UDK 61

ISSN 0031-6857

HRVATSKO DRUŠTVO FARMAKOLOGA
CROATIAN PHARMACOLOGICAL SOCIETY

HDKFiT

INTERNATIONAL SOCIETY OF DRUG BULLETINS

10. HRVATSKI KONGRES FARMAKOLOGIJE I
1. HRVATSKI KONGRES KLINIČKE FARMAKOLOGIJE
S MEĐUNARODNIM SUDJELOVANJEM

10TH CROATIAN CONGRESS OF PHARMACOLOGY AND THE
1ST CROATIAN CONGRESS OF CLINICAL PHARMACOLOGY
WITH INTERNATIONAL PARTICIPATION

pharmaca

GLASILO HRVATSKOG DRUŠTVA ZA
KLINIČKU FARMAKOLOGIJU I TERAPIJU

HRVATSKI ČASOPIS ZA FARMAKOTERAPIJU

Pharmaca 2022; 52 Suppl 2

Zagreb, 2022.

Final programme and abstracts from the

10th Croatian Congress of Pharmacology and the 1st Croatian Congress of Clinical Pharmacology with International Participation

Opatija, September 22 – 25, 2022

Guest Editors: Jasenka Mršić-Pelčić

Dinko Vitezić

Tamara Janković

ORGANIZERS

CONGRESS ORGANIZERS

Croatian Pharmacological Society

Croatian Society of Clinical Pharmacology and Therapeutics, Croatian Medical Association

Faculty of Medicine, University of Rijeka

Agency for Medicinal Products and Medical Devices (HALMED)

ORGANIZING COMMITTEE

Presidents: Jasenka Mršić-Pelčić (Rijeka), Dinko Vitezić (Rijeka)

Members: Melita Šalković-Petrišić (Zagreb), Darko Modun (Split), Lidija Bach-Rojecky (Zagreb), Suzana Matanović Mimica (Osijek), Kristina Peroš (Zagreb), Pero Draganić (Zagreb), Matea Nikolac Perković (Zagreb), Dubravka Švob Štrac (Zagreb), Viktorija Erdeljić Turk (Zagreb), Ksenija Makar-Aušperger (Zagreb), Iveta Merćep (Zagreb), Goran Hauser (Rijeka), Siniša Tomić (Zagreb)

LOCAL ORGANIZING COMMITTEE

Renata Jurišić-Grubešić, Elitza Petkova Markova Car, Marko Skelin, Petra Dolenec, Jelena Rajič Bumber, Tamara Janković, Lea Juretić, Andrej Belančić, Igor Rubinić, Anja Harej Hrkać

SCIENTIFIC COMMITTEE

President: Marijan Klarica (Zagreb)

Members: Zdravko Lacković (Zagreb), Vera Vlahović Palčevski (Rijeka), Kristina Pilipović (Rijeka), Mladen Boban (Split), Nada Božina (Zagreb), Ivana Šutej (Zagreb), Vesna Eraković (Zagreb), Vladimir Trkulja (Zagreb), Robert Likić (Zagreb), Jasna Križ (Kanada), Jean Pierre Julien (Kanada), Tabassome Simon (Francuska), Luka Čičin Šain (Njemačka)

UNDER THE AUSPICES

Croatian Academy of Sciences and Arts

CONTENTS

EDITORIAL

I am very proud to present the second supplement of our journal this year. This one is dedicated, or rather, connected to the 10th congress of pharmacology, but also to the 1st congress of clinical pharmacology, which is particularly important for us. Fundamental/basic pharmacology has been closely related to clinical pharmacology for a long time, as it must be, and we have always participated in the previous pharmacological congresses with great representation and value.

But this time, our Croatian Society for Clinical Pharmacology and Therapy, with its official journal Pharmaca, is jointly organizing a congress for the first time with the Croatian Pharmacological Society. It is needless to emphasize how good, useful, necessary and valuable this is. The field of pharmacology is perhaps more important than ever, especially because it is necessary to quickly gain and translate scientific results into clinical reality. It is difficult to predict how many tasks, unknowns and work is to be done still, but there is no shortage in young people in both professions, and I am sure that with joint efforts, pharmacology and clinical pharmacology will move forward with full impulse.

The congress will be held in Opatija, from September 22 to 25, 2022, and it seems to me that it is precisely in Opatija, with its long history, a wonderful present, and a bright future, and the past, present, and future of both associated scientific disciplines, are symbolically combined.

On behalf of myself and the Editorial Board, we wish the congress participants and organizers success, fruitful discussions, prestigious lectures and, above all, pleasant socializing.

Ksenija Makar-Aušperger

Chief editor of the journal Pharmaca

WELCOME NOTE

Dear colleagues and friends,

It is our pleasure to welcome you to Opatija for the 10th Croatian Congress of Pharmacology and the 1st Croatian Congress of Clinical Pharmacology with international participation!

The Croatian Pharmacological Society has a long tradition of organising successful congresses that bring together leading national and international experts in the field of basic and clinical pharmacology and related disciplines. We are proud that the Croatian Pharmacological Society and the Croatian Society of Clinical Pharmacology and Therapeutics of the Croatian Medical Association are for the first time jointly organising this Congress.

More than 100 distinguished scientists and experts of various profiles from Croatia and abroad have the opportunity to discuss current achievements and trends in basic and clinical pharmacology, pharmacotherapy, drug safety and regulation, as well as in the education of physicians, pharmacists and other experts in the field of pharmacology. We have four plenary lectures (one supported by EPHAR), 19 symposia, two roundtables, one workshop and four popular lectures. In addition, there will be three poster sessions including student presentations with the aim of popularisation pharmacology among young professionals. The Congress is an ideal opportunity in exchange of knowledge in pharmacology between experienced as well as young scientists, professionals in different fields of medicine and representatives of the pharmaceutical industry. We have no doubt that lively discussions will spark new ideas for future research and collaborations.

The Agency for Medicinal Products and Medical Devices of Croatia (HALMED) is presenting its activities and topics of interest in two symposia, a workshop and a roundtable discussion.

All these activities will help to promote and improve our knowledge about the efficacy, quality and safety of possible therapeutic strategies and human health in general.

In addition to the scientific and formal part of the Congress, we look forward to spending time together in charming Opatija, known for its natural beauty, Mediterranean climate, historical monuments, long coastal promenades and more than 170 years of tradition in tourism.

Finally, we would like to thank everyone who contributed and supported the organisation of the Congress, including institutions, companies, sponsors and donators.

Welcome to Opatija!

Prof. Jasenka Mršić-Pelčić, MD, PhD

President of the Croatian Pharmacological Society

Prof. Dinko Vitezić, MD, PhD

President of the Croatian Society for Clinical Pharmacology and Therapeutics of the CMA

GENERAL INFORMATION

Congress venue

Amadria Park Grand Hotel 4 Opatijska Cvijeta

Viktora Cara Emina 6, 51410, Opatija

Congress official languages

Croatian and English

Professional Congress Organizer

O-TOURS PCO d.o.o. | Gajeva 6/1, 10000 Zagreb

Tel: +385 1 4831 444 | Email: tatjana.koprtla@otours.hr

Congress web sites

https://events.otours.hr/FARMAKO2022

http://hdf-pharma.mef.hr/

REGISTRATION

Congress pre-registration

On-line registration via Congress website:

https://events.otours.hr/FARMAKO2022

TOPICS OF PLENARY LECTURES, SYMPOSIA, ROUND TABLES, POPULAR LECTURES AND WORKSHOP

Plenary lectures

P 1	Development of antibody approaches to target TDP-43 proteinopathy in ALS and dementia, Jean-Pierre Julien (Canada)
P 2	Pharmacological and immunological interventions targeting COVID-19 disease, Luka Čičin-Šain (Germany)
P 3	Transfusion strategies and cardiovascular outcomes following an acute myocardial infarction, Tabassome Simon (France), EPHAR lecture 2022
P 4	Pharmacogenomics for personalized medicine: From bench... to the drug label... to bedside, Julia Carolin Stingl (Germany)

Symposia

Symposia	Organiser	Title
S 01 Precongress symposium	Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)	Drug regulation
S 02	Melita Šalković-Petrišić, Jelena Osmanović Barilar (Zagreb)	Pharmacology of central and peripheral metabolism in neurodegenerative disorders
S 03	Vera Vlahović Palčevski (Rijeka), Milan Čižman (Ljubljana)	Rational antimicrobial drug use - antimicrobial stewardship
S 04	Ivana Šutej, Kristina Peroš (Zagreb)	Pharmacology in dental medicine - pandemic response
S 05	Suzana Mimica (Osijek)	The place of biologic and biosimilar drugs in current medicine practice
S 06	Dubravka Jurišić Eržen (Rijeka)	Modern approach to the treatment of diabetes and metabolic diseases - new challenges and opportunities
S 07	Dubravka Švob Štrac (Zagreb)	Recent findings in neuropsychopharmacology of mental disorders

S 08	Stjepko Pleština (Zagreb)	News in the treatment of malignant diseases
S 09	Mladen Boban (Split)	Pharmacological approaches to cardiometabolic disorders
S 10	Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)	GMP mini symposium
S 11	Predrag Sikirić (Zagreb)	BPC157
S 12	Viktorija Erdeljić Turk (Zagreb)	Immunopharmacology: from vaccines to immunotherapy
S 13	Renata Jurišić Grubešić, Marko Skelin (Rijeka)	Rational pharmacotherapy: the role of the pharmacist
S 14	Dinko Vitezić (Rijeka)	Rare diseases: opportunities and challenges in the treatment
S 15	Kristina Pilipović, Jasenka Mršić-Pelčić (Rijeka)	Novel insights into the function of glial cells in health and disease
S 16	Nada Božina (Zagreb)	Pharmacogenomics in personalised medicine: how far have we come and how far could we go?
S 17	Iveta Merćep (Zagreb)	Development of new medicines
S 18	Lidija Bach Rojecky, Ivica Matak (Zagreb)	Clostridial neurotoxins and their role in sensory and motor functions in the central nervous system
S 19	Marijan Klarica (Zagreb)	Symposium "Marin Bulat": The influence of interstitial and cerebrospinal fluid movement on the distribution of drugs, metabolites and biomarkers within the craniospinal space

Round tables

RT 01 HALMED

Vaccines against Covid-19 - lessons learned

RT 02 Croatian Pharmacological Society

Croatian programme for EuCP qualification

Popular lectures

PL 01/1 We have a cure for obesity: the use of liraglutide 6.0mg/ml in the treatment of obesity – Miličić D, Klobučar Majanović S

PL 01/2 Communication between gut microbiota and neurons: the toll-like story – Giron MC

PL 02/1 Chinese traditional medicine-music therapy - Zhao Simonić R, Simonić A

PL 02/2 Traditional chinese medicine (TCM) as a vital component of integrative medicine - Simonić A, Zhao Simonić R

Workshop

W 01 HALMED

Pharmacovigilance

TIMETABLE OF CONGRESS ACTIVITIES

Thursday, September 22, 2022	
12:00-18:00	**Registration of Congress participants**
14:00-17:30	**Precongress symposium S 01**
S 01 **Hall 1A**	**DRUG REGULATION** Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)
	S 01/1 HALMED'S PAST ACHIVEMENTS AND FUTURE CHALLENGES - Lovrek Romčević M, Tomić S (Croatia)
	S 01/2 REVISION OF THE EU GENERAL PHARMACEUTICALS LEGISLATION – Uzeirbegović S, Lovrek Romčević M, Marušić Kontent G, Tomić S (Croatia)
	S 01/3 PHARMACOVIGILANCE UPDATE - Margan Koletić Ž, Tomić S (Croatia)
	Refreshments
	S 01/4 THE ROLE OF CLINICAL PHARMACOLOGISTS IN THE AUTHORISATION OF INNOVATIVE MEDICINES - Juričić Nahal D (Croatia)
	S 01/5 SPECIFICS AND TENDENCIES OF DRUG CONSUMPTION IN CROATIA IN THE LAST FIVE YEARS - Draganić P (Croatia)
	S 01/6 MANAGEMENT OF MEDICINES SHORTAGES – Cvek J, Kontek A, Bilandžija B (Croatia)
	S 01/7 MEDICINAL PRODUCT DATA STANDARDISATION – PRECONDITION FOR EFFICIENT DATA EXCHANGE BETWEEN ALL STAKEHOLDERS – Sudić D, Grčić Plečko S (Croatia)
18:00-18:45 **Hall 1A**	**Opening ceremony**
18:45-19:30	**Plenary lecture P 1** Chairperson: Jasenka Mršić-Pelčić (Croatia)
P 1 **Hall 1A**	**DEVELOPMENT OF ANTIBODY APPROACHES TO TARGET TDP-43 PROTEINOPATHY IN ALS AND DEMENTIA - Jean-Pierre Julien (Canada)**
19:30-21:00	**Welcome reception**

Friday, September 23, 2022	
08.30-10:00	**Round table RT 01 / Symposium S 02 / Symposium S 03**
RT 01 **Hall 1A**	**VACCINES AGAINST COVID-19 - LESSONS LEARNED** Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)
	RT 01/1 VACCINES AGAINST COVID-19 - LESSONS LEARNED FROM SAFETY MONITORING – Mirošević Skvrce N (Croatia)
	RT 01/2 VACCINES DEVELOPMENT – LESSONS FROM THE COVID-19 PANDEMIC – Šlezak T (Croatia)
	RT 01/3 CHALLENGES OF VACCINES QUALITY ASSESSMENT IN THE CONTEXT OF PANDEMIC – Derganc D (Croatia)
S 02 **Hall 1B**	**PHARMACOLOGY OF CENTRAL AND PERIPHERAL METABOLISM IN NEURODEGENERATIVE DISORDERS** Chairpersons: Melita Šalković-Petrišić (Croatia), Jelena Osmanović Barilar (Croatia)
	S 02/1 INTRODUCTION TO METABOLIC AND OTHER NON-COGNITIVE PATHOLOGY IN NEURODEGENERATIVE DISORDERS – Šalković-Petrišić M (Croatia)
	S 02/2 CROSSTALK BETWEEN OXIDATIVE STRESS AND ABERRANT INSULIN SIGNALLING IN THE BRAIN: INSIGHTS FOR NEURODEGENERATION – Barone E (Italy)
	S 02/3 METABOLIC EFFECTS OF ACUTE CENTRAL INCRETIN RECEPTORS INHIBITION IN A RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE – Osmanović Barilar J, Knezović A, Babić A, Homolak J, Šalković-Petrišić M (Croatia)
	S 02/4 GASTROINTESTINAL CHANGES IN THE RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE – AN OPPORTUNITY FOR THERAPEUTIC INTERVENTION WITH D-GALACTOSE? – Homolak J, Joja M, Virag D, Babić Perhoč A, Knezović A, Osmanović Barilar J, Šalković-Petrišić M (Croatia)
	S 02/5 MODELLING OF PARKINSON'S DISEASE BY INTRASTRIATAL ADMINISTRATION OF A DIABETOGENIC COMPOUND – Knezović A, Osmanović Barilar J, Farkas V, Bagaric R, Virag D, Babić Perhoč A, Homolak J, Šalković-Petrišić M (Croatia)
S 03 **Hall 1C**	**RATIONAL ANTIMICROBIAL DRUG USE - ANTIMICROBIAL STEWARDSHIP** Chairpersons: Vera Vlahović Palčevski (Croatia), Milan Čižman (Slovenia)

	S 03/1 ECDC PERSPECTIVE ON ANTIMICROBIAL STEWARDSHIP (on-line) – Monnet D (ECDC)
	S 03/2 THE ROLE OF EDUCATION IN ANTIMICROBIAL STEWARDSHIP – Beović B (Slovenia)
	S 03/3 USE OF ANTIBIOTICS DURING PANDEMIC COVID-19 – Baršić B (Croatia)
10:00-10:30	**Coffee break**
10:30-11:15	**Plenary lecture P 2** Chairperson: Viktorija Erdeljić Turk (Croatia)
P 2 **Hall 1A**	**PHARMACOLOGICAL AND IMMUNOLOGICAL INTERVENTIONS TARGETING COVID-19 DISEASE - Luka Čičin-Šain (Germany)**
11:20-12:50	**Symposium S 04 / Symposium S 05 / Symposium S 06**
S 04 **Hall 1A**	**PHARMACOLOGY IN DENTAL MEDICINE - PANDEMIC RESPONSE** Chairpersons: Ivana Šutej (Croatia), Kristina Peroš (Croatia)
	S 04/1 PANDEMIC RESPONSE - ADJUSTMENT IN PHARMACOTHERAPY AND PRESCRIBING – Šutej I (Croatia)
	S 04/2 ORAL ANTISEPTICS AGAINST CORONAVIRUS – ARE THEY JUSTIFIED – Bašić K (Croatia)
	S 04/3 STRENGHTS AND LIMITATIONS OF COVID SALIVA TESTING – Peroš K (Croatia)
	S 04/4 SALIVA DIAGNOSTICS ON EVERYONE'S LIPS: COVID-19 TESTING AND BEYOND – Hofner M, Kegler U, Huber J, Krainer J, Klausberger M, Regele V, Dürkop M, Vierlinger K, Weinhäusel A, Noehammer C (Austria)
S 05 **Hall 1B**	**THE PLACE OF BIOLOGIC AND BIOSIMILAR DRUGS IN CURRENT MEDICINE PRACTICE** Chairperson: Suzana Mimica (Croatia)
	S 05/1 THE CHALLENGES OF BIOSMILAR DRUGS USE: 16 YEARS LATER – Mimica S (Croatia)
	S 05/2 ADVERSE REACTIONS TO BIOLOGICAL MEDICINES – Juričić Nahal D (Croatia)
	S 05/3 NOVEL BIOLOGICAL MEDICINAL PRODUCTS FOR THE TREATMENT OF MALIGNANT AND AUTOIMMUNE DISEASES – Arapović Džakula S (Croatia)
	S 05/4 BIOLOGIC DRUGS FOR THE TREAMENT OF COVID-19: CURRENT KNOWLEDGE AND CHALLENGES FOR THE FUTURE – Havidić A (Croatia)

S 06 **Hall 1C**	**MODERN APPROACH TO THE TREATMENT OF DIABETES AND METABOLIC DISEASES – NEW CHALLENGES AND OPPORTUNITIES** Chairperson: Dubravka Jurišić Eržen (Croatia)
	S 06/1 INCRETIN THERAPY: EFFECTS BEYOND GLYCEMIC CONTROL –Tičinović Kurir T (Croatia)
	S 06/2 SGLT2 INHIBITORS - MECHANISM OF CARDIO AND RENAL PROTECTION – Rahelić D (Croatia)
	S 06/3 PAST, PRESENT AND FUTURE OF INSULIN THERAPY – Jurišić Eržen D (Croatia)
	S 06/4 IMMUNE CHECKPOINT INHIBITOR MEDIATED ENDOCRINOPATHIES – Nazlić J (Croatia)
12:50-14:10	**Lunch**
14:10-15:10	**Poster session 1 with organized discussion**
15:10-16:40	**Symposium S 07 / Symposium S 08 / Symposium S 09**
S 07 **Hall 1A**	**RECENT FINDINGS IN NEUROPSYCHOPHARMACOLOGY OF MENTAL DISORDERS** Chairperson: Dubravka Švob Štrac (Croatia)
	S 07/1 INTRODUCTION: RECENT FINDINGS IN NEUROPSYCHOPHARMACOLOGY OF MENTAL DISORDERS – Švob Štrac D (Croatia)
	S 07/2 BENEFICIAL EFFECT OF ESTROGEN DERIVATES IN ALZHEIMER DISEASE: STUDIES IN MICE MODEL – Zelena D, Farkas S, Szabó A, Török B, Sólyomvári C, Fazekas CL, Bánrévi K, Correia P, Chaves T, Ábrahám I (Hungary)
	S 07/3 SIDE EFFECTS OF PSYCHOPHARMACS: RECOGNIZE, PREVENT, TREAT – Uzun S, Kozumplik O, Mimica N (Croatia)
	S 07/4 MULTIMODAL APPROACH TO THE DEPRESSION TREATMENT: FOCUS ON VORTIOXETINE – Nikolac Perković M, Dvojković A, Nedić Erjavec G, Mihaljević Peleš A, Vuksan Čusa B, Tudor L, Kušević Z, Konjevod M, Živković M, Jakšić N, Pivac N, Šagud M (Croatia)
	S 07/5 METABOLOMICS IN ALZHEIMER'S DISEASE AS A TOOL FOR BIOMARKER DISCOVERY AND EARLY DIAGNOSIS – Nedić Erjavec G, Nikolac Perković M, Uzun S, Barbas C, Pivac N (Croatia)
	S 07/6 EPIGENETIC, GENETIC AND EXPRESSION ANALYSIS OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN ALZHEIMER'S DISEASE – Tudor L, Nikolac Perković M, Babić Leko M, Videtič Paska A, Kouter K, Miloš T, Nedić Erjavec G, Vuić B, Konjevod M, Šimić G, Borovečki F, Pivac N (Croatia)

S 08 **Hall 1B**	**NEWS IN THE TREATMENT OF MALIGNANT DISEASES** Chairperson: Stjepko Pleština (Croatia)
	S 08/1 ONCOLOGY DURING THE DEVELOPMENT OF PERSONALIZED MEDICINE – Pleština S (Croatia)
	S 08/2 MOLECULAR TUMOR PROFILE IN THE ERA OF PRECISION MEDICINE – THE EXAMPLE OF CHOLANGIOCELLULAR CARCINOMA – Belev B (Croatia)
	S 08/3 ANTIBODY DRUG CONJUGATES IN THE TREATMENT OF METASTATIC BREAST CANCER – Dedić Plavetić N (Croatia)
	S 08/4 IMMUNE CHECKPOINT INHIBITORS IN TREATMENT OF NON-SMALL CELL LUNG CANCER PATIENTS - THE MECHANISMS, EFFICACY, AND SAFETY OF ICI AGENTS AND COMBINATIONS – Pleština S (Croatia)
S 09 **Hall 1C**	**PHARMACOLOGICAL APPROACHES TO CARDIOMETABOLIC DISORDERS** Chairperson: Mladen Boban (Croatia)
	S 09/1 CHANGES IN THE MYOCARDIAL METABOLISM IN TYPE 2 DIABETES MELLITUS – Ljubkovic M, Bulat C, Ćavar M, Grkovic I, Lemaire C, Marinovic J (Croatia)
	S 09/2 ANTIDIABETICS IN CARDIOVASCULAR DISEASE THERAPY – Knežević A (Croatia)
	S 09/3 WINE CONSUMPTION IN TYPE 2 DIABETES MELLITUS: FRIEND OR FOE – Boban M (Croatia)
	S 09/4 HEPCIDIN: A NEW SITE OF ACTION OF WINE IN PATIENTS WITH DIABETES MELLITUS TYPE 2 – Gujinović D (Croatia)
	S 09/5 EFFECT OF MODERATE WHITE WINE CONSUMPTION ON THE EXPRESSION OF HSP70, GPX, CAT AND NQO1 IN RAT CARDIOMYOCYTES – Benzon B, Mastelić A, Grahovac M, Matijević J, Marinović Ljubković J, Ljubković M, Mudnić I, Grković I, Boban M (Croatia)
16:40-17:00	**Coffee break**
17:00-17:45	**Plenary lecture P 3** Chairperson: Dinko Vitezić (Croatia)
P 3 **Hall 1A**	**TRANSFUSION STRATEGIES AND CARDIOVASCULAR OUTCOMES FOLLOWING AN ACUTE MYOCARDIAL INFARCTION - Tabassome Simon (France),** EPHAR lecture 2022
17:50-18:20 **Hall 1A**	**Annual HDF Assembly (for HDF members only)**

Saturday, September 24, 2022	
08:30-10:00	**Symposium S 10 / Symposium S 11 / Symposium S 12**
S 10 **Hall 1A**	**GMP MINI SYMPOSIUM** Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)
	S 10/1 INSPECTION OD GOOD MANUFACTURING PRACTICE – Kolonić T, Bencetić Marijanović M (Croatia)
	S 10/2 SERIOUS GMP NON-COMPLIANCE – Hodak Lj (Croatia)
	S 10/3 CROSS-CONTAMINATION RISKS IN PHARMACEUTICAL PRODUCTION, GMP PERSPECTIVE – Jukić S (Croatia)
	S 10/4 IMPORTATION, QUALITY CONTROL AND BATCH RELEASE OF MEDICINAL PRODUCTS – Trbojević Krpanić T (Croatia)
S 11 **Hall 1B**	**BPC157** Chairperson: Predrag Sikirić (Croatia)
	S 11/1 GASTRIC PENTADECAPEPTIDE BPC 157 IN CYTOPROTECTION TO RESOLVE MAJOR VESSEL OCCLUSION DISTURBANCES, ISCHEMIA-REPERFUSION INJURY – Sikirić P (Croatia)
	S 11/2 THE NEUROLEPTICS, AMPHETAMINE AND DOMPERIDONE APPLICATION AS INNATE VASCULAR FAILURE, AND THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157, AS THERAPY, MIGHT BE THE PARTICULAR KEY – Strbe S (Croatia)
	S 11/3 STABLE GASTRIC PENTADECAPEPTIDE BPC 157 AND MUSCLE HEALING FOR POSSIBLE THERAPY – Skrtic A (Croatia)
	S 11/4 THE HEARTH DISTURBANCES, MYOCARDIAL INFARCTION, ARRHYTHMIAS, CONGESTIVE HEART FAILURE, PULMONARY HYPERTENSION AND THROMBOSIS PRESENTATION FOR THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157 AS USEFUL PEPTIDE THERAPY – Seiwerth S (Croatia)
S 12 **Hall 1C**	**IMMUNOPHARMACOLOGY: FROM VACCINES TO IMMUNOTHERAPY** Chairperson: Viktorija Erdeljić Turk (Croatia)
	S 12/1 NEW THERAPIES FOR IMMUNE-MEDIATED DISEASES – Mimica S (Croatia)
	S 12/2 TARGETED THERAPIES FOR ALLERGIC DISEASES – Čegec I (Croatia)
	S 12/3 DEVELOPMENT OF IMMUNO-ONCOLOGY DRUGS – Erdeljić Turk V (Croatia)
	S 12/4 VACCINES: PREVENTIVE, THERAPEUTIC, PERSONALIZED – Macolić- Šarinić V (EMA)

	S 12/5 IMMUNE-MEDIATED ADVERSE EFFECTS OF COVID-19 VACCINE – Strikić D, Erdeljić Turk V (Croatia)
10:00-10:30	**Coffee break**
10:30-12:00	**Symposium S 13 / Popular lectures PL 01 / Popular lectures PL 02**
S 13 **Hall 1A**	**RATIONAL PHARMACOTHERAPY: THE ROLE OF THE PHARMACIST** Chairpersons: Renata Jurišić Grubešić (Croatia), Marko Skelin (Croatia)
	S 13/1 THE FUTURE OF THE CENTRAL PREPARATION OF ANTINEOPLASTIC DRUGS IN THE ERA OF DIGITIZATION AND ROBOTIZATION – Pavlica V (Croatia)
	S 13/2 RATIONAL PHYTOTHERAPY IN THE MAINTENANCE OF MENTAL HEALTH – Vladimir-Knežević S (Croatia)
	S 13/3 POTENTIALLY INAPPROPRIATE MEDICINES IN OLDER PEOPLE – LESSONS LEARNED FROM EUROAGEISM PROJECT – Ortner Hadžiabdić M (Croatia)
	S 13/4 COMPREHENSIVE MEDICATION MANAGEMENT AT THE PRIMARY CARE LEVEL - IMPLEMENTATION AT THE HEALTH CARE CENTRE ZAGREB CENTRE – Mucalo I, Brajković A (Croatia)
	S 13/5 INFLUENCE OF QUALITY OF LIFE ON ADHERENCE TO ADJUVANT ENDOCRINE THERAPY IN WOMEN WITH EARLY BREAST CANCER – Dugonjić Okroša A, Silovski T, Dedić Plavetić N, Mucalo I (Croatia)
	S 13/6 RATIONAL DRUG USE IN A PATIENT WITH TYPE 2 DIABETES AND CARDIOVASCULAR DISEASES - A CASE STUDY – Mucalo I, Bićanić LA, Brajković A (Croatia)
PL 01 **Hall 1B**	**Popular lectures PL 01** Chairperson: Goran Hauser (Croatia)
10:30-11:00	**PL 01/1** WE HAVE A CURE FOR OBESITY: THE USE OF LIRAGLUTIDE 6.0MG/ML IN THE TREATMENT OF OBESITY – Miličić D, Klobučar Majanović S (Croatia)
11:00-11:30	**PL 01/2** COMMUNICATION BETWEEN GUT MICROBIOTA AND NEURONS: THE TOLL-LIKE STORY – Giron MC (Italy)
PL 02 **Hall 1C**	**Popular lectures PL 02** Chairperson: Kristina Pilipović (Croatia)
10:30-11:00	**PL 02/1** CHINESE TRADITIONAL MEDICINE-MUSIC THERAPY - Zhao Simonić R, Simonić A (Croatia)
11:00-11:30	**PL 02/2** TRADITIONAL CHINESE MEDICINE (TCM) AS A VITAL COMPONENT OF INTEGRATIVE MEDICINE - Simonić A, Zhao Simonić R (Croatia)

12:00-12:45	**Plenary lecture P 4** Chairperson: Nada Božina (Croatia)
P 4 **Hall 1A**	**PHARMACOGENOMICS FOR PERSONALIZED MEDICINE: FROM BENCH... TO THE DRUG LABEL... TO BEDSIDE - Julia Carolin Stingl (Germany)**
12:45-14:00	**Lunch**
14:00-15:00	**Poster session 2 with organized discussion**
15:00-16:30	**Workshop W 01 / Symposium S 14 / Symposium S 15**
W 01 **Hall 1A**	**PHARMACOVIGILANCE** Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)
	W 01/1 MEDICATION ERRORS IN CHILDREN AND ADOLESCENTS – Mirošević Skvrce N, Margan Koletić Ž, Prpić S (Croatia)
S 14 **Hall 1B**	**RARE DISEASES: OPPORTUNITIES AND CHALLENGES IN THE TREATMENT** Chairperson: Dinko Vitezić (Croatia)
	S 14/1 ORPHAN DRUGS: FROM RESEARCH TO APPLICATION – Vitezić D (Croatia)
	S 14/2 EUROPEAN INITIATIVES IN A COMPREHENSIVE APPROACH TO THE TREATMENT OF RARE DISEASES – Barišić I (Croatia)
	S 14/3 AVAILABILITY OF ORPHAN MEDICINES IN CROATIA – Strbad T (Croatia)
	S 14/4 FROM DIAGNOSIS TO TREATMENT OF NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 (CLN2) - CLINICAL AND ADMINISTRATIVE CHALLENGES – Prpić I (Croatia)
	S 14/5 REAL-WORLD EVALUATION OF PHARMACOLOGICAL TREATMENT FOR SPINAL MUSCULAR ATROPHY – CROATIAN EXPERIENCE – Belančić A, Strbad T, Vitezić D (Croatia)
S 15 **Hall 1C**	**NOVEL INSIGHTS INTO THE FUNCTION OF GLIAL CELLS IN HEALTH AND DISEASE** Chairpersons: Kristina Pilipović (Croatia), Jasenka Mršić-Pelčić (Croatia)
	S 15/1 INTRODUCTION - BRAIN INJURY: NEUROPROTECTIVE STRATEGIES - Mršić-Pelčić J (Croatia)
	S 15/2 DRUG REPURPOSING MODEL: NEURO-IMMUNO-METABOLIC ROLE OF NALTREXONE – Kučić N, Rački V, Grahovac I, Mršić-Pelčić J (Croatia)

	S 15/3 THE EFFECTS OF CHEMICALLY-FUNCTIONALIZED SINGLE-WALLED CARBON NANOTUBES ON PRIMARY MOUSE ASTROCYTES IN AN IN VITRO MODEL OF SEVERE TRAUMATIC BRAIN INJURY – Pilipović K, Gržeta N, Harej Hrkać A, Parpura V (Croatia)
	S 15/4 IMMUNITY IN AMYOTROPHIC LATERAL SCLEROSIS: BLURRED LINES BETWEEN EXCESSIVE INFLAMMATION AND INEFFICIENT IMMUNE RESPONSES – Munitić I (Croatia)
	S 15/5 TRAUMATIC BRAIN INJURY AND PIOGLITAZONE: BENEFITS AND LIMITATIONS OF NEUROPROTECTIVE THERAPY – Dolenec P, Pilipović K, Delač Lj, Slavić A, Župan Ž, Župan G (Croatia)
	S 15/6 EFFECTS OF A SINGLE MODERATE TRAUMATIC BRAIN INJURY IN MOUSE ON THE TAR DNA-BINDING PROTEIN 43 AND ITS CONNECTION WITH NEUROINFLAMMATION AND SYNAPTIC PLASTICITY – Janković T, Gržeta N, Rajič Bumber J, Dolenec P, Križ J, Župan G, Pilipović K (Croatia)
16:30-17:00	**Coffee break**
17:00-18:30	**Symposium S 16 / Symposium S 17 / Symposium S 18**
S 16 **Hall 1A**	**PHARMACOGENOMICS IN PERSONALISED MEDICINE: HOW FAR HAVE WE COME AND HOW FAR COULD WE GO?** Chairperson: Nada Božina (Croatia)
	S 16/1 PHARMACOGENOMICS IN ADVERSE DRUG REACTIONS LEADING TO EMERGENCY HOSPITAL VISITS – Stingl JC (Germany)
	S 16/2 PRECISION MEDICINE IN RENAL TRANSPLANT PATIENTS - ROLE OF ABCG2 LOSS OF FUNCTION POLYMORPHISM – Borić Bilušić A, Božina N, Lalić Z, Nađ-Škegro S, Penezić L, Barišić K, Trkulja V (Croatia)
	S 16/3 PHARMACOGENOMICS IN THE PREDICTION OF CARDIOVASCULAR DRUGS ADVERSE REACTIONS - PGX-CARDIODRUG: PRELIMINARY RESULTS – Božina T, Vrkić Kirhmajer M, Šimičević L, Ganoci L, Palić J, Bićanić LA, Mucalo I, Samardžić J (Croatia)
	S 16/4 INFLUENCE OF ABCG2 421C>A POLYMORPHISM AND VALPROATE ON STEADY-STATE DISPOSITION OF LAMOTRIGINE - Šušak Sporiš I, Božina N, Trkulja V, Klarica Domjanović I, Sporiš D, Bašić S, Marković I, Lovrić M, Čolak Romić Z (Croatia)
S 17 **Hall 1B**	**DEVELOPMENT OF NEW MEDICINES** Chairperson: Iveta Merćep (Croatia)
	S 17/1 CLINICAL TRIALS AND THE NEW EUROPEAN UNION DIRECTIVE – Merćep I, Strikić D (Croatia)

	S 17/2 DRUG DEVELOPMENT – Radačić Aumiler M (Croatia)
	S 17/3 WHY DO CLINICAL DRUG TRIALS SO OFTEN FAIL? – Makar-Aušperger K (Croatia)
	S 17/4 IN SILICO METHODS IN DEVELOPMENT OF NEW THERAPEUTIC COMPOUNDS – Likić R (Croatia)
	S 17/5 INTERPRETING RESULTS OF CLINICAL TRIALS: COMMON STATISTICAL CONCERNS – Erdeljić Turk V (Croatia)
S 18 **Hall 1C**	**CLOSTRIDIAL NEUROTOXINS AND THEIR ROLE IN SENSORY AND MOTOR FUNCTIONS IN THE CENTRAL NERVOUS SYSTEM** Chairpersons: Lidija Bach Rojecky (Croatia), Ivica Matak (Croatia)
	S 18/1 BOTULINUM TOXIN TYPE AXONAL TRANSPORT FROM THE PERIPHERY TO THE BRAIN: IS IT GOOD OR BAD? – Lacković Z (Croatia)
	S 18/2 CORTICAL REWIRING FOLLOWING PERIPHERAL INJECTION OF BOTULINUM TOXIN TYPE A – Tiberi A, Massa V, Pirazzini M, Rossetto O, Caleo M, Restani L (Italy)
	S 18/3 FABS FROM PURIFIED HUMABS OPEN TO THE INTRATHECAL THERAPY OF TETANUS – Pirazzini M, Fabris F, Šoštarić P, Meglić P, Tonellato M, Grinzato A, Corti D, Lanzavechhia A, Schiavo G, Rossetto O, Zanotti G, Montecucco C, Matak I (Italy)
	S 18/4 LONG TERM CENTRAL EFFECTS OF BOTULINUM TOXIN TYPE A ON MUSCULAR FUNCTION AND RECOVERY IN RAT – Šoštarić P, Matić M, Matak I (Croatia)
	S 18/5 UPDATE ON BOTULINUM TOXIN TYPE A CENTRAL ACTION ON PAIN – ARE THE PRIMARY AFFERENTS IN THE SPINAL CORD ITS FINAL DESTINATION? – Vađunec D, Matak I, Bach-Rojecky L (Croatia)
20:00	**Congress dinner**

Sunday, September 25, 2022	
09:00-10:15	**Round table RT 02**
RT 02 **Hall 1A**	**CROATIAN PROGRAMME FOR EuCP QUALIFICATION** Croatian Pharmacological Society Moderators: Vladimir Trkulja, Melita Šalković Petrišić, Jasenka Mršić-Pelčić, Mladen Boban, Dubravka Švob Štrac, Jelena Osmanović Barilar
10:15-11:15	**Poster session 3 with organized discussion: Students section "HDF youth programme"**
11:15-11:30	**Coffee break**
11:30-13:00	**Symposium S 19**
S 19 **Hall 1A**	**SYMPOSIUM "MARIN BULAT" - THE INFLUENCE OF INTERSTITIAL AND CEREBROSPINAL FLUID MOVEMENT ON THE DISTRIBUTION OF DRUGS, METABOLITES AND BIOMARKERS WITHIN THE CRANIOSPINAL SPACE** Chairperson: Marijan Klarica (Croatia)
	S 19/1 DISTRIBUTION OF VARIOUS SUBSTANCES BETWEEN CSF AND INTERSTITIAL SPACE AFTER THEIR APPLICATION IN DIFFERENT CSF COMPARTMENTS – Klarica M, Radoš M, Jurjević I, Orešković D (Croatia)
	S 19/2 DYNAMICS OF BLOOD AND CEREBROSPINAL FLUID BIOMARKERS OF ALZHEIMER'S DISEASE – Šimić G, Babić Leko M, Mihelčić M (Croatia)
	S 19/3 SUBSTANCE DISTRIBUTION CHANGES AFTER CSF PATHWAY IMPAIREMENT IN DIFFERENT PARTS OF CRANIOSPINAL SPACE – Klarica M, Radoš M, Jurjević I, Kudelić N, Orešković D (Croatia)
	S 19/4 ROLE OF ARACHNOID GRANULATIONS IN CEREBROSPINAL FLUID PHYSIOLOGY: ANALYSIS BY MAGNETIC RESONANCE IMAGING – Radoš M, Živko M, Periša A, Orešković D, Klarica M (Croatia)
13:00-13:15 **Hall 1A**	**Best poster awards**
13:15-14:00 **Hall 1A**	**Closing ceremony**

POSTER SECTIONS

Friday, September 23, 2022	
Poster session 1 with organized discussion **Chairpersons: Suzana Mimica (Croatia), Dubravka Švob Štrac (Croatia)**	
P1 01	PHARMACOGENOMICS OF ROSUVASTATIN – IMPACT OF ABCG2 AND SLCO1B1 POLYMORPHISMS AND DRUG-DRUG INTERACTIONS ON DEVELOPMENT OF ADVERSE DRUG REACTIONS - Ganoci L, Mucalo I, Bićanić LA, Palić J, Šimičević L, Vrkić Kirhmajer M, Samardžić J, Božina T
P1 02	RHABDOMYOLYSIS IN KIDNEY TRANSPLANT PATIENT WITH COVID-19: POSSIBLE ROLE OF REMDESIVIR AND ATORVASTATIN DRUG-DRUG-GENE INTERACTIONS - Fištrek Prlić M, Osmanović Barilar J, Ganoci L, Šimičević L, Božina N
P1 03	THE ROLE OF PHARMACOGENETICS AS POSSIBLE RISK FACTOR FOR RIVAROXABAN – ASSOCIATED BLEEDING - Šimičević L, Slišković AM, Vrkić Kirhmajer M, Ganoci L, Holik H, Samardžić J, Božina T
P1 04	ASSOCIATION OF PERIOD CIRCADIAN GENES WITH CHEMORESISTANCE OF COLON CANCER CELLS WITH BRAFV600E MUTATION - Markova-Car EP, Ripić M, Sedić M
P1 05	CONSUMPTION OF ALLERGY MEDICINE IN EUROPE, 2017-2020: IS THERE A SIMILAR PATTERN OF ALLERGY MEDICINE CONSUMPTION IN THREE EUROPEAN COUNTRIES? - Pelčić G, Draganić P, Rožmanić V, Ragulj M
P1 06	ORAL CHALLENGE WITH TRIMETHOPRIM-SULFAMETHOXAZOLE IN A PATIENT WITH ALLERGY IN DRUG HISTORY - Čagalj Z, Mimica S, Havidić A
P1 07	NOVEL AGENTS IN DYSLIPIDAEMIA THERAPY - ARE WE SWITCHING DAILY TREATMENT TO WEEKLY OR EVEN MONTHLY? – Strikić D, Slišković AM, Merćep I

P1 08	KNOWLEDGE, ATTITUDES AND AWARENESS REGARDING FOOD-DRUG INTERACTIONS AMONG PHARMACISTS IN CROATIA - Pavičić Žeželj S, Kenđel Jovanović G, Mašković S, Skočibušić N, Belančić A, Rubinić I, Vlahović-Palčevski V
P1 09	PHYTOCHEMICAL ANALYSIS AND PHYTOTHERAPEUTIC POTENTIAL OF SELECTED *VERONICA* L. SPECIES (PLANTAGINACEAE) FROM CROATIA - Jurišić Grubešić R, Molc N, Nazlić M, Kremer D, Juretić L, Dunkić V
P1 10	IMPACT OF PHARMACIST-LED MEDICATION MANAGEMENT ON ADVERSE DRUG REACTIONS REPORTED BY ELDERLY CARDIOVASCULAR PATIENTS AT A PRIMARY CARE LEVEL - Strgačić M, Pupačić A, Nalo L, Brajković A, Mucalo I
P1 11	THE ASSESSMENT OF SALIVARY PARAMETERS IN OBSTRUCTIVE SLEEP APNEA PATIENTS AFTER CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT: A 6-MONTH FOLLOW-UP STUDY - Tranfić M, Pecotić R, Lušić Kalcina L, Pavlinac Dodig I, Valić M, Rogić D, Lapić I, Grdiša K, Peroš K, Đogaš Z
P1 12	METHODS OF DETERMINATION OF PROGESTERONE AND ESTRADIOL IN SALIVA - Smajli Vokshi K, Peroš K
P1 13	EFFECT OF CALCIUM PRETREATMENT ON ENAMEL FLOURIDE REACTIVITY AND IN REMINERALIZATION DEMINERALIZATION PROCESSES - Kullashi Spahija F, Peroš K
P1 14	DYSTONIA IN EUROPE: A SURVEY TOWARDS DIAGNOSIS AND THERAPY FROM A PATIENTS' PERSPECTIVE - Relja M, Dressler D, Albanese A, Morgante F, Trkulja V
P1 15	ASPARAGINASE ACTIVITY IN ALL TREATMENT - Lovrić M, Glasovac D, Jelić M, Ščavničar A, Bilić E, Rogić D
P1 16	THE EFFECTS OF PROLONGED ANTISEPTIC USE DURING COVID-19 PANDEMIC ON SKIN PARAMETERS – Modun D, Bročić I, Mićanović M, Bukić J, Rušić D, Šešelja Perišin A, Leskur D
P1 17	NON-INTERVENTIONAL PILOT STUDY EVALUATING THE EFFICACY AND SAFETY OF LYSOZYMEBASED THERAPY IN PATIENTS WITH NON-INFECTIOUS SORE THROAT - Karakaš S, Huduti DZ, Mehic M, Šukalo A, Dzananovic Jaganjac J, Tanovic Avdic A, Skopljak A, Dupovac A, Sarajlic Z, Glamoclija U, Limo S

P1 18	THE EFFECTS OF TOPICAL APPLICATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS ON THE CONCENTRATION OF IMMUNE PARAMETERS IN A MODEL OF COLLAGEN-INDUCED ARTHRITIS – RESEARCH PLAN - Maleškić Kapo S, Rakanović-Todić M, Burnazović-Ristić L, Loga-Zec S, Kusturica J, Limo S, Kulo Ćesić A
P1 19	NO FEAR TO EXPLORE THE UNSAFE WITH CEFTRIAXONE! - Tvrdeić A, Miše B, Babacanli A, Poljak LJ
P1 20	ELEVATED C MAZE - TO TEST OR NOT TO TEST IN THE MORNING? - Tvrdeić A, Miše B, Babacanli A, Poljak LJ
P1 21	COX-2 RS689466 POLYMORPHISM AND METABOLIC SYNDROME-RELATED PARAMETERS AMONG MEDICATED SCHIZOPHRENIA PATIENTS - Zatković L, Nadalin S, Dević Pavlić S, Peitl V, Karlović D, Rebić J, Buretić-Tomljanović A
P1 22	THE EFFECTS OF MODERATE RED WINE CONSUMPTION ON ARTERIAL STIFFNESS AND HEMODYNAMIC PARAMETERS IN TYPE 2 DIABETES MELLITUS – Mudnić I, Nazlić J, Boban Z, Gujinović D, Dželalija AM, Boban M
P1 23	THE PROTECTIVE ACTIONS OF DHEA/S AND BDNF IN AN IN VITRO MODEL OF PARKINSON'S DISEASE – Miloš T, Vuić B, Bacelj N, Nedić Erjavec G, Tudor L, Konjevod M, Švob Štrac D, Nikolac Perković M
P1 24	MOLECULAR MECHANISMS OF THE RENAL EFFECT OF EMPAGLIFLOZIN ON LLC-PK1 CELLULAR MODEL OF DIABETIC NEPHROPATHY - Mihaljević V, Omanović Kolarić T, Smolić M, Kuna L, Kizivat T, Petrović A, Smolić R, Včev A, Bilić Ćurčić I
P1 25	EFFECTS OF DIFFERENT DOSES OF PIOGLITAZONE ON NEURONAL DAMAGE, INFLAMMATION AND MOTOR PERFORMANCE FOLLOWING TRAUMATIC BRAIN INJURY IN THE RAT - Dolenec P, Pilipović K, Župan Ž, Župan G
P1 26	CHARACTERIZATION OF ASTROCYTIC RESPONSE TO EXPOSURE TO CHEMICALLY FUNCTIONALIZED SINGLE-WALLED CARBON NANOTUBES IN AN IN VITRO STRECH INJURY MODEL - Harej Hrkać A, Gržeta N, Mladenić T, Jurički I, Parpura V, Pilipović K
P1 27	THE EFFECTS OF REPETITIVE MILD TRAUMATIC BRAIN INJURY ON SOME PROTEINOPATHY SUSCEPTIBLE PROTEINS IN THE MOUSE FRONTAL CORTEX – Janković T, Gržeta N, Rajič Bumber J, Dolenec P, Križ J, Župan G, Pilipović K

P1 28	THE ROLE OF CLINICAL PHARMACOLOGIST IN ASSESSMENT OF CONTRAINDICATIONS FOR VACCINATION AGAINST COVID-19 - Strujić E, Pastović M, Petrinović M, Mimica S
P1 29	PROCEDURES AT SUSPECTED HYPERSENSITIVITY TO LOCAL ANESTHETICS - Petrinović M, Strujić E, Pastović M, Mimica S

Saturday, September 24, 2022

Poster session 2 with organized discussion

Chairpersons: Kristina Pilipović (Croatia), Pero Draganić (Croatia), Viktorija Erdeljić Turk (Croatia)

P2 01	NEUROPROTECTIVE ACTIONS OF DHEA AND DHEAS IN PRIMARY MOUSE NEURONS AND SHSY5Y CELLS EXPOSED TO TOXIC AMYLOID BETA OLIGOMERS - Vuić B, Miloš T, Nikolac Perković M, Nedić Erjavec G, Tudor L, Konjevod M, Pivac N, Švob Štrac D
P2 02	OVER-DOSE CAFFEINE TOXICITY IN RATS AND TRETMENT WITH STABLE GASTRIC PENTADECAPEPTIDE BPC 157 - Vukovic V, Sablic M, Krezic I
P2 03	THE ASSOCIATION OF PLATELET SEROTONIN (5-HT) AND 5HT2A GENE POLYMORPHISMS WITH ASTHMA – Konjevod M, Sreter K, Popovic-Grle S, Lampalo M, Jukic I, Bingulac-Popovic J, Safic Stanic H, Markeljevic J, Pivac N, Svob Strac D
P2 04	THE EFFECTS OF PHLORIDZIN, A SODIUM-GLUCOSE COTRANSPORTER INHIBITOR IN AN ORAL GALACTOSE-TREATED RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE - Babić Perhoč A, Homolak J, Knezović A, Osmanović Barilar J, Virag D, Šalković-Petrišić M
P2 05	ANTISTEATOTIC EFFECT OF LIRAGLUTIDE IS MEDIATED THROUGH ACSL1 and SREBP-1c SIGNALING PATHWAY IN A CELL CULTURE MODEL OF TAMOXIFEN-INDUCED STEATOSIS - Omanović Kolarić T, Ninčević V, Kizivat T, Kuna L, Zjalić M, Bilić-Ćurčić I, Smolić R, Roguljić H, Petrović A, Včev A, Wu G, Smolić M
P2 06	IS VASCULAR RESPONSIVENESS OF THE ISOLATED RAT AORTA AFFECTED BY 4 WEEKS OF MODERATE STANDARD AND MACERATED WHITE WINE CONSUMPTION? – Mornar M, Filipović N, Grahovac M, Gujinović D, Dželalija AM, Grković I, Boban M, Mudnić I
P2 07	AWARENESS AND ATTITUDES OF NURSES ABOUT DIET THERAPY AND NUTRITIONAL SUPPORT OF PERSONS WHIT CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN HOSPITAL ENVIROMENT - Kocić Z, Fistonić T, Jovanović Ž
P2 08	PREVALENCE OF ANXIOLYTICS USE BY HEALTH PROFESSIONALS - Jovanović Ž, Pešut S, Kocić Z

P2 09	PATIENTS ATTITUDES TOWARDS ANTIPSYCHOTIC MEDICATION: A CROSS-SECTIONAL STUDY - Bukic J, Rusic D, Leskur D, Šešelja Perisin A, Herceg D, Cohadzic T, Modun D, Herceg M
P2 10	DO FINAL-YEAR MEDICAL STUDENTS IN CROATIA FEEL SUFFICIENTLY PREPARED TO PRESCRIBE ANTIMICROBIALS PRUDENTLY? – COMPARISON BETWEEN FOUR CROATIAN MEDICAL SCHOOLS - Belančić A, Palčevski D, Likić R, Vlahović-Palčevski V
P2 11	EFFECTS OF LOW DOSE TETANUS TOXIN INJECTIONS INTO THE RAT MOTOR CORTEX AND BASAL GANGLIA ON MOTOR PERFORMANCE - Meglić P, Šoštarić P, Virag D, Matak I
P2 12	EXPERIMENTAL FOCAL MUSCLE HYPERTONIA OFFERS NOVEL INSIGHTS INTO MOTOR EFFECTS OF BOTULINUM TOXIN TYPE A – Matak I, Meglić P, Šoštarić P
P2 13	TETANUS NEUROTOXIN ACTS AT THE NEUROMUSCULAR JUNCTION AND ON BRAINSTEM CENTERS THAT CONTROL MUSCLE MOVEMENT, RESPIRATION AND SWALLOWING IN A MURINE MODEL OF CEPHALIC TETANUS - Fabris F, Varani S, Tonellato M, Matak I, Šostaric P, Meglic P, Simonato M, Rubini A, Caleo M, Megighian A, Rossetto O, Montecucco C, Pirazzini M
P2 14	CALCIUM CHLORIDE-INDUCED RAT MODEL OF ABDOMINAL AORTIC ANEURYSM AND THE EFFECT OF PENTADECAPEPTIDE BPC 157 - Zizek H, Sjekavica I, Smoday I, Oroz K, Boban Blagaic A
P2 15	BRAIN EDEMA AND BLOOD PRESSURE DISTURBANCES INDUCED BY ACUTE WATER INTOXICATION IN A RAT MODEL AND THE EFFECT OF PENTADECAPAPTIDE BPC 157 - Yago H, Zizek H, Smoday IM, Durasin T
P2 16	TREATMENT OF ULCER, INTRACRANIAL, PORTAL AND CAVAL HYPERTENSION AND AORTAL HYPOTENSION WITH BPC 157 AFTER STOMACH PERFORATION - Vranes H, Kalogjera L, Chiddenton MH, Buric S
P2 17	STABLE GASTRIC PENTADECAPEPTIDE BPC 157 THERAPY EFFECT ON REPERFUSION FOLLOWING MAINTAINED INTRA-ABDOMINAL HYPERTENSION, GRADE III AND IV - Tepes M, Madzar Z, Miskic B, Miskic S, Duzel A, Sever M, Dretar V
P2 18	BPC 157 IN PSORIASIS MODEL - Šola M, Skroza N, Mangino G, Boban Blagaic A

P2 19	THERAPEUTIC EFFECT OF BPC 157 ON MANDIBULAR FRACTURE HEALING - Suman O, Staresinic M, Kocman I, Jadrijevic S
P2 20	PENTADECAPEPTIDE BPC 157 AS THERAPY OF THE INFERIOR CAVAL VEIN EMBOLIZATION POST-EMBOLIZATION SYNDROME WITH SODIUM LAURATE IN RATS - Smoday IM, Kalogjera L, Buric S, Vranes H
P2 21	THERAPY EFFECT OF THE PENTADECAPEPTIDE BPC 157 ON DEVELOPMENT OF ABDOMINAL AORTIC ANEURYSM AND VASCULAR FAILURE SYNDROME CAUSED BY CIPROFLOXACIN - Skorak I, Brizic I, Hriberski K, Krezić I, Žižek H, Smoday IM, Meštrović T, Pavić P, Sikirić P
P2 22	THE EFFECT OF PENTADECAPEPTIDE BPC 157 ON ALCOHOL-INDUCED LESIONS OF BREAST AND SOURROUNDING TISSUE IN RATS - Samara M, Zic R, Sikiric P
P2 23	„OCCLUSION-LIKE“ SYNDROME IN RAT LOWER LEG FRACTURE AND THE THERAPEUTIC EFFECT OF PENTADECAPEPTIDE BPC 157 - Prtoric A, Dobric I, Jurjevic I, Durasin T
P2 24	SOTALOL-INDUCED GENERAL OCCLUSION-LIKE SYNDROME AND QTC PROLONGATION IN RATS ARE COUNTERACTED BY PENTADECAPEPTIDE BPC 157 - Premuzic Mestrovic I, Smoday IM, Mestrovic T, Skorak I, Haluzan D, Figl J, Brizic I, Staresinic M, Pavic P
P2 25	PROTECTIVE EFFECTS OF PENTADECAPEPTIDE BPC 157 ON CAUSTIC LESIONS OF THE ESOPHAGUS IN RATS - Peklic M, Krezic I, Boban Blagaic A, Vranes H, Smoday IM
P2 26	TOURNIQUET-INDUCED COMPARTMENT SYNDROME OF RATS' LIMB AND ITS COUNTERACTION WITH PENTADECAPEPTIDE BPC 157 THERAPY - Oroz K, Coric L, Dretar V
P2 27	BPC 157 COUNTERACTS RADIATION-INDUCED ORAL MUCOSITIS IN RATS - Milatic K, Alajbeg I, Sobat H, Andabak-Rogulj A, Reić T
P2 28	CYTOPROTECTIVE EFFECTS OF BPC 157 ON MULTIORGAN DAMAGE CAUSED BY HIGH DOSES OF MEGESTROL ACETATE IN RATS - Krtalic B, Koprivanac A, Kalogjera L, Oroz K, Durasin T
P2 29	NEUROPROTECTIVE EFFECT OF PENTADEKAPEPTIDE BPC 157 ON 3-NITRO PROPRIONIC ACID-INDUCED MODEL OF HUNTINGTONS DISEASE - Krezic I, Jurjevic I, Chiddenton HM

P2 30	EFFECT OF PENTADECAPEPTIDE BPC 157 ON LUNG REEXPANSION IN RIGHT-SIDED PNEUMOTHORAX IN RATS WITH PENETRATING CHEST INJURY - Koprivanac A, Krtalic I, Zizek H, Boban Blagaic A, Oroz K, Coric L
P2 31	STABLE GASTRIC PENTADECAPEPTIDE BPC 157 THERAPY EFFECT ON REPERFUSION FOLLOWING OCCLUSION OF SUPERIOR MESENTERIC ARTERY, SUPERIOR MESENTERIC VEIN, AND SUPERIOR MESENTERIC ARTERY AND VEIN - Knezevic M, Knezevic T, Kolak T, Prtoric A, Sever M, Giljanovic A, Gojkovic S, Muzinic D, Boban Balagaic A
P2 32	PENTADECAPEPTIDE BPC 157 AS THERAPY OF THE AIR EMBOLIZATION AND POST-EMBOLIZATION SYNDROME IN RATS - Kalogjera L, Smoday I, Chiddenton HM, Buric S, Coric L
P2 33	EFFECT OF PENTADECAPEPTIDE BPC 157 ON APICAL PERIODONTITIS CAUSED BY PULP EXPOSURE IN RATS - Juzbasic M, Talapko J, Krezic I, Zizek H, Tomas M
P2 34	SYNDROME ARISING AFTER CATALEPTOGENIC DOSE OF L-NAME APPLICATION IN RATS AND THE EFFECT OF PENTADECAPEPTIDE BPC 157 - Jurca I, Zizek H, Sjekavica I, Coric L
P2 35	THERAPEUTIC EFFECT OF PENTADECAPEPTIDE BPC157 ON KREON INDUCED MODEL OF ABDOMINAL AORTA ANEURYSM IN RATS - Hriberski K, Brizic I, Skorak I, Haluzan D, Figl J, Pavic P, Mestrovic T
P2 36	OCCLUSION OF SUPERIOR SINUS SAGITTAL SINUS IN RATS AND THERAPY WITH THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157, L-NAME AND L-ARGININE - Gojkovic S, Dretar V, Krezic I
P2 37	FOURIER TRANSFORM INFRARED SPECTROSCOPY MEASUREMENTS OF INFLUENCE OF THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157 ON RAT THORACIC AORTA - Gamulin O, Maria Krajacic M, Skrabic M, Oroz K, Coric H
P2 38	INFLUENCE OF PENTADECAPEPTIDE BPC 157 ON THE HEALING OF COLON-COLONIC ANASTOMOSIS UNDER VENOUS CONGESTION CONDITIONS IN RATS - Duzel A, Artukovic B, Rakic M, Kolovrat M, Begovic A, Andabak M, Sabic A
P2 39	THE EFFECT OF PENTADECAPEPTIDE BPC 157 ON GLYCEROL INDUCED ACUTE KIDNEY INJURY - Dretar V, Durasin T, Vranes H
P2 40	THE EFFECT OF BPC-157 ON SURGICALLY INDUCED LUMBAR SPINE INSTABILITY IN A RAT MODEL - Dokuzovic S, Krezic I, Smoday IM, Durasin T, Dretar V

P2 41	PILOCARPINE AND LITHIUM STATUS EPILEPTICUS IN RATS AND PENTADECAPEPTIDE BPC 157, L-NAME, AND L-ARGININE THERAPY EFFECT - Chiddenton HM, Buric S, Kalogjera L, Vranes H
P2 42	THERAPEUTIC EFFECT OF PENTADECAPEPTIDE BPC 157 IN RATS WITH ISCHEMIA-REPERFUSION INJURY AFTER OCCLUSION OF THE INFRARENAL ABDOMINAL AORTA – Brižić I, Škorak I, Hriberski K, Pavić P, Meštrović T, Krezić I, Žižak H, Sikirić P
P2 43	SEVERE ULCERATIVE COLITIS AND PENTADECAPEPTIDE BPC 157 THERAPY - Bekic D, Kalogjera L, Vranes HS
P2 44	THE EFFECT OF BPC-157 ON THE SISTEMIC EFFFECTS OF INDUCED OPEN ANGLE GLAUCOMA IN RAT MODEL - Sablic M, Vukovic V, Kokot A

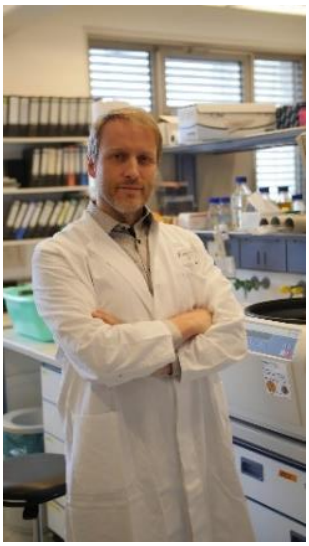
Sunday, September 25, 2022	
Poster session 3 with organized discussion: Students section "HDF youth programme" **Chairpersons: Petra Dolenec (Croatia), Jelena Osmanović Barilar (Croatia)**	
P3 01	THE EFFECT OF MUSIC AND SOUNDS ON ANXIETY AND STRESS LEVELS - Bacelj N, Tudor L
P3 02	SAFETY PROFILE OF JAK INHIBITORS BASED ON THE RECEIVED REPORTS OF SUSPECTED SIDE EFFECTS - Pavlinovic L, Mirošević Skvrce N
P3 03	ATTITUDES TOWARDS USE OF SUPPLEMENTS DURING COVID- 19 PANDEMICS - Matijević A, Mimica S
P3 04	THE EFFECT OF ORAL GALACTOSE ON THE INSULIN SIGNALLING PATHWAY IN THE PARIETAL CORTEX OF A TRANSGENIC MICE MODEL OF ALZHEIMER'S DISEASE – Ipša A, Babić Perhoč A
P3 05	USE OF CANNABIS FOR MEDICINAL PURPOSES - Valković F, Mršić-Pelčić J
P3 06	REDOX HOMEOSTASIS PRESERVATION ALONG THE GASTROINTESTINAL TRACT OF THE RAT BRAIN-FIRST 6-HYDROXYDOPAMINE MODEL OF PARKINSON'S DISEASE - Grabarić G, Homolak J, Šalković-Petrišić M
P3 07	ADHERENCE TO CHRONIC THERAPY DURING COVID-19 PANDEMICS - Balić I, Mimica S
P3 08	INTESTINAL REDOX PARAMETERS IN THE ALZHEIMER'S DISEASE RATS RECEIVING ORAL D-GALACTOSE - Joja M, Homolak J, Šalković-Petrišić M
P3 09	ASSESSMENT OF PATIENTS ON ORAL ANTITHROMBOTIC THERAPY REFERRED TO THE DEPARTMENT OF ORAL SURGERY FOR SIMPLE TOOTH EXTRACTION – A PRELIMINARY REPORT- Burja Vladić M, Salarić I, Zdunić E, Perić B, Vuletić L
P3 10	COMPLEX MECHANISMS OF BOTULINUM TOXIN TYPE A ACTION ON EXPERIMENTAL PAIN -TIME TO LOOK BEYOND THE FIRST SYNAPSE - Mustapić M, Skenderović M, Vađunec D, Bach-Rojecky L
P3 11	BIOCHEMICAL PROPERTIES OF RAT FECAL PELLETS ACCOMPANYING THE DEVELOPMENT OF MOTOR DEFICITS IN A

	6-HYDROXYDOPAMINE-INDUCED RAT MODEL OF PARKINSON'S DISEASE - Marković P, Babić Perhoč A
P3 12	THE NEUROPROTECTIVE POTENTIAL OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN AN *IN VITRO* MODEL OF ALZHEIMER'S DISEASE - Pendelić R, Nedić Erjavec G
P3 13	ANTIBIOTIC THERAPY IN THE COVID-19 PANDEMIC: RETROSPECTIVE COHORT STUDY OF PATIENTS HOSPITALIZED AT THE UNIVERSITY HOSPITAL OF SPLIT - Starčević D, Pranić S, Pinjatela J, Skelin M, Mudnić I
P3 14	EXPLORATION OF THE ANTIOXIDATIVE AND ANTI-INFLAMMATORY EFFECTS OF ARONIA MELANOCARPA EXTRACT IN AN *IN VITRO* MODEL OF PARKINSON'S DISEASE – Glavan T, Harej Hrkać A, Pilipović K
P3 15	TESTING THE POSSIBILITY OF LOADING AND SUBSEQUENT RELEASE OF FLUORIDE IONS FROM BIOACTIVE DENTAL MATERIALS AFTER COATING WITH HIGHLY CONCENTRATED FLUORIDE GEL - Kelić M, Kilić D, Peroš K

PLENARY LECTURES SPEAKERS

Jean-Pierre Julien (Canada)

Professor Jean-Pierre Julien holds a Canada Research Chair in Neurodegeneration at Laval University. He obtained his doctorate in biochemistry from McGill University and completed a postdoctoral fellowship in molecular genetics at the National Institute for Medical Research (London). He was first recruited as a researcher at the Institut du cancer de Montréal (now CRCHUM) and then in the department of Neurology and Neurosurgery at McGill University. In 2003, he moved to Laval University which offered him a Canada Research Chair and since 2013 he has been director of the integrative neuroscience axis of the CERVO research center affiliated with Laval University. Dr. Julien was a pioneer in the creation of genetically modified mice to study the regulation and functions of neurofilaments. He was the first to discover that disorganization of neurofilaments can cause neurological diseases (Cell 1993). His studies with mouse models led to the unexpected discovery that non-neuronal cells contribute to motor neuron loss in ALS (Science 2003). This breakthrough has prompted several laboratories to look into the role of glial and immune cells in ALS, and to test stem cell therapies for ALS. Subsequently, he proposed a new pathogenesis model for ALS based on the secretion of misfolded proteins (Nature Neuroscience 2006). This led him to develop immunization and immunotherapy approaches to target toxic proteins in ALS. Thus, he was the first to experiment an immunization for the treatment of ALS (PNAS 2007). In the past few years, Dr. Julien has been working on the development of new experimental treatments for ALS, such as immunotherapy to target misfolded proteins and natural product therapies to target inflammatory pathway signaling. His article in J Clin Invest on nano-antibodies to treat ALS was selected as one of the scientific discoveries of the year 2019 by Quebec Science. His work has led to several patents that could have clinical implications in the diagnosis and treatment of ALS. On the other hand, he is co-founder of a new company based in Quebec whose mission is to find cures for neurodegenerative diseases. His career productivity is outstanding with over 230 articles that are highly cited. Dr. Julien has received several awards including the prestigious Sheila Essey Prize for ALS Research from the American Academy of Neurology, the Léo-Pariseau Prize from ACFAS and the Jonas Salk Prize. He is a Fellow of the Royal Society of Canada and of the Canadian Academy of Health Sciences. In short, Dr. Julien has a remarkable career path that has evolved from basic research to a fine example of translational biomedical research.

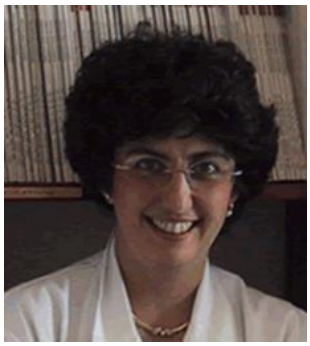


Luka Čičin-Šain (Germany)

Luka Čičin-Šain studied medicine at the University of Rijeka in Croatia and attained subsequently a PhD in Biomedicine under the supervision of Stipan Jonjić at the same university. Upon training in the Koszinowski lab in Munich, Germany and in the Nikolich-Zugich lab at the Oregon Health and Science University (OHSU) in Portland, OR, USA, he became a research assistant professor at OHSU in 2007. He started his own lab at the Helmholtz Institute for Infection Research (HZI) in Braunschweig, Germany in 2010, funded by starting grants from the Helmholtz Association and from the European Research Council (ERC). From 2011 he was an adjunct junior professor at the Institute for Virology of the Medical School in Hannover (MHH) and since 2016 a tenured faculty member of HZI. He became an associate professor in immunology at MHH in 2019, a visiting professor at the University of Rijeka in 2020, and since 2021 he leads the Department of Viral Immunology at HZI. Furthermore, he is the main coordinator of the Helmholtz Research Topic Immune Responses and Intervention at his home institute and co-coordinator of the Vaccine Study Group within the German Immunological Society.

Luka Čičin-Šain focuses on innate and adaptive immune responses to viruses, and in particular cytomegalovirus (CMV) and SARS-CoV-2. He has contributed to our understanding of the effects of CMV infection on the aging immune system, on the molecular mechanisms regulating virus in vivo infection and latency, and on T-cell responses and homeostasis in the latently infected host.

Since the advent of SARS-CoV-2, his lab has developed experimental models to study viral evolution in experimental settings and COVID immunity from the molecular to the organismal level. Luka Čičin-Šain has authored more than 80 peer-reviewed publications, with more than 3000 citations in the last 5 years.



Tabassome Simon (France)

Tabassome Simon is Professor of Medicine and Clinical Pharmacology at AP-HP, Saint-Antoine Hospital, Sorbonne University in Paris, France, and Past-Chair of the European Association for Clinical Pharmacology and Therapeutics (EACPT). In addition to teaching pharmacology for medical students, T. Simon coordinates the Master Diploma of Clinical Research for physicians, pharmacists, and scientists, the university diploma for pharmacogenetics and personalized medicine, and the university diploma for the education of research nurses in France.

Dr Simon is currently Head of the Department of Pharmacology, APHP. Sorbonne University, the Head of the Clinical Research platform of the East of Paris, including the Clinical Research Unit, the clinical Research Center, and the BioBank Research Center, that coordinates several multicenter national and international studies. She is also the Co-Vice President Research for Assistance Publique-Hôpitaux de Paris (APHP, the first sponsor for clinical studies in Europe).

She is a member of several Executive Committee of national and international studies (MINT, THEMIS, TIGRIS, Reality, RHU IVASC with several nested clinical trials, Fast-MI programs, ..). She is also the Co-coordinator of the academic research organization « French Alliance for Cardiovascular Trials » (FACT) in collaboration with other academic research organizations such as Duke (USA), PHRI (Canada), Uppsala (Sweden)., .. FACT is labelled d by F-Crin (French Clinical Research Infrastructure Network) which is the French component of the European structure ECRIN, that support the organization of multinational clinical trials in Europe.

Dr Simon has received several awards from the French Society of Cardiology, the French Society of Pharmacology, the French Society of Angiology, and the EACPT. The editors of Circulation have chosen one of her publications as Groundbreaking Studies in the Practice of Cardiovascular Medicine in 2009. She has published more than 230 articles in international peer-reviewed journals, including The New England Journal of Medicine, The Lancet, JAMA, Nature Med, Circulation, JACC, European Heart Journal, Hypertension, Atherosclerosis, Arterioscler Thromb Vasc Biol, Clinical Pharmacology and Therapeutics, Heart, J Clin Endocrinol Metab, etc.

Julia Carolin Stingl (Germany)

University professor in clinical pharmacology, Julia Stingl is director of the Institute of Clinical Pharmacology at the University hospital of RWTH University Aachen, Germany. Before her move to the University RWTH Aachen, Dr. Stingl worked for seven years in drug regulation and research as vice president at the German drug regulatory authority, BfArM. Her research mostly focuses on Personalized Medicine and individual pharmacogenetic diagnostics. She pioneered the systematic development of personalized dose adjustments based upon differences in drug clearances caused by pharmacogenetic polymorphisms promoting the way of pharmacogenetics from bench to bedside. She explored individual variability in molecular or genetic influences on drug response and also worked on characterization of the physiological role of genetic polymorphisms in cytochrome P450 enzymes such as the brain expressed CYP2D6. She integrated new methods into pharmacogenetic research such as brain imaging techniques for visualization of individual drug effects and pharmacogenetic modulation.

She was recipient of the Utrecht Award for Pharmaceutical Research 2009; recipient of the Leon I. Goldberg Young Investigator Award 2010 of the American Society for Clinical Pharmacology and Therapeutics (ASCPT). She is involved in several European projects on pharmacogenetics and personalized medicine and is currently coordinator of the EraPerMed project Artipro on Artificial Intelligence methods for the prediction of response to antidepressant drugs involving multimodal biomarkers in several European countries and Israel.

She has authored more than 260 publications in peer-reviewed scientific journals, has been cited more than 10,000 times with an average citation of 30 per article and an H-index of 53.

PLENARY LECTURES ABSTRACTS

P1

DEVELOPMENT OF ANTIBODY APPROACHES TO TARGET TDP-43 PROTEINOPATHY IN ALS AND DEMENTIA

Jean-Pierre Julien (CERVO Brain Research Centre, Québec, Québec, Canada and Department of Psychiatry and Neuroscience, Université Laval, Québec City, Québec, Canada)

Cytoplasmic aggregates of TDP-43 are a pathological hallmark of degenerating neurons in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). With the objective to mitigate TDP-43 aggregation, we have generated antibodies (Abs), full length Abs and single chain scFv Abs against the RRM1 domain of TDP-43. One of our full length Ab, called E6 Ab, was found to detect specifically cytoplasmic TDP-43 species, but not nuclear TDP-43. Our data demonstrated that full length Ab E6 and scFv Ab E6 can attenuate cytoplasmic TDP-43 accumulations in part by inducing degradation of TDP-43 via autophagic and proteasomal pathways. We showed that intrathecal AAV viral-mediated delivery of a scFv Ab E6 against TDP-43 RRM1 region mitigated TDP-43 pathology, and it ameliorated cognitive and motor performance of transgenic mice expressing ALS-linked TDP-43 mutants. To achieve pan-neuronal expression in the CNS of E6 scFv, we recently generated an AAV vector bearing a recombinant capsid designed to achieve efficient transduction in large neuronal populations after intravenous injection. Few weeks following single intravenous injection of AAV vector encoding scFv E6 into transgenic mice expressing TDP-43G348C, microscopy results confirmed the wide spread detection of scFv E6 antibodies in CNS neurons and preliminary results suggest an attenuation of TDP-43 mislocalization. We are also exploring a treatment based on administration of full length Abs against TDP-43 into the cerebrospinal fluid (CSF). We are testing this approach on a new mouse model of sporadic ALS based on intracerebroventricular (i.c.v.) infusion of CSF from ALS patients. Intrathecal injection of E6 Abs in such mice infused with ALS-CSF alleviated gait deficits and increased the nuclear to cytoplasmic ratio of TDP-43 in spinal neurons. Moreover, the addition of E6 Abs to ALS-CSF before infusion into hTDP-43WT mice led to amelioration of cognitive deficits raising up the possibility that E6 Abs might neutralize the toxicity of ALS-CSF.

P2

PHARMACOLOGICAL AND IMMUNOLOGICAL INTERVENTIONS TARGETING COVID-19 DISEASE

Luka Čičin-Šain (Helmholtz Centre for Infection Research)

Since its emergence in late 2019, SARS-CoV-2 has caused more than 6 million known fatalities, tens of millions of hospitalizations and countless sick-days, either during the acute infection or as post-infection, long-COVID sequelae. While vaccines were rolled out with unprecedented speed and showed remarkable success in the early months upon deployment, waning immunity compounded with viral mutations and immune escape has resulted in a progressive vaccine failure to provide protection. Therefore, a new wave of COVID-19 is rolling throughout Europe at the time of this writing, causing numerous infections, hospitalizations and fatalities. Better preventive and therapeutic strategies against COVID-19 remain as necessary as ever.
Available antiviral therapy relies on corticosteroids alleviating inflammation and thus disease manifestations, or on compounds directly targeting the virus. While monoclonal antibodies against the spike protein on the virion surface were rapidly rolled out, mutations in newly emerging variants of concern and in particular those in Omicron subvariants, rendered most (but not all) monoclonal antibodies ineffective. Numerous small compounds were tested against COVID, but only two orally administered antiviral drugs that act on non-structural viral molecules have been EMA-approved so far. Paxlovid (ritonavir + nimatrelvir) targets the viral protease, and lowers the risk of severe disease by approximately 90% when administered early upon diagnosis, but shows numerous interactions with commonly prescribed pharmaceuticals that act on Cytochrome P450 3A4. Molnupiravir, a nucleoside analogue that blocks viral RNA replication, shows substantially less interactions and side effects, but also a lower efficacy, where the risk of severe disease is lowered by merely 30%. Both of the drugs are resistant to VoC mutations, most effective when used within the first days of diagnosis, and thus suitable for pre-emptive treatment of at-risk patients. Pros and cons of various compounds and strategies will be discussed in light of virological and clinical considerations.

P3

TRANSFUSION STRATEGIES AND CARDIOVASCULAR OUTCOMES FOLLOWING AN ACUTE MYOCARDIAL INFARCTION

Tabassome Simon (Saint-Antoine Hospital, Sorbonne University in Paris, France)

EPHAR lecture 2022

Rationale Anemia is common in patients with acute myocardial infarction (AMI° and is associated with worse short- and long-term outcomes. Substantial uncertainty remains in this target population regarding the optimal transfusion strategy for reducing outcome events, as well as the consequences of the transfusion strategies on costs and quality of life. Moreover, whether the effects on outcomes and cost effectiveness vary over time is unknown.
Methods and results: The reality was an international randomized, multicenter trial designed to assess the hypothesis that a “restrictive” transfusion strategy (triggered by hemoglobin [Hb] ≤ 8 g/dL) is clinically non-inferior to a “liberal” transfusion strategy (triggered by Hb ≤ 10 g/dL) but less costly at 30 days. The primary endpoint was the incremental cost-effectiveness ratio (ICER) at 30 days, using the primary composite clinical outcome of major adverse cardiac events (MACE) all-cause death, non-fatal stroke, non-fatal recurrent MI, and emergency revascularization prompted by ischemia as the effectiveness criterion. Secondary endpoints included the rates of MACE and the ICER at 1 year.
Conclusion: The results of all avaivable data including the Reality trial evaluating transfusions strategies and cardiovascular in anemic patients with acute myocardial infarction will be presented and discussed during the meeting.

P4

PHARMACOGENOMICS FOR PERSONALIZED MEDICINE: FROM BENCH... TO THE DRUG LABEL... TO BEDSIDE

Julia Carolin Stingl (Institute of Clinical Pharmacology, University Hospital of RWTH Aachen)

Introduction

The role of pharmacogenetic diagnostics has changed during the past decades. Starting with a more explorative role of explaining variability in drug metabolism affecting individual drug response and safety, pharmacogenomics is nowadays developing into Personalized Medicine Practice.

With the knowledge on our pharmacogenome, also new methods for genetic diagnostics arose, and large genome analyses now became convenient, easy to handle, and relatively cheap. In the Summary of Medicinal Product Characteristics issued by the European Medicines Agency as precursor of the drug leaflet, more and more pharmacogenetic information is given. This pharmacogenetic information may be relevant to treatment with a specific drug in different ways:

1. indication or contraindication according to the drug approval
2. therapy strategy (selection and dosage of a drug)
3. cause clarification of adverse drug reactions during the course of therapy.

According to the available evidence, the following consequences for pharmacogenetic testing can be distinguished:

- Mandatory, i.e., pharmacogenetic testing must be performed based on the available evidence,- recommended, i.e. pharmacogenetic testing can or should be performed if it results in an improvement in the efficacy of the drug substance or if a treatment needs to be monitored, - informative, i.e., in individual cases, pharmacogenetic testing may also be useful on the basis of preliminary evidence.

Conclusion

Genome medicine is now in its clinical implication phase with the use of pharmacogenetic tests in clinical practice in different fields of drug therapy. It may help to derive the indication for drug therapy, to identify the individual optimal dose and to avoid side effects in patients.

SYMPOSIA ABSTRACTS

S01

DRUG REGULATION

Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)

S 01/1

HALMED'S PAST ACHIVEMENTS AND FUTURE CHALLENGES

Maja Lovrek Romčević (Agency for Medicinal Products and Medical Devices of Croatia (HALMED)), Siniša Tomić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

The past few years represented a uniquely challenging period for the national competent authorities responsible for medicinal products and medical devices as two unprecedented events, Brexit and COVID-19 pandemic, occurred closely one after the other. Both events required robust allocation of increased workload across the EU network in evaluation and monitoring of medicinal products and medical devices. Brexit necessitated alignment of all medicinal products with the post-Brexit requirements as well as taking over the responsibility of a reference member state for a certain number of marketing authorisation procedures from the UK's competent authority. Both Brexit and COVID-19 pandemic demanded greater contribution by HALMED to the assessment of medicinal products within the centralised procedure coordinated by the European Medicines Agency (EMA), including COVID-19 vaccines and therapeutics. Ensuring adequate safety monitoring of new vaccines and therapeutics, securing a supply of medicinal products and medical devices and providing timely information to the public and healthcare community in times of the COVID-19 pandemic represented additional challenges for the whole EU regulatory network. In addition to the regular workload and emerging tasks, HALMED was also engaged in the Croatian Presidency of the Council of the European Union, Twinning project to support Montenegrin competent authority, changes in the legislation for medical devices and clinical trials and actions related to nitrosamine impurities in medicinal products. In the upcoming period, HALMED's strategy is focused further on availability and safety, contribution to the EU regulatory network, operational excellence, strengthening HALMED's role and regulatory framework as well as process optimization.

S 01/2

REVISION OF THE EU GENERAL PHARMACEUTICALS LEGISLATION

Sabina Uzeirbegović (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia), Maja Lovrek Romčević (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia), Goranka Marušić Kontent (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia), Siniša Tomić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia)

In November 2021, the European Commission adopted the Pharmaceutical Strategy outlining the reforms that intend to reinforce the European pharmaceutical system's patient-centred focus and to make it future-proof and crisis-resistant. The Strategy also takes into account learnings from the COVID-19 pandemic which has clearly demonstrated how critical it is to ensure timely access to safe, high quality and affordable medicines. As part of the EU pharmaceuticals strategy, the Commission has started to evaluate and revise the EU's general legislation on medicines for human use to ensure a futureproof and crisis-resistant medicines regulatory system. The revision aims to: ensure access to affordable medicines; enable innovation for the development of high quality, safe and effective medicines, harnessing the benefits of digital and emerging science and technology while reducing the environmental footprint; enhance the security of supply of medicines and address shortages; reduce the regulatory burden and provide a flexible regulatory network. The strategy anticipates that a new Regulation replacing Directive 2001/83/EC and Regulation 726/2004 will be adopted in Q4 2022. In addition, revisions are anticipated to the Orphan Regulation, the Paediatric Regulation and the Supplementary Protection Certificate Regulation to target incentives in areas of unmet medical needs. In conclusion, the aim of a new pharmaceutical legislation is to fit current world ensuring that all patients have access to safe, high quality and affordable medicines.

S 01/3

PHARMACOVIGILANCE UPDATE

Željana Margan Koletić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED)), Sinisa Tomić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

Pharmacovigilance, also known as drug safety, is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.
COVID-19 pandemic required regulatory network to adapt its mechanisms for safety monitoring by developing Pharmacovigilance plan for COVID-19 vaccines. In the presentation, brief summary of conducted pharmacovigilance activities regarding COVID-19 vaccines will presented, such as ACCESS project. Also, information about proposed
changes to pharmacovigilance legislation, further development of HALMED's electronic system for Adverse Drug Reaction reporting from healthcare professionals and projects in which HALMED participates will presented.
At the end of the presentation, participants will be informed about the new trends and developments in field of pharmacovigilance.

S 01/4

THE ROLE OF CLINICAL PHARMACOLOGISTS IN THE AUTHORISATION OF INNOVATIVE MEDICINES

Danica Jurčić Nahal (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Croatia)

Introduction

In the European Union (EU), innovative medicines are almost in all cases submitted for authorisation under the centralised procedure. The centralised procedure means that a single marketing-authorisation application is submitted to the European Medicines Agency (EMA). EMA's Committee for Medicinal products for Human Use (CHMP) carries out a scientific assessment of the application and gives recommendation to the European Commission on whether the medicine should be authorised. Assessor teams from two EU Member States, appointed by the CHMP, carry out the initial assessment of each application independently.

Materials and methods

The aim of this overview is to present the involvement of Croatian clinical pharmacologists in the initial assessment of safety and efficacy of innovative medicines submitted to the EMA under the centralised procedure.

Results

In the period of 3 years (from June 2019 to June 2022), Agency for medicinal products and medical devices of Croatia (HALMED) carried out initial assessment of safety and efficacy for 10 innovative medicines submitted to the EMA under the centralised procedure. Additionally, 3 new assessments are to be performed in the second half of 2022. Clinical pharmacologists are involved in the safety and efficacy assessment of all these medicines. The assessed medicines are intended for use in diverse therapeutic areas (dermatology, gastroenterology, haematology, oncology, neurology, immunology and women's health). Conclusions

Clinical pharmacologists provide indispensable contribution to the safety and efficacy assessment as well as to the conclusion on the overall benefit-risk balance of new medicines in different therapeutic areas.

S 01/5

SPECIFICS AND TENDENCIES OF DRUG CONSUMPTION IN CROATIA IN THE LAST FIVE YEARS

Pero Draganić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia)

OBJECTIVES: In relation to the symposium theme of this Congress „Drug regulation", we have examined the outliers within the drug consumption in Croatia in the last five years. This consideration gives an extensive insight into drug utilization, as an economic and a public health issue, thus detecting the possible specifics of consumption. Our target is to investigate the utilization tendencies of drugs in Croatia during the period 2017 - 2021, thus focusing on the drugs with references that are outside the usual consumption tendencies. METHODS: The data of drug utilization in Croatia are collected and analysed in HALMED. By applying the ATC methodology (ATC), the given data are used to calculate the number of defined daily doses (DDD) and the financial expenditure in the period 2017-2021.
RESULTS: The drugs most expended, according to DDD / TID, in the period 2017-2021 are Agents acting on renin-angiotensin system, Psycholeptics, Lipid modifying agents and Drugs used in diabetes. According to spending in Kunas, the most expended drugs in the period 2017-2021 were Antineoplastic agents, Immunosuppressant drugs, Drugs used in diabetes and Psycholeptics. The utilization of Antineoplastic drugs (L01) indicate a huge increase of more than three times in the period 2017 to 2021.
CONCLUSIONS: During the period 2017-2021, the majority of the drugs had moderate increase of consumption. The utilization of drugs for cancer therapy increased continuously and significantly. The biggest expenditure is noticed in Antineoplastic agents group, which includes the most of new, efficient, specific and, after all, expensive drugs.

S 01/6

MANAGEMENT OF MEDICINES SHORTAGES

Josipa Cvek (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia), Ana Kontek (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia), Barbara Bilandžija (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia)

Shortages of medicinal products present a rising public health concern in many European Union (EU) countries. The causes are multifactorial, ranging from the manufacturing of raw materials to national pricing and procurement practices.
Consequences of shortages include a decreased quality of patient care and an increased burden on healthcare professionals, who need to identify and provide alternative treatments if there are any. The COVID-19 pandemic has further spotlighted problems with the availability of medicines and vulnerabilities in pharmaceutical supply chains.
In recognition of the problem and the need for coordinated action at the EU level, the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) established a single point of contact (SPOC) network to improve information sharing between the Member States, EMA and the Commission on preventing and managing shortages.
Measures to secure the supply of medicines across the EU and avoid shortages are also included under the EU Pharmaceutical Strategy for Europe 2020. Based on the Strategy, a new Regulation (EU) 2022/123 entered into force in March 2022 to strengthen the EMA's role in responding to health threats. This includes monitoring and mitigating the risk of shortages of critical medicines and medical devices. It also foresees electronic monitoring and reporting system through which national agencies and marketing authorisation holders should provide information regarding shortages of a specific list of medicines in times of crisis.
The lecture addresses the above-described initiatives within the EU regulatory network as well as monitoring the medicines shortages at the national level.

S 01/7

MEDICINAL PRODUCT DATA STANDARDISATION – PRECONDITION FOR EFFICIENT DATA EXCHANGE BETWEEN ALL STAKEHOLDERS

Dubravka Sudić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia), Sanja Grčić Plečko (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia)

Medicinal products identification is a global challenge as healthcare stakeholders capture in their information systems different sets of data on medicinal products, using different codebooks, different languages and different abbreviations to describe them. Simple example might be pharmaceutical form described as “Film-coated tablet” that can be presented as “Coated tablet”, “Tablet,” or even “Tabl.” or “Tbl.”. Also, the same product might be available in different countries under different brand names or even the same name might be used for different products. When a medicinal product is dispensed or used inappropriately due to mistakes related to medicinal product data, patient’s safety might be jeopardized.
Moreover, different standards and different languages used to describe medicinal products, cause challenges in business processes to industry as well as to regulatory network members. EC Regulation (EU) 520/2012 addresses the above-described challenges by requiring national competent authorities in the EU and Marketing Authorization Holders to apply the ISO IDMP (Identification of Medicinal Products) standards for identification and describing of medicinal products.
The European Medicines Agency (EMA) is leading the implementation of the ISO IDMP standards for the identification of medicinal products in a phased programme, based on the four domains of master data in pharmaceutical regulatory processes: Substance, Product, Organisation and Referential (SPOR) data.
ISO IDMP standards were introduced with the goal to have a standardized set of information on medicinal products across the world, across regulatory and medicinal communities, in order to fulfil the needs of wide healthcare areas.

ROUND TABLE 01

VACCINES AGAINST COVID-19 - LESSONS LEARNED

Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)

RT 01/1

VACCINES AGAINST COVID-19 - LESSONS LEARNED FROM SAFETY MONITORING

Nikica Mirošević Skvrce (The Agency for Medicinal Products and Medical Devices)

European Pharmacovigilance system was well prepared for COVID-19 pandemic, which resulted in early detection and confirmation of new signals and timely implementation of risk minimisation measures.
Expedited approval of a vaccine administered to large population requires not only monitoring of adverse drug reactions through spontaneous reporting, but also cohort event monitoring (CEM) and epidemiological studies, especially those using rapidly available data in healthcare databases.
Preparedness activities for safety surveillance of COVID-19 vaccines included protocols development, as part of ACCESS project, before approval of vaccines. This enabled timely start and rapid results of studies. Additionally, due to previous work from ADVANCE project, data from large databases were available and prepared for data linkage thus enabling calculation of background incidences and confirmation of very rare risks. Background incidences were combined also with reporting rates from spontaneous reporting resulting in improved signal detection. CEM can generate additional data on course and impact of the adverse events. Disadvantages of CEM include extensive use of resources and inadequate inclusion of participants in case of lack of awareness of this newer method. CEM could have an important role in next phase with adaptive COVID-19 vaccines, as less data from clinical trials would be available and less real life dana due to vaccine use mainly in high-risk groups.
Epidemiological studies enabled confirmation of risks with high background incidence and identification of risk factors. In conclusion, COVID-19 pandemic once again showed importance of Pharmacovigilance and continuous investments in this filed especially in view of increased workload in pandemic.

RT 01/2

VACCINES DEVELOPMENT – LESSONS FROM THE COVID-19 PANDEMIC

Tihana Šlezak (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

COVID-19 pandemic rapidly grew into a global crisis with long term health, social and economic consequences.
Incredible global effort was made to develop and deploy vaccines to battle COVID-19 in record time which is unprecedented in the history of vaccines. Pathogen surveillance and quick and seamless sharing of data across borders as well as regulatory flexibility and collaboration among the leading agencies, proved invaluable in bringing these breakthroughs to people. Next to fast vaccines deployment, we witnessed constant viral strains evolution. It is an urgent reminder that nobody is safe until everybody is safe.
Scientific community's ability to combine speed and accuracy, sharing new data quickly through various research hubs was crucial. EMA and the European medicines regulatory network introduced a variety of measures and regulatory flexibilities as part of their response to the COVID-19 crisis. Two extremely important tools implemented by the EMA enabled faster vaccines approval - rolling review and conditional marketing authorization. Major lesson was that one can be faster without taking shortcuts. Innovation is essential for preparedness and response. Regulatory agencies have to be able to provide rapid and coordinated feedback to medicine developers during a crisis. Mechanisms to enable rapid advice and approval of large, well-designed trials, to avoid fragmentation in clinical research, should be established. Collection, coordination and analysis of health data across the EU should be improved. The collaboration and communication with ECDC, national public authorities and the NITAGs should be strengthened as vaccine confidence is critical for success.

RT 01/3

CHALLENGES OF VACCINES QUALITY ASSESSMENT IN THE CONTEXT OF PANDEMIC

Dijana Derganc (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

EU authorities are making significant contribution to global efforts in combating COVID-19 pandemic, investing resources in accelerating development and authorizing vaccines of appropriate quality, safety and efficacy.
Existing EU regulatory framework, which allows granting of conditional authorization for medicines in defined situations, was further adapted with new elements such as rolling review, accelerated procedures and regulatory flexibility. However, regulatory flexibility did not imply reduced regulatory requirements, but increased involvement of the pharmaceutical industry and competent authorities in the common goal of accelerating the availability of COVID-19 vaccines.
Unlike the usual marketing authorization procedure in which assessment begins when testing is fully completed, data in support of COVID-19 vaccines authorization is assessed gradually, as it becomes available, in order to provide advice to manufacturers in a timely manner and to speed up the authorization process.
In addition to short deadlines and procedural adaptations, implementation of new manufacturing technologies for COVID- 19 vaccines also presented challenge for the competent authorities. Innovative manufacturing processes, new formulations and analytical methodologies were presented as part of quality dossiers.
First approved vaccines had unconventional presentations and storage conditions. Although distribution-demanding, such vaccines were more stable and could be manufactured in appropriate quantities due to high demands. However, manufacturers continued optimizing the vaccines after the authorization in order to make them easier to use and more available. Consequently, high number of variations of the dossiers followed. New variants and consequent need to adapt regulatory framework represent today’s greatest challenge in development and authorization of COVID-19 vaccines.

S02

PHARMACOLOGY OF CENTRAL AND PERIPHERAL METABOLISM IN NEURODEGENERATIVE DISORDERS

Chairpersons: Melita Šalković-Petrišić (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Jelena Osmanović Barilar (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia)

S 02/1

INTRODUCTION TO METABOLIC AND OTHER NON-COGNITIVE PATHOLOGY IN NEURODEGENERATIVE DISORDERS

Melita Šalković-Petrišić (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia)

Neurodegenerative disorders (NDs) and Alzheimer's disease (AD) in particular, are incurable diseases affecting elderly. AD is the most common cause of dementia characterised by progressive memory loss but the complex etiopathogenesis of its prevailing sporadic form (sAD) and frequently occurring comorbidities of different origin have paved a way to the research of central and peripheral non-cognitive pathology/symptoms in sAD. sAD has considered as a metabolic disease caused by brain insulin resistance (BRI). Type 2 diabetes mellitus (T2DM) doubles the risk of sAD, and T2DM and sAD share some overlapping pathophysiology in the brain including dysregulation of glucose and insulin signals, neuroinflammation, mitochondrial dysfunction and oxidative stress but the crosstalk between them and BRI is still unresolved. Altogether this has led to the increased interest in exploring of the therapeutic potential of antidiabetic drugs in AD treatment, particularly of the incretin glucagon-like peptide-1 (GLP-1) analogues which have a neuroprotective role in the brain. Although data on incretins in animal sAD and other NDs models are very promising, the results of incretin-clinical trials in AD/PD patients are inconsistent. One of the major drawbacks of preclinical and clinical studies on incretins' effects in NDs is the lack of knowledge on the incretins' dyshomeostasis in sAD condition in general, particularly their dysfunction in the brain and the alterations in the incretins' brain - gut axis. The need for further research on incretins' pathophysiology and related therapy as well as on animal models manifesting both cognitive and non-cognitive NDs pathology is discussed in the Symposium. Supported by HRZZ-IP-2018-01-8938.Co-financed by the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain", GA KK01.1.1.01.0007 funded by the European Union).

S 02/2

CROSSTALK BETWEEN OXIDATIVE STRESS AND ABERRANT INSULIN SIGNALLING IN THE BRAIN: INSIGHTS FOR NEURODEGENERATION

Eugenio Barone (Department of Biochemical Sciences “A. Rossi-Fanelli”, Sapienza University of Rome)

Introduction:
Alterations of brain insulin signalling are a common pathophysiological mechanism leading to dementia in AD and Type 2-Diabetes Mellitus (T2DM). These alterations are often associated with mitochondrial stress, failure of energy metabolism, synaptic loss and ultimately neurodegeneration. Our group identified the impairment of BVR-A – a regulator of insulin signalling – as an early event leading to brain insulin resistance. Here, we tested the hypothesis that reduced BVR-A levels link failure of insulin signalling with mitochondrial stress resulting in AD neuropathology.
Materials and methods:
Alterations of brain insulin signalling, autophagic flux, oxidative stress levels, mitochondrial functions, and AD neuropathology were analyzed in animal models for AD and T2DM, as well as in human samples. Correlations with peripheral metabolic measurements (fasting glucose, insulin and OGTT) and cognitive tasks (spatial memory) were performed. The role for BVR-A, was confirmed in BVR-A-/- mice and cells.
Results:
Reduced BVR-A levels along with IRS1 hyper-activation and loss of Akt-mediated inhibition of GSK3b were observed in the hippocampus before brain insulin resistance development, consistent with a regulatory role for BVR-A. As result, hyperactive GSK3b accumulated responsible for mitochondrial impairment and increased oxidative stress levels. Similar observations were collected in BVR-A-/- mice and confirmed in Sh-Sy5y cells lacking BVR-A. Conversely, by rescuing BVR-A levels we ameliorated the observed dysfunctions.
Conclusions:
These results suggest that early BVR-A loss impairs brain insulin signalling favoring the development of brain insulin resistance and mitochondrial stress. These alterations lead to impaired energy metabolism and development of cognitive dysfunctions both in AD and T2DM.

S 02/3

METABOLIC EFFECTS OF ACUTE CENTRAL INCRETIN RECEPTORS INHIBITION IN A RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE

Jelena Osmanović-Barilar (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Ana Knezović (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Ana Babić (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Jan Homolak (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Melita Šalkovic-Petrišić (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia)

Introduction

The incretin system in sporadic Alzheimer's disease (sAD) is unexplored and its research contributes to understanding of the sAD pathophysiology and new therapeutic strategies. We aimed to explore the role of central glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) on cell metabolism/energy in the hippocampus (HPC) and hypothalamus (HPT) by inhibiting the central incretins receptors (GLP-1R, GIP-R) in streptozotocin intracerebroventricularly-treated (STZ-icv) rat model of sAD.

Materials and Methods

One month after STZ-icv, (3 mg/kg) male Wistar rats were icv treated with vehicle or incretin receptor antagonist Exendin (9-39) amide (Ex9/GLP-1R) or Pro-3 GIP/GIP-R and sacrificed 30 minutes afterward. Protein expression of cell metabolism/energy markers CytC, COXIV, PDH, and cAMP was measured by Western-blot and plasma levels of insulin, glucose, GLP-1, GIP and brain levels of ATP by commercial kits. Data were analyzed by Kruskal-Wallis one-way ANOVA and Mann-Whitney U test ($p<0.05$).

Results

Only Pro-3 GIP increased plasma insulin in STZ-icv and control groups. Plasma active GLP-1 form was increased in STZ-icv group versus controls and decreased by Ex9. Pro-3 GIP increased the GIP concentration in STZ-icv and control groups. CytC and ATP remained unchanged after both inhibitors. PDH levels were altered only after GLP-1R inhibition; decreased in (HPC) controls and increased (HPT) in STZ-icv group. cAMP was decreased (HPC) only following GIP-R inhibition in STZ-icv and control groups.

Conclusions

Central inhibition of GIP-R and GLP-1R in healthy and STZ-icv animals indicated a region-dependent role of incretins in the brain cell energy/metabolism and central incretin-dependent modulation of peripheral hormone homeostasis.

Supported by HRZZ-IP-2018-01-8938.Co-financed by the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain", GA KK01.1.1.01.0007 funded by the European Union)

S 02/4

GASTROINTESTINAL CHANGES IN THE RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE – AN OPPORTUNITY FOR THERAPEUTIC INTERVENTION WITH D-GALACTOSE?

Homolak J (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Joja M (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Virag D (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Babić Perhoč A (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Knezović A (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Osmanović Barilar J (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Šalkovic-Petrišić M (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia)

Introduction: Accumulating evidence highlights the importance of the gastrointestinal tract in the etiopathogenesis and progression of neurodegenerative disorders including Alzheimer's disease (AD), and our preliminary results indicate that gastrointestinal homeostasis is altered in the rat model of sporadic AD induced by intracerebroventricular administration of the diabetogenic toxin streptozotocin (STZ-icv). The aim was to explore the pathophysiological alterations of the gastrointestinal tract and potential protective effects of orally administered D-galactose.
Materials and methods: In the first cohort, 3-month-old male Wistar rats (N=10/group) were administered either STZ-icv (3mg/kg) or vehicle and sacrificed after 1 month. In the second cohort, a 2x2 factorial design was used to understand the effects of chronic oral D-galactose (200 mg/kg/day) in the STZ-icv rats sacrificed two months after model induction. Duodenum, ileum, and colon were dissected and biochemical systems responsible for the maintenance of redox homeostasis were analyzed.
Results: Redox homeostasis seems to be altered (decreased total antioxidant capacity and nucleophilic substrates; increased lipid peroxidation) primarily in the upper small intestine of the STZ-icv rat model of sporadic AD both 1 and 2 months upon model induction. Chronic oral D-galactose shows modest potential to alleviate redox dyshomeostasis in the most affected region of the gastrointestinal tract.
Conclusion: The upper gastrointestinal tract seems to be affected in the rat model of sporadic AD and chronic oral D-galactose does not seem to provide neuroprotective effects by modulating gut redox homeostasis. This work was funded by the Croatian Science Foundation (IP-2018-01-8938). Research was co-financed by the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain"; GA KK01.1.1.01.0007 funded by the European Union through the European Regional Development Fund).

S 02/5

MODELING OF PARKINSON'S DISEASE BY INTRASTRIATAL ADMINISTRATION OF A DIABETOGENIC COMPOUND

Ana Knezović (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Jelena Osmanović Barilar (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Vladimir Farkas (Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia.), Robert Bagaric (Department of Experimental Physics, Rudjer Boskovic Institute, Zagreb, Croatia), Davor Virag (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Ana Babić Perhoč (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Jan Homolak (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Melita Šalković-Petrišić (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia)

Neurodegenerative diseases (NDs) share a number of molecular and cellular pathologies and therapeutic approaches have not been too successful. Recently, metabolic dysfunction was proposed as a common fundamental threat of NDs development and type 2 diabetes as a risk factor for Parkinson's disease (PD). Diabetes in animals is generated by peripheral administration of streptozotocin, while its intracerebroventricular administration induces insulin resistance in the brain (Alzheimer's disease animal model). The aim of this project is to examine whether metabolic dysfunction caused by direct application of streptozotocin to brain region affected in PD (striatum) can induce symptoms characteristic of PD (motoric deficit, cognitive and behavioural alterations). Adult Male Wistar rats were given intrastriatally (is) streptozotocin (3 mg/kg; STZis) or vehicle and one month after, cognitive, behavioural and motoric functions were tested by Rota Rod, Novel Object Recognition, Passive Avoidance, Morris Water Maze, Elevated Plus Maze and CatWalk, and glucose uptake assessed by PET scan. Data were analyzed by Kruskal-Wallis and Mann-Whitney U test. STZis rats showed deficits in motoric functions, spatial learning and memory, fear conditioned and recognition memory, and anxiety-like behaviour and additionally impaired brain glucose uptake/metabolism. The results demonstrate for the first time the development of PD hallmark symptoms after instrastriatal STZ administration, indicating its possible use to generate a new model of PD with both motor and non-motor symptoms The STZis rat model could provide a better translation value in testing of novel drugs so its further characterization is needed to elucidate the underlying mechanisms of PD pathology development.
This work was funded by the Croatian Science Foundation (IP-2018-01-8938) and co-financed by University of Zagreb and the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain"; GA KK01.1.1.01.0007 funded by the European Union through the European Regional Development Fund).

S 03

RATIONAL ANTIMICROBIAL DRUG USE - ANTIMICROBIAL STEWARDSHIP

Chairpersons: Vera Vlahović Palčevski (Department for Basic and Clinical Pharmacology and Toxicology, University of Rijeka Medical Faculty and Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, Rijeka, Croatia), Milan Čižman (Ljubljana University Medical Centre)

S 03/1

ECDC PERSPECTIVE ON ANTIMICROBIAL STEWARDSHIP

Dominique L. Monnet (Head of Section Antimicrobial Resistance and Healthcare-Associated Infections, European Centre for Disease Prevention in Control (ECDC), Solna, Sweden)

The European Centre for Disease Prevention and Control (ECDC) is an EU agency with the mandate to 'identify, assess and communicate current and emerging threats to human health from communicable diseases' (Regulation (EC) No 851/2004). Antimicrobial resistance is a priority disease area of the agency. ECDC contributes to the implementation of the 2017 European One Health Action Plan against antimicrobial resistance.
ECDC contributed to the development of the EU guidelines for the prudent use of antimicrobials in human health that provide a set of principles of prudent and appropriate use of antimicrobials to support good clinical practice and health systems developments for improvement of antimicrobial stewardship.
ECDC also organises regular point prevalence surveys of healthcare-associated infections and antimicrobial use in European acute care hospitals and long-term care facilities, which include collection of data on structure and process indicators of infection prevention and control and of antimicrobial stewardship.
Since 2008, ECDC coordinates the European Antibiotic Awareness Day, in partnership with the World Antimicrobial Awareness Week since 2015, with new materials such as the animation video "Antibiotic Resistance | What can you do as a healthcare specialist?" (https://www.youtube.com/watch?v=3yxRL2TAGOQ).
New EU policy developments include proposals from the European Commission for a regulation on a new ECDC mandate as well as for a new regulation on serious cross-border threats to health.

S 03/2

THE ROLE OF EDUCATION IN ANTIMICROBIAL STEWARDSHIP

Bojana Beović (University Medical Centre Ljubljana)

Education has been recognized as a vital part of antimicrobial stewardship. The topics in education on antimicrobial stewardship include microbiology, pharmacology of antimicrobial drugs, management of infectious diseases as well as communication skills and behaviour science. Elementary knowledge on antibiotic prescribing and stewardship should be embedded in the education of health-care professionals throughout their educational curricula from undergraduate studies, internship, specialty training and continuous postgraduate education. In most parts of the world education in antimicrobial prescribing and stewardship is still deficient. Additional knowledge and skills are needed for experts who lead antimicrobial stewardship programmes. At the same time education is one of the antimicrobial stewardship interventions.

Small group education has been recognized as most effective type of education in AMS. Innovative methods of education include e-learning, smart-phone applications and social media. Education is embedded in some other AMS interventions such as prospective audit and feedback and in antibiotic rounds. Barriers to education in antimicrobial stewardship include cost of education, lack of time and lack of personnel. Several steps to improve education in AMS have been taken recently by various national and international organisations.

S 03/3

USE OF ANTIBIOTICS DURING PANDEMIC COVID-19

Bruno Baršić (University Hospital Dubrava and School of Medicine Zagreb, Zagreb, Croatia)

An enormous increase in the use of antibiotics was observed during COVID-19 pandemic. Still rudimentary concept of antibiotic policy at least in Croatia was unfortunatelly aborted. There are number of reasons for this phenomena:

1. At the beginning of pandemic azithromycin was considered useful controling early viral replication. Four controlled studies did not support that practice, amd its use was abandoned. However, azitromycin use remained widespread, particularly in general practice setting. Combined with hidroxychloroquine it caused a number od QT prolongations with high risk of cardiac arrhytmias.
2. It is difficult to discern bacterial from viral pneumonia in COVID-19 patients since many patients satisfy sepsis criteria and have increased levels of inflammatory biomarkers such as CRP, procalcitonin and IL-6. Although x-ray of the chest is suggestive for COVID-19 pneumonia lot of patients received antimicrobial therapy for severe bacterial pneumonia such as ceftriaxone or co-amoxylav.
3. The risk of nosocomial infections is increased in hospitalized patients with COVID-19. The reasons are huge number of mechanically ventilated patients, central and peripheral venous lines, arterial lines. We observed increased number of *A.baumannii*, MR *K.pneumoniae*, and reappearance of MRSA. That led to increased consumption of reserve antibiotics such as amikacin, penems, 5th generation cephalosporins, colistin.

Grouping of COVID-19 in dedicated (*Nightingale*) hospitals, lack of staff, invlovement of personal not educated for the treatment of infectious disease and critically ill patients caused difficulties in infection control procedures. Fear of nosocomial infections and inability to discriminate primary from secondary infections led to enormous increase in antibiotic consumption. However, during the course of pandemic antibiotic prescription practice improved although we shall observe the consequences of inapproipriate use of antibiotics in years to come.

S04

PHARMACOLOGY IN DENTAL MEDICINE - PANDEMIC RESPONSE

Chairpersons: Ivana Šutej (University of Zagreb School of Dental Medicine, Zagreb, Croatia), Kristina Peroš (University of Zagreb School of Dental Medicine, Zagreb, Croatia)

S 04/1

PANDEMIC RESPONSE - ADJUSTMENT IN PHARMACOTHERAPY AND PRESCRIBING

Ivana Šutej (University of Zagreb School of Dental Medicine, Zagreb, Croatia)

The objectives: During the 2-year time of the Covid-19 pandemic, everyday clinical work was affected by the restriction measures. We investigated the impact of the pandemic on the prescribing pattern of dentists in Croatia during 2 pandemic years and compared those with a pre-covid time period.
Materials and methods: Data used in this research were obtained from the Croatian Health Insurance Institute, for the years of 2013. - 2021. The number of dentists' prescriptions, the cost of medicines in Croatian Kuna (HRK), and the number of packages prescribed were analyzed.
Results: Results showed changes in the prescription pattern that could be attributed to the behavior of patients and practitioners during the Covid-19 pandemic. The most prescribed medications were antibiotics with a steady increase through all observed years, with no significant changes during the pandemic period. Pandemic has made an impact only on prescribing of azithromycin, the reason for this anomaly is to be investigated. For most pain-relief and antiseptic medications, the increase was significant only for the first pandemic year while the measures were strict, while in the second year the trend in increase significantly dropped.
Conclusions: Restricted access to dental care due to COVID-19 resulted in changes to the prescription pattern of dental medications. The changes that could be attributed to the restriction measures are seen in the utilization of pain relief medications, antiseptics, and wide-spectrum antibiotic azithromycin. Adaptation to the Covid-19 pandemic setting in dentistry is now over, and observed abnormalities have to be corrected primarily through evidence-based dental prescribing protocols and guidelines.

S 04/2

ORAL ANTISEPTICS AGAINST CORONAVIRUS – ARE THEY JUSTIFIED

Krešimir Bašić (Department of Pharmacology, School of dental medicine University of Zagreb, Zagreb, Croatia)

The coronavirus disease 2019 (COVID-19) pandemic is major health, political and economic issue in last 3 years. Since there is no effective cure to this disease, most public health measures to contain the pandemic are based on preventing the spread of the SARS-CoV-2 infection.

ACE2 receptors, cellular receptors for SARS-CoV-2, are highly expressed in the oral mucosa, which makes oropharyngeal cavity a potential high-risk route for SARS-CoV-2 infection. Also, virus can be detected in saliva, even before symptoms appear, which is presenting high risk of virus transmission. Reducing oral viral load could help reduce transmission risk. Oral antiseptics are proven to be effective against oral microorganisms in prevention of infection of soft and hard tissues in oral cavity. They are used widely in form of mouthwashes. Only question that needs to be answered is virucidal activity of oral antiseptics on SARS-CoV-2. Povidone-iodine and cetylpyridinium chloride showed best results and they are recommended to use in professional clinical settings, such as dental office, prior to dental treatment. Still, it is not recommended to use oral antiseptics as a measure in prevention against SARS-CoV-2 infection in general population since their use could provide a false sense of security.

Although there is sufficient in-vitro evidence to support the use of antiseptics to potentially reduce the viral load of SARS-CoV-2 there is need for further research since in-vivo evidence for most oral antiseptics is limited. Effective protocol and recommendations for oral antiseptics is yet to be determined.

S 04/3

STRENGHTS AND LIMITATIONS OF COVID SALIVA TESTING

Kristina Peroš (University of Zagreb School of Dental Medicine, Zagreb, Croatia)

The use of saliva as a sample material has well known advantages (easy, non-invasive, low cost, more acceptable for patients) that motivates researchers to try to develop saliva testing for current COVID-19 pandemic. Several commercial diagnostic assays for saliva COVID testing are currently available but none of these is accepted as mutually recognised test when compared to assays for nasopharyngeal specimens. The tests for samples are based on different laboratory procedures available for saliva COVID testing as well: RT-PCR testing, RT-LAMP testing, rapid antigen testing, antibody testing and isolation of viable virus.
Issues as sampling techniques, sampling times, population characteristics, presence and time of symptoms onset, and the height of viral load significantly affect the sensitivity of testing associated with the use of saliva samples. Lower sensitivity associated with the use of saliva samples is suggested by meta-analyses of numerous saliva testing studies. Adequate sensitivity of saliva tests to those using nasopharyngeal swabs is noticed for RT-PCR tests in case of symptomatic patients, in the sample collection during the first five days from onset of symptoms, and in case of high viral load.
The accepted standard for COVID-19 testing for use with RT-PCR and rapid antigen diagnostic tests is nasopharyngeal swab. The use of saliva as an alternative sample material for rapid antigen or antibody tests is not supported although is promising. Ther is a need for further clinical studies on the saliva tests for COVID-19.

S 04/4

SALIVA DIAGNOSTICS ON EVERYONE'S LIPS: COVID-19 TESTING AND BEYOND

Manuela Hofner (AIT – Austrian Institute of Technology GmbH; Molecular Diagnostics – Vienna, Austria), Ulrike Kegler (AIT – Austrian Institute of Technology GmbH; Molecular Diagnostics – Vienna, Austria), Jasmin Huber (AIT – Austrian Institute of Technology GmbH; Molecular Diagnostics – Vienna, Austria), Julie Krainer (AIT – Austrian Institute of Technology GmbH; Molecular Diagnostics – Vienna, Austria), Miriam Klausberger (BOKU - University of Natural Resources and Life Sciences; Department of Biotechnology – Vienna, Austria), Valerie Regele (AIT – Austrian Institute of Technology GmbH; Molecular Diagnostics – Vienna, Austria), Mark Dürkop (BOKU - University of Natural Resources and Life Sciences; Department of Biotechnology – Vienna, Austria)), Klemens Vierlinger (AIT – Austrian Institute of Technology GmbH; Molecular Diagnostics – Vienna, Austria), Andreas Weinhäusel (AIT – Austrian Institute of Technology GmbH; Molecular Diagnostics – Vienna, Austria), Christa Noehammer (AIT – Austrian Institute of Technology GmbH; Molecular Diagnostics – Vienna, Austria)

Our research group Molecular Diagnostics at AIT, the Austrian Institute of Technology, started to explore the advantages and potential of saliva for diagnostic biomarker development already quite some time before saliva became familiar and popular to everyone as a convenient sample matrix for COVID-19 testing. Given our previous years of saliva and multiplex assay experience we were able in short time not only to establish a reverse-transcription (RT) PCR assay for COVID-19 testing from gurgle solutions but also to implement a serological test based on Luminex® xMAP® technology, which allows highly efficient multiplexed detection of antibodies directed against SARS-CoV-2 spike protein (SP), receptor binding domain (RBD) and nucleocapsid protein (NP) simultaneously. We will report on technical details of the gurgle PCR test and also glance over other PCR based COVID tests we have been evaluating. Further we will introduce the technical set up of our newly developed Luminex Sars-CoV-2 antibody test and present data on IgG titers measured from 232 serum samples taken after second shot of SARS-CoV-2 vaccine and a comparative study of IgG and IgA reactivities in 22 paired saliva and serum samples. Last but not least we will give a short overview of selected saliva diagnostics projects of our research group which go beyond COVID-19 testing.

S05

THE PLACE OF BIOLOGIC AND BIOSIMILAR DRUGS IN CURRENT MEDICINE PRACTICE

Chairperson: Suzana Mimica (University hospital center Osijek, Department of Clinical Pharmacology and Faculty of Medicine Osijek, Department of Internal Medicine and History of Medicine, Osijek, Croatia)

S 05/1

THE CHALLENGES OF BIOSMILAR DRUGS USE: 16 YEARS LATER

Suzana Mimica (University hospital center Osijek, Department of Clinical Pharmacology and Faculty of Medicine Osijek, Department of Internal Medicine and History of Medicine, Osijek, Croatia)

A biosimilar medicine is highly similar to another already marketed biological medicine (i.e. reference medicine). European Medicines Agency has approved the first biosimilar in 2006 (growth hormone – Omnitrope) and the landmark decisions of EMA represented the approval of a first monoclonal antibody biosimilar – infliximab in 2013 followed by biosimilar monoclonal antibodies for use in Haematology and Oncology. Within the period of the last 16 years, EMA has approved 88 biosimilar drugs, i.e enoxaparin sodium, proteins (growth factors – epoetin, filgrastim, pegfilgrastim, hormones - follitropin alfa, insulin glargine, somatropin, teriparatide, insulin lispro, fusion proteins – etanercept, monoclonal antibodies
– adalimumab, infliximab, rituximab, bevacizumab and trastuzumab).
The evidence acquired over 16 years of clinical experience shows that biosimilars can be used as safely and effectively in all their approved indications as other biological medicines. Biosimilars enabled more patients to be treated and reduced price of the reference products. Interchangeability and switching of biosimilar monoclonal antibodies and fusion proteins is regulated by individually EU Member States and has been a subject to debate since their approval. In a recent study where data on EU-licensed mAbs and fusion proteins using European Public Assessment Reports (EPARs) and postmarketing safety surveillance reports from EMA were analyzed, it was demonstrated that the efficacy, safety, and immunogenicity of biosimilars compared with the reference products is comparable. The authors concluded that biosimilars approved in the EU are highly similar to and interchangeable with their reference products and that therefore additional systematic switch studies are not required.

S 05/2

ADVERSE REACTIONS TO BIOLOGICAL MEDICINES

Danica Juričić Nahal (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia)

Introduction

Biological medicines contain active substances from a biological source. Most biological medicines used today contain active substances made of proteins. These differ in size and complexity, from simple proteins like insulin to complex ones such as monoclonal antibodies. Biological medicines are essential for the treatment of many serious conditions such as autoimmune diseases and cancers.

Materials and methods

A short overview of adverse reactions to biological medicines will be presented. The process of establishing the list of adverse drug reactions in the Summary of product characteristics during marketing authorisation process will be described.

Results

Potential adverse reactions to biological medicines include infusion reactions, infections, autoimmunity, cytokine release syndrome, immune-related effects and other. Immune-related effects include a number of dermatologic, gastrointestinal, endocrine and other inflammatory reactions. Recognition of these reactions is important since treatment with immunosuppressive medications might be needed.

Clinical trials performed to support the marketing authorisation of a new biological medicine will not be able to identify all possible adverse reactions. Clinical trials include a limited number of patients with usually strict and narrow eligibility criteria. These and other relevant information are placed in the Summary of product characteristics.

Conclusions

Healthcare professionals need to be aware of the wide spectrum of possible adverse reactions in patients treated with biological medicines. Summary of product characteristics is a valuable source of information regarding adverse reactions for all medicines.

S 05/3

NOVEL BIOLOGICAL MEDICINAL PRODUCTS FOR THE TREATMENT OF MALIGNANT AND AUTOIMMUNE DISEASES

Selma Arapović Džakula (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia)

Introduction

The field of medicinal products is constantly evolving. That is particularly evident for biological medicinal products for the treatment of malignant and autoimmune diseases. Biological therapies provide new treatment options in burdensome indications. The overview gives insight in the novel biological medicines authorised in the EU, together with a brief overview of the regulatory pathway for the marketing authorisation.

Materials and Methods

The website of the European Medicines Agency (EMA) was searched for new authorised biological medicines by date of authorisation and by therapeutic areas. European Public Assessment Reports (EPARs) together with summaries of opinion and product information of concerned medicinal products were reviewed. Period from 1 January 2021 until 30 June 2022 was covered.

Results

The overview of the newly authorised biological medicines for the treatment of malignant diseases and for the treatment of autoimmune diseases is presented. Particularly significant novel therapies for the concerned therapeutic indications are emphasized. Selected details of the clinical development programme for selected medicinal products are extracted.

Conclusions

Novel biological medicinal products for the treatment of malignant and autoimmune diseases are constantly being developed. The European regulatory pathway for the marketing authorisation of biological medicinal products is well defined and assures thorough assessment of quality, efficacy, safety and benefit - risk balance. Biological medicines represent valuable treatment options of particular importance for the treatment of malignant and autoimmune diseases.

S 05/4

BIOLOGIC DRUGS FOR THE TREAMENT OF COVID-19: CURRENT KNOWLEDGE AND CHALLENGES FOR THE FUTURE

Ana Havidić (Clinical hospital centre Osijek, Osijek, Croatia)

COVID-19 is an infectious disease caused by the SARS-CoV2 virus. Since the outbreak in December 2019, COVID- 19 represents public health crisis and demands rapid development of new treatment options.

Some monoclonal antibodies have been approved for prophylaxis and treatment of some viral diseases, e.g. those caused by RSV, HIV and Ebola virus. This therapy was also recognized as an important therapeutic option in COVID-19.

SARS-CoV2 infection can lead to development of cytokine storm with further deterioration of the disease. European Medicines Agency (EMA) has approved extended indication for two monoclonal antibodies, anakinra and tocilizumab, previously registered and use din management of various inflamatory conditions.

Casirivimab/imdevimab and regdanvimab were the first monoclonal antibodies authorised by EMA – for administration in patients with COVID-19, followed by sotrovimab. These antibodies target the spike protein of SARS-CoV2, thus preventing the viral entry into cells. These monoclonal antibodies have been approved in patients with increased risk of progression to severe COVID-19.

Tixagevimab/cilgavimab has recently been approved by EMA for pre-exposure prophylaxis in immunocompromised patients and individuals with contraindication to vaccination.

Results of randomised trials of those monoclonal antibodies show moderate efficacy and good safety, but with the emergence of delta and omicron variant of SARS-CoV2, some of the monoclonal antibodies lost their activity against SARS-CoV2.

In conclusion, monoclonal antibodies are important part of COVID-19 treatment, especially in prevention of progression to severe COVID-19 disease. Their use is limited by high costs and variability of SARS-CoV2. Combining different antibodies could be an important strategy in the future.

S 06

MODERN APPROACH TO THE TREATMENT OF DIABETES AND METABOLIC DISEASES - NEW CHALLENGES AND OPPORTUNITIES

Chairperson: Dubravka Jurišić Eržen (Department of Internal Medicine, Clinical Hospital Centre Rijeka, Rijeka, Croatia)

S 06/1

INCRETIN THERAPY: EFFECTS BEYOND GLYCEMIC CONTROL

Tina Tičinović Kurir (Department of Pathophysiology, Faculty of Medicine, University of Split and Department of Endocrinology, Diabetes and Metabolic Diseases, University Hospital of Split, Split, Croatia)

Incretin-based therapies (glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 inhibitors) have become an important treatment option for patients with type 2 diabetes mellitus. Glucagon-like peptide (GLP-1) plays a role in multiple physiologic systems. The actions of GLP-1 RA in type 2 diabetes include: stimulating glucose-dependent insulin secretion, inhibiting glucose-dependent release of glucagon, reducing release of glucose from the liver, decreasing gastric emptying, increasing glucose uptake in muscle and adipose tissue and enhancing satiety and decreasing appetite and food intake. In addition to glucose-lowering effect, GLP-1 and GLP-1 RAs exerts many protective biological functions in accord with the wide expression of GLP-1R throughout the gastrointestinal tract and in many other tissues including vascular endothelium, cardiomyocytes, endocardium, and smooth muscle cells. Studies in both animals and humans have repeatedly demonstrated the ability of GLP-1 to improve endothelial function, and beneficial effects on the cardiovascular system by improving and protecting cardiac function from ischemic injury and by its anti-atherogenic and vasodilatory effects. In particular, GLP-1 RAs determined a reduction of the risk of cardiovascular events and mortality in large prospective outcome trials in type 2 diabetes mellitus patients. Regarding neuroprotective actions in degenerative neurological disease models for Parkinson's- or Alzheimer's disease or neurovascular complications like stroke, animal studies have shown positive results.

S 06/2

SGLT2 INHIBITORS - MECHANISM OF CARDIO AND RENAL PROTECTION

Dario Rahelić (Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases Merkur University Hospital, Zagreb, Croatia; Catholic University of Croatia School of Medicine, Zagreb, Croatia and Josip Juraj Strossmayer University of Osijek School of Medicine, Osijek, Croatia)

The modern treatment of type 2 diabetes include antihyperglycemic therapy with low risk of hypoglycemia, beneficial effect on weight loss and additional extraglycemic effects like cardioprotective and nephroprotective effects.
After the results from the EMPA-REG OUTCOME trial which demonstrated that empagliflozin (SGLT-2 inhibitor) reduced major cardiovascular and renal outcomes in patients with type 2 diabetes and established cardiovascular disease in comparison to placebo, the treatment of type 2 diabetes has changed dramatically. Sodium glucose co-transporter 2 (SGLT-2) inhibitors inhibit glucose reabsorption in the proximal tubule of the kidney and have beneficial effects on albuminuria and renal outcomes. The number of mechanisms have been proposed to explain the cardioprotective effects of SGLT-2 inhibitors, including effect on glycemia, blood pressure, hyperuricemia, weight loss, diuresis, natriuresis, erythropoiesis, cardiac energy metabolism, oxidative stress and inflammation, vascular function, cardiac Naþ/Hþ exchanger, increasing autophagy and lysosomal degradation, decreasing epicardial fat mass, increasing number of circulating provascular progenitor cells, preventing ischemia and reperfusion injury, preventing adverse cardiac remodeling, reducing sym-pathetic nervous system (SNS) activity. Proposed mechanisms of nephroprotection are reduced intraglomerular pressure, improved tubular oxygenation and metabolism and reduced inflammation and fibrosis.
SGLT-2 inhibitors reduce risk of heart failure and have cardioprotective and nephroprotective effects. As cardiovascular and renal disease are common and serious complications of diabetes, SGLT-2 inhibitors are highly recommended for patients with type 2 diabetes and cardiovascular and/or renal disease.

S 06/3

PAST, PRESENT AND FUTURE OF INSULIN THERAPY

Dubravka Jurišić Eržen (Department of Internal Medicine, Clinical Hospital Centre Rijeka, Rijeka, Croatia)

In the last 100 years we have witnessed tremendous progress in insulin therapy, as a pivotal therapy for diabetes, from the initial crude, yet life-saving, animal insulin extracts to novel human insulin analogues. Although the complete physiologic replacement of insulin is inherently difficult to achieve with open-loop subcutaneously administered insulin, the continued development of improved injectable insulin formulations with superior pharmacokinetics and pharmacodynamics will enhance glucose control, and represents important clinical advances in the treatment of both type 1 and type 2 diabetes. There is also, consistent innovation in the technological advances such as new pumps, pens and connected care have eased the burden of care for people with diabetes all over the world. In the coming century, new innovations including glucose-sensing insulins and artificial islets will lead the way toward a future where life is a normal as possble for people living with diabetes.

S 06/4

IMMUNE CHECKPOINT INHIBITOR MEDIATED ENDOCRINOPATHIES

Jurica Nazlić (University Hospital of Split, Split, Croatia)

Anticancer immunotherapy, in the form of immune checkpoint inhibition is a paradigm shift that has transformed the care of patients with different types of solid and hematologic cancers. Immune checkpoint molecules have an important function in regulating immune response. After binding to their ligands, these proteins can initiate either inhibitory or stimulatory pathways that modulate T-cell function. CTLA-4, PD-1 and PD-L1 play a key role in the maintenance of immunological tolerance to self-antigens, preventing autoimmune disorders. Therefore, at the same time that Immune checkpoint inhibitors (ICI) are able to unleash T cells to fight cancer, they also can trigger autoimmune like manifestations in different organ systems, generally referred to as immune-related adverse events (irAEs). Endocrine dysfunctions are among the most common irAEs that have been reported in clinical trials with ICI, including hypothyroidism, hyperthyroidism, hypophysitis, primary adrenal insufficiency, and insulin-deficient diabetes . Immune-mediated endocrinopathies can cause acute and persistent morbidity and, rarely, death. Clinical suspicion and routine hormonal testing are crucial for the early diagnosis. Understanding of ICI-induced endocrinopathies is critical, not only, for oncologists and endocrinologists, but also the other specialists who may be called upon to diagnose and manage these growing number of patients.

S07

RECENT FINDINGS IN NEUROPSYCHOPHARMACOLOGY OF MENTAL DISORDERS

Chairperson: Dubravka Švob Štrac (Laboratory for Molecular Neuropsychiatry, Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia)

S 07/1

INTRODUCTION: RECENT FINDINGS IN NEUROPSYCHOPHARMACOLOGY OF MENTAL DISORDERS

Dubravka Švob Štrac (Laboratory for Molecular Neuropsychiatry, Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia)

According to International Classification of Diseases, 11th Revision (ICD-11), the mental, behavioral and neurodevelopmental disorders are syndromes characterized by a clinically significant disturbance in an individual's cognition, emotional regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes, which underlie mental and behavioral functioning. They are heterogeneous disorders, ranging from anxiety, mood and psychotic disorders to stress-related, personality, substance use and neurocognitive disorders, which represent significant health, social and economic burden to the individual, their relatives and society. Despite many studies, their multifactorial etiology is still poorly understood, although it is probably due to a complex interplay of environmental and genetic factors. The elucidation of their biological background pose some of the toughest challenges in neuroscience research; however, it may contain keys for identifying risk factors, offering new diagnostic or prognostic biomarkers, as well as providing novel and specific targets for their prevention and treatment. Therapeutic strategies for mental disorders frequently demonstrate high variability in the treatment response, as well as development of side effects, and are often limited to only alleviating the symptoms. Choosing their adequate therapy is challenging and personalized, polytherapeutic and multimodal interventions should be tailored in order to help increase the treatment efficacy and safety and minimize drug adverse effects. This symposium will present recent findings, obtained by both preclinical and clinical studies, and give a selection of new advances in the field of neuropsychopharmacology of mental disorders, covering integrative and psychopharmacology research areas, as well as various study models and approaches.

S 07/2

BENEFICIAL EFFECT OF ESTROGEN DERIVATES IN ALZHEIMER DISEASE: STUDIES IN MICE MODEL

Dóra Zelena (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), Szidónia Farkas (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), Adrienn Szabó (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), Bibiána Török (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), Csenge Sólyomvári (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), Csilla Lea Fazekas (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), Krisztina Bánrévi (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), Pedro Correia (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), Tiago Chaves (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary), István Ábrahám (Institute of Physiology, Medical School, University of Pécs, Centre for Neuroscience, Szentágothai Research Centre, Pécs, Hungary)

Alzheimer's disease is the most common form of dementia being highly prevalent in elderly women. The advanced progression may be due to decreased hormone synthesis during post-menopause as estradiol (E2) has neuroprotective potentials. However, E2 might have several side-effects (stroke, venous thromboembolism, and breast cancer), therefore newer compounds with more focused effects are needed.

We hypothesized that activators of non-genomic estrogen-like signaling (ANGELS) might have several health-benefit with more favourable side-effect profile.

First, we found that removal of the ovaries in young (3-month-old) triple transgenic Alzheimer's mice (3xTg-AD) aggravated the neurodegeneration in the cholinergic somatosensory cortical fibres (AChE), without deep influence on behaviour confirming the role of E2. Next, we found that some ANGELS compounds prevented the one-sided intracerebral (into the nucleus basalis magnocellularis) amyloid β injection-induced cholinergic fibre loss in AChE, similarly to E2. However, these compounds did not have uterotrop side-effects. Next, we have chosen one possible candidate (A2), and confirmed the neuroprotective effect of its single dose at structural level (AChE) using ovariectomized, 6-month-old 3xTg-AD mice. The chronic treatment with the same compound was similarly effective in females and males suggesting that this effect of A2 is independent from classical sexual function.

We identified a compound with neuroprotective potential without peripheral side-effect.

Funding: NKFIH K141934, K138763 and K 120311; TKP2021-EGA-16

S 07/3

SIDE EFFECTS OF PSYCHOPHARMACS: RECOGNIZE, PREVENT, TREAT

Suzana Uzun (University Psychiatric Hospital Vrapce, Zagreb, Croatia and School of Medicine Zagreb, Zagreb, Croatia), Oliver Kozumplik (University Psychiatric Hospital Vrapce, Zagreb, Croatia), Ninoslav Mimica (University Psychiatric Hospital Vrapce, Zagreb, Croatia and School of Medicine Zagreb, Zagreb, Croatia)

Side effects of psychopharmacs represent a significant problem during the treatment of mental disorders, as they can affect the patient's cooperation and the results of the treatment itself. Most often, side effects are a consequence of the very mechanism of action of psychopharmacs. Older antipsychotics are associated with extrapyramidal side effects due to D2 receptor blockade. The most common extrapyramidal side effects are parkinsonism, acute dystonia, akathisia, tardive dyskinesia, neuroleptic malignant syndrome, and they can be acute or early and chronic or late. It is necessary for the doctor to know the possible side effects of the drugs he prescribes and to inform the patient about them in advance and to advise him on how to behave in that case. In this way, premature rejection of a drug that could be useful will be prevented, trust will increase, a better therapeutic alliance will be created, and all of this is necessary for the overall outcome of the treatment. Other experts who do not prescribe drugs, but participate in the treatment of patients with mental disorders, should be aware of possible side effects. Side effects affect the quality of life of the patient and his family, and it is necessary to recognize them in time, especially to prevent and treat them.

S 07/4

MULTIMODAL APPROACH TO THE DEPRESSION TREATMENT: FOCUS ON VORTIOXETINE

Matea Nikolac Perković (Ruđer Bošković Institute, Zagreb, Croatia), Anja Dvojković (Psychiatric Clinic Vrapče, Zagreb, Croatia), Gordana Nedić Erjavec (Ruđer Bošković Institute, Zagreb, Croatia), Alma Mihaljević Peleš (School of Medicine, University of Zagreb, Zagreb, Croatia and University Hospital Centre Zagreb, Department of Psychiatry and Psychological Medicine, Zagreb, Croatia), Bjanka Vuksan Čusa (School of Medicine, University of Zagreb, Zagreb, Croatia and University Hospital Centre Zagreb, Department of Psychiatry and Psychological Medicine, Zagreb, Croatia), Lucija Tudor (Ruđer Bošković Institute, Zagreb, Croatia), Zorana Kušević (School of Medicine, University of Zagreb, Zagreb, Croatia and University Hospital Centre Zagreb, Department of Psychiatry and Psychological Medicine, Zagreb, Croatia), Marcela Konjevod (Ruđer Bošković Institute, Zagreb, Croatia), Maja Živković (University Hospital Centre Zagreb, Department of Psychiatry and Psychological Medicine, Zagreb, Croatia), Nenad Jakšić (University Hospital Centre Zagreb, Department of Psychiatry and Psychological Medicine, Zagreb, Croatia), Nela Pivac (Ruđer Bošković Institute, Zagreb, Croatia), Marina Šagud (School of Medicine, University of Zagreb, Zagreb, Croatia and University Hospital Centre Zagreb, Department of Psychiatry and Psychological Medicine, Zagreb, Croatia)

Introduction: Major depressive disorder (MDD) is a common, highly prevalent, and recurrent mental illness. Medication options for the treatment of MDD include different antidepressant drugs, including selective serotonin reuptake inhibitors (SSRIs). Escitalopram and vortioxetine are efficacious SSRIs and they directly target serotonin (5-HT) system. However, vortioxetine has a multimodal mechanism of action and better effect on cognitive dysfunction. This study aimed to compare the effects of treatment with these two SSRIs on plasma BDNF and platelet 5-HT concentration, and to assess their effect on cognitive function in patients with MDD.
Materials and Methods: Cognitive function was evaluated using the F-A-S test, Digit Span test, and Digit Symbol Coding Test. Plasma BDNF was measured using ELISA and platelet 5-HT concentration was determined fluorometrically and evaluated at baseline and after 4 weeks of treatment with vortioxetine (N=61) or escitalopram (N=60).
Results: The results revealed that vortioxetine significantly increased plasma BDNF concentration ($p=0.018$) and significantly decreased platelet 5-HT concentration ($p<0.001$). Treatment with escitalopram significantly decreased platelet 5-HT concentration ($p<0.001$), but it did not affect plasma BDNF concentration ($p=0.379$). Vortioxetine treatment displayed better effects on cognitive functions in MDD patients then the treatment with escitalopram.
Conclusions: These effects might be due to vortioxetine unique mechanism of action, but the clinical implications are unclear. A better knowledge and understanding of the underlying effects of different treatment strategies could not only provide answers to the neurobiology of depression, but also serve to design and develop more effective and faster-acting new-generation antidepressants with fewer adverse side effects.

S 07/5

METABOLOMICS IN ALZHEIMER'S DISEASE AS A TOOL FOR BIOMARKER DISCOVERY AND EARLY DIAGNOSIS

Gordana Nedić Erjavec (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia), Matea Nikolac Perković (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia), Suzana Uzun (University Psychiatric Hospital Vrapce, Zagreb, Croatia and School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Coral Barbas (Centre of Metabolomics and Bioanalysis (CEMBIO), Faculty of Pharmacy, University San Pablo CEU, Madrid, Spain), Nela Pivac (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia)

Alzheimer's disease (AD), as a predominant form of dementia, is a complex and heterogeneous neurodegenerative disorder often diagnosed in its advanced phase leaving patients and their physicians with narrow treatment options.
Pathological processes associated with dementia primarily affect the central nervous system, but are also reflected at the periphery. Metabolomics is the emerging scientific discipline dealing with metabolites which represent the final products of all biochemical reactions in organism, highly reflecting different pathologies. Pharmacometabolomics captures environmental and microbiome-level effects on response to drug therapy contributing to the development of personalized therapy. The aim of this study was to investigate and compare the metabolic profiles of patients with AD and subjects diagnosed with mild cognitive impairment (MCI) and healthy subjects. Metabolic profiling was conducted using the liquid (LC) and gas (GC) chromatography coupled with mass spectrometry (MS) based untargeted metabolomics approach on blood plasma samples from AD patients (N=40), subjects with MCI (N=40) and healthy control subjects (N=40). The results suggested altered lipid, amino acid and energy metabolism indicating destabilization of membranes in AD and alterations in the neurotransmitters' biosynthesis, urea cycle, metabolism of purines, polyamines and bile acids. The study proposes metabolomics as a promising approach for studying the biological background of AD pathogenesis and discovering the novel easy obtainable biomarkers for the diagnosis, prognosis and therapy follow-up in AD patients.
Study was partially funded by Croatian science foundation project Therapeutic potential of neurosteroids and neurotrophins in dementia, IP-2019-04-6100.

S 07/6

EPIGENETIC, GENETIC AND EXPRESSION ANALYSIS OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN ALZHEIMER'S DISEASE

Lucija Tudor (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia), Matea Nikolac Perković (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia), Mirjana Babić Leko (Croatian Institute for Brain Research, Faculty of Medicine Zagreb), Alja Videtič Paska Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, Ljubljana), Katarina Kouter (Institut za biokemiju i molekularnu genetiku, Medicinski fakultet Ljubljana), Tina Miloš (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia), Gordana Nedić Erjavec (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia), Barbara Vuić (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia), Marcela Konjevod (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia), Goran Šimić (Croatian Institute for Brain Research, Faculty of Medicine Zagreb), Fran Borovečki (Department of Neurology, Clinical Hospital Center Zagreb), Nela Pivac (Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia)

Introduction

The most common dementia type is Alzheimer's disease (AD), characterized by the progressive cognitive decline and neuronal death, which is often attributed to the accumulation of beta amyloid (Aβ) plaques and neurofibrillary tangles in the brain. Brain derived neurotrophic factor (BDNF) is a neurotrophin that plays an important role in the neurogenesis and neuroplasticity. Therefore, our aim was to investigate the BDNF alternations in AD, at the genetic, epigenetic, and expression levels.

Materials and methods

The study included 254 patients with AD and mild cognitive impairment (MCI), as comparative group. Plasma BDNF and cerebrospinal fluid (CSF) Aβ1–42 protein levels were measured with enzyme-linked immunosorbent assay. Quantitative PCR was used to determine the five BDNF gene polymorphisms and BDNF mRNA expression in peripheral white blood cells. The methylation status of nine amplicons covering 169 CpG sites in the BDNF gene region was determined by the next generation sequencing. The data were analyzed using GraphPad Prism 4.00 software.

Results

The results demonstrated increased BDNF plasma concentration in AD patients compared to MCI group, and its positive correlation with Aβ1–42 CSF levels. Tested BDNF polymorphisms were not associated with AD; however, lower methylation levels, especially in BDNF3 and BDNF9 amplicon region, and lower expression of BDNF gene in peripheral blood were detected in AD patients, compared to MCI subjects.

Conclusions

These findings could help to elucidate the complex role of BDNF in AD, as well as its potential as an easily accessible peripheral biomarker and novel therapeutic strategy for AD.

S08

NEWS IN THE TREATMENT OF MALIGNANT DISEASES

Chairperson: Stjepko Pleština (Department of Oncology, University Hospital Centre Zagreb and School of Medicine, Zagreb, Croatia)

S 08/1

ONCOLOGY DURING THE DEVELOPMENT OF PERSONALIZED MEDICINE

Stjepko Pleština (Department of Oncology, University Hospital Centre Zagreb and School of Medicine, Zagreb, Croatia)

Malignant diseases are a very significant growing public health problem in Croatia, they are the second leading cause of death following cardiovascular diseases. According to data from the HZJZ Cancer Registry, there were 25,352 newly diagnosed cancer cases and 13,344 cancer deaths in 2019. Unlike the most developed countries in Croatia, in addition to an increase in incidence, an increase in mortality from malignant diseases may be noted. The worrying trend of increasing mortality prompted the adoption of the National Strategic Framework Against Cancer, the implementation of which should have a significant impact on improving outcomes. Recent scientific breakthroughs and technological advancements have improved our disease knowledge and altered diagnostics and treatment approaches, resulting in a more precise, predictive and personalised health care, customized for the individual patient. As an evolution of healthcare, personalised medicine is a medical model for tailoring the right therapeutic strategy for the right person at the right time. Changing the treatment paradigm should lead to better outcomes, improve the patient's quality of life, but also reduce costs by eliminating unnecessary treatment. Technologies such as comprehensive genomic profiling are the drivers of this shift. Thanks to the dramatic progress in the knowledge of key metabolic pathways and the discovery of drugs that can target them, previously non-selective, both relatively weakly effective and toxic chemotherapy is increasingly being replaced by targeted therapy with so-called "smart" drugs. Also, by acting on the control points of the immune system, previously unimaginable results have been achieved.

S 08/2

MOLECULAR TUMOR PROFILE IN THE ERA OF PRECISION MEDICINE – THE EXAMPLE OF CHOLANGIOCELLULAR CARCINOMA

Borislav Belev (Dpt of Medical Oncology, Clinic of oncology, Clinical Hospital Center Zagreb, Zagreb, Croatia)

Biliary carcinoma is prognosis disease with very limited treatment options. Therefore, chemotherapy doublet, cisplatine and gemcitabine, is the golden standard in the first line treatment of metastatic or inoperable disease. Very recently TOPAZ clinical trial showed progress in improved outcomes using durvalumab in addition to standard treatment. During the progress of molecular diagnostics there have been found many molecular mutations in different subtypes of biliary tract carcinoma (BTC). Today we know that there are about 40% of patients having targetable alterations. IDH1-mutations occur in some 15-20% of iCC and there is inhibitor ivosidenib specific for this mutation. In ClarIDHy clinical trial, phase III, ivosidenib showed improved overall survival (OS) what was the reason for FDA approval of this drug for IDH1-mutation positive, previously treated metastatic disease. Another important genetic alterations are FDFR2-fusions or rearrangements, seen in approximately 10-15% of iCCA. Infigratinib as monotherapy after progression on chemotherapy showed objective response rate of 46% and median progression-free survival of 7,3 months. Pemigatinib is also tested in metastatic CCC. Pertuzumab with trastuzumab in HER2-positive, metastatic biliary cancer, phase 2a, open label, multiple basket study, showed mPFS of 4 months and ORR 22%. Most recently, ROAR-trial showed dabrafenib/trametinib combination efficacy in BRAF 600V mutation positive tumor with durable effect and thus approved in June 2022 by FDA. The future of this field is profiling of all BTC patients and more basket trials to capture multiple targets. Although we have clear options for some mutations, chemotherapy is still very important option for many patients.

S 08/3

ANTIBODY DRUG CONJUGATES IN THE TREATMENT OF METASTATIC BREAST CANCER

Natalija Dedić Plavetić (Department of Oncology, University Hospital Centre Zagreb and School of Medicine, Zagreb, Croatia)

Despite great advances in treatment, metastatic breast cancer (mBC) is still an incurable disease. When choosing systemic oncological treatment for advanced breast cancer, we are guided by an immunohistochemistry-based surrogate classification. Conjugates of cytostatics and antibodies (antibody-drug conjugate, ADC) are a newer group of drugs that have made progress in the treatment of several subtypes of breast cancer.
In the treatment of metastatic HER2 positive breast cancer, the greatest improvement in clinical studies has been shown by trastuzumab deruxtecan (T-Dx), which first showed an advantage over trastuzumab emtansine (T-DM1) in the Destiny-BREAST001 study in previously overtreated patients, and then proved superior better than the current standard of the second line trastuzumab emtansine T-DM1 in the Destiny-BREAST003 study.
The results of the DESTINY-Breast04 clinical trial have showed that HER2 receptor-directed trastuzumab deruxtecan therapy in patients with mBC that has low expression of the HER-2 receptor, showed a benefit in terms of prolonging progression-free survival and overall survival compared to previous standard treatment, regardless of expression of hormone receptors. The subtype with low HER-2 becomes a therapeutically accessible subgroup of mBC.
The ADC sacituzumab govitecan (Trodelvy) is directed against the TROP-2 molecule on TNBC cells and has shown good tolerability. Efficacy was demonstrated in phase III trial ASCENT. The first results of the effectiveness of the new ADC molecule, datopotamab deruxtecan, were presented, which proved to be effective in terms of the overall response rate for the treatment of metastatic TNBC.

S 08/4

IMMUNE CHECKPOINT INHIBITORS IN TREATMENT OF NON-SMALL CELL LUNG CANCER PATIENTS - THE MECHANISMS, EFFICACY, AND SAFETY OF ICI AGENTS AND COMBINATIONS

Sanja Pleština (University Hospital Centre Zagreb, Zagreb, Croatia)

Introduction

Immune-checkpoint inhibitors (ICI) have altered the management of solid tumors over the last 10 years. First demonstrated to improve outcomes of NSCLC patients in second-line or later therapy of advanced disease, ICIs were also shown to improve OS in first-line therapy for patients whose tumors express PD-L1 on at least 50% of cells, and combining with chemotherapy in patients with NSCLC regardless of PD-L1 expression.

Materials and methods

Lung cancer has been shown to be immunogenic and responsive to checkpoint blockade therapy. Checkpoint signals such as CTLA-4 and PD-1/PD-L1 dampen T cell activation and allow tumors to escape the adaptive immune response. We summarize the latest efficacy and safety data for early and advanced NSCLC in both the treatment-naïve and pretreated settings.

Conclusions

Immune checkpoint inhibitors such as antibodies to programmed cell death-1 (PD-1), or to its ligand PD-L1, or to cytotoxic T lymphocyte-associated protein-4 (CTLA-4) are an evolving treatment option for several types of cancer. Combinations of cytotoxic chemotherapy and PD-1/PD-L1 inhibitors are now used in clinical practice for the treatment of non-small cell lung cancer on the basis of positive results of large-scale clinical trials. The majority of patients who do respond to immunotherapy have a durable response attributed to the effect of adaptive immune system's memory. However, a large proportion of NSCLC patients still do not respond to PD-1/PD-L1 inhibition leaving an unmet need for a large and growing population. The identification of patients likely to achieve a sufficient benefit from this therapy remains a challenge.

S09

PHARMACOLOGICAL APPROACHES TO CARDIOMETABOLIC DISORDERS

Chairperson: Mladen Boban (Department of Basic and Clinical Pharmacology, University of Split School of Medicine, Split, Croatia)

S 09/1

CHANGES IN THE MYOCARDIAL METABOLISM IN TYPE 2 DIABETES MELLITUS

Marko Ljubkovic (University of Split School of Medicine, Split, Croatia), Cristijan Bulat (University Hospital Split, Split, Croatia), Marija Ćavar (University of Split School of Medicine, Split, Croatia), Ivica Grkovic (University of Split School of Medicine, Split, Croatia), Cristophe Lemaire (INSERM UMR-S 1180, Uni- versité Paris-Sud, France), Jasna Marinovic (University of Split School of Medicine, Split, Croatia)

Introduction: Deterioration of cardiac function occurs in patients with Type II diabetes mellitus even in the absence of coronary artery disease or other cardiac pathology. The underlying mechanism is still unknown, and probably includes altered substrate utilization. However, very little data were obtained on human diabetic hearts - mostly using PET monitoring of cardiac metabolism or atrial tissue (energetically different from the ventricular muscle). Here, we directly assessed mitochondrial capacity for oxidation of fatty acid and carbohydrate substrates in samples of left ventricular myocardium obtained from patients undergoing open-heart surgery.
Materials and Methods: Cardiac biopsies were obtained from 37 patients undergoing CABG surgery; 16 of them diabetic (DM). Mitochondrial respiration was assessed via oxygen-sensitive electrode, in permeabilized myocardial samples, using substrates from fatty acid and carbohydrate metabolic pathways. Expression of key metabolic enzymes was evaluated by Western blot and intracellular accumulation of fat using appropriate dyes.
Results: In diabetic patients, mitochondrial oxidation of fatty acyl was significantly lower than in non-diabetic group, while there was no difference when respiration was fueled with carbohydrate metabolite pyruvate. Diminished capacity for fat oxidation in DM hearts was also suggested by reduced activity of beta-oxidation enzyme HADHA. On the other hand, activity of pyruvate dehydrogenase, a key enzyme of carbohydrate metabolism, was unaltered. Myocardial staining revealed increased intracellular accumulation of triglycerides and ceramide in diabetic myocardium.
Conclusions: Diabetic hearts develop reduced capacity for oxidation of fatty acids, which likely results in excessive intracellular accumulation of fat. This may lead to lipotoxicity and contribute to development of diabetic cardiomyopathy.

S 09/2

ANTIDIABETICS IN CARDIOVASCULAR DISEASE THERAPY

Aleksandar Knežević (Faculty of Dental Medicine and Health, Osijek and General Hospital Šibenik, Croatia)

Earlier clinical trials have shown the effect of glycemic control in patients with diabetes wich reduced microvascular complications, while the effect on macrovascular complications was neutral or even exacerbate them. ACCORD study has shown that intensive glycemic control increases overall and cardiovascular mortality; and an analysis of the use of rosiglitazone from 2007. found an increased incidence of myocardial infarction in the use of the drug. That's why the FDA adopted guidelines in 2008., that require proof of cardiovascular safety when applying all new antidiabetics.

A number of studies have further been published to show that new antidiabetics do not increase cardiovascular morbidity and mortality, but without evidence of its reduction.

Views changed, with the publication of the EMPA-REG OUTCOME study in 2015, which showed that the SGLT-2 inhibitor empagliflozin has an impressive effect on the reduction of cardiovascular mortality, overall mortality and hospitalization due to heart failure in diabetic patients. In later clinical trials, this was also proven for another SGLT-2 inhibitor, dapagliflozin. The effectiveness of the treatment was also shown in patients with heart failure who do not have diabetes, so that in the 2021. ESC guidelines for the treatment of heart failure, dapagliflozin and empagliflozin were added to the standard heart failure therapy (ACE-I, ARNI, beta-blockers, MRAs). It is considered they reduce the risk of cardiovascular mortality and worsening of heart failure in patients with reduced ejection fraction (EF) of the left ventricle, and that they are recommended for all such patients, regardless of the presence of diabetes.

Based on the results of the EMPEROR-Preserved study, in which the use of empagliflozin showed a decrease in cardiovascular mortality and heart failure in patients with preserved EF, this year it was the first drug to receive an indication for treatment in patients with heart failure with preserved EF. So far, we have not registered therapy for this entity, but have treated the causes, primarily hypertension.

Another group of antidiabetics, GLP-1 agonists so far have good evidence in the reduction of cardiovascular risk in patients with diabetes.

In the last 15 years, new antidiabetics from drugs that can potentially increase cardiovascular risk, become drugs for prevention and treatment of cardiovascular diseases, both in patients with and without of diabetes.

S 09/3

WINE CONSUMPTION IN TYPE 2 DIABETES MELLITUS: FRIEND OR FOE

Mladen Boban (Department of Basic and Clinical Pharmacology, University of Split School of Medicine, Split, Croatia)

Dietary habits are a crucial lifestyle factor that is strongly related to the incidence and prevalence of type 2 diabetes mellitus (T2DM). In that context, a number of well-done prospective studies indicate that moderate alcohol consumption, particularly wine, is associated with the reduced risk of T2DM. Wine taken with meals is also an important part of the Mediterranean diet, a dietary pattern with proven beneficial effects on components of the metabolic syndrome. Despite prevailing scientific evidence on benefits of moderate wine consumption on different health outcomes, no conclusive recommendations exist regarding wine consumption by patients with T2DM. Moreover, in an attempt to reduce harm associated with alcohol-abuse in the population, there is an ever-increasing indiscriminate campaign against any alcohol use. All this often cause confusion in both, the general public and health professionals.
Here we will summarize the latest information regarding the effects of wine on different health parameters in patients with T2DM. Also, an overview of the proposed mechanisms for the observed biological effects of wine in patients with T2DM will be presented.

S 09/4

HEPCIDIN: A NEW SITE OF ACTION OF WINE IN PATIENTS WITH DIABETES MELLITUS TYPE 2

Diana Gujinović (Department of Pharmacology, University of Split School of Medicine, Split, Croatia)

Type 2 diabetes (T2D) is a complex and multifactorial disease, requiring the orchestration of pharmacological and nonpharmacological treatment approaches. Along with low-grade chronic inflammation, T2D is often associated with iron overload. This indicates a potential role of hepcidin, the key iron-regulatory hormone and acute-phase protein, in the pathogenesis of T2D. Hepcidin reduces iron bioavailability by promoting the degradation of ferroportin, the only mammalian iron exporter identified to date. According to the evidence, alcohol consumption may also lead to body iron excess. On the other side, moderate consumption of red wine, an important component of the Mediterranean dietary pattern, has been associated with the cardiometabolic benefits in T2D. These effects have been mainly attributed to both ethanol and polyphenolic compounds, that are present in particularly high content in red wine. In this lecture it will be discussed how changes in hepcidin levels associated with moderate consumption of wine might influence wine's cardiometabolic effects.

S 09/5

EFFECT OF MODERATE WHITE WINE CONSUMPTION ON THE EXPRESSION OF HSP70, GPx, CAT AND NQO1 IN RAT CARDIOMYOCYTES

B. Benzon (Dtp. of Anatomy, Histology and Embryology, School of Medicine, University of Split), A. Mastelić (Dtp. of Medical Chemistry and Biochemistry, School of Medicine, University of Split), M. Grahovac (Dtp. of Basic and Clinical Pharmacology, School of Medicine, University of Split), J. Matijević (Dtp. of Basic and Clinical Pharmacology, School of Medicine, University of Split), J. Marinović Ljubković (Dtp. of Integrative Physiology, School of Medicine, University of Split), M. Ljubković (Dtp. of Integrative Physiology, School of Medicine, University of Split), I. Mudnić (Dtp. of Basic and Clinical Pharmacology, School of Medicine, University of Split), I. Grković (Dtp. of Anatomy, Histology and Embryology, School of Medicine, University of Split), M. Boban (Dtp. of Basic and Clinical Pharmacology, School of Medicine, University of Split)

Introduction: There is strong epidemiological evidence that moderate consumption of wine has beneficial effects on human health, particularly on cardiovascular system. Increase in antioxidant defence is one of the proposed biological pathways that may contribute to the observed health benefits. The aim of our study was to determine the effect of moderate white wine consumption on the expression of GPx (glutathione peroxidase), CAT (catalase), NQO1 (NAD(P)H Quinone Oxidoreductase 1) and HSP-70 (heat shock protein) in cardiomyocytes.
Materials and methods: Male Sprague Dawley rats were given either a combination of white wine (Graševina, Krauthaker, 13% alcohol vol.) and water (n= 6) or only water (n=7) for 28 days. After that, the animals were sacrificed. From the harvested hearts, cardiomyocytes were isolated, fixated and stored at -20 ^{o}C. When all the samples were collected, cells were permeabilized, incubated with antibodies and analysed by flow cytometry.
Results: Consumption of white wine increased HSP-70 expression by 1.46 ± 0.29-fold ($p=0.0002$) when compared to control group. Furthermore, expressions of CAT, GPx and NQO1 were increased in wine consuming rats by 1.3 ± 0.21 ($p=0.008$), 1.45 ± 0.33 ($p=0.0006$), and 1.36 ± 0.12 ($p=0.003$) fold, respectively.
Conclusion: Moderate white wine consumption for 4 weeks resulted in increased expression of the enzymes that are important in the cell protection from the oxidative stress.

S10

GMP MINI SYMPOSIUM

Agency for Medicinal Products and Medical Devices (HALMED, Zagreb)

S 10/1

INSPECTION OF GOOD MANUFACTURING PRACTICE

Teo Kolonić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED)), Martina Bencetić Marijanović (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

Good Manufacturing Practice (GMP) is a set of different guidelines, rules and standards that guarantee effectiveness, quality, safety and consistency in medicinal products' manufacturing and quality control. HALMED's responsibilities derive from the Medicinal Products Act and the Veterinary Medical Products Act, i.e. the acquis communautaire of the EU. Consequently, the supervision of good manufacturing practice for human and veterinary medicines is carried out by the Inspection Department of the Agency for medicinal products and medical devices (HALMED) Inspection is a complete procedure from preparing the inspection to issuing relevant documents, including conducting an official audit of records, personnel, premises and quality assurance mechanisms, preferably at manufacturing sites. Due to the Covid- 19 pandemic and the inability of inspectors to travel to third countries, the inspections were carried out as distant assessments, i.e. remotely, with the use of teleconferences and camera recording of premises and equipment as requested by the inspector. The Agency inspectors are trained and experienced accordingly and are continuously educated. Except at the applicant’s request for issuing specific permits/certificates, inspections are carried out ex officio as regular (periodic) inspections and those in extraordinary (incidental) circumstances. After an inspection has been completed, in case of a positive conclusion, HALMED issues a GMP certificate or in case of a negative conclusion, issues a Statement of non-compliance, whether for manufacturers located in the Republic of Croatia or a third country.

S 10/2

SERIOUS GMP NON-COMPLIANCE

Ljubica Hodak (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

Manufacturers of human and veterinary medicinal products are obliged to implement good manufacturing practice (GMP) principles and guidelines with the main goal of protecting public and animal health. Also, the manufacturers of medicinal products are obliged to use active pharmaceutical ingredients (APIs) manufactured in line with GMP.
Compliance with GMP is checked by regulatory inspectors during GMP inspections, and in case serious GMP noncompliance is determined, a Statement of Non-compliance with GMP is issued to a manufacturing site.
Serious GMP non-compliance is a non-compliance with GMP that is of such a nature that urgent interim supervisory measures may be necessary to remove a potential risk to public or animal health or where final measures may be needed to prohibit further supply of the medicinal product. Serious GMP non-compliance may include deficiencies as a result of evidence of falsification gathered by inspectors during GMP inspection. Measures issued by regulatory authorities may include but are not limited to prohibition of manufacture or importation, suspension of an existing manufacturer or import authorisation, prohibition of supply or withdrawal of medicinal products, decisions to revoke, or vary an existing marketing authorisation/manufacturer or import authorisation or refuse an application for marketing authorisation /manufacturer or import authorisation.
The aim of this presentation will be to familiarize the attendees with the administrative and regulatory measures taken after the serious GMP non-compliance is determined.

S 10/3

CROSS-CONTAMINATION RISKS IN PHARMACEUTICAL PRODUCTION, GMP PERSPECTIVE

Suzana Jukić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

Contamination control is one of the main challenges in pharmaceutical production since uncontrolled and undetected contamination could potentially represent a significant threat to the health and safety of patients. Cross-contamination is defined as contamination of a starting material, intermediate product or finished product with another starting material or product during the production.

Throughout a GMP inspection, a significant amount of attention is paid to the risk management of cross-contamination.

The manufacturer should prove that risks are controlled and recognized and that practices applied at the manufacturing site take into account the hazard level of the molecules, the type and number of products handled, and the complexity of production processes. Various sources/origins of cross-contamination should be evaluated; surface to surface, airborne to air/surface, process or equipment failure, and movement and mix-up of personnel, materials or equipment.

Cross-contamination should be prevented by attention to the premises and equipment design, which should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes. To confirm the effectiveness of any cleaning procedure for all product contact equipment, the manufacturers should perform cleaning validation. The purpose of cleaning validation is to demonstrate that the cleaning process consistently removes product and process residues and environmental contaminants from the manufacturing equipment so that it can be safely used for the manufacture of the following product.

S 10/4

IMPORTATION, QUALITY CONTROL AND BATCH RELEASE OF MEDICINAL PRODUCTS

Tanja Trbojević Krpanić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

The importation of medicinal products is subject to GMP requirements. In addition to the requirements stated in the main chapters and annexes of the EU GMP Guidelines, the specific requirements explaining the application of GMP principles to the importation of medicinal products are summarized and published in a new Annex 21 “Importation of medicinal products”.
The requirements for the manufacturing authorization holders related to quality control of the medicinal products are defined within the Chapter 6 “Quality Control”[1]. Quality Control is not confined solely to laboratory operations, but must be involved in all decisions which may concern the quality of the product. In addition to the quality control of medicinal products performed by the MIA holders, quality control for the products on the market is performed by the HALMED according to the Article 173 of the Medicinal Product Act and Ordinance on the Quality Control of Medicinal Products.
EU GMP Annex 16 “Certification by a Qualified Person and Batch Release“ defines the main duties and responsibilities of a Qualified Person (QP) in the certification and batch release of medicinal products holding a MA within the EU or made for export. The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the MAH. However, the QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State where certification takes place, in accordance with the requirements of the MA and with GMP.

S11

BPC157

Chairperson: Predrag Sikirić (Department of Pharmacology, Medical Faculty University of Zagreb, Zagreb, Croatia)

S 11/1

GASTRIC PENTADECAPEPTIDE BPC 157 IN CYTOPROTECTION TO RESOLVE MAJOR VESSEL OCCLUSION DISTURBANCES, ISCHEMIA-REPERFUSION INJURY

Predrag Sikirić (Department of Pharmacology, Medical Faculty University of Zagreb, Zagreb, Croatia)

The stable gastric pentadecapeptide BPC 157 counteracts various venous occlusion-induced syndromes. Summarized are all these arguments, in the Robert's cytoprotection concept terms, to substantiate the resolution of different major vessel occlusion disturbances, in particular ischemia-reperfusion injury following the Pringle maneuver and Budd-Chiari syndrome, which was obtained by BPC 157 therapy. Conceptually, there is new point (bypassed occluded or ruptured vessel, the equation endothelium maintenance → epithelium maintenance = blood vessel recruitment and activation towards defect or bypassing vessel occlusion), the recruitment of collateral blood vessels to compensate for vessel occlusion and reestablish blood flow. Here, we summarize the evidence of the native cytoprotective gastric pentadecapeptide BPC 157, resistant and stable in the human gastric juice, membrane stabilizer, counteracting gut-leaky syndrome, as a particular target. BPC 157 is distinctive from the standard peptide growth factors, with particular molecular pathways involved, controlling VEGF- and NO-pathways. In the early 1990s, BPC 157 appeared as a late outbreak of the Robert's and Szabo's cytoprotection-organoprotection concept, epithelium, endothelium protection as previous theoretical/practical breakthrough in the 1980s, and brain-gut axis and gut-brain axis. As the time went on, BPC 157, with its reported effects, is likely most useful theory practical implementation and justification. Meantime, several reviews suggest that BPC 157, which does not have a lethal dose (LD1), has profound cytoprotective activity, used to be demonstrated in ulcerative colitis and invented to multiple sclerosis trials. Likely, it may bring the theory to practical application, starting with the initial argument, no degradation in human gastric juice for more than 24 h, and thereby, the therapeutic effectiveness (including therapeutic per-oral regimen) and pleiotropic beneficial effects.

S 11/2

THE NEUROLEPTICS, AMPHETAMINE AND DOMPERIDONE APPLICATION AS INNATE VASCULAR FAILURE, AND THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157, AS THERAPY, MIGHT BE THE PARTICULAR KEY

Sanja Strbe (Department of Psychiatry, Clinical Hospital Rebro, Zagreb, Croatia)

The neuroleptics, amphetamine and domperidone application as innate vascular failure, and the stable gastric pentadecapeptide BPC 157, as therapy, might be the particular key. Recently, we reported the BPC 157 particular therapy effect in the neuroleptic or L-NAME-induced catalepsy, lithium intoxication and in the schizophrenia positive and negative symptoms, and its particular therapy effect (i.e. activation of the collateral pathways, “bypassing vascular key”) in the recovery of the multiorgan failure syndrome in the rats with vascular failure. Vascular failure was either by major vessel(s) occlusion or with other noxious procedures. There were occlusion/occlusion-like syndrome of the multiorgan failure (i.e. the brain, heart, lung, liver, kidney and gastrointestinal lesions), arrhythmias, blood pressure disturbances (intracranial (superior sagittal sinus), portal and caval hypertension, aortal hypotension), arterial and venous thrombosis, peripherally and centrally, rapidly acting Virchow triad circumstances. As particular points appeared the major vessel occlusion (inferior caval vein, portal vein and hepatic artery, superior mesenteric vein and artery, superior sagittal sinus, both carotid arteries, and cauterized episcleral veins). As additional particular points appeared the variety of the other severe procedures (i.e. the intoxication with endothelium damaging agents, alcohol or lithium, isoprenaline-induced myocardial infarction, bile duct occlusion acute pancreatitis, and maintained severe intra-abdominal hypertension), and also neuroleptics, amphetamine and domperidone, all as occlusion-like syndrome. Whatever the cause, there were all organs lesions, progressing venous/arterial thrombosis/stasis, peripherally and centrally, all counteracted by BPC 157 therapy application, along with the ECG disturbances, intracranial (superior sagittal sinus) hypertension, portal and caval hypertension, and aortal hypotension eliminated/attenuated.

S 11/3

STABLE GASTRIC PENTADECAPEPTIDE BPC 157 AND MUSCLE HEALING FOR POSSIBLE THERAPY

Anita Skrtic (Department of Pathology, Medical Faculty, University of Zagreb, Zagreb, Croatia)

Recently, we focused on the myotendinous junction recovery and we reported the myotendinous junction recovered by the stable gastric pentadecapeptide BPC 157 therapy, which was known to heal both transected and detached tendon and transected muscle, applied alone, as native peptide therapy, effective in rat injury, given intraperitoneally or in drinking water. Here, as a follow up, we reviewed these myotendinous junction combined points, their therapy effect significance on the specific healing of the muscle, tendon, ligament and bone injuries, along with the other BPC 157 muscle effects, beyond the direct trauma-injured muscle, tendon, ligament and bone damage, in particular that on the distinctive etiopathology muscle disabilities and weakness. To provide a general clue for the BPC 157 muscle therapy potential and the background against various noxious causes, in addition to the direct trauma-injured muscle, tendon, ligament and bone damage, we reviewed the recovered muscle disabilities and weakness, which were induced in rats by the succinylcholine, vascular occlusion, severe electrolyte disturbances, and neuroleptics. Further, we reviewed the BPC 157 therapy effect on the disable heart functioning, and disable smooth muscle functioning, and muscle disabilities after neurotoxins, stroke, spinal cord injury and tumor-cachexia. Finally, pentadecapeptide BPC 157, always given alone, as a prototype of anti-ulcer cytoprotective peptide, native and stable in human gastric juice, has very safe profile (lethal dose LD1 not achieved), and an apparent curing potential, a wide range of µg-ng dose and ways of application, intraperitoneal, intragastric, in drinking water or topically, at the site of injury.

S 11/4

THE HEARTH DISTURBANCES, MYOCARDIAL INFARCTION, ARRHYTHMIAS, CONGESTIVE HEART FAILURE, PULMONARY HYPERTENSION AND THROMBOSIS PRESENTATION FOR THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157 AS USEFUL PEPTIDE THERAPY

Sven Seiwerth (Department of Pathology, Medical Faculty, University of Zagreb, Zagreb, Croatia)

In the hearth disturbances, stable gastric pentadecapeptide BPC 157 especial therapy effect is combining together the therapy of the myocardial infarction, arrhythmias, congestive heart failure, pulmonary hypertension and thrombosis, prevention and reversal. Shared therapy effect occurred as part of its even larger cytoprotection (cardioprotection) therapy effect (direct epithelial cell protection; direct endothelium cell protection) that BPC 157 exerts as novel cytoprotection mediator, native and stable in human gastric juice, easy applicable. Accordingly, there is the interacting with many molecular pathways, combining maintained endothelium function and maintained thrombocytes function, counteracted thrombocytopenia in rats underwent major vessel occlusion and deep vein thrombosis, and counteracted thrombosis in all vascular studies, and coagulation pathways not affected. These appeared as having modulatory effects on NO-system (NO-release, NOS-inhibition, NO-over-stimulation all affected), controlling vasomotor tone and the activation of Src-Caveolin-1-eNOS pathway) and modulatory effects on prostaglandins-system (BPC 157 counteracted NSAIDs-toxicity, counteracted bleeding, thrombocytopenia and leaky gut syndrome, in particular). As essential novelty, noted in the vascular studies, there was the activation of the collateral pathways. This might be the upgrading of the minor vessel to take over the function of the disable major vessel, competing with the Virchow triad circumstances devastatingly present, making possible the recruitment of collateral blood vessels, compensating vessel occlusion and reestablish blood flow or bypass the occluded or ruptured vessel. As a part of the severe multiorgan failure syndrome counteraction, there was counteraction of the brain, lung, liver, kidney and gastrointestinal lesions, and in particular, the counteraction of the heart arrhythmias and infarction.

S12

IMMUNOPHARMACOLOGY: FROM VACCINES TO IMMUNOTHERAPY

Chairperson: Viktorija Erdeljić Turk (Division of Clinical pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia)

S 12/1

NEW THERAPIES FOR IMMUNE-MEDIATED DISEASES

Suzana Mimica (University hospital center Osijek, Department of Clinical Pharmacology and Faculty of Medicine Osijek, Department of Internal Medicine and History of Medicine, Osijek, Croatia)

After decades of using conventional immunosupressant and immunomodulatory medicines for immune-mediated diseases (e.g. glucocorticoids, azathioprine, mycophenolate mofetil), many new breakthough therapies have received market approval. Among them, various monoclonal antibodies (mAbs) are now the cornerstone of treatment for inflammatory bowel disease (IBD), psoriasis, inflamamatory rheumatoid diseases etc. Important small molecules recently approved for these conditions are various JAK inhibitors (e.g. baricitinib or upadacitinib) and sphingosine 1-phosphate receptor (S1P) modulators (fingolimod and siponimod for the treatment of multiple sclerosis).
With new discoveries in basic science, new potential targets have been identified and drug candidates explored in clinical trials. Several mAbs against IL-23 as well as S1P modulators and next-generation anti-integrin therapy are being evaluated in phase 3 clinical trials of IBD. In Phase 2 of different autoimmune diseases, examples of novel molecular targets are mAb targeting fractalkine (FKN), a CX3C chemokine, humanized mAb blocking tumor necrosis factor (TNF)-like ligand 1A (TL1A), oral irreversible inhibitor of JAK3/TEC, human IL-22Fc fusion protein and selective inhibitors of tyrosine kinase 2. A number of investigational medicinal products (IMPs) targeting different chemokines are being investigated in clinical trials in patients with autoimmune diseases. Most advanced in clinical trials are IMPs targeting chemokines CCR1, CCR2 and CC5. Bruton's tyrosine kinase (BTK) plays a key role in B-cell receptor and Fc receptor signaling pathways. Some BTK inhibitors are being investigated in the Phase 3 studies in multiple sclerosis and some other autoimmune disease.
This presentation will give overview of the most promising new targets for immune-mediated diseases and their respective stage of development.

S 12/2

TARGETED THERAPIES FOR ALLERGIC DISEASES

Ivana Čegec (University Hospital Centre Zagreb, Department of Internal medicine, Division of Clinical Pharmacology, Zagreb, Croatia)

Allergy today is a public health concern of pandemic proportions, affecting more than 150 million people in Europe alone.
The established therapeutic approaches (allergen avoidance, antihistamines, and corticosteroids) do not address the underlying causes of the pathology, highlighting the need for other long-term treatment options.
Allergen specific immunotherapy is the only currently available medical intervention that has the potential to affect the natural course of the disease.
To understand the mode of action of allergen specific immunotherapy, it is essential to understand the mechanism of the disease. In allergic disease, type 2 differentiated T-helper cells, via IL-4 and IL-13, drive the formation of allergen-specific immunoglobulin E (IgE). This IgE binds to mast cells and basophils and triggers allergen-induced degranulation. Released mediators as well as IL-4 and IL-13 lead to tissue eosinophilia. In nonallergic type 2 inflammation, type 2 differentiated innate lymphoid cells drive the same cell types and mediators to produce eosinophilic inflammation sustained by IL-5. The recruitment, activation, and secretion of these inflammatory cells lead to tissue damage and a cycle of chronic inflammation.
Biologic therapy includes the anti-IgE agent omalizumab, the anti-IL-5 agents reslizumab, mepolizumab, and benralizumab, and the anti-IL4/13 agent dupilumab.
Clinical trials have demonstrated that these biologic agents improve objective and subjective parameters of disease, particularly in severe cases and provide a new and promising modality for patients with severe eosinophilic diseases and other inflammatory conditions.

S 12/3

DEVELOPMENT OF IMMUNO-ONCOLOGY DRUGS

Viktorija Erdeljić Turk (Division of Clinical pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia)

The regulatory approval of the anti–CTLA-4 monoclonal antibody ipilimumab in 2011, has permanently changed the oncology treatment landscape. Immunotherapy agents do not directly attack the tumour but instead mobilize the immune system - this can be achieved through various approaches that utilize adaptive or innate immunity.
The scientific turning point came with the understanding that T cell immune responses are controlled through on and off switches, so called 'immune checkpoints' that protect the body from possibly damaging immune response. The master
switch for T cell activation and modulation was found to be the CD28–cytotoxic T lymphocyte-associated antigen 4 (CTLA4) interaction. In the following years, additional immune checkpoints were identified, such as programmed cell death protein 1–programmed cell death 1 ligand 1 (PD1–PDL1) and several others, which work at different stages of the immune system. However, CTLA4 and PD1–PDL1 both are negative regulators of T-cell immune function, and inhibition
of these targets results in increased activation of the immune system.
The modulation of immune checkpoints using monoclonal antibodies induces an immune response that is not dependent on tumour histologies or individual cancer-specific antigens. Due to its potential for a large and sustained clinical benefit, immuno-oncology has become the fastest-growing area in oncology that encompasses a broad range of agents, including antibodies, peptides, proteins, small molecules, adjuvants, cytokines, oncolytic viruses, bi-specific molecules, and cellular therapies.
This presentation will discuss emerging immunotherapies with emphasis on new mechanisms and modalities under investigation, and present future directions for immune oncology.

S 12/4

VACCINES: PREVENTIVE, THERAPEUTIC, PERSONALIZED

Viola Macolić Šarinić (European Medicines Agency, Amsterdam, Netherlands)

Vaccination is one of the most effective and widespread public health intervention, whose benefits for individuals and public health have been proven in the past decades, mainly in the prevention of infectious diseases caused by viruses and bacteria. Prominent examples are the global eradication of smallpox and the elimination of poliomyelitis in most countries of the world.

The lecture will present vaccines in the prophylaxis of infectious diseases focusing on approved vaccines in the European Union and the development of new vaccines in the prevention of COVID-19 and monkeypox. Vaccines that are used in the prevention of malignant diseases caused by viruses (HPV, hepatitis B), as well as the use of vaccines as one of the methods in immunotherapy in oncology (BCG) and new research in the field of personalized vaccines based on neoantigens and the treatment of malignant diseases will be presented. .

As vaccines are produced by biotechnological processes in the indication of prevention of infectious diseases and are expanding to the prevention and treatment of malignant diseases, they are exclusively approved for the European Union market through a centralized procedure through the European Medicines Agency (EMA), which also provides scientific advice to applicants during the development of vaccines for different therapeutic indications.

S 12/5

IMMUNE-MEDIATED ADVERSE EFFECTS OF COVID-19 VACCINE

Dominik Strikić (Division of Clinical pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia), Viktorija Erdeljić Turk (Division of Clinical pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia)

COVID-19 pandemic began in early 2020 and is still ongoing, with vaccination being one of the most effective measures to prevent severe illness and death. Two main types of SARS-CoV-2 vaccines are licenced and in use in Europe: those developed by Pfizer and Moderna use a new mRNA technology and lipid nanoparticles as delivery systems, while the formulations developed by AstraZeneca and Janssen contain DNA delivered in non-replicating adenovirus vector systems. Both vaccines code to produce the SARS-COV-2 spike (S) protein, the primary target for neutralising antibodies produced during natural infection.

As vaccination programmes have been rolled out worldwide, many COVID-19 vaccine-related adverse events (AEs) have been reported, most commonly mild local reactions at the administration site and flu-like symptoms. Very rare adverse events also include serious clinical autoimmune phenomena such as immune thromboembolism, autoimmune liver disease, Guillan-Barre syndrome, Bell's palsy, myocarditis/pericarditis, IgA nephropathy, rheumatoid arthritis, and systemic lupus erythematosus. However, these AEs are significantly less frequent than analogous immune reactions that occur after severe COVID-19. Based on available research data, autoimmune phenomena after vaccination could be related to a pro-inflammatory effect of the vaccine adjuvants, the S protein produced and molecular mimicry. Research into the molecular and cellular basis of the rare side effects should be a public health priority to ensure safety and maintain public confidence.

There is no doubt that the COVID-19 vaccines have reduced COVID-19 related morbidity and mortality, but the medical community needs to be aware of the risk of immune-mediated AEs, as it is important to detect and treat them in a timely manner.

S13

RATIONAL PHARMACOTHERAPY: THE ROLE OF THE PHARMACIST

Chairpersons: Renata Jurišić Grubešić (University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Marko Skelin (General Hospital Šibenik and University of Rijeka, Faculty of Medicine, Rijeka, Croatia)

S 13/1

THE FUTURE OF THE CENTRAL PREPARATION OF ANTINEOPLASTIC DRUGS IN THE ERA OF DIGITIZATION AND ROBOTIZATION

Vesna Pavlica (Community Pharmacy Chain Farmacia, Training Center, Zagreb, Croatia)

Introduction. More than 19.3 million new cases of cancer were diagnosed in 2020. Cancer was responsible for almost 10 million deaths worldwide in 20201.A record 30 novel antineoplastic drugs were initially launched globally in 2021, and a total of 159 have been launched since 20122. Many of antineoplastic drugs belong to the group of hazardous drugs.Hazardous drugs require safe handling precautions.The goal is to indicate the new application systems, the application of robots and the connection with the hospital information system.
Materials and methods. For the purpose of creating this work, a search was made of scientific and professional literature using databases: PabMed, Up ToData, Mediscap.
Results. The published evidence suggests that the implementation of chemotherapy compounding automation solutions may reduce compounding errors and reduce costs; however, this is highly variable depending on the form of automation. The positive effects of integration are reflected in the reduction of unnecessary or multiple manual data entry, then work with documentation in paper form, and the elimination of the possibility of human error, which ultimately facilitates work and raises the quality of service in the process of preparing antineoplastic drugs.
Conclusions. Both the automated and manual procedures for preparing antineoplastic preparations proved to be accurate and precise. The automated procedure resulted in substantial advantages in terms of quality and risk lowering.An additional challenge is the proper integration with hospital information systems.

S 13/2

RATIONAL PHYTOTHERAPY IN THE MAINTENANCE OF MENTAL HEALTH

Sanda Vladimir-Knežević (Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia)

The prevalence of mental disorders has increased and remains a major contributor to the global burden of disease. The coronavirus pandemic, war events, global economic crises, and climate change are all contributing factors to the increasing demand for mental health services. Anxiety, mild depression, stress, insomnia, mood disorders and cognitive impairment are the most common mental health problems that can be treated with herbal medicines which generally have minimal side effects and are low in toxicity compared to most conventional psychiatric drugs. Plant extracts contain a variety of bioactive ingredients with different mechanisms of action. They act on the GABA system or on 5-hydroxytryptophan, enhance the action of acetylcholine, or facilitate adaptation to stress by modulating the hypothalamic-pituitary-adrenal axis.

St. John's wort is commonly used to treat mild to moderate depression, valerian is recommended to relieve mild nervous tension and sleep disturbances, while ginkgo is used to improve age-related cognitive abilities and quality of life in mild dementia. Mild symptoms of mental stress and fatigue can be relieved by herbal medicines containing lavender or passionflower, which may also promote sleep. Evidence-based use of herbal medicines of high pharmaceutical quality in consultation with physicians and pharmacists can help maintain mental health and alleviate symptoms of mental illness.

S 13/3

POTENTIALLY INAPPROPRIATE MEDICINES IN OLDER PEOPLE – LESSONS LEARNED FROM EUROAGEISM PROJECT

Maja Ortner Hadžiabdić (Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia)

Introduction

The rapid aging of the population on a global scale presents a number of challenges. One of them is the use of potentially inappropriate medicines in older people, which is highly prevalent, especially in those having multiple chronic diseases and using multiple medications. It is associated with worse health outcomes, lower health related quality of life and higher healthcare costs. The aim of this lecture is to present the findings on potentially inappropriate prescribing in communitydwelling older patients of Croatian cohort of the EuroAgeism H2020 project.

Materials and methods

We analysed Croatian data of multinational conducted H2020 EuroAgeism project. Data were collected in community pharmacies in three Croatian's regions: Slavonia, Istria and City of Zagreb, using standardised EuroAgeism protocol based on comprehensive geriatric assessment. Here, we analysed, potentially inappropriate prescribing using validated tools for identification of fall-risk-increasing drugs (FRIDs), and drug burden index (DBI) due to drugs with anticholinergic and sedative properties.

Results

We analysed data of 388 patients (63.7% female; median age 73 (IQR 69-80)) in whom high prevalence of FRID (71%) and DBI drugs (57%) was identified. The most common FRIDs and/or DBI drugs were hydrochlorothiazide (18.4%), indapamide (17.1%), diazepam (15.5%) and tramadol (14.7%). The calculated DBI score was 0.54±0.65 indicating an anticholinergic and sedative burden similar to that identified in other studies.

Conclusion

The prevalence of potentially inappropriate medicines is high in Croatian sample and indicates the need for rationalisation of drug therapy in older patient population in order to reduce risk of worsening health outcomes.

S 13/4

COMPREHENSIVE MEDICATION MANAGEMENT AT THE PRIMARY CARE LEVEL - IMPLEMENTATION AT THE HEALTH CARE CENTRE ZAGREB CENTRE

Iva Mucalo (University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Andrea Brajković (University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia)

Introduction

Due to an increase in the prevalence of chronic diseases, medication use and their cost is rising rapidly. This scenario renders chronic patients at an increased risk of experiencing drug therapy problems, subsequently leading to unfavourable clinical and economic outcomes. Thus, to ensure patients' optimal medication use and improve their clinical outcomes, a comprehensive and systematic management of medications is deemed crucial and was tested at the Croatian primary care ambulatory clinic, Health Care Centre Zagreb – Centre.

Materials and methods

Collaborative practice between pharmacists and general practitioners, together with patients' active participation in the definition of treatment regimens, plays an important role in the effectiveness of CMM services. It includes an individualized care plan that achieves the intended goals of therapy with appropriate follow-up to determine actual patient outcomes.

Results

The CMM intervention significantly improved clinical outcomes and reduced the number of hospital admissions and unplanned GPs visits. Furthermore, the budget impact analysis performed on our patient sample showed that CMM services are an affordable intervention.

Conclusion

Hence, as CMM services can significantly contribute to better clinical outcomes and lower healthcare utilisation, it appears to be an affordable intervention for addressing medication mismanagement and irrational drug use. For CMM services to become a reality in Europe and elsewhere, numerous prerequisites need to be accomplished, including policies and legal regulations supporting the provision of CMM services, clearly defined and standardized professional practice and common language shared among the pharmacists, and well trained and experienced practitioners providing full-time, direct patient care.

S 13/5

INFLUENCE OF QUALITY OF LIFE ON ADHERENCE TO ADJUVANT ENDOCRINE THERAPY IN WOMEN WITH EARLY BREAST CANCER

Ana Dugonjić Okroša (Agency for Medicinal Products and Medical Devices of Croatia, Zagreb, Croatia), Tajana Silovski (Oncology Clinic, University Hospital Centre Zagreb, Zagreb, Croatia), Natalija Dedić Plavetić (Oncology Clinic University Hospital Centre Zagreb, Zagreb, Croatia, University of Zagreb, School of Medicine, Zagreb, Croatia), Iva Mucalo (University of Zagreb, Faculty of Pharmacy and Biochemistry, Centre for Applied Pharmacy, Zagreb, Croatia)

Introduction
High survival rate in early breast cancer is a direct consequence of highly effective adjuvant endocrine treatment (AET) recommended to be taken 5 to 10 years. However, AET has numerous side effects that adversely affect the quality of life (QoL) and preclude long-term adherence. This study aimed to investigate the QoL in early-stage breast cancer in women receiving AET and to explore its association with adherence.
Materials and methods
This cross-sectional study included women with early hormone-dependent breast cancer treated with AET for more than 3 months. The research was conducted at the University Hospital Centre (UHC) Zagreb. Validated instruments, the Medication Adherence Report scale (MARS-5) and the Functional Assessment of Cancer Therapy, endocrine symptoms
- FACT-ES, were used. The collected data were processed and presented with descriptive statistics and an independent t-test.
Results
Overall, 329 respondents completed the survey. In line with the MARS score participants were divided into 4 groups: 56.3% of adherers (taking all indicated doses), unintentional non-adherers (26.3%), intentional non-adherers (3.9%) and intentional/unintentional non-adherers (13.5%). Total QoL score was generally high (score range 138 - 146 out of 184) and not significantly different between the groups (t-test, $p<0.05$). The FACT-ES endocrine symptom subscale (ESS) score was statistically lower among intentional non-adherers ($t=1.86$, $p=0.03$) and intentional/unintentional non-adherers ($t= 2.26$, $p=0.01$) as opposed to adherers.
Conclusions
QoL was generally high and similar across participants indicating that adherence to therapy is not associated with the overall QoL. However, the ESS score indicated a higher adverse effects burden, hence rendering participants intentionally non-adherent. Further investigation of specific adverse events and their association with adherence could shed light on possible intervention targets for adherence behaviour change.

S 13/6

RATIONAL DRUG USE IN A PATIENT WITH TYPE 2 DIABETES AND CARDIOVASCULAR DISEASES - A CASE STUDY

Iva Mucalo (University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Lucija Ana Bićanić (University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Andrea Brajković (University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia)

Introduction

Type 2 diabetes (T2DM) is a complex metabolic disorder characterized by elevated blood glucose levels and a marked increase in the risk of cardiovascular disease (CVD). Additionally, CVDs are the number one cause of global mortality, responsible for an estimated 17.9 million deaths each year. Hence, to reduce the risk of cardiovascular complications in patients with T2DM, comprehensive medication management (CMM) is deemed crucial. The purpose of this case-study is to present the process of pharmaceutical care and clinical outcomes in a patient with T2DM and CVD who received CMM services.

Methods

In CMM services, the fundamental purpose of pharmacist's work is to address all of a patient's medication-related needs, optimise their medication use, and improve their health outcomes. The provision of CMM involves a logical and patientcentered approach to medication optimization that ensures every medication used by a patient is appropriate, effective, safe and convenient to be taken. A patient with T2DM and CVD who has undergone an extensive CMM over a 2 year period at the Health care Centre Zagreb is hereby described.

Results

Patient who participated in more than eleven follow-up visits had her clinical outcomes (blood pressure, HbA1c, LDL and weight) significantly improved through CMM provision.

Conclusion

As previously shown by an extensive body of evidence, CMM services have demonstrated the positive impact of pharmacists' interventions on the management of chronic diseases by improving individual cardiovascular risk factors such as blood pressure, glycated haemoglobin and lipid profile.

POPULAR LECTURES

PL 01

Chairperson: Goran Hauser (Department of Gastroenterology, Clinical Hospital Centre Rijeka and Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

PL 01/1

WE HAVE A CURE FOR OBESITY: THE USE OF LIRAGLUTIDE 6.0MG/ML IN THE TREATMENT OF OBESITY

Davor Miličić (University Hospital Centre Zagreb and University of Zagreb School of Medicine, Zagreb, Croatia), Sanja Klobučar Majanović (Clinical Hospital Centre Rijeka, Rijeka Croatia)

Obesity is a chronic metabolic disease characterized by abnormal and excessive adipose tissue accumulation associated with a wide range of complications and shorter life expectancy. Obesity management goals emphasize the importance of a realistic approach to weight loss in order to reduce health risks. They include promoting weight loss, maintenance of achieved lower/optimal body weight and prevention of weight regain. Obesity treatment is primarily based on lifestyle modifications and the permanent acceptance of healthy habits. Pharmacotherapy for weight loss is indicated as an adjunct to a low-calorie diet and increased physical activity in adults with a BMI ≥30 kg/m2, but also in overweight adults with a BMI ≥27 to <30 kg/m2 in the presence of at least one obesity-related comorbidity. Liraglutide 3.0 mg is a human glucagon-like peptide-1 (GLP-1) analog with 97% amino acid sequence identity to endogenous human GLP-1. Endogenous GLP-1 belongs to the group of incretin hormones and is secreted by intestinal cells in response to food intake. Liraglutide 3.0 mg regulates the appetite by increasing the feeling of fullness and satiety and simultaneously alleviating the feeling of hunger and potential food consumption, which leads to reduced food intake. In clinical studies, treatment with liraglutide lead to a 10% reduction in body weight and significantly improved cardiometabolic parameters and health-related quality of life scores. It is generally well tolerated, except for gastrointestinal side effects, which in most cases are transient and of mild to moderate intensity.

PL 01/2

COMMUNICATION BETWEEN GUT MICROBIOTA AND NEURONS: THE TOLL-LIKE STORY

Maria Cecilia Giron (Department of Pharmaceutical & Pharmacological Sciences, University of Padova, Italy)

Gut microbiota and the enteric nervous system (ENS) communicate with each other to maintain a homeostatic relationship and ensure host development and function. However, we are still far from understanding how gut bacteria influence these systems throughout life. Changes in gut microbial composition has been associated to several gut disorders, including inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) while an altered microbiome during childhood/adolescence, caused by infections or antibiotics, predisposes at the onset of these diseases. Furthermore, dysfunctions of the enteric nervous system (ENS) such as structural abnormalities and/or changes in the content of neurotransmitters have been revealed with the onset of IBD or IBS. A sophisticated system of proteins, so-called Toll-like receptors (TLRs), plays a key role in mediating the inflammatory response against pathogens and activates beneficial signals to ensure tissue integrity in physiological and pathological conditions. Polymorphisms in the genes, encoding TLR2 and TLR4, have been associated with different gut disease phenotypes. Lately, we have shown that TLR2 and/or TLR4 signaling appear to be highly involved in the detrimental effects induced by colitis underlining its pivotal role in ENS homeostasis. Intriguingly, among all alterations determined in the structural and functional integrity of ENS, antibiotic-induced enteric dysbiosis determines anomalies of glial network, GI transit time and iNOS-produced NO neuromuscular relaxation, similar to those found in mice deficient of TLR4 and /or TLR2 signaling. Therefore, the modulation of TLRs signaling appears an interesting target for exploitation in immunotherapy in order to ameliorate the pathophysiology of gut disorders.

POPULAR LECTURES

PL 02

Chairperson: Kristina Pilipović (Department for Basic and Clinical Pharmacology and Toxicology, University of Rijeka Medical Faculty, Rijeka, Croatia)

PL 02/1

CHINESE TRADITIONAL MEDICINE-MUSIC THERAPY

Rita Zhao Simonić (Rijeka University, Rijeka, Croatia), Ante Simonić (Rijeka University, Rijeka, Croatia)

According to the 4000-year-old traditional Chinese medicine book “Yellow Empire’s Canon of Medicine”: music is regarded as a great remedy for preventing physical and mental illnesses and enhancing immune system, and it has been practiced consecutively for thousands of years.
Besides using relaxing and soothing music in daily life in China, it is discovered also that natural, pleasing and uplifting sounds are also essential to the well-being of the human nerves system.
With the proof of modern technology, music therapy is more and more used in conjunction with current medicinal treatments, and has become one of the most practical ways to uplifting the quality of human life. It can be used for better coping with stress, depression and many other mental disorder. In the post Covid era, music therapy is also a very useful way to help people recovering and rejuvenating effiently. It can even help to reduce the budget pressure of health care in all countries.

PL 02/2

TRADITIONAL CHINESE MEDICINE (TCM) AS A VITAL COMPONENT OF INTEGRATIVE MEDICINE

Ante Simonić (Rijeka University, Rijeka, Croatia), Rita Zhao Simonić (Rijeka University, Rijeka, Croatia)

In biomedical research, enormous achievements are presented daily. However, everyday clinical activities are facing enormous challenges. We require drastic changes to the total medical and health care system and to the public acceptance and understanding of medical and health care. Health care should become integrated, personalized, cheaper, more efficient and accessible to all, and should help people to live longer with high quality life.
The integrative medicine should be based on the interconnection of the achievements of scientific-evidence-based medicine and of a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. Among them TCM is one of the most prominent.
Integrative medicine includes cooperation of clinical medicine, research and education of physicians and other medical staff, pharmacists, students and the population in general. The major issue of such programs remains a low-cost access to effective integrative therapies available to everyone all over the globe.
Policy makers, legislators, health-authorities, scientific communities, pharmaceutical organizations, insurance companies and public bodies are encouraged to enter the cross-sectorial debate and facilitate the large public discussion. Namely, we need the implementation of all global beneficial concepts in clinical medicine, i.e. to combine wise state-of the-art, scientific knowledge with other therapies that are carefully selected and shown to be effective and safe.
The projects can be carried on through various initiatives on the international level (in all interested countries), and from
Chinese institutions too.

WORKSHOP

PHARMACOVIGILANCE

Agency for Medicinal Products and Medical Devices of Croatia (HALMED, Zagreb)

W 01/1

MEDICATION ERRORS IN CHILDREN AND ADOLESCENTS

Nikica Mirošević Skvrce (Agency for Medicinal Products and Medical Devices of Croatia (HALMED)), Željana Margan Koletić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED)), Sanja Prpić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED))

Introduction

A medication error (ME) is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient [1]. Use of medicinal products in children is identified as a risk factor for occurrence of medication errors [2, 3].

Materials and methods

Aim of this pharmacovigilance workshop is to analyse reports of medication errors in children and adolescents spontaneously reported to HALMED, until 30 April 2022, and to discuss potential risk minimisation measures.

Results

HALMED's adverse drug reaction database contained 8603 cases reported in patients up to 18 years of age, out of which 1684 cases included terms pertaining to MEs. The most commonly reported terms are Accidental exposure to product by child (65%) and Accidental overdose (19%). Grouping of cases was observed for the salbutamol nebuliser solution, paracetamol solution for infusion, cholecalciferol oral drops, valproate oral solution/syrup and lipid emulsion for intravenous infusion. Identified root causes were: misinterpretation of prescribed dosage for salbutamol, due to very small volume resulting in 10 times higher administered dose, confusion between units millilitres and milligrams for paracetamol, interchange between medicinal products due to primary package similarities for cholecalciferol (e.g. swapping with simethicone, dimetindene, bromhexidine), interchange between oral solution and syrup for valproate and wrong dose administered for lipid emulsion.

Conclusion

At the end of this workshop, attendees would be able to identify root causes of most common medication errors in children and adolescents and to implement risk minimisation measures in order to prevent them.

S14

RARE DISEASES: OPPORTUNITIES AND CHALLENGES IN THE TREATMENT

Chairperson: Dinko Vitezić (Department for Basic and Clinical Pharmacology and Toxicology, University of Rijeka Medical Faculty and Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, Rijeka, Croatia)

S 14/1

ORPHAN DRUGS: FROM RESEARCH TO APPLICATION

Dinko Vitezić (Department for Basic and Clinical Pharmacology and Toxicology, University of Rijeka Medical Faculty and Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, Rijeka, Croatia)

Introduction: EU definition for a rare disease is the one that affects less than 5 in 10000 of the general population and in the United States a rare disease is that affects less than 200,000 people. It is estimated that 5000 to 8000 distinct rare diseases exist, and affect 27 to 36 million people (6-8 % of the population of the EU). In this field European Medicines Agency (EMA) is responsible for reviewing applications from sponsors for orphan designation and this assessment is done by the Committee for Orphan Medicinal Products (COMP). To qualify for orphan designation, a product must meet a number of criteria which are defined and assessed during this process.
Materials and methods: Literature search and EMA collected data have been analysed and presented.
Results: Regulation orphan medicinal products (OMPs) benefit from the incentives and the result of this approach is that from 2000 to 2021 the COMP discussed 3929 applications with 2572 positive opinions, 1132 applications withdrawn, 36 negative opinions, 2552 designations, 207 designated OMPs with the EU marketing authorisations and 38 extensions of indication. After the medicine approval, the next important step for availability and access of orphan drugs to patients is depending to decisions on reimbursement from HTA organisations, and/or national payers (financial possibilities of health insurance). During the process of developing the recommendation HTA will evaluate, besides others, for specific orphan drug, their relative effectiveness (RE) which usually include a clinical assessment i.e. the benefit of the new medicine to comparators already available in the same indication.
Conclusion: Because the average price of ODs is several times higher than for non-orphan it is important to set the criteria for assessing the value of new ODs. These criteria need to include disease-specific factors (i.e. incidence or prevalence, aetiology, pathogenesis, clinical severity etc.), analysis of costs to manufacturer and benefits to patient. A general method for establishing a reasonable price need to include adjusted cost-effectiveness thresholds which includes incremental cost-effectiveness ratio (ICER). This is important for availability and access of ODs to patients (a value-based pricing policy, etc.), because the rising of budget impact of ODs is a challenge for public insurance.

S 14/2

EUROPEAN INITIATIVES IN A COMPREHENSIVE APPROACH TO THE TREATMENT OF RARE DISEASES

Ingeborg Barišić (Children's Hospital Zagreb, Medical School University of Zagreb, Zagreb, Croatia)

Introduction: Rare diseases (RD) are affecting 6%-8% of the European population and are an important public health issue. Due to their severity and complexity RD are an area where collaboration at the European level provides a major integrated added value. We present the main areas for policy actions at the European level that are progressively improving care for patients with a RD with special emphasis on policy provisions to foster research and development of orphan drugs.
Materials and methods: A review of the state of the art of RD policy and activities at national, European and international levels was conducted.
Results: Kay actions that have established the framework for action in the field of orphan medicinal products at the European level include the development of European Reference Networks (2017), the launch of the European Platform for Rare Disease Registration (2018), the progress of Orphanet information service, the creation of the Horizon 2020 European Joint Programme on Rare Diseases (EJP RD) (2019), policy provisions like PRIority MEdicines (PRIME) or Health technology assessment (HTA), the evaluation and ongoing revision of on the legislation for medicines for rare diseases and for children (2020) initiatives to evaluate and improve the European Orphan Medicinal Product landscape (2021) and the new clinical trial Regulation applying as of 1 February 2022 to promote research and development of orphan drugs.
Conclusions: All these European achievements are instrumental in guiding policy and research in the field of development of new therapies for rare diseases in the forthcoming years.

S 14/3

AVAILABILITY OF ORPHAN MEDICINES IN CROATIA

Tea Strbad (Croatian Health Insurance Fund, Zagreb, Croatia)

Introduction: The mission of the Croatian Health Insurance Fund (CHIF) is rationally invest financial resources through high quality and efficient health services and programs that will contribute to increasing life expectancy and contribute to the general health of people. The insured person, under the right to health care from the mandatory health insurance, has the right to use medicines that have been established in current reimbursed list which is publicly available on the CHIF web site https://hzzo.hr/zdravstvena-zastita/lijekovi/objavljene-liste-lijekova.

Materials and methods: On reimbursement list are numerous orphan medicines for the treatment of rare diseases. All these medicines are 100% available to insured persons. To ensure the availability of new, innovative, smart but expensive medicines, in 2005. CHIF has established the “List of very expensive medicines” (VEM) and costs of all VEMs are excluded from the hospital budgets. This list and all the data which are collected and analysed in CHIF have been presented as well as the system how the VEMs are available to the patients in Croatia.

Results: Based on the recommendation of the hospital specialist, the use of VEMs must be approved by the Hospital Medicines Committee. For the use of VEMs within compulsory health insurance, the patient must meet certain criteria, which are listed with each VEM on the CHIF reimbursement list of medicines. Also, CHIF recognizes the cost of certain VEM if it shows the expected effectiveness (cure, stop the progression of the disease, improvement of functional status, steady state of malignant diseases, etc.).

In the deciding process of putting medicines on the reimbursement list of medicines and VEMs list, CHIF applies different types of Managed Entry Agreements (MEAs) to make new drugs available to patients. The contract is concluded between CHIF and Market Authorisation Holder (MAH). The contract determines the relationship and the amount of MAH's participation in financing the cost of an individual VEM.

Conclusion: For the past three years, many new medicines have been added to the CHIF reimbursement list and list of VEMs to treat several rare diseases, some of which are intended for a completely new indication and with a new mechanism of action. The VEMs list includes, among other medicines, VEM for the treatment of mucopolysaccharoidosis, spinal muscular atrophy, haemophilia, Duchenne muscular dystrophy, Batten disease, cystic fibrosis, neuroblastoma, and also includes VEMs for various malignancies, for the treatment of rare haematological diseases, VEMs used as gene therapy, etc.

S 14/4

FROM DIAGNOSIS TO TREATMENT OF NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 (CLN2) - CLINICAL AND ADMINISTRATIVE CHALLENGES

Igor Prpić (Clinical Hospital Center Rijeka, University of Rijeka, Faculty of Medicine, Department of Paediatrics, National Referral Centre for Childhood Epilepsy, Rijeka, Croatia)

Introduction: Neuronal ceroid lipofuscinosis type 2 (CLN2 disease; OMIM#204500) is an autosomal recessive disease, caused by deficiency of the lysosomal enzyme tripeptidyl peptidase (TPP1). In the classic late-infantile form of CLN2 disease this results in a rapidly progressive neurodegenerative disorder. Patients exhibit a rapid decline in cognitive, language, motor and visual function, with complete loss of motor and speech functions by 6–7 years of age, followed by blindness and premature death between 8 and 13 years. In 2017, the first intracerebroventricular enzyme replacement therapy with cerliponase alfa, a recombinant human TPP1 enzyme, was approved based on the results of the pivotal trial conducted in 23 CLN2 patients.
Materials and methods: Analysis of the literature and the results of two patients treated with cerliponase alfa have been presented.
Results: Treating our two patients we followed strict protocols for intracerebroventricular device reservoir and with biweekly intracerebroventricular infusion of cerliponase alfa. Antihistamines and antipyretics were administered as premedication 30 min before each infusion. During administration, heart rate, oxygen saturation, blood pressure and temperature were monitored. During the first infusions, patients remained hospitalized overnight, but thereafter infusions were given in a day-care setting with observations for some extra couple hours after completion of the infusion. We did not have any intracerebroventricular access device-related infections. In one patient, due to material degradation, the intracerebroventricular access device reservoir was replaced after three years of treatment, and patients resumed treatment.
Conclusion: With the advent of treatment for CLN2 disease, it is now imperative to ensure that patients are diagnosed as early as possible to allow treatment to be initiated. A multidisciplinary approach, including physicians, pharmacy and nurses are essential to the approach of the care of children with CLN2 disease. Lifetime duration of this treatment modality and cost are challenges to families, institutions, and national health care system.

S 14/5

REAL-WORLD EVALUATION OF PHARMACOLOGICAL TREATMENT FOR SPINAL MUSCULAR ATROPHY – CROATIAN EXPERIENCE

Andrej Belančić (Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, Rijeka, Croatia and University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Tea Strbad (Croatian Health Insurance Fund, Zagreb, Croatia), Dinko Vitezić (Department for Basic and Clinical Pharmacology and Toxicology, University of Rijeka Medical Faculty and Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, Rijeka, Croatia)

Introduction: Spinal muscular atrophy (SMA) is a rare hereditary motor neuron disorder, with an estimated incidence of 1 in 10000 live births, caused by an insufficient level of survival motor neuron (SMN) protein due to SMN1 gene homozygous deletion or mutation. Based on age of onset and disease severity, SMA can be classified into five types (0-4). Nusinersen was the first drug approved for treatment of SMA. It initially demonstrated efficacy (motor response, time to death or the use of permanent assisted ventilation) in infants with SMA type 1 in ENDEAR study. Real-world data pointed towards nusinersen effectiveness in SMA type 1 and 2 (especially for presymptomatic/early-symptomatic individuals). However, due to noticeable public, political and media pressure, latter product was ultimately registered for all types/stages of SMA in Croatia, despite lack of adequate evidence regarding effectiveness for other types of the disease. Bearing this in mind, there is an unmet need for regional and local data collection as well as disease registry networks; especially now when even newer and more expensive therapeutic options (rispidlam, onasemnogene abeparvovec) are available on the market.
Methods and results: We have retrospectively and anonymously collected and analysed relevant demographic (age at onset of disease, age when therapy was introduced, gender), and clinical (SMN genotype, SMA type and stage, SMA drug data, motor response, need for permanent assisted ventilation and/or feeding device, safety data, etc.) Croatian Health Insurance Fund data for all patients treated with one of the drugs registered for SMA up to 2022.
Conclusion: Long-term robust prospective studies are still required to draw final conclusions regarding SMA therapeutic options' effectiveness and pharmacoeconomic aspects.

S15

NOVEL INSIGHTS INTO THE FUNCTION OF GLIAL CELLS IN HEALTH AND DISEASE

Chairpersons: Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka Croatia), Jasenka Mršić-Pelčić (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

S 15/1

INTRODUCTION - BRAIN INJURY: NEUROPROTECTIVE STRATEGIES

Jasenka Mršić-Pelčić (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

Neuroprotective strategies are based on procedures and/or mechanisms used to protect the brain from damage caused by either acute conditions (stroke, trauma) or chronic neurodegeneration. Stroke is the most common cause of disability and the second leading cause of death in humans. It is a complex cerebral disease characterized by the simultaneous activation of multiple deleterious signaling cascades in both the core and penumbra. Despite recent advances in the recanalization therapy of acute ischemic stroke by pharmacological and mechanical thrombolysis, the concept of neuroprotection as a potentially valuable adjunctive therapy has been the subject of extensive in vitro and in vivo research. It is based on prolonging the time window for recanalization therapy or preventing neuronal death caused by either acute ischemic brain injury or reperfusion injury after successful therapy. Targets for reducing or preventing reperfusion injury should include multiple drugs involved in regulating intracellular signaling pathways to reduce edema, excitotoxicity, oxidative stress, inflammatory responses, and/or apoptosis, suppress microglia, and identify epigenetic factors involved in the etiopathogenesis and progression of stroke. In addition, experimental and clinical studies have shown that control of physiological parameters (brain and body temperature, partial pressure of oxygen and carbon dioxide, mean arterial blood pressure, and glucose metabolism) in the early poststroke period may have a direct impact on the treatment of stroke patients. Potential implications of pharmacological and nonpharmacological methods for neuroprotection of ischemic stroke and advances in preclinical and clinical trials will be discussed.

Supported by grant uniri-biomed-18-115 "Molecular mechanisms of ischemic brain injury and neuroprotection" to Jasenka Mršić-Pelčić.

S 15/2

DRUG REPURPOSING MODEL: NEURO-IMMUNO-METABOLIC ROLE OF NALTREXONE

Natalia Kučić (Department of Physiology and Immunology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Valentino Rački (Department of Neurology, Clinical Hospital Center Rijeka, University of Rijeka, Rijeka, Croatia), Irena Grahovac (Pharmacy Irena Grahovac, Pula, Croatia), Jasenka Mršić-Pelčić (Department of Pharmacology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

Naltrexone is an opioid receptor antagonist commonly used to treat dependence. The use of low dose naltrexone (LDN) was found to have anti-neuroinflammatory properties possibly acting via Toll-like receptor 4 antagonism, widely expressed on microglia.
The aim of our study was to assess the immunometabolic effects of naltrexone on microglia cells in in vitro conditions. All experiments were performed in the BV-2 microglial cell line. The cells were treated with naltrexone at 100 µM concentrations corresponding to low dose for 24 h with assessment of cell viability. To induce activation, the cells were pretreated with LPS and IFN-γ. Immunofluorescence was used to analyze the microglial activation markers iNOS and CD206, while Seahorse was used for real-time cellular metabolic assessments. mTOR activity measured over the expression of a downstream target S6K was assessed by western blot. LDN induced a shift from highly activated proinflammatory phenotype (iNOShighCD206low) to quiescent anti-inflammatory (iNOSlowCD206high) phenotype in BV-2 cells. Changes in the inflammatory profile were accompanied by cellular metabolic switching based on the transition from high glycolysis to mitochondrial oxidative phosphorylation (OXPHOS). LDN-treated cells maintain a metabolically suppressive phenotype by supporting OXPHOS with high oxygen consumption and a lower energetic state due to lower lactate production. The metabolic shift was more prominent in cells pretreated with immunometabolic modulators such as LPS and IFN-γ. Also, naltrexone modulated mTOR/S6K expression.
By modulating the phenotypic features by metabolic switching of activated microglia, naltrexone could be an effective tool for immunometabolic reprogramming and a promising treatment for various neuroinflammatory conditions.

S 15/3

THE EFFECTS OF CHEMICALLY-FUNCTIONALIZED SINGLE-WALLED CARBON NANOTUBES ON PRIMARY MOUSE ASTROCYTES IN AN IN VITRO MODEL OF SEVERE TRAUMATIC BRAIN INJURY

Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Nika Gržeta (Department of Basic and Clinical Pharmacology and Toxicology, University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Anja Harej Hrkać (Department of Basic and Clinical Pharmacology and Toxicology, University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Vladimir Parpura (Department of Neurobiology, University of Alabama at Birmingham, Birmingham, United States)

Extensive research has proven that astrocytes, one of the key regulators of brain homeostasis, influence synaptic plasticity of the brain after traumatic brain injury (TBI). It has also been shown that dysregulation of the astrocyte function can lead to negative outcomes of brain trauma. Recently, a promising approach in TBI therapy is tissue engineering, which focuses on connecting the damaged parts of the brain and restoring its structure, and certain nanomaterials, such as the chemically-functionalized single-walled carbon nanotubes (SWCNTs), show potential for use in such cases. It was previously discovered that the application of SWCNTs decreases lesion volume and promotes neurite outgrowth in the rat model of spinal cord injury, and when applied to the culture medium, they modulate morpho-functional properties of astrocytes. However, it is still unknown how would the injured astrocytes react to SWCNTs exposure and if these effects would persist in pathological conditions.

The purpose of the investigations of our research group is to determine whether the chemically-functionalized SWCNTs can affect the survival of the astrocytes and their proliferation, as well as influence their function in the *in vitro* model of TBI. In this presentation, the results of our research regarding the effects of SWCNTs on the astrocytes' survival rate and oxidative stress following stretch injury will be shown. Also, we explored the changes in the secretory function of injured astrocytes and the influence of the application of the investigated nanomaterials. This research was fully supported by the Croatian Science Foundation grant UIP-2017-05-9517 to KP.

S 15/4

IMMUNITY IN AMYOTROPHIC LATERAL SCLEROSIS: BLURRED LINES BETWEEN EXCESSIVE INFLAMMATION AND INEFFICIENT IMMUNE RESPONSES

Ivana Munitić (Laboratory of Molecular Immunology, Department of Biotechnology, University of Rijeka, Rijeka, Croatia)

Amyotrophic lateral sclerosis (ALS) is a rapidly fatal neurodegenerative disease targeting motoneurons. It is marked by a wide genetic, environmental and clinical heterogeneity. However, a prominent common feature of all ALS cases is neuroinflammation, which presents as glial activation, T cell infiltration and systemic immune system activation, and leads to collateral neuronal damage. Despite this, various anti-inflammatory or immunosuppressive therapies in ALS or related neurodegenerative disease have failed to prevent or slow down the disease progression. This is likely because immune system also has an important neuroprotective function, and different phases and/or different subtypes of neurodegenerative process can be marked with either excessive inflammation, autoimmunity or inefficient immune responses. In this lecture, I will review the evidence on several recently characterized ALS-linked mutations in TBK1, OPTN, CYLD and C9orf72 genes, which could directly lead to inefficient immune responses and/or failed damage clearance, suggesting that an innate immunodeficiency may also be a trigger and/or disease modifier. The topic of immunity in amyotrophic lateral sclerosis is highly relevant as the immune system presents one of most interesting targets in ALS and related neurodegenerative diseases.

S 15/5

TRAUMATIC BRAIN INJURY AND PIOGLITAZONE: BENEFITS AND LIMITATIONS OF NEUROPROTECTIVE THERAPY

Petra Dolenec (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Ljerka Delač (Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Solna, Stockholm County, Sweden), Ante Slavić (PrimeVigilance d.o.o., Zagreb, Croatia), Željko Župan (Department of Anesthesiology, Reanimatology and Intensive Care Medicine, Faculty of Medicine, University of Rijeka, Rijeka, Croatia; Clinics of Anesthesiology and Intensive Care Medicine, Clinical Hospital Center Rijeka, Rijeka, Croatia), Gordana Župan (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

Traumatic brain injury (TBI) affects millions of people worldwide. Despite numerous preclinical and clinical research of pathophysiology and therapy of TBI, it remains the most significant cause of mortality and long-term disability, especially in previously healthy young people. One of the possible reasons why there is no effective neuroprotective agent proven to improve outcomes in TBI patients could be the complex and heterogenous pathobiology of TBI. That includes different cellular, molecular, biochemical and metabolic events that lead to progressive tissue damage and associated cell death. Because the primary injury is irreversible and cannot be pharmacologically affected, novel pharmacological options have been focused on the secondary injury. The recent pharmacological investigations are directed mainly toward multifunctional drugs that could affect different harmful pathomechanisms included in TBI. Here, our studies on the effects of the multifunctional compound, a peroxisome proliferator-activated receptor γ agonist, pioglitazone, on the different parameters of the rat brain damage will be presented. This work was supported by University of Rijeka, project uniri-biomed-18-204 to Ž.G. (from 2021 to D.P.).

S 15/6

EFFECTS OF A SINGLE MODERATE TRAUMATIC BRAIN INJURY IN MOUSE ON THE TAR DNA-BINDING PROTEIN 43 AND ITS CONNECTION WITH NEUROINFLAMMATION AND SYNAPTIC PLASTICITY

Tamara Janković (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Nika Gržeta (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Jelena Rajič Bumber (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Petra Dolenec (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Jasna Križ (Department of Psychiatry and Neuroscience, University Laval, Faculty of Medicine, Quebec, Canada), Gordana Župan (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

Traumatic brain injury (TBI) is a lifelong condition that leads to progressive brain damage and cognitive disturbances. TBI has been recognized as a risk factor for the development of numerous neurodegenerative diseases, such as Alzheimer and Parkinson's disease, amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Proteinopathy of TAR DNA binding protein 43 (TDP-43) is considered the most important pathological characteristic of ALS and FTLD, that is characterized by permanent translocation of TDP-43 in the cytoplasm where this protein undergoes hyperphosphorylation, ubiquitination and fragmentation with subsequent inclusion formation. Toxic effects of TDP-43 inclusions have been demonstrated in the neurons and microglia, but deficiency of nuclear TDP-43 has numerous cell consequences too. Although cellular processes that induce TDP-43 proteinopathy are still unclear, it has been proven that inflammation can induce these changes. Interconnection of TDP-43 with some synaptic proteins has also been found. TDP-43 inclusions have been detected in the brain tissue after repetitive trauma in numerous clinical and preclinical investigations and it is mostly considered that this type of proteinopathy is only a consequence of repetitive, but with single TBI, results have thus far been inconclusive. The aim of this study was to investigate the changes in the TDP-43 localization, fragmentation, and phosphorylation in different brain regions after single moderate TBI in mouse. Additionally, we examined the association of TDP-43 expression with some markers of synaptogenesis and inflammation. This work was supported by the University of Rijeka, Croatia, project-uniri-biomed-18-199 to K.P. and Croatian Science Foundation project-IP-2016-06-4602 to GŽ.

S16

PHARMACOGENOMICS IN PERSONALISED MEDICINE: HOW FAR HAVE WE COME AND HOW FAR COULD WE GO?

Chairperson: Nada Božina (Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia)

S 16/1

PHARMACOGENOMICS IN ADVERSE DRUG REACTIONS LEADING TO EMERGENCY HOSPITAL VISITS

Julia Carolin Stingl (Institute of Clinical Pharmacology, University Hospital of RWTH Aachen, Germany)

Adverse drug reactions (ADRs) and medication errors are a relevant problem in the context of health. Estimates approximately 5%-15% of emergency hospitalizations are due to ADRs.
Methods
The basis for this evaluation was the recording of suspected cases of ADR in patients who came to the hospital emergency department in four large hospitals in Germany. Suspected cases of ADR were documented if considered "possible", "probable", or "certain" according to WHO-UMC criteria for associations with drug therapy. A biosample for pharmacogenetic analyses was taken if patients had provided informed consent.
Results
In the participating emergency departments, 6.5% of all treatment cases were detected as suspected ADRs during the observation period of the feasibility analysis. The majority of the study cases collected involved patients who were, older (median: 73 years) and multimorbid (72.4%). Accordingly, most of the cases are also polymedicated (median: 7 drugs).
Pharmacogenetic analyses were done in n=776 of the total sample of n=2215. It turned out that drugs affected by pharmacogenetic polymorphisms were more frequently suspected being causative for the ADR in patients who turned out to be pharmacogenetic risk allele carriers in the pharmacogenetic analyses done retrospectively.
Conclusion
Certain groups of drugs, such as psychotropic drugs, antithrombotic drugs or antineoplastic and immunomodulatory drugs have a high potential to cause ADRs due to their mechanism of action. Here, knowledge of which drug is affected by pharmacogenetic polymorphism could make a decisive contribution to the recognition of ADRs in the emergency room setting, but also to the selection of drugs for use in certain pharmacogenetic risk groups.

S 16/2

PRECISION MEDICINE IN RENAL TRANSPLANT PATIENTS - ROLE OF ABCG2 LOSS OF FUNCTION POLYMORPHISM

Ana Borić Bilušić (Agency for Medicinal Products and Medical Devices of Croatia, Zagreb, Croatia), Nada Božina (Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia), Zdenka Lalić (Department of Laboratory Diagnostics, Analytical Toxicology and Pharmacology Division, University Hospital Center Zagreb, Zagreb, Croatia), Sandra Nađ-Škegro (Department of Urology, University Hospital Center Zagreb, Zagreb, Croatia), Luka Penezić (Department of Urology, University Hospital Center Zagreb, Zagreb, Croatia), Karmela Barišić (Department of Medical Biochemistry and Hematology, Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia), Vladimir Trkulja (Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia)

Introduction: Breast cancer resistance protein (BCRP/ABCG2) is an efflux transporter important in pharmacokinetics of a number of drugs. We evaluated effect of a loss-of-function polymorphism ABCG2 c.421C>A on exposure to mycophenolic acid (MPA) in stable adult renal transplant recipients of Croatian origin.

Materials and methods: Patients (n=68; 43 co-treated with cyclosporine, 25 with tacrolimus) were genotyped for ABCG2 c.421C>A and 11 polymorphisms in genes encoding enzymes and transporters implicated in MPA pharmacokinetics.

Donors were genotyped for polymorphisms suggested to affect renal MPA secretion. ABCG2 c.421C>A variant vs. wildtype (wt) patients were matched in respect to demographic, biopharmaceutic and genetic variables (full optimal combined with exact matching) and compared for dose-adjusted steady-state MPA pharmacokinetics (frequentist and Bayes [skeptical neutral prior] estimates of geometric means ratios, GMR).

Results: Raw data (12 variant vs. 56 wt patients) indicated by around 40% higher total exposure (frequentist GMR=1.45, 95%CI 1.10-1.91; Bayes = 1.38, 95%CrI 1.07-1.81) and by around 30% lower total body clearance (frequentist GMR=0.66, 0.58-0.90; Bayes=0.71, 0.53-0.95) in variant carriers than in wt controls. The estimates were similar in matched data (11 variant vs. 43 wt patients): exposure GMR=1.41 (1.11-1.79) frequentist, 1.39 (1.15-1.81) Bayes, with 85.5% probability of GMR >1.20; clearance GMR=0.73 (0.58-0.93) frequentist, 0.71 (0.54-0.95) Bayes. Raw data indicated exposure difference in tacrolimus-treated but not in cyclosporine-treated patients (P for genotype-calcineurin type interaction 0.045 frequentist, 92.7% Bayes).

Conclusions: Loss-off-function polymorphism ABCG2 c.421C>A increases steady-state exposure to MPA in stable renal transplant patients. The effect might be conditional on the type of calcineurin inhibitor.

S 16/3

PHARMACOGENOMICS IN THE PREDICTION OF CARDIOVASCULAR DRUGS ADVERSE REACTIONS - PGX-CARDIODRUG: PRELIMINARY RESULTS

Tamara Božina (University of Zagreb School of Medicine, Zagreb, Croatia), Majda Vrkić Kirhmajer (University of Zagreb School of Medicine, Zagreb, Croatia), Livija Šimičević (University Hospital Centre Zagreb, Zagreb, Croatia), Lana Ganoci (University Hospital Centre Zagreb, Zagreb, Croatia), Jozefina Palić (University of Zagreb School of Medicine, Zagreb, Croatia), Lucija Ana Bićanić (University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Iva Mucalo (University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Jure Samardžić (University of Zagreb School of Medicine, Zagreb, Croatia)

Introduction: To investigate the multiple drug-drug-gene interactions (DDI) and their relevance for predicting cardiovascular drugs' adverse drug reactions (ADRs). Preliminary data from our prospective nested case-control study are presented.
Patients and methods: The primary cohort of cardiovascular disease patients is represented by subjects who have a new indication for the administration of direct oral anticoagulants (DOACs); platelet aggregation inhibitors (PAI), HMG-CoA reductase inhibitors (statins). Patients were enrolling during the 16 months. The cases represent subjects that developed ADRs during the follow-up period: bleeding from DOACs and PAIs, myotoxicity and hepatotoxicity from statins, other serious ADRs. Control subjects are recruited from the same cohort, without ADRs. All subjects were genotyped for relevant ADME gene variants: CYP2C9*2*3, CYP2C19*2*3*17, CYP2D6*3*4*5*6*9*10*41 and xN, CYP2J2*7, CES1 (rs2244613, rs8192935), ABCB1 (c.1236C>T, c.2677G>T/A, c.3435C>T, rs4148738), ABCG2 c.421C>A, SLCO1B1 c.521T>C by Real-Time PCR methods, depending on the used therapy, and were monitored for clinical and laboratory parameters. For DDI The Lexicomp® Clinical Decision Support System was applied.
Results: 450 patients were recruited (female=215, male=235). Among them were genotyped according to prescribed drug substrates for CYP2C9 (47%), CYP2C19 (58%), CYP3A4 (74%), CYP3A5 (66%), CYP2D6 (22%), CES1 (7%), ABCB1 (63%), ABCG2 (79%), SLCO1B1 (48%). ADRs observed were: myotoxicity (n=84, 17%), hepatotoxicity (n=14, 3%), bleeding (n=36, 9%). Potential DDI with increased risk for ADRs were found in group of statins (n=39/182), DOACs (n=133/135) and PAIs (n=68/76).
Conclusions: Our preliminary data point to the drug-drug-gene interactions as an important risk factor for cardiovascular drug adverse reactions.

S 16/4

INFLUENCE OF ABCG2 421C>A POLYMORPHISM AND VALPROATE ON STEADY-STATE DISPOSITION OF LAMOTRIGINE

I. Šušak Sporiš (Department of Neurology, Dubrava University Hospital, Zagreb, Croatia and Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), N. Božina (Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia), V. Trkulja (Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia), I. Klarica Domjanović (Croatian Agency for Medicinal Products & Medical Devices, Zagreb, Croatia), D. Sporiš (Department of Neurology, Dubrava University Hospital, Zagreb, Croatia and Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), S. Bašić (Department of Neurology, Dubrava University Hospital, Zagreb, Croatia), I. Marković (Department of Neurology, Dubrava University Hospital, Zagreb, Croatia and Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), M. Lovrić (Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia), Z. Čolak Romić (Department of Neurology, Dubrava University Hospital, Zagreb, Croatia)

Introduction: We aimed to re-evaluate a previously suggested interaction between valproate and a loss-of-function single nucleotide polymorphism (SNP) in the breast cancer resistance protein gene (ABCG2 421C>A, rs2231142) in their effects on exposure to lamotrigine in adults with epilepsy. Materials and methods: Consecutive, otherwise generally healthy adults with epilepsy on lamotrigine monotherapy or on lamotrigine+valproate, free of other drugs known to interfere with exposure to lamotrigine were genotyped for ABCG2 421C>A and for three additional SNPs in P-glycoprotein (ABCB1 1236C>T, rs1128503) and metabolizing enzymes (UGT2B7 -161C>T, rs7668258; UGT1A4*3 142T>G, rs2011425) suggested to affect lamotrigine pharmacokinetics.

Lamotrigine and valproate troughs were determined at steady-state and ABCG2 variant allele carriers were matched exactly to wild-type controls in respect to demographics, other SNPs and valproate troughs [none (not co-treated), low (<364 mmol/L) or normal-high (≥364 mol/L)].

Results: Of the 471 included patients (age 39±15 years, 39.9% men, 69.6% monotherapy), 93 (19.8%) were ABCG2 421C>A variant allele carriers and were matched exactly to 322/378 wt controls. Dose-adjusted lamotrigine troughs in ABCG2 variant carriers vs. wt controls were by 25% lower if no valproate treatment (GMR=0.75, 95%CI 0.63-0.88), were comparable if valproate troughs were low (GMR=1.07, 0.86-1.33) and were by 47% higher at high valproate troughs (GMR=1.47, 1.08-1.94). The difference between variant carriers and wt controls at high valproate troughs was by 93% (95%CI 38-170) greater than in patients not co-treated with valproate.

Conclusion: There is a qualitative interaction between valproate and ABCG2 421C>A SNP in their effects on exposure to lamotrigine.

S17

DEVELOPMENT OF NEW MEDICINES

Chairperson: Iveta Merćep (Division of Clinical Pharmacology, Department of Internal medicine, University of Zagreb, School of Medicine, Zagreb, Croatia)

S 17/1

CLINICAL TRIALS AND THE NEW EUROPEAN UNION DIRECTIVE

Iveta Merćep (Division of Clinical Pharmacology, Department of Internal medicine, University of Zagreb, School of Medicine, Zagreb, Croatia), Dominik Strikić (Division of Clinical Pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia)

Modern medicine, and pharmacology in particular, relies on new developments in therapeutics. Every day we observe innovative treatment approaches and the approval of new therapeutics. The most important part of any approval and introduction of a new drug is the clinical trial, which is highly regulated nowadays. Furthermore, on 31 January 2022, new European Union Directive for clinical trials will come into force.
Currently, every single or multi-centre clinical trial in Croatia must be approved by the Central Ethical Committee, an independent committee appointed by the Minister of Health. This allows for unification of clinical trials with a single application form, standardised requirements and uniform assessment and is a much more efficient model. It also allows for a single national database for clinical trials.
The new European Union Clinical Trials Directive (EC) No 2001/02/ EC aims to ensure that Europe becomes an encouraging and attractive environment for clinical research. The emphasis is on better efficiency and more transparency in clinical trials to enable the development of better and safer new therapeutics. It is hoped that the new directive will ensure consistent rules across all European Union countries and introduce Clinical Trials Information System (CTIS). From January 2023, all new clinical trial applications in Croatia will be submitted through CTIS. The benefits of this new Directive are a single application for trials conducted in different EU countries, reduction of administrative burden for researchers, facilitation of patient recruitment and coordinated and faster approval of clinical trials, with a focus on transparency and full visibility to the public.

S 17/2

DRUG DEVELOPMENT

Matea Radačić Aumiler (University Hospital Centre Zagreb, Department of Internal medicine, Division of Clinical Pharmacology, Zagreb, Croatia)

New drug development is a time consuming, expensive and complicated process, which involves drug discovery, drug development, preclinical and clinical testing.
First, a lead compound should be found. The main ways to find it include from nature, with high throughput screening or through the biotechnology. In order to try and make a safe and effective drug, the lead compound should be optimized. Preclinical trials focusing on research in animals are conducted, where numerous test are performed to determine potential efficacy and safety in humans, to reveal pharmacokinetics, pharmacodynamics and toxicology.
Toxicity studies consist of tests of acute and chronic toxicity. Preclinical studies involve also reproductive toxicity and teratogenicity studies, immunogenicity, carcinogenicity and sometimes immunotoxicity. After preclinical studies, an application is made to the regulatory Agencies to request permission to further test the drug in humans. If successful, the clinical development of a new drug can begin. Clinical trials have an enormous role in drug development and they are conducted in three phases. Phase I is the most important as it is the first time a new compound is being administered in humans and it is conducted on a small number of healthy volunteers to access safety of the drug. Phase II involves larger number of participants, further assessing efficacy and safety. Phase III is performed on a significantly larger number of patients to confirm efficacy/safety. If the new compound is proven safe and effective, the results are documented and submitted to the Regulatory authorities to grant approval for marketization.

S 17/3

WHY DO CLINICAL DRUG TRIALS SO OFTEN FAIL?

Ksenija Makar-Aušperger (Clinical Hospital Center Zagreb, Zagreb, Croatia)

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. The process itself is very long, highly risky and costly. However, nine out of ten drug candidates after they have entered clinical studies would fail during phase I, II, III clinical trials and drug
approval process but it is important to note that the 90% failure rate is for candidate drugs that have already advanced to Phase I clinical trials, and does not include candidate drugs in preclinical stages. If we include drugs from preclinical studies in the statistics the failure rate of drug discovery/development is even higher than 90%.
More than one-third of new drugs fail between phase III and launch, which can force sponsors to abandon programs after investing hundreds of millions of dollars.
Possible reasons attributes to the clinical failures of drug development are: lack of clinical efficacy (40%-50%), unmanageable or unacceptable toxicity (30%), poor drug -like properties (10%-15%) and lack of commercial needs and poor strategic planning (10%).
In accordance with the given data, the possible successful strategies to improve each aspect of drug development process are selecting best drug candidate to achieve adequate clinical efficacy, best candidate with minimal clinical toxicity, candidate with optimal drug-like properties and good strategic planning in drug development.

S 17/4

IN SILICO METHODS IN DEVELOPMENT OF NEW THERAPEUTIC COMPOUNDS

Robert Likić (University of Zagreb School of Medicine and Clinical Hospital Centre Zagreb, Zagreb, Croatia)

Identifying new drug candidates with good safety and efficacy profiles early in the new compound development process can significantly boost success rates and portfolio value while simultaneously decreasing research time and lowering drug development costs. In silico methods based on big data analysis of potential treatment targets among cellular functions through comparative genomics and natwork-based methods present a promising approach to the development of new drugs in infectious and non-infectious diseases. Considering the increasing availability and user-friendliness of in silico resources, it is very likely that the utilisation of computational methods in the identification of new therapeutic targets will rise significantly in the near future.

S 17/5

INTERPRETING RESULTS OF CLINICAL TRIALS: COMMON STATISTICAL CONCERNS

Viktorija Erdeljić Turk (Division of Clinical pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia)

Statistical concepts can be difficult for health professionals to understand due to inadequate level of medical training in biostatistics in most medical schools curricula. However, it is important that clinicians understand fundamental statistical issues to be able to critically review the design, endpoints, and results of clinical trials. Evidence from clinical trials directly impacts clinical decision making, which ultimately guides patient management.

There are several common statistical concerns in clinical trials including poor p-value interpretation, the need for presenting confidence intervals, adherence to the intent-to-treat principle, missing data, multiplicity, subgroup analyses, association vs. causation, appropriate reporting of trial results, probability, and Bayesian statistics.

Identifying sources of error and understanding study limitations helps clinicians evaluate the validity of clinical data, ultimately influencing clinical decision making and patient care.

S18

CLOSTRIDIAL NEUROTOXINS AND THEIR ROLE IN SENSORY AND MOTOR FUNCTIONS IN THE CENTRAL NERVOUS SYSTEM

Chairpersons: Lidija Bach Rojecky (University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Ivica Matak (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

S 18/1

BOTULINUM TOXIN TYPE AXONAL TRANSPORT FROM THE PERIPHERY TO THE BRAIN: IS IT GOOD OR BAD?

Zdravko Lacković (Department of Pharmacology, University of Zagreb, School of Medicine, Zagreb, Croatia)

Introduction
In the second half of the last century, botulinum toxin type (BoNT-A) A was found to have an analgesic effect that is independent of muscle relaxation. In the last 20 years a number of experimental and clinical data have been collected that the effect on pain takes place primarily in the CNS. According to numerous behavioral and immunohistochemical findings, the toxin travels to the CNS by axonal transport. In fact, at least in experimental conditions, transsynaptic transport can reach more distant places in the CNS.
Methods
In this review, we present a literature search and selected examples of the data from our laboratory in Zagreb, Croatia.
Results
(1) As shown experimentally and clinically, BoNT-A has analgesic effects on various forms of chronic pain, characterized by a very long duration of action. Parallel behavioral and immunohistochemical data clearly indicate that effects are centrally mediated. (2) There are several preclinical data that intracerebroventricular administration could cause cognitive impairment that develops very slowly but could be permanent. (3) Results from several dozens of controlled clinical trials, where BoNT-A has been used for cosmetic purposes, suggest that it has a positive effect on depressive disorders. However, so far there is only one report from our laboratory that the toxin changes the activity of certain neurotransmitter systems in the brain.
Conclusion
After the discovery of axonal and transsynaptic transport, it is reasonable to expect that the central effect after peripheral application will lead to unexpected new discoveries.

S 18/2

CORTICAL REWIRING FOLLOWING PERIPHERAL INJECTION OF BOTULINUM NEUROTOXIN TYPE A

Alexia Tiberi (Neuroscience Institute, National Research Council (CNR), Pisa, Italy and Scuola Normale Superiore, Pisa, Italy), Verediana Massa (Neuroscience Institute, National Research Council (CNR), Pisa, Italy and Scuola Normale Superiore, Pisa, Italy), Marco Pirazzini (Department of Biomedical Sciences, University of Padua, Padua, Italy), Ornella Rossetto (Department of Biomedical Sciences, University of Padua, Padua, Italy), Matteo Caleo (Department of Biomedical Sciences, University of Padua, Padua, Italy and Neuroscience Institute, National Research Council (CNR), Pisa, Italy), Laura Restani (Neuroscience Institute, National Research Council (CNR), Pisa, Italy and Scuola Normale Superiore, Pisa, Italy)

Introduction: BoNT/A1 is widely use in human therapy for treating neurological conditions characterized by neuronal hyperactivity. A fraction of BoNT/A1 can undergo long-distance axonal transport, possibly mediating a direct effect on central circuits. Here, we assessed whether BoNT/A1 peripheral injections can influence motor cortical areas, affecting the morpho-functional physiology of pyramidal cortical neurons connected with BoNT/A1-affected central nuclei. Methods: We used Thy1-GFP mice, injected with BoNT/A1 (5 U/kg) in the whisker pad, to perform an ex vivo analysis of spine morphology 30 days after the injection. Alternatively, two-photon imaging of GFP-positive dendrites was performed through a 3-mm cranial window over the motor cortex at different time points to image spine dynamics. Results: Ex vivo dendritic spine analysis revealed a striking decrease in spine density in cortical motor areas 30 days after BoNT/A1 injection, while whisker paralysis lasted only around 10 days. Moreover, we observed an increase in stubby spines, known to be an immature spine type that could either be new or in the process of being eliminated. Longitudinally measures of spine dynamics in awake mice using two-photon microscopy revealed a decrease in spine density and an increase in spine elimination at day 15 after BoNT/A1 injection. Conclusions: Overall, our data reveal profound morphological changes in cortical neurons after intramuscular BoNT/A1 injection, which persist longer than the peripheral effect at the NMJ. Our hypothesis is that cortical spine remodeling plays a key role in the therapeutic action of BoNT/A1 in neuropathologies and contributes to the long-lasting benefits observed in patients.

S 18/3

FABS FROM PURIFIED HUMABS OPEN TO THE INTRATHECAL THERAPY OF TETANUS

Marco Pirazzini (University of Padova - Department of Biomedical Sciences), Federico Fabris (University of Padova, Department of Biomedical Sciences, Italy), Petra Šoštarić (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Patrik Meglić (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Marika Tonellato (University of Padova, Department of Biomedical Sciences, Italy), Alessandro Grinzato (University of Padova, Department of Biomedical Sciences, Italy), Davide Corti (Humabs BioMed SA, Bellinzona, Switzerland), Antonio Lanzavechhia (Humabs BioMed SA, Bellinzona, Switzerland), Giampietro Schiavo (UCL-Institute of Neurology and Dementia Research Institute, London, United Kingdom), Ornella Rossetto (University of Padova, Department of Biomedical Sciences, Italy), Giuseppe Zanotti (University of Padova, Department of Biomedical Sciences, Italy), Cesare Montecucco (CNR-Institute of Neuroscience, Padova, Italy), Ivica Matak (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Tetanus neurotoxin (TeNT) is the causative agent of tetanus, a fatal disease characterized by neuromuscular spastic paralysis caused by TeNT activity in inhibitory interneurons in the spinal cord. Although tetanus can be prevented using a highly effective vaccine, a worldwide clinical practice is the administration of anti-TeNT immunoglobulins (TIG) for prophylaxis and/or treatment of patients already experiencing tetanus symptoms. TIG neutralizes TeNT in peripheral body fluids before it enters peripheral nerves and is retrotransported to the spinal cord. Intrathecal administration of TIG to block TeNT at its site of action would be more effective, but this approach is limited by the low level of anti-TeNT antibodies present in TIG and the amount of protein that can be safely injected into the cerebrospinal fluid. All of these drawbacks can be overcome by highly purified human monoclonal antibodies (humAbs), which are emerging as superior therapeutics against several diseases. By screening immortalized memory B cells pooled from the blood of immunized human donors, we isolated TT104 and TT110, two humAbs that display an unprecedented neutralization ability against TeNT. We produced the Fab derivatives to determine the epitopes they recognize using cryo-electron microscopy, i.e. epitopes essential for toxin binding to target neurons and light chain translocation inside the neuronal cytosol. TT104 and
TT110 humAbs display in mice a prophylactic activity comparable to TIG when injected long before TeNT and the combination of TT104-Fab and TT110-Fab prevent tetanus in post-exposure experiments if injected within 6 hours after TeNT, again comparably to TIG. Crucially, none of these treatments can prevent tetanus when administered later than 12
hours after TeNT inoculation, while it can be prevented by the TT104-Fab and TT110-Fab combination administered via the intrathecal route. In rats, intrathecal Fabs administered up to 24 hours after TeNT reduce the severity and duration of tetanus symptoms to a greater degree than intramuscular TIG. In conclusion, TT104 and TT110 humAbs meet all the
requirements to improve the current prophylaxis and therapy of human tetanus and are ready for clinical trials while TT104- and TT110-Fab derivatives open to effective intrathecal therapy of symptomatic tetanus.

S 18/4

LONG TERM CENTRAL EFFECTS OF BOTULINUM TOXIN TYPE A ON MUSCULAR FUNCTION AND RECOVERY IN RAT

Petra Šoštarić (Laboratory of Molecular Neuropharmacology, Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia), Magdalena Matić (Laboratory of Molecular Neuropharmacology, Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia), Ivica Matak (Laboratory of Molecular Neuropharmacology, Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia)

Introduction: Due to presumable action on local neuromuscular terminals, botulinum toxin type A (BoNT-A) is widely used in different muscle hyperactivity disorders. However, clinical observations suggest possible central effects. Herein, we examined the contribution of BoNT-A long term central effects on normal muscle function and recovery from paralysis, as well as tetanus neurotoxin (TeNT) evoked spasticity.

Materials and methods: BoNT-A was bilaterally injected into rat gastrocnemius muscle (2 U/kg) or sciatic nerve (5 U/kg). To prevent spinal transcytosis, BoNT-A-neutralizing antitoxin was administered into the lumbar intrathecal (i.t.) spine. To examine late antispastic action on disinhibited muscle tone and stretch reflex, 1.5 ng TeNT was injected unilaterally into gastrocnemius muscle on day 62 post BoNT-A. BoNT-A enzymatic activity was examined in injected muscle and spinal cord by cleaved synaptosomal-associated protein 25 (cSNAP-25) immunohistochemistry.

Results: I.t. antitoxin significantly accelerated the flaccid paralysis and motor performance recovery in different motor tests (gait ability score, digit abduction score, rota-rod, beam walking and swimming performance). Dependently on its central effects, BoNT-A reduced the TeNT-evoked increased muscle tone, however, did not affect the disinhibited stretch reflex. In contrast to cSNAP-25 continuous presence in injected muscle, BoNT-A action in second order spinal cord cholinergic neurons depended on the toxin's central transcytosis.

Conclusion: Normal motor performance (day 1-62), as well as the spastic paralysis (days 62-78), are influenced by BoNT-A ongoing central action, suggesting a clinically relevant benefit resulting from combined peripheral and central toxin effects.

Funding: Croatian Science Foundation (project ID: UIP-2019-04-8277)

S 18/5

UPDATE ON BOTULINUM TOXIN TYPE A CENTRAL ACTION ON PAIN – ARE THE PRIMARY AFFERENTS IN THE SPINAL CORD ITS FINAL DESTINATION?

Dalia Vađunec (University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Ivica Matak (University of Zagreb, School of Medicine, Zagreb, Croatia), Lidija Bach-Rojecky (University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia)

Introduction

The mechanism of botulinum toxin type A (BoNT-A) antinociceptive effect in the central nervous system is yet to be clarified. This study aimed to investigate possibility of BoNT-A transcytosis at the level of the spinal cord after its peripheral application in rats.

Materials and methods

Male Wistar rats were unilaterally injected into the plantar surface of the hind paws (i.pl.) with BoNT-A (7 IU/kg) one day before intrathecal administration of antitoxin against BoNT-A (2 IU/10µL). After six days carrageenan solution (2%) was injected i.pl. bilaterally and three hours later sensitivity to mechanical stimuli was measured. Animals were sacrificed and immunohistochemistry of c-Fos, (marker of neural activation) and cleaved SNAP-25 (marker of BoNT-A biological activity) were performed in the lumbar spinal cord sections. Experiments were approved by Ethical Committee of University of Zagreb School of Medicine.

Results

Peripheral unilateral BoNT-A significantly reduced the mechanical hypersensitivity on both, ipsilateral and contralateral paws. Antitoxin prevented this effect of BoNT-A on both sides. Immunohistochemical data showed reduction of c-Fos positive neurons bilaterally in dorsal horn at L4/L5 segments in BoNT-A pre-treated animals, which was also prevented by antitoxin. Additionally, quantification of cleaved SNAP-25-positive neurons showed strong signal on both sides of the dorsal horns of BoNT-A-treated rats, which was significantly lower in antitoxin-treated group.

Conclusion

Here we provide evidence for complex BoNT-A's central action on pain, which probably involves the toxin transsynaptic transport within the spinal cord. Further in-depth studies are needed to elucidate this possibility.

This research is supported by Croatian Science Foundation (project no. HRZZ-UIP-2019-04-8277).

ROUND TABLE 02

CROATIAN PROGRAMME FOR EUCP QUALIFICATION

Croatian Pharmacological Society

Moderators: Vladimir Trkulja (Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia), Melita Šalković Petrišić (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Jasenka Mršić-Pelčić (Department of Basic and Clinical Pharmacology and Toxicology, University of Rijeka Faculty of Medicine, Rijeka, Croatia), Mladen Boban (Department of Basic and Clinical Pharmacology University of Split School of Medicine, Split, Croatia), Dubravka Švob Štrac (Laboratory for Molecular Neuropsychiatry, Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia), Jelena Osmanović Barilar (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia)

S19

SYMPOSIUM "MARIN BULAT" - THE INFLUENCE OF INTERSTITIAL AND CEREBROSPINAL FLUID MOVEMENT ON DISTRIBUTION OF DRUGS, METABOLITES AND BIOMARKERS INSIDE OF CRANIO-SPINAL SPACE

Chairperson: Marijan Klarica (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia)

S 19/1

DISTRIBUTION OF VARIOUS SUBSTANCES BETWEEN CSF AND INTERSTITIAL SPACE AFTER THEIR APPLICATION IN DIFFERENT CSF COMPARTMENTS

Klarica M (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Radoš M (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Jurjević I (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Orešković D (Ruđer Bošković Institute, Department of Molecular Biology, Zagreb, Croatia)

Introduction: The manner of cerebrospinal fluid (CSF) movement and its influence on different substances distribution into CNS tissue have been analyzed and discussed.
Methods: Investigations were done on freely moving animals. Distribution of various molecular weight substances was observed after their application into different CSF compartments.
Results: Investigated substances moved freely in all directions. That included both the classically imagined circulation path from the brain ventricles into the subarachnoid space, as well as the opposite direction. The fast disappearance of organic anions (brain metabolites) from the central CSF compartment (cisterna magna), and the very low concentration of tested substances in "peripheral" CSF compartments (cortical and lumbar subarachnoid space) were observed in control conditions. When the active transport was blocked, the concentration of monitored substances in CNS tissue and in „peripheral" CSF compartments was significantly increased. Results suggest that key role in process of substances elimination from CSF/interstitial fluid (ISF) belongs to transport mechanisms at CNS microvessels. Substance distribution was more pronounced along the interhemispheric space (intensive pulsatile movement), and significantly reduced in the temporal and parietal subarachnoid space.
Conclusions: Described results imply that systolic-diastolic pulsatile movement of the CSF is responsible for the distribution of different substances through the CSF system, as well as their passage from the CSF into ISF of the CNS tissue. The brain metabolites are probably removed from CSF/ISF by means of active transport that takes place at the capillary level, which has the most important role in providing CNS homeostasis.

S 19/2

DYNAMICS OF BLOOD AND CEREBROSPINAL FLUID BIOMARKERS OF ALZHEIMER'S DISEASE

Šimić G (Department of Neuroscience, Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Babić Leko M (Department of Neuroscience, Croatian Institute for Brain Research, University of Zagreb School of Medicine and Department of Medical Biology, University of Split School of Medicine, Split, Croatia), Mihelčić M. (Department of Mathematics, Faculty of Science, University of Zagreb, Zagreb, Croatia)

Introduction: Dyshomeostasis of essential metals has been proposed to be directly related to Alzheimer's disease (AD) pathological changes.
Materials and methods: We analyzed cerebrospinal fluid (CSF) and venous blood samples of AD, mild cognitive impairment (MCI) subjects, and healthy controls. Eleven AD biomarkers were measured in CSF by using the enzyme-linked immunosorbent assay: Aβ42, VILIP-1, t-tau, p-tau181, p-tau231, p-tau199, NF-L, S100B, YKL-40, PAPP-A, and albumin. Inductively coupled plasma mass spectroscopy was used for the measurement of CSF and plasma levels of the following elements: As, B, Ca, Cd, Co, Cu, Fe, Hg, Li, Mg, Mn, Mo, Na, Ni, P, Pb, S, Se, Sr, Tl and Zn, and CSF levels of Al, Ba, and K. Correlation and linear regression were used for testing of the association between protein biomarkers and elements measured. The principal component analysis was used to reduce the dimensionality.
Results: The elements that correlated with the high number of AD biomarkers in CSF were As, Hg, Zn, Cu, Fe, S, K, Se, Co, Mn, Ni, Na, Mg, Tl, and Li. Factor analysis of CSF included 23 parameters that explained around three-quarters of the total variance, whereas factor analysis of elements in plasma included 21 parameters, which explained around two-thirds of the total variance. Using redescription mining, we found six potentially interesting co-occurrences between AD protein biomarkers and elements analyzed.
Conclusions: Using three different methods of data analysis on a relatively large data set we confirmed dyshomeostasis of essential elements in CSF and plasma in AD and MCI subjects.

S 19/3

SUBSTANCE DISTRIBUTION CHANGES AFTER CSF PATHWAY IMPAIREMENT IN DIFFERENT PARTS OF CRANIOSPINAL SPACE

Klarica M (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Radoš M (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia), Jurjević I (Department of Pharmacology and Croatian Brain Research Institute, Faculty of Medicine, University of Zagreb, Zagreb, Croatia), Kudelić N (Department of Neurosurgery, General Hospital Varaždin, Varaždin, Croatia), Orešković D (Department of Molecular Biology, Ruđer Bošković Institute, Zagreb, Croatia)

Introduction: It is unclear how obstruction and stenosis in different parts of craniospinal space affect the CSF movement and distribution of substances within the CSF and interstitial fluid (ISF).
Material and methods: In experimental animals with acute and subchronic blockage or stenosis of the aqueduct of Sylvii and/or cervical subarachnoid space, changes in dye distribution, size of ventricles and CSF pressure were examined. Contrast dynamics and changes in the CSF system anatomy were investigated in patients with obstruction or severe aqueductal stenosis.
Results: According to the classic concept, obstruction or severe stenosis of unidirectional CSF circulation should lead to an increase in CSF pressure and dilation of ventricles proximal to the site of obstruction. Experimental acute aqueductal blockage showed lack of increase in the CSF pressure and ventricular dilatation. Long-term blockage and stenosis of the cervical space resulted in slight enlargement of ventricles. The obstructions within CSF system limited the distribution of the dye along the CSF system and increased its penetration into the tissue. MR studies in some patients showed the existence of aqueductal obstruction or stenosis, without development of clinical and radiological signs of the three-ventricular hypertensive hydrocephalus.
Conclusion: Classical hypothesis of constant CSF secretion inside the ventricles, unidirectional circulation, and dominantly passive absorption through the arachnoid granulations of the dural sinuses cannot explain the described results, while they can be easily explained by a new concept of CSF/ISF physiology.

S 19/4

ROLE OF ARACHNOID GRANULATIONS IN CEREBROSPINAL FLUID PHYSIOLOGY: ANALYSIS BY MAGNETIC RESONANCE IMAGING

Radoš M (Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Živko M (Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Periša A (Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia), Orešković D (Department of Molecular Biology, Ruđer Bošković Institute, Zagreb, Croatia), Klarica M (Department of Pharmacology and Croatian Institute for Brain Research, School of Medicine University of Zagreb, Zagreb, Croatia)

Introduction: The study aims to quantify changes in the number, size, and distribution of arachnoid granulations (AG) during the human lifespan.
Material and Methods: 3T magnetic resonance imaging of the brain was performed in 120 subjects of different ages (neonate, 2 years, 10 years, 20 years, 40 years, 60 years, and 80 years) all with the normal findings of the cerebrospinal fluid system (CSF Group scanned at neonatal age was re-scanned at the age of two, while all other groups were scanned once. AG were analyzed on T2 coronal and axial sections.
Results: Our study shows that 85% of neonates and 2-year-old children do not have visible AG. With age, the percentage of patients with AG in the superior sagittal sinus increases significantly, but there is no increase in the sigmoid and transverse sinuses. However, numerous individuals in different age groups do not have AG in dural sinuses. From the age of 60 onwards, AG were more numerous in the cranial bones than in the dural sinuses.
Conclusions: The results show that the number, size, and distribution of AG in the superior sagittal sinus and surrounding cranial bones change significantly over a lifetime. Numerous individuals with a completely normal CSF system do not have AG in the dural sinuses, which calls into question their role in CSF physiology. It can be assumed that AG do not play an essential role in CSF absorption as it is generally accepted.

POSTER ABSTRACTS

POSTER SESSION 1 WITH ORGANIZED DISCUSSION

Chairpersons: Suzana Mimica (University hospital center Osijek, Department of Clinical Pharmacology and Faculty of Medicine Osijek, Department of Internal Medicine and History of Medicine), Dubravka Švob Štrac (Laboratory for Molecular Neuropsychiatry, Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia)

P1 01

PHARMACOGENOMICS OF ROSUVASTATIN – IMPACT OF ABCG2 AND SLCO1B1 POLYMORPHISMS AND DRUG-DRUG INTERACTIONS ON DEVELOPMENT OF ADVERSE DRUG REACTIONS

Lana Ganoci (Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia), Iva Mucalo (Centre for Applied Pharmacy, Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia), Lucija Ana Bićanić (Centre for Applied Pharmacy, Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia), Jozefina Palić (Department of Medical Chemistry, Biochemistry and Clinical Chemistry, University of Zagreb School of Medicine, Zagreb, Croatia), Livija Šimičević (Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia), Majda Vrkić Kirhmajer (Department of Cardiovascular Diseases, University Hospital Centre Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia), Jure Samardžić (Department of Cardiovascular Diseases, University Hospital Centre Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia), Tamara Božina (Department of Medical Chemistry, Biochemistry and Clinical Chemistry, University of Zagreb School of Medicine, Zagreb, Croatia)

Introduction: ABCG2 c.421C>A and SLCO1B1 c.521T>C polymorphisms are associated with a reduced transporter function and higher exposure to rosuvastatin. We investigated the relationship between ABCG2 and SLCO1B1 polymorphisms, drugdrug interactions (DDIs) and rosuvastatin-related myotoxicity and hepatotoxicity.
Patients and methods: In this case-control study, cases were subjects that developed rosuvastatin-related myotoxicity and hepatotoxicity and control subjects were rosuvastatin-treated patients free of adverse drug reactions (ADRs). Patients were enrolled retrospectively and prospectively for 3,5 years, and their clinical data, concomitant therapy and rosuvastatin-related myotoxicity and hepatotoxicity occurrence were evaluated. All subjects were genotyped for ABCG2 c.421C>A and SLCO1B1 c.521T>C by TaqMan® real-time PCR method. Using the individuals' medication lists and Lexicomp® clinical decision support system, the prevalence of DDI and drug-drug-gene interactions (DDGIs) were analysed.
Results: A total of 356 subjects were recruited (cases (n=128), controls (n=228)). SLCO1B1 c.521T>C variant carriers had 1,4- times greater odds (95% CI: 0,92-2,20; χ^2 = 6,333; p=0,042), and ABCG2 c.421C>A variant carriers had 1,9-times greater odds (95% CI: 1,18-3,33; χ^2 = 6,814; p=0,009) of developing rosuvastatin ADRs. The number of clinically relevant DDI that could have contributed to ADRs was low, both in a group of cases (n=16) and in a control group (n=50). There was no statistically significant difference in the rate of DDGIs between both groups.
Conclusions: In our study, preliminary data showed an association between ABCG2 c.421C>A and SLCO1B1 c.521T>C polymorphisms and rosuvastatin-related myotoxicity and hepatotoxicity. At the same time, there was no association between rosuvastatin DDIs, ABCG2 and SLCO1B1 polymorphisms and rosuvastatin-related ADRs.

P1 02

RHABDOMYOLYSIS IN KIDNEY TRANSPLANT PATIENT WITH COVID-19: POSSIBLE ROLE OF REMDESIVIR AND ATORVASTATIN DRUG-DRUG-GENE INTERACTIONS

Margareta Fištrek Prlić (University Hospital Centre Zagreb, Department of Nephrology, Hypertension, Dialysis, and Transplantation, Zagreb,Croatia), Jelena Osmanović Barilar (School of Medicine, Department of Pharmacology, University of Zagreb, Zagreb, Croatia), Lana Ganoci (University Hospital Centre Zagreb, Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, Zagreb, Croatia), Livija Šimičević (University Hospital Centre Zagreb, Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, Zagreb, Croatia), Nada Božina (School of Medicine, Department of Pharmacology, University of Zagreb, Zagreb, Croatia)

Introduction
Because of very variable clinical presentation of Covid-19 and polypharmacy in elderly, sometimes is difficult to distinguish between the drug-drug, disease- drug or drug-drug-gene induced side effects.
Description
A 63 –year old Caucasian woman with kidney transplant, was hospitalized due to Covid-19 infection. She was treated with remdesivir for 10 days along with meropenem and methylprednisolone. Mycophenolate was excluded for 10 days.
Tacrolimus, atorvastatin, ramipril and ezetimibe were continued and furosemide and pantoprazole were added. After discharge, she started to feel muscle weakness in her extremities and laboratory results at admission showed elevated value of creatinine kinase (CK-MM 6975 U/L). CK returned to the normal range in two weeks following the cessation of atorvastatin and ezetimibe.
Discussion
In this case atorvastatin and remdesivir were the most prominent candidates for drug-drug and drug-drug-gene interactions resulting in elevated CK and rhabdomyolysis. Pharmacogenetic analysis showed that patient was a carrier of inactivating alleles of CYP2D6*1/*4, CYP3A4*1/*22, SLCO1B1 *5/*5. Remdesivir is substrate of CES1, CYP2D6, CYP3A4, OATP1B1(SLCO1B1) and inhibitor of CYP3A4 and SLCO1B1. Atorvastatin is substrate of CYP3A4 and OATP1B1 and can moderately inhibit the CES1 enzyme, the main metabolic pathway of remdesivir. Other concomitantly prescribed drugs, such as ezetimibe, furosemide and proton pump inhibitors could have added to the drug-drug-gene interactions.
Conclusions
The pharmacogenetic profiling along with the assessment of drug interactions and pharmacokinetics in polypharmacy can significantly contribute to the minimization of the risk of developing side effects especially in a vulnerable subpopulation of patients such as the kidney transplant patients.

P1 03

THE ROLE OF PHARMACOGENETICS AS POSSIBLE RISK FACTOR FOR RIVAROXABAN – ASSOCIATED BLEEDING

Livija Šimičević (Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia), Ana Marija Slišković (Department of Cardiology, University Hospital Centre Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia), , Majda Vrkić Kirhmajer (Department of Cardiology, University Hospital Centre Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia), Lana Ganoci (Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia), Hrvoje Holik (Department of Internal Medicine, "Dr. Josip Benčević" General Hospital, Slavonski Brod, Croatia), Jure Samardžić (Department of Cardiology, University Hospital Centre Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia), Tamara Božina (Department of Medical Chemistry, Biochemistry and Clinical Chemistry, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Rivaroxaban has large interindividual trough concentration variability affecting its efficacy and safety, especially bleeding events. This variability could be associated with age, liver and kidney function, concomitant illness and therapy, and pharmacogenetic predisposition. Rivaroxaban is a substrate of ABCB1 and ABCG2 transporters, and CYP2J2, CYP3A4/5 enzymes. The polymorphisms of these genes may affect the pharmacokinetics of rivaroxaban and its safety profile. Aim of the study is to evaluate role of pharmacogenetics as possible risk factor for rivaroxaban-associated bleeding in patients treated for cardiovascular diseases.
Patients and Methods: Presented data are part of the larger prospective nested case-control study "Pharmacogenomics in Prediction of Cardiovascular Drugs Adverse Reaction". Clinical and laboratory data were collected. Pharmacogenetic analyses were performed using specific TaqMan® DME and SNP Assays on 7500 Real-Time PCR System for genotyping of CYP3A4*1B*22, CYP3A5*3, CYP2J2*7, c.1331-2201T>C, ABCB1 (c.1236C>T, c.2482-2236G>A, c.2677G>T/A, c.3435C>T) and ABCG2 (c.421C>A) variants. For drug-drug interactions (DDI), The Lexicomp®
Clinical Decision Support System was applied.
Results: Sixteen patients (median age 73 years, range 61-80) with rivaroxaban-associated bleeding: gastrointestinal (N=9), epistaxis (N=5), haematuria (N=1) and gynaecological (N=1) were analysed. In 9/16 DDI with increased bleeding risk were found. Two patients had eGFR>90, while six patients had eGFR<60. Only three patients who experienced bleeding did not have any of investigated risk factors including gene variants.
Conclusions: Our data suggest a possible role of pharmacogenetic and clinical factors and their interactions in predicting bleeding on rivaroxaban treatment. These findings indicate the need for further comprehensive research.

P1 04

ASSOCIATION OF PERIOD CIRCADIAN GENES WITH CHEMORESISTANCE OF COLON CANCER CELLS WITH BRAFV600E MUTATION

Elitza Petkova Markova-Car (Department of Basic and Clinical Pharmacology and Toxicology, University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Martin Ripić (University of Rijeka, Department of Biotechnology, Rijeka, Croatia), Mirela Sedić (Institute for Anthropological Research, Zagreb, Croatia)

Introduction: Colorectal cancer is one of the most common cancers worldwide with approximately 5-10% of all cases carrying BRAFV600E mutation. Despite increasingly improved chemotherapy options, no significant advancement was observed in the treatment outcome of BRAF mutated patients, mainly due to the development of chemoresistance. The circadian system is involved in a number of cellular processes such as the cell cycle, DNA repair, metabolism and regulation of apoptosis. Consequently, in recent years there has been a growing interest in exploring possible links between the circadian system and tumorigenesis. Here, we investigated the relationship between circadian clock genes and acquired resistance to vemurafenib in colon cancer cells with the BRAFV600E mutation.
Materials and methods: The expression profiles of circadian clock genes in chemosensitive versus chemoresistant RKO colon cancer cells with BRAFV600E mutation were analyzed using the qPCR method. In silico analysis of selected genes was performed using the TCGA Colorectal Adenocarcinoma (TCGA, PanCancer Atlas) dataset.
Results: The expression of PER genes was significantly higher in chemoresistant cells. Among these, PER3 gene showed the highest expression level in chemoresistant cells. Importantly, mRNA levels of PER3 were also significantly increased in BRAFV600E mutated colon cancer patients in comparison with an unaltered group in the TCGA colorectal cancer dataset. Higher mRNA level of PER3 was also associated with shorter overall survival of BRAF mutated colon cancer
patients.
Conclusions: Our results suggested a possible role for PER3 in acquired resistance to vemurafenib and survival outcomes in BRAFV600E-mutated colon cancer.

P1 05

CONSUMPTION OF ALLERGY MEDICINE IN EUROPE, 2017-2020: IS THERE A SIMILAR PATTERN OF ALLERGY MEDICINE CONSUMPTION IN THREE EUROPEAN COUNTRIES?

Pelčić G (Health Care Center of Primorsko Goranska County and Department of Social Sciences and Medical Humanities, Faculty of Medicine of the University of Rijeka), Draganić P (Agency for Medical Product and Medical Devices of Croatia (HALMED) and Department of Biotechnology, University of Rijeka), Rožmanić V (Health Care Center of Primorsko Goranska County), Ragulj M (Department of Pediatrics, University Hospital Center Split, Croatia)

Introduction: The aim of this study was to review the trend in allergy medication consumption in three European countries (2017 - 2020) and to analyze the consumption trends of allergy medications in the countries studied.

Materials and Methods: Data on allergy medication consumption were obtained from the HALMED database. We used the Anatomical Therapeutic Chemical (ATC) classification system and Defined Daily Doses per 1000 inhabitants per day (DDD) as a metric tool to monitor medication consumption.

Results: The consumption trend of allergy medications during 2017-2020 is expressed by the annual average percentage: antihistamines increased by 5.3% in Croatia, 7.1% in Norway, and 1.9% in Slovenia; adrenergics for systemic use decreased by 24.9% in Croatia, 0.7% in Norway, and 3.7% in Slovenia; adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics, increased by 7.5% in Croatia, by 0.3% in Norway, and by 6.3% in Slovenia; adrenergics in combination with anticholinergics including triple combinations with corticosteroids increase by 68% in Croatia, 28% in Norway and 2.9% in Slovenia; glucocorticoids increase by 7.1% in Croatia, 1.2% in Norway and 1.3% in Slovenia per year; anticholinergics decrease by 0.9% in Croatia, 4.3% in Norway, and 1.7% in Slovenia while leukotriene receptor antagonists increase by 5.8% in Croatia, 2.5% in Norway, and dropped by 2.2% in Slovenia.

Conclusion: Consumption of allergy medications varies by country and type of medication. Possible reasons include the influence of epidemiological circumstances, changes in therapeutic guidelines, environmental factors and climate changes, pharmaceutical marketing, and the financial burden on patients.

P1 06

ORAL CHALLENGE WITH TRIMETHOPRIM-SULFAMETHOXAZOLE IN A PATIENT WITH ALLERGY IN DRUG HISTORY

Zvonimir Čagalj (Clinical Hospital Centre Osijek and University of Josip Juraj Strossmayer in Osijek, School of Medicine Osijek), Suzana Mimica (University hospital center Osijek, Department of Clinical Pharmacology and Faculty of Medicine Osijek, Department of Internal Medicine and History of Medicine, Osijek, Croatia), Ana Havidić (Clinical Hospital Centre Osijek and University of Josip Juraj Strossmayer in Osijek, School of Medicine Osijek)

Introduction: Sulfonamide antibiotics can cause allergic reactions ranging from mild to severe. Allergy testing for this group of antimicrobials is not frequently conducted due to the risk of allergic reactions and alternative treatment options. A patient in active treatment for non-Hodgkin lymphoma was referred to a clinical pharmacologist regarding the workup of her possible allergy to „sulfa" antibiotics. Trimethoprim-sulfamethoxazole (TMP-SMX) was recommended for this patient for prophylaxis against opportunistic pathogens. Her drug history shows that her reaction to TMP-SMX occurred 25 years ago and was mild. The patient reported developing redness of the face, palms, and feet, with pruritus, probably after taking the first dose of the drug.
Materials and methods: We decided to perform an oral challenge test with TMP-SMX. The patient was examined in our department. An intravenous line was placed and the oral challenge test was performed in a single-blind study. The patient received ascending doses of TMP-SMX.
Results: The oral challenge was conducted until the patient received full single doses of drugs (160 mg TMP+800 mg SMX). There were no recorded side effects during the testing and observation period.
Conclusions: Literature data are scarce regarding allergy testing to sulfonamide antibiotics. Allergy testing for sulfonamide antibiotics should be considered in cases where these antibiotics are the most suitable treatment option for prophylaxis and treatment of infections caused by certain organisms. Rechallenge may be appropriate for patients with mild reactions to sulfonamide antibiotics, like maculopapular eruptions, while alternative treatment protocol may be advisable for more severe reactions.

P1 07

NOVEL AGENTS IN DYSLIPIDAEMIA THERAPY - ARE WE SWITCHING DAILY TREATMENT TO WEEKLY OR EVEN MONTHLY?

Dominik Strikić (Division of Clinical pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia), Ana Marija Slišković (Department of Cardiology, University Hospital Centre Zagreb, Zagreb, Croatia), Iveta Merćep (Division of Clinical pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia)

Dyslipidaemia is a disease of modern man and leading risk factor for the cardiovascular disease. For a long time, successful treatment options were used, with statin therapy being the cornerstone. Nowadays, more and more new agents are being discovered and approved for the treatment of dyslipidaemia.
For this research, online databases were searched using the keywords ''dyslipidaemia'', ''statins'', ''PCSK9 inhibitors'' and ''inclisiran''.
Statins have been used for over 30 years. Studies have shown excellent results in lowering LDL cholesterol levels and reducing cardiovascular risk. Thus, statins became main preventive therapeutics in high-risk patients. However, changes in people's lifestyles and the fast pace of life have presented us with new challenges and shown us that statins are not enough in some cases. The first monoclonal antibodies approved for the treatment of dyslipidaemia were the PCSK9 inhibitors evolocumab and alirocumab. In trials, great results were observed in lowering blood LDL cholesterol levels, and administered once every two weeks, the PCSK9 inhibitors gradually became a second-line treatment option. Recently, the EMA approved a new siRNA molecule called inclisiran, which interferes with and PCSK9 mRNA translation, thereby lowering LDL cholesterol levels. The main advantage of inclisiran is its dosing scheme of once every three months.
The reduction in cardiovascular risk with PCSK9 inhibition and inclisiran therapy is still unknown, but its effect on lowering LDL cholesterol levels is evident. As statins remain the first therapeutic choice for dyslipidaemia, we should ask ourselves whether we are switching from daily to weekly or even monthly treatment.

P1 08

KNOWLEDGE, ATTITUDES AND AWARENESS REGARDING FOOD-DRUG INTERACTIONS AMONG PHARMACISTS IN CROATIA

Sandra Pavičić Žeželj (Department of Health Ecology, Faculty of Medicine, University of Rijeka), Gordana Kenđel Jovanović (Department of Health Ecology, Teaching Institute of Public Health of Primorsko-Goranska County), Silvija Mašković (Department of Clinical Pharmacology, Clinical hospital centre Rijeka, Rijeka, Croatia), Nataša Skočibušić (Department of Clinical Pharmacology, Clinical hospital centre Rijeka, Rijeka, Croatia), Andrej Belančić (Department of Clinical Pharmacology, Clinical hospital centre Rijeka, Rijeka, Croatia), Igor Rubinić (Department of Clinical Pharmacology, Clinical hospital centre Rijeka, Rijeka, Croatia), Vera Vlahović-Palčevski (Department of Clinical Pharmacology, Clinical hospital centre Rijeka, Rijeka, Croatia)

Introduction: This cross-sectional study aimed to investigate knowledge, attitudes, and awareness regarding food-drug interactions among pharmacists in Croatia.
Materials and methods: The anonymous questionnaire consisted of socio-demographic determinants, 10 subjective and 35 objective domains (17 on food-drug interactions in general and some of the most frequently present in practice – category A, 13 on the time of taking certain drugs depending on the meal - category B and 5 on the alcohol-drug interactions - category C). It was distributed in April 2021 among the members of the Croatian Chamber of Pharmacists through a local newsletter and e-mail addresses.
Results: The study included 114 subjects (median age 37 years; 87.7% women). The majority of respondents were masters of pharmacy (93.0%) and employed in a pharmacy (89.5%). Their median work experience was 12 years.
Approximately one third of respondents (32.5%) felt that they did not have enough knowledge about food-drug interactions, while almost half of respondents (44.7%) were unsure of their knowledge. All respondents agreed that it is important to improve pharmacists' knowledge of food-drug interactions. Only half of the pharmacists (46.4%) inform their patients/customers about food-drug interactions whenever necessary. The average number of correct answers overall was 22.4 ± 4.4 out of 35; whilst the average number of correct answers according to individual question categories (A-C) was
11.4 ± 2.8, 7.2 ± 2.0, and 3.8 ± 1.0, respectively.
Conclusions: Obtained results indicate the need for continuous education and evaluation of the knowledge of pharmacists and other health professionals about food-drug interactions.

P1 09

PHYTOCHEMICAL ANALYSIS AND PHYTOTHERAPEUTIC POTENTIAL OF SELECTED *VERONICA* L. SPECIES (PLANTAGINACEAE) FROM CROATIA

Renata Jurišić Grubešić (University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Nives Molc (University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Marija Nazlić (University of Split, Faculty of Science, Split, Croatia), Dario Kremer (University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Lea Juretić (University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Valerija Dunkić (University of Split, Faculty of Science, Split, Croatia)

Introduction. *Veronica* species have been used in traditional medicine for the treatment of various diseases, including influenza, respiratory diseases, and cancer. In this study, a qualitative analysis of various polyphenolic components and a quantitative analysis of phenolic acids were carried out on selected *Veronica* L. species growing in Croatia (*V. longifolia*, *V. cymbalaria*, *V. chamaedrys*, *V. hederifolia*, *V. polita*, *V. persica*, *V. serpyllifolia*, and *V. arvensis*) to evaluate their phytotherapeutic potential.
Materials and methods. The presence of polyphenols was investigated using appropriate chemical reactions and thin-layer chromatography (TLC). Quantitative analysis of total phenolic acids (TPA) was performed spectrophotometrically, according to official pharmacopoeial method for determination of hydroxycinnamic derivatives.
Results. The polyphenols were detected in all investigated plant samples by general chemical reactions of developing colored products and precipitates. The strongest intensity of the reaction was observed for the sample of *V. persica*, which indicates a higher content of polyphenols in that sample. TLC analysis proved the presence of phenolic acids in methanolic extracts of all investigated *Veronica* species. Spectrophotometrically determined TPA content varied from 0.44% (*V. cymbalaria*) to 3.59% (*V. chamaedrys*), when expressed as rosmarinic acid (at 505 nm), and from 0.81% (*V. cymbalaria*) to 7.18% (*V. chamaedrys*), when expressed as chlorogenic acid (at 525 nm).
Conclusions. This study is a contribution to the research of *Veronica* species and increases the previous knowledge about the phytotherapeutic potential of the analyzed plant species, especially in relation to the significant content of bioactive phenolic substances.
This research was supported by the project “Croatian *Veronica* species: Phytotaxonomy and Biological Activity”, CROVeS-PhyBA, funded by the Croatian Science Foundation. Project number IP-2020-02-8425.

P1 10

IMPACT OF PHARMACIST-LED MEDICATION MANAGEMENT ON ADVERSE DRUG REACTIONS REPORTED BY ELDERLY CARDIOVASCULAR PATIENTS AT A PRIMARY CARE LEVEL

Strgačić M (Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia), Pupačić A (Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia), Nalo L (Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia), Brajković A (Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia), Mucalo I (Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia)

Introduction
Although adverse drug reaction (ADR) reporting is a legal obligation of all healthcare professionals, studies have shown that only around 6% of all ADRs are actually reported, hence contributing to a limited data on the epidemiology of ADRs. Therefore, the primary aim of this study was to determine the frequency and provide an in-depth analysis of ADRs reported by elderly cardiovascular patients receiving Comprehensive Medication Management (CMM) services at a primary care level. The secondary aim was to evaluate the impact of CMM services on the frequency of ADRs.
Materials and methods
A prospective, pre and post intervention study was conducted in the period from January 2018 to December 2020. Once identified, suspected ADRs were coded into the related Preferred Term using the MedDRA terminology and further analysed in respect to the baseline characteristics of patients, System Organ Class (SOC), occurrence mechanism, seriousness, expectedness and sequence number of consultations.
Results
Sixty-five patients who met the eligibility criteria completed the study. A total of 596 suspected ADR reports were found (9.2 ± 16.9 per patient). There was a strong, positive correlation between the number of drugs used and the rate of ADRs ($r = 0.823$; $p < 0.001$). According to SOC, the leading ADRs pertained to General disorders and administration site conditions (N = 103). Type A ADRs made the majority of the total number of ADRs (75%), while serious and unexpected ADRs represented a lower ratio of the total number of ADRs (12% and 19%, respectively). CMM services significantly reduced the rate of ADRs throughout the course of time, that is between the first and the last consultation ($p < 0.001$).
Conclusions
Through more careful selection and more frequent monitoring of patients' therapy, CMM services could serve as a solution to the evergrowing clinical, financial and humanistic burden of ADRs.

P1 11

THE ASSESSMENT OF SALIVARY PARAMETERS IN OBSTRUCTIVE SLEEP APNEA PATIENTS AFTER CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT: A 6-MONTH FOLLOW-UP STUDY

Tranfić M (University of Split School of Medicine, Split, Croatia), Pecotić R (University of Split School of Medicine, Split, Croatia), Lušić Kalcina L (University of Split School of Medicine, Split, Croatia), Pavlinac Dodig I (University of Split School of Medicine, Split, Croatia), Valić M (University of Split School of Medicine, Split, Croatia), Rogić D (University Hospital Center Zagreb, Zagreb, Croatia), Lapić I (University Hospital Center Zagreb, Zagreb, Croatia), Grdiša K (University Hospital Center Zagreb, Zagreb, Croatia), Peroš K (University of Zagreb School of Dental Medicine, Zagreb, Croatia), Đogaš Z (University of Split School of Medicine, Split, Croatia)

Introduction: One of the most common treatment modalities for obstructive sleep apnea (OSA) is continuous positive airway pressure (CPAP). However, a few studies have reported oral health side effects during CPAP treatment such as oral dryness and changes in saliva composition. The aim of this study is to establish the changes of the salivary parameters in CPAP- treated OSA patients.
Materials and methods: Unstimulated saliva was collected from 16 patients diagnosed with severe OSA following a whole-night polysomnography. All patients were treated with CPAP treatment for 6 months. Salivary flow rate, salivary pH, salivary calcium, phosphate, magnesium and cortisol levels were measured. All of the patients completed a questionnaire for evaluating their subjective assessment of dry mouth.
Results: Following a 6-month CPAP treatment patients had significantly lower levels of salivary calcium (0,5 vs. 0,3; p=0,010), as well as the ratio of salivary calcium and phosphate levels (0,09 vs. 0,06; p=0,03). There were no significant changes in salivary flow rate, salivary pH, salivary phosphate and cortisol levels. Furthermore, there was a reduction of subjective assessment of dry mouth upon awakening during CPAP treatment compared to baseline results (3(2-3) vs. 0,5(0-1); p=0,002).
Conclusions: CPAP treatment was associated with lower salivary calcium and lower ratio of salivary calcium and phosphate levels. Although there was no significant change in salivary flow rate, subjective assessment of dry mouth appears to be lower after CPAP treatment. Further studies should investigate true clinical value of these findings of salivary parameters.

P1 12

METHODS OF DETERMINATION OF PROGESTERONE AND ESTRADIOL IN SALIVA

Kaltrina Smajli Vokshi (School of Dental Medicine, Zagreb, Croatia), Kristina Peroš (School of Dental Medicine, Department of Pharmacology, Zagreb, Croatia)

The aim of this study was to analyze methods used to determine the female sex hormones, progesterone and estradiol, in saliva. The literature search was conducted on the PubMed website (US National Library of Medicine, National Institute of Health) in July 2022 using the keywords “female sex hormones, methods of determination, saliva”. The literature search included human studies published in the last 10 years.
In this process, 20 published papers were reviewed. According to these articles, saliva samples were stored at -20 °C before analysis, thawed at room temperature, and then centrifuged. The vast majority of articles offer enzyme linked immunosorbent assay (ELISA) kits for the determination of female salivary hormones, although this method is limited to the measurement of only one analyte at a time and smaller samples. In contrast, determination by chromatographic assays has higher sensitivity and multiple hormones can be measured simultaneously. The use of the combined method LC-MS /MS for the measurement of salivary hormones has recently increased, as it has a higher sample throughput and sensitivity and is capable of quantifying small amounts of hormones in saliva.
Determination of hormones in saliva has recently become the most attractive method for various
medical conditions. Several laboratory methods (ELISA, chromatography, LC-MS /MS) are available for the precise determination of estradiol and progesterone in saliva. The choice of method depends on the study design and the characteristics of the saliva sample.

P1 13

EFFECT OF CALCIUM PRETREATMENT ON ENAMEL FLOURIDE REACTIVITY AND IN REMINERALIZATION DEMINERALIZATION PROCESSES

Fjolla Kullashi Spahija (School of Dental Medicine, Zagreb, Croatia), Kristina Peroš (School of Dental Medicine, Department of Pharmacology, Zagreb, Croatia)

Introduction: the aim of this literatures search was to evaluate the calcium regimens for dental pretreatment currently in use.
There are several forms of calcium pretreatment that aim to improve fluoride reactivity during treatment: dicalcium phosphate dihydrate (DCPD), calcium lactate, monocalcium phosphate monohydrate (MCPM), calcium glycerophosphate (CGP), calcium phosphate solution (CPS), etc.
Materials and Methods: The literature search using the keywords "calcium pretreatment fluoride reactivity enamel and dentine" was conducted through the PubMed website (US National Library of Medicine, National Institute of Health) in July 2022. The literature search using the keywords "calcium dental remineralization/demineralization processes" was also conducted via the same website.
Results: A total of 40 studies published showed a significant relationship between calcium pretreatment and fluoride reactivity, remineralization/demineralization processes, and anti-caries efficacy. Among these, there were studies that showed a statistically significant relationship between calcium pretreatment and both processes, fluoride reactivity and remineralization/demineralization. In 25 of these studies, enamel fluoride concentration was significantly increased after calcium pretreatment, while in 21 of these studies, enamel calcium activity and intraoral remineralization significantly increased.
Conclusions: Pretreatment with a calcium solution prior to fluoridation can be used as an effective anti-caries agent to increase the labile fluoride concentration in enamel and oral fluid, thus improving tooth remineralization. A precipitation reaction with calcium after fluoridation did not increase fluoride uptake in enamel.

P1 14

DYSTONIA IN EUROPE: A SURVEY TOWARDS DIAGNOSIS AND THERAPY FROM A PATIENTS' PERSPECTIVE

Maja Relja (University of Zagreb Medical School), Dirk Dressler (Hannover Medical School, DE), Alberto Albanese (Humanitas Research Hospital Rozzano Milan, Italy), Franceska Morgante (St George's University London, UK), Vladimir Trkulja (University of Zagreb Medical School)

Introduction: Although an under-diagnosed condition, dystonia syndromes (DS) represent the third most common disorder in movement disorder centres We have reported a lack of specific training in dystonia by general neurologist and family doctors (Valadas et al. Eur J Neurol 2016). But there are no data of care from a patients' perspective. Our aim was to investigate diagnosis, treatment and quality of life (QoL) of dystonia patients in Europe using patients' on-line questionnaire

Material and Methods: The validated on-line questionnaire (available in 24 languages on Dystonia Europe web site) was distributed to dystonia patients. Questionnaire was divided into three parts (I. General questions: name, age etc. II.

Specific questions: type of dystonia, time to correct diagnosis etc. III. Therapy, quality of life, etc.). Data were collected from 2017- 2019.

Results: A total 3120 questionnaire were received from 30 countries. Women outnumbered men by about 3 to 1, while cervical dystonia was the most common type (48%) followed by generalised dystonia (15%). Only 24% patients obtained a correct diagnosis within one year after first symptoms, while 14% waited longer than 10 years. Consequently therapy was delaied. Botulinum toxin was the most common type of treatment (45% of patients) followed by drugs and DBS. But only 30% of patients are satisfied with treatment.

Conclusions: First European online questionnaire in dystonia patients shows a long interval to diagnosis and treatment and consequently pure QoL of dystonia patients. Early dystonia is important for patient treatment and QoL.

P1 15

ASPARAGINASE ACTIVITY IN ALL TREATMENT

Lovrić M (Department of Laboratory Diagnostics, University Hospital Centre Zagreb and Faculty of Pharmacy and Biochemistry, University of Zagreb and School of Medicine, University of Zagreb), Glasovac D (Department of Laboratory Diagnostics, University Hospital Centre Zagreb), Jelić M (Department of Pediatrics, University Hospital Centre Zagreb), Ščavničar A (Department of Laboratory Diagnostics, University Hospital Centre Zagreb), Bilić E (. School of Medicine, University of Zagreb and Department of Pediatrics, University Hospital Centre Zagreb), Rogić D (Department of Laboratory Diagnostics, University Hospital Centre Zagreb and Faculty of Pharmacy and Biochemistry, University of Zagreb)

Introduction

Asparaginase plays an important role in the treatment of pediatric acute lymphoblastic leukemia (ALL). The drug starves leukemic cells by converting extracellular asparagine which is essential for these cells. Therapeutic drug monitoring of asparaginase activity can accurately determine if a patient has reached adequate depletion of asparagine (asparaginase activity > 100 U/L).

Materials and methods

Using a gradient fluorescence HPLC assay, the enzymatic activity was quantified by measurement of the asparagine acid produced after incubation of plasma samples with asparagine.

Results

A ten-year-old girl with diagnosis of acute lymphoblastic leukemia (“pre-B” ALL) was treated in Department of Pediatrics, UHC Zagreb, according to protocol ALL-IC-BFM 2009. The asparaginase activities measured after the first and second dose were: after 7 days 534 and 236 U/L; after 14 days 152 and 40 U/L, respectively. For comparison, the median of the asparaginase activity after 7 days for other patients was 781 U/L, and after 14 days it was 423 U/L. On the 105th day of the treatment protocol, the patient received the third dose of asparaginase and developed symptoms of an allergic reaction during administration (the asparaginase activity was lower than the lower limit of quantitation, < 20 U/L).

Conclusions

The results presented in the case report suggest inadequate asparaginase activity in induction, but it is questionable whether it is silent inactivation and/or increased clearance due to the inflammatory state that was present. Given the low predictive value of one sample for evidence of silent inactivation, the third dose was administered with high caution for an allergic reaction which ultimately occurred.

P1 16

THE EFFECTS OF PROLONGED ANTISEPTIC USE DURING COVID-19 PANDEMIC ON SKIN PARAMETERS

Darko Modun (Department of Pharmacy, University of Split School of Medicine, Split, Croatia), Ivana Bročić (Department of Pharmacy, University of Split School of Medicine, Split, Croatia), Mislav Mićanović (Department of Pharmacy, University of Split School of Medicine, Split, Croatia), Josipa Bukić (Department of Pharmacy, University of Split School of Medicine, Split, Croatia), Doris Rušić (Department of Pharmacy, University of Split School of Medicine, Split, Croatia), Ana Šešelja Perišin (Department of Pharmacy, University of Split School of Medicine, Split, Croatia), Dario Leskur (Department of Pharmacy, University of Split School of Medicine, Split, Croatia)

Introduction: The global coronavirus disease pandemic has put an enormous burden on healthcare workers who faced the increased workload with limited resources, mental exhaustion, stress and a risk of acquiring an infection. Further, there was an increased need to wear protective equipment and practicing hygiene measures such as more frequent use of antiseptics. These measures can lead to changes in the skin, the development of new or exacerbation of an existing inflammatory skin disease.

The aim of the study was to determine the changes in the skin parameters after the prolonged use of antiseptics, with and without emollient cream treatment.

Materials and methods: Adult participants who had no active skin disease or damage and gave written informed consent were recruited. Effects of the antiseptic use were determined using the repeated exposure model. Antiseptic was applied daily, for three weeks, to the both volar forearms of the participants under occlusion with Finn chambers. One volar forearm was treated with commercially available emollient cream while the other was left untreated. Skin transepidermal water loss - TEWL, hydration and erythema were followed for five weeks.

Results: Antiseptic elevated the TEWL values ($F(1, 22)=6.743$; $p=0.0165$) signifying skin barrier disruption and lowered the skin hydration values ($F(1, 22)=13.97$; $p=0.0011$), in comparison to undamaged skin. Emollient treatment significantly improved the skin hydration when applied daily after the antiseptic ($F(1, 22) = 24.19$; $p<0.001$).

Conclusions: Prolonged antiseptic use negatively affected the skin parameters while the emollient cream improved some parameters after the concomitant use with antiseptics.

P1 17

NON-INTERVENTIONAL PILOT STUDY EVALUATING THE EFFICACY AND SAFETY OF LYSOZYMEBASED THERAPY IN PATIENTS WITH NON-INFECTIOUS SORE THROAT

Selma Karakas (Javna ustanova Zavod za medicinu rada Kanton Sarajevo), Dzenana Huduti (Javna ustanova Zavod za medicinu rada Kanton Sarajevo), Meliha Mehic (Bosnalijek d.d.), Aziz Sukalo (Bosnalijek d.d.), Jasna Dzananovic Jaganjac (Bosnalijek d.d.), Amna Tanovic Avdic (Bosnalijek d.d.), Amira Skopljak (Javna ustanova Dom zdravlja Kanton Sarajevo), Azra Dupovac (Javna ustanova Dom zdravlja Kanton Sarajevo), Zehra Sarajlic (Klinika za bolesti uha, nosa i grla sa hirurgijom glave i vrata kliničkog centra univerziteta Sarajevo), Una Glamoclija (Bosnalijek d.d.), Samra Limo (Javna ustanova Zavod za zdravstvenu zaštitu zaposlenika ministarstva unutrašnjih poslova kantona Sarajevo)

lntroduction: This study aimed to evaluate the efficacy and safety of lysozyme-based oral antiseptic in the therapy of noninfectious sore throat in teachers.
Materials and Methods: A non-interventional, prospective, pilot study was conducted with two examinations. The first was performed as part of a general medical examination. If a non-infectious sore throat was confirmed by clinical checkup and all other inclusion and non-exclusion criteria confirmed, patients were offered to be enrolled in the study. After signing the informed consent form, patients were advised to use lysozyme-based lozenges, six times a day, for a period of five days.
A telephone call follow-up examination was performed within 24 hours from the therapy completion. Results: The study involved 25 adult patients of both genders. Lysozyme-based lozenges showed positive effects in relieving the symptoms of non-infectious sore throat in teachers. At the same time, the lozenges showed excellent tolerability, and no side effects were reported during the study. 92% of patients confirmed they would take the same medicine again due to the same problem.
Conclusion: The results of this “proof-of-concept” study indicated that lysozyme-based antiseptic could be effective and safe in the treatment of non-infectious sore throat in teachers and should be further evaluated as a treatment option in this condition.

P1 18

THE EFFECTS OF TOPICAL APPLICATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS ON THE CONCENTRATION OF IMMUNE PARAMETERS IN A MODEL OF COLLAGEN-INDUCED ARTHRITIS – RESEARCH PLAN

Sanita Maleškić Kapo (University of Sarajevo, Medical Faculty, Department of Pharmacology, Toxicology and Clinical pharmacology), Maida Rakanović-Todić (University of Sarajevo, Medical Faculty, Department of Pharmacology, Toxicology and Clinical pharmacology), Lejla Burnazović-Ristić (University of Sarajevo, Medical Faculty, Department of Pharmacology, Toxicology and Clinical pharmacology), Loga-Zec Svjetlana (University of Sarajevo, Medical Faculty, Department of Pharmacology, Toxicology and Clinical pharmacology), Jasna Kusturica (University of Sarajevo, Medical Faculty, Department of Pharmacology, Toxicology and Clinical pharmacology), Samra Limo (Institute for health protection of employees of Ministry of interior affairs of Sarajevo Canton), Aida Kulo Ćesić (University of Sarajevo, Medical Faculty, Department of Pharmacology, Toxicology and Clinical pharmacology)

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and cartilage destruction. Animal models are used to evaluate the mechanisms involved in the pathogenesis of the disease, but also predict the potency of topically applied nonsteroidal anti-inflammatory drugs (NSAIDs). The aim of the study is to evaluate the effect of topical application of NSAID on the concentration of tissue immune parameters in collagen-induced arthritis in Wistar rats.
Materials and Methods: Bovine collagen type II and Freund's Incomplete Adjuvant will be used for induction of arthritis and 0,9% NaCl for contol group. RA will be induced in rats by subcutaneous injection of with type II collagen.
Subsequently, patches containing diclofenac, ketoprofen, piroxicam or placebo will be applied after randomization. The tissue level of interleukin 17 (IL-17), prostagladine E2 (PGE2) and the transporter signal transducer 3 (STAT3) will be determined using the ELISA method after the animals are sacrified. Statistical data processing will be performed using the SPSS Statistics v 20.0 software.
Results: This study should provide an insight into the changes in the concentration of tissue immune factors (IL-17, STAT3, PGE2). It will indicate the potential efficacy and pathway of action of NSAID in the collagen-induced arthritis model.
Also, differences in concentrations compared to the administered drug may affect the selection of one of the three NSAILs tested as the first choice drug.
Conclusion: The obtained results will provide additional knowledge of the impact of immunological parameters on the pathophysiology of the disease.

P1 19

NO FEAR TO EXPLORE THE UNSAFE WITH CEFTRIAXONE!

Ante Tvrdeić (University in Zagreb, School of Medicine, Department of Pharmacology, Zagreb), Branko Miše (University Hospital for Infectious Diseases “Fran Mihaljević”, Zagreb), Alen Babacanli (Clinical Hospital “Sisters of Mercy”, Zagreb), Ljiljana Poljak (University in Zagreb, School of Medicine, Department of Physiology and Immunology, Zagreb)

Antibiotic ceftriaxone enhances the expression of GLT1 glutamate membrane transporter in the brain and decreases the availability of synaptic glutamate. To investigate whether this anti glutamate effect of ceftriaxone could modulate anxiety, we used elevated plus maze (EPM) and elevated T maze (ETM) tests. EPM is a plus sign shape elevated 60 cm from the floor with two opposite enclosed arms (50x10 cm with 30 cm high walls) vertical to two opposite open arms (50x10 cm) and intersection zone (10x10 cm). The individual rat was left in the intersection zone to investigate EPM for 5 minutes.
Avoidance of open, unsafe arms in EPM suggests anxiety. ETM is the same as EPM with one blocked enclosed arm.
ETM measure avoidance behaviour in 4 subsequent avoidance sessions and escape behaviour in 4 escape sessions. In the avoidance ETM session, the rat starts at the distal end of the enclosed arms. But in the escape ETM session at the distal end of the open arms. Both avoidance and escape individual sessions last 5 minutes. We assigned 21 or 22 male Wistar rats for ETM or EPM in groups treated with ceftriaxone (200 mg/kg IP., 1 x daily in 9 days) or saline (5mL/kg IP.).
Behavioural data were collected and analysed by camera and video tracking software Any maze 4.82. Results revealed that ceftriaxone significantly increases exploration behaviour (number of head dipping) in unsafe zones of EPM (open arms and intersection zone) without influencing avoidance, escape, locomotion or defensive behaviour in EPM or ETM.

P1 20

ELEVATED C MAZE - TO TEST OR NOT TO TEST IN THE MORNING?

Ante Tvrdeić (University in Zagreb, School of Medicine, Department of Pharmacology, Zagreb), Branko Miše (University Hospital for Infectious Diseases “Fran Mihaljević”, Zagreb), Alen Babacanli (Clinical Hospital “Sisters of Mercy”, Zagreb), Ljiljana Poljak (University in Zagreb, School of Medicine, Department of Physiology and Immunology, Zagreb)

To find out whether different testing periods during an active (dark) phase of the day might modulate anxiety-like behaviour in an elevated C maze (ECM), we assigned 30 male Wistar rats to groups of 10 animals tested in ECM during the morning (10-12 hrs), early afternoon (14-16 hrs) or late afternoon (18-20 hrs). ECM have the shape of the letter C, it is 80 cm elevated from the floor, enclosed in the middle third (22 cm long, 15 cm wide) with two side walls of 30 cm in height. Two-thirds of the maze (each 22 x15 cm) are open, without walls. For testing, individual rats were allowed to freely explore ECM for 5 minutes. Behaviour data were collected and analysed by camera and video tracking software Any maze 4.82. Results showed that independent of testing time, rats had a significantly higher number of entrances, spend more time and travel a longer distance in the safe, enclosed zone of ECM as compared to unsafe open zones. Also, we
found no differences in horizontal or vertical rat locomotion in ECM or ECM zones. But freezing time (defensive behaviour) was longer in the morning and early afternoon than in the late afternoon for ECM. In the enclosed ECM zone, the number of faecal boli (a sign of emotionality), the number of head dipping (exploration) and the number of entrances (avoidance) were lower during the morning and early afternoon testing period. In conclusion, testing of Wistar rats during different periods within the active (dark) phase of the day might modulate anxiety-like behaviour in ECM.

P1 21

COX-2 RS689466 POLYMORPHISM AND METABOLIC SYNDROME-RELATED PARAMETERS AMONG MEDICATED SCHIZOPHRENIA PATIENTS

Zatković L (Hospital pharmacy, Clinical Hospital Center Rijeka, Rijeka, Croatia), Nadalin S (Department of Psychiatry, General Hospital "Dr. Josip Benčević", Slavonski Brod, Croatia), Dević Pavlić S (Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Peitl V (Department of Psychiatry, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia and Faculty of Medicine, Catholic University of Croatia, Zagreb, Croatia), Karlović D (Department of Psychiatry, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia and Faculty of Medicine, Catholic University of Croatia, Zagreb, Croatia), Rebić J (Psychiatry Clinic, Clinical Hospital Center Rijeka, Rijeka, Croatia), Buretić-Tomljanović A (Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

Introduction: Altered dopaminergic neurotransmission and metabolic disturbances, such as weight gain, lipid disturbance, and glucose dysregulation are frequently observed in schizophrenia individuals. Antipsychotic medications have also been causatively linked to metabolic disturbances in schizophrenia. The use of selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib, has been reportedly associated with favourable effects on dopaminergic neurotransmission and insulin sensitivity. Functional rs689466 polymorphism (A/G polymorphism) of the COX-2 gene has been extensively investigated in schizophrenia. We previously reported that female smokers with schizophrenia from the Croatian population carrying the COX-2-G allele (COX-2-GG homozygous and COX-2-AG heterozygous) manifested an earlier disease onset. We also found that schizophrenia individuals under antipsychotic treatment carrying the COX-2-G allele manifested higher skin flush response to niacin and that schizophrenia individuals manifesting higher skin flush response to niacin had higher plasma triglyceride levels. Therefore, here we investigated whether metabolic syndrome-related parameters such as body mass index (BMI) and fasting plasma total cholesterol, LDL cholesterol, HDL cholesterol and glucose levels might be influenced by the COX-2 polymorphism among medicated schizophrenia patients.
Materials and methods: Genotyping was performed by polymerase chain reaction/restriction fragment length polymorphism analysis for 275 patients (males/females: 143/132).
Results: We observed no significant associations between COX-2 polymorphism, BMI, and plasma lipid and glucose levels in any male or female patients ($p > 0.05$, respectively).
Conclusions: Our results indicate that COX-2 polymorphism may not be of relevance in determining metabolic syndrome-related parameters among medicated schizophrenia patients.

P1 22

THE EFFECTS OF MODERATE RED WINE CONSUMPTION ON ARTERIAL STIFFNESS AND HEMODYNAMIC PARAMETERS IN TYPE 2 DIABETES MELLITUS

Ivana Mudnić (Department of Basic and Clinical Pharmacology University of Split School of Medicine), Jurica Nazlić (Department of Basic and Clinical Pharmacology University of Split School of Medicine; Department of Internal Medicine University Hospital of Split), Zvonimir Boban (Department of Biophysics University of Split School of Medicine), Diana Gujinović (Department of Basic and Clinical Pharmacology University of Split School of Medicine), Ana Marija Dželalija (Department of Basic and Clinical Pharmacology University of Split School of Medicine), Mladen Boban (Department of Basic and Clinical Pharmacology University of Split School of Medicine)

Introduction

Assessment of carotid-femoral pulse wave velocity (PWV), a direct measure of arterial stiffness, could serve as useful tool in the early detection of type 2 diabetes mellitus (T2DM) patients at high risk of cardiovascular events. Moderate red wine consumption has been linked to cardiovascular benefits among both healthy persons and diabetic patients.

We aimed to determine whether the daily intake of a 300 ml of red wine for 3 weeks affect PWV and hemodynamic parameters in T2DM patients.

Subjects and Methods

In the 5-weeks cross-over interventional trial of 18 T2DM participants we assessed changes in PWV and hemodynamic parameters (heart rate, peripheral and central systolic, diastolic and pulse pressures). All participants underwent an initial 2 weeks-drive in period with no alcohol consumption (baseline) followed by 3-weeks of wine consumption period. The measurements were performed at the end of each period by applanation tonometry using the SphygmoCor® device.

Results

Moderate RW consumption was associated with significant decrease in PWV from 7.42±1.44 m/s at baseline to 6.98±1.44 m/s at the end of wine consumption period. Peripheral arterial diastolic pressure also decreased from baseline 79.72±11.47 mmHg to 76.39±11.15 mmHg at the end of wine consumption period.

Conclusion

In a cohort of diabetic patients without clinical symptoms of cardiovascular disease, relatively short period of moderate red wine consumption resulted in improvement of cardiovascular hemodynamics.

P1 23

THE PROTECTIVE ACTIONS OF DHEA/S AND BDNF IN AN IN VITRO MODEL OF PARKINSON'S DISEASE

Tina Miloš (Ruder Boskovic Institute), Barbara Vuić (Ruder Boskovic Institute), Nora Bacelj (Ruder Boskovic Institute), Gordana Nedić Erjavec (Ruder Boskovic Institute), Lucija Tudor (Ruder Boskovic Institute), Marcela Konjevod (Ruder Boskovic Institute), Dubravka Švob Štrac (Ruder Boskovic Institute), Matea Nikolac Perković (Ruder Boskovic Institute)

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disorder that is characterized by the degeneration of dopaminergic neurons in the substantia nigra. Inducing an in vitro model of PD is a valuable tool for investigating the mechanisms involved in pathogenesis of disease, which is the key to identifying potential therapeutic strategies for PD. Rotenone and 6-hydroxydopamine are neurotoxins commonly used to generate the in vitro model of PD. Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), and brain-derived neurotrophic factor (BDNF) are involved in neuroprotection and neuroregeneration, while their levels decrease with age and in neurodegenerative diseases such as PD. The aim of this study was to investigate potential neuroprotective actions of these agents in an in vitro model of PD.
Materials and methods: Primary mouse neurons derived from C57BL/ 6 mice embryos and rat dopaminergic N27 cell line were injured with rotenone or 6-hydroxdopamine to induce in vitro model of PD. Both cell cultures were treated with DHEA(S) and BDNF, separately and combined, 16 h before injury. Alterations in cell viability were analyzed using the MTT test while oxidative stress parameters were determined using Cellular ROS Assay Kit 2',7'-dichlorofluorescein diacetate (DCFHDA). Fluorescent dyes Hoechst 33342 and Propidium Iodide were used for staining apoptotic and necrotic cells.
Results: Induced injury by rotenone or 6-hydroxydopamine showed lower metabolic activity and higher ROS levels, while DHEA(S), BDNF showed neuroprotective effect separately or combined on both cell cultures.
Conclusion: Our results suggest that DHEA(S) and BDNF may play important role in prevention and treatment of PD.

P1 24

MOLECULAR MECHANISMS OF THE RENAL EFFECT OF EMPAGLIFLOZIN ON LLC-PK1 CELLULAR MODEL OF DIABETIC NEPHROPATHY

Mihaljević V (Department of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia and Department of Pharmacology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Omanović Kolarić T(Department of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia and Department of Pharmacology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Smolić M (Department of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia and Department of Pharmacology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Kuna L (Department of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia) Kizivat T (Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Osijek, Osijek, Croatia and Department for Nuclear Medicine and Oncology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Petrović A (Department of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Smolić R (Department of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Včev A (Department of Pathophysiology, Physiology and Immunology, Faculty of Dental Medicine and Health Osijek, J.J. Strossmayer University of Osijek, Osijek), Bilić Ćurčić I (Department of Pharmacology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia and Department of Diabetes, Endocrinology and Metabolism Disorders, University Hospital Osijek, Osijek, Croatia)

Introduction: Diabetic nephropathy (DN) is a major cause of chronic kidney disease and end-stage renal failure. In this study, the effects of empagliflozin (SGLT2i) on cell viability and oxidative stress were investigated in the LLC-PK1 model of DN.
Materials and methods: Cells were exposed to high glucose (HG30 mM) followed by 0.5 mM H_2O_2 and a combination of glucose and H_2O_2 for 24 hours. Cells were treated with various combinations of glucose and empagliflozin (100 and 500 nM) and combinations of glucose, H_2O_2, and empagliflozin. Colorimetric MTT assay was used to determine cell viability. Glutathione (tGSH) and TGF-β1 concentrations were measured using a spectrophotometric/microplate assay and an ELISA kit, respectively.
Results: After initial exposure of cells to glucose and oxidative stress, addition of both concentrations improved cell viability and also increased the accumulation of GSH concentration ($p < 0.001$, $p < 0.05$). In addition, empagliflozin treatment caused a decrease in TGF- β1 levels in both concentrations of injured cells ($p < 0.001$).
Conclusions: Cellular viability indicates that empagliflozin has a protective effect on renal injury. The renoprotective effect of empagliflozin is mainly mediated by the reduction of antioxidant stress and the antifibrotic properties of the drug.

P1 25

EFFECTS OF DIFFERENT DOSES OF PIOGLITAZONE ON NEURONAL DAMAGE, INFLAMMATION AND MOTOR PERFORMANCE FOLLOWING TRAUMATIC BRAIN INJURY IN THE RAT

Petra Dolenec (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Željko Župan (Department of Anesthesiology, Reanimatology and Intensive Care Medicine, Faculty of Medicine, University of Rijeka, Rijeka, Croatia; Clinics of Anesthesiology and Intensive Care Medicine, Clinical Hospital Center Rijeka, Rijeka, Croatia), Gordana Župan (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

Introduction: Pioglitazone, agonist of the peroxisome proliferator-activated receptor-gama, has shown to exhibit beneficial effects in various animal models of brain injury. This study was performed to determine effects of pioglitazone on the cortical damage and activation of the glial cells, as well as on motor performance following traumatic brain injury (TBI) in the rat. Methods: TBI of moderate severity was performed over the left parietal cortex using the lateral fluid percussion brain injury model. Animals were i.p. injected with either pioglitazone (1 or 3 mg/kg) or vehicle 10 minutes, 12, 24 and 48 hours after the TBI. Motor functions were evaluated at post-injury day (PID) 1, 2 and 3 using the modified neurological severity score (mNSS) and rotarod test (RRT). Rats were sacrificed 72 h after TBI and their brains were prepared for histologic analyses. Sham-operated used as the control group. Results: Brain trauma caused significant neuronal loss, apoptosis, astrocytosis and microgliosis. Pioglitazone treatment exerted significant effects on astrocytes and microglia but didn't effect apoptotic changes and neuronal loss. All brain-injured animals exhibited statistically significant decrease in the overall motor functioning in mNSS and RRT, with pioglitazone having some limited effects on RRT performance on PID3. No significant differences between the different doses of pioglitazone were detected. Conclusions: Preliminary results of our study imply beneficial effects of pioglitazone on inflammatory reaction, limited effects on motoric performance and no effects on the neuronal loss and apoptosis in traumatized rats in used experimental conditions. This work was supported by project uniri-biomed-18-204 to PD.

P1 26

CHARACTERIZATION OF ASTROCYTIC RESPONSE TO EXPOSURE TO CHEMICALLY FUNCTIONALIZED SINGLE-WALLED CARBON NANOTUBES IN AN *IN VITRO* STRECH INJURY MODEL

Anja Harej Hrkać (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka), Nika Gržeta (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka), Tea Mladenić (Department of Biology and Medical Genetics, University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Ivana Jurički (Combino Pharm Malta Ltd., Birżebbuġa, Malta), Vladimir Parpura (Department of Neurobiology, Heersink School of Medicine, University of Alabama at Birmingham), Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka)

One of the most commonly used nanomaterials, carbon nanotubes (CNTs), specifically single-walled CNTs (SWCNTs) might be a promising material for biomedical applications. Chemical functionalization of SWCNTs with polyethylene glycol (PEG) or poly-m-amynobenzene sulfonic acid (PABS) makes them more soluble in aqueous solutions, which is necessary for their application in the brain tissue e.g. after traumatic brain injury (TBI). Our research aimed to evaluate the effects of the PEG- and PABS-SWCNTs colloid solutes on the mouse astrocytes in an in vitro TBI model.
Primary mouse astrocytes were severely injured by rapid stretching, and SWCNTs were added to the cell culture medium one hour following injury. Injured and non-injured untreated cells were used as the TBI and the control groups, respectively. Astrocytes' survival rates within the first 24 h were determined by lactate dehydrogenase assay. Changes in the protein expression of glial marker GFAP and glutamate transporter EAAT1 were measured by western blotting, and the cytokine/chemokine secretion profiles were evaluated by microarray.
The main results of our studies are that both types of SWCNTs had no significant effect on the astrocytes' survival rate, with differing effects on the GFAP and EAAT1 expressions as PEG-SWCNTs caused an increase in EAAT1, and PABS-SWCNTs enhanced GFAP expression. Injured astrocytes exposed to PEG-SWCNTs released more of the anti-apoptotic and neurotrophic factor GM-CSF compared to both control and non-treated injured cells, while the PABS-SWCNTs stimulated the release of the RANTES chemokine.
Results of this study suggest that SWCNTs cause molecular changes in astrocytes exposed to in vitro TBI, altering the expression of EAAT1 and GFAP and influencing the secretory function of these cells. This research was fully supported by the Croatian Science Foundation grant UIP-2017-05-9517 to KP.

P1 27

THE EFFECTS OF REPETITIVE MILD TRAUMATIC BRAIN INJURY ON SOME PROTEINOPATHY SUSCEPTIBLE PROTEINS IN THE MOUSE FRONTAL CORTEX

Tamara Janković (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Croatia), Nika Gržeta (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Croatia), Jelena Rajič Bumber (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Croatia), Petra Dolenec (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Croatia), Jasna Križ (Department of Psychiatry and Neuroscience, University Laval, Faculty of Medicine, Quebec, Canada), Gordana Župan (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Croatia), Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Croatia)

Introduction: Traumatic brain injury (TBI) is an important healthcare problem leading to lifelong repercussions that burden society. Primary brain injury is irreversible, but secondary TBI includes many pathophysiological processes, including the development of proteinopathies that contribute to cognitive impairment. This study aimed to investigate the expression of amyloid-beta precursor protein (APP), phosphorylated Tau protein (pTau) and TAR-DNA binding protein 43 (TDP-43) in the frontal cortex of C57BL/6 mice 14 days after mild repetitive traumas. Selected proteins are susceptible to pathological misfolding and are proven to contribute to the clinicopathological spectrum of dementias developing after TBI.

Materials/Methods: Repetitive mild brain traumas were applied by the weight drop method, twice per day, 5 days in a row. Injured animals were sacrificed 14 days after the last brain trauma and their frontal cortices were prepared for western blot or immunohistological analyses. Control group of animals were sacrificed one day after the sham injury procedure.

Results: At 14 days post-injury, a significant increase in the cortical expression levels of total and mature APP was detected, while pTau positive cells were not found. A significant increase in the TDP-43 levels was detected only in the nucleus, but cytoplasmic mislocalization and phosphorylation were not found after mild repetitive TBI.

Conclusions: Our preliminary results showed that repetitive brain traumas lead to changes in APP levels at 14 days, without the formation of pathological pTau and TDP-43 species. This work was supported by the University of Rijeka, Croatia, project-uniri-biomed-18-199 to K.P. and Croatian Science Foundation project-IP-2016-06-4602 to GŽ.

P1 28

THE ROLE OF CLINICAL PHARMACOLOGIST IN ASSESSMENT OF CONTRAINDICATIONS FOR VACCINATION AGAINST COVID-19

Strujić E (Faculty of Medicine Osijek,Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Pastović M (Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Petrinović M (Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Mimica S (Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia and University Hospital Centre Osijek, Clinic of Internal Medicine, Department of Clinical Pharmacology, Osijek, Croatia)

Introduction: In cases of possible contraindications to vaccination against COVID-19 epidemiologists and general practitioners have referred patients to our clinical pharmacology department for evaluation.
Materials and methods: We performed a cross-sectional study with historical data. Overall, 137 patients referred between November 2021 and February 2022 for assessing possible contraindications to vaccination against COVID-19 were included.
Results: The study included 108 (78.8%) women and 29 (21.2%) men. Majority of the patients, 106 (77.4%) were referred to the Department of Clinical Pharmacology before vaccination against COVID-19 and 31 (22.6%) after previous vaccination against COVID-19. The most common referral diagnoses were suspected side effects of previously received vaccine against COVID-19, hypersensitivity to other allergens and medicines, and coagulation disorders. Only for 27 (19.7%) assessed patients the conclusion was that there was an absolute or relative contraindications for the COVID-19 vaccine. Among those patients, the majority developed a side effect to a previously received vaccine against COVID-19 (24/27). The patients with thrombophilia were mostly recommended to receive mRNA or protein vaccines, while for almost all patients with previous allergies to medications it was concluded that there was no contraindication for the vaccination. After receiving the expertise of a clinical pharmacologist, only 25 (18.2%) patients were eventually vaccinated against COVID-19.
Conclusion: Majority of the patients did not have any contraindications for the COVID-19 vaccine. Therefore, they were needlessly referred to the Department of Clinical Pharmacology. After clinical pharmacologist's evaluation, a small number of patients received COVID-19 vaccine.

P1 29

PROCEDURES AT SUSPECTED HYPERSENSITIVITY TO LOCAL ANESTHETICS

Petrinović M (Faculty of Medicine, J.J. Strossmayer University of Osijek, Croatia), Strujić E (Faculty of Medicine, J.J. Strossmayer University of Osijek, Croatia) Pastović M (Faculty of Medicine, J.J. Strossmayer University of Osijek, Croatia) Mimica S (Faculty of Medicine, J.J. Strossmayer University of Osijek, Croatia and University Hospital Center Osijek, Department of Clinical Pharmacology, Osijek, Croatia)

Introduction: Hypersensitivity reactions account for less than 1% of all adverse reactions to local anesthetics. Skin tests used to diagnose hypersensitivity are prick and intradermal tests, followed by subcutaneous exposure.
Materials and methods: This cross-sectional study included patients who were tested for hypersensitivity to local anesthetics in Clinical Pharmacology outpatient clinic in the period from October 2016 to the end of December 2020. The total number of subjects was 73. The data collected from medical records for each patients included demographic dana, with comorbidities, data on hypersensitivity to other allergens and other groups of drugs, description of previous adverse reactions to local anesthetic, time interval from reaction to testing and outcomes of skin tests and subcutaneous exposure. Local anesthetics considered in this study were lidocaine, articaine, bupivacaine, levobupivacaine and mepivacaine. The collected data were analyzed in relation to the outcome of skin testing.
Results: Among the observed subjects, the most common adverse reaction to local anesthetics for which they were referred for testing were skin changes. Although the percentage of positive tests was very low (3 %), a higher percentage of positive intradermal tests is recorded compared to the prick tests, with the highest number of positive intradermal tests for articaine. Subcutaneous exposure was well tolerated in all subjects.
Conclusion: This study confirmed that the frequency of positive skin test results for hypersensitivity to local anesthetics was low, i.e. that true hypersensitivity to local anesthetics is extremely rare.

POSTER SESSION 2 WITH ORGANIZED DISCUSSION

Chairpersons: Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Croatia), Pero Draganić (Agency for Medicinal Products and Medical Devices of Croatia (HALMED), Zagreb, Croatia), Viktorija Erdeljić Turk (Division of Clinical pharmacology, Department of Internal medicine, University Hospital Centre Zagreb, Zagreb, Croatia)

P2 01

NEUROPROTECTIVE ACTIONS OF DHEA AND DHEAS IN PRIMARY MOUSE NEURONS AND SHSY5Y CELLS EXPOSED TO TOXIC AMYLOID BETA OLIGOMERS

Barbara Vuić (Ruder Boskovic Institute, Zagreb, Croatia), Tina Milos (Ruder Boskovic Institute, Zagreb, Croatia), Matea Nikolac Perković (Ruder Boskovic Institute, Zagreb, Croatia), Gordana Nedić Erjavec (Ruder Boskovic Institute, Zagreb, Croatia), Lucija Tudor (Ruder Boskovic Institute, Zagreb, Croatia), Marcela Konjevod (Ruder Boskovic Institute, Zagreb, Croatia), Nela Pivac (Ruder Boskovic Institute, Zagreb, Croatia), Dubravka Švob Štrac (Ruder Boskovic Institute, Zagreb, Croatia)

Introduction: Alzheimer´s disease (AD) is neurodegenerative disease characterized by cognitive impairment and progressive synaptic damage accompanied by neuronal loss. The causes of amyloid beta aggregation that form amyloid plaques in the pathogenesis of AD has been debated for more than 25 years and it is supposed that amyloid beta oligomers may be the toxic factors acting on a very early stage of AD. Currently available therapy provides only symptomatic treatment, while many studies of new effective drugs have so far been unsuccessful. Therefore, neurosteroids dehydroepiandrosterone (DHEA) and its sulfated form dehydroepiandrosterone sulfate (DHEAS) are of a great interest
due to their potential to modulate neurogenesis, neuronal growth and differentiation, as well as neuroprotection.
Materials and methods: Neuroprotective effects of DHEA and DHEAS were investigated using primary mouse neurons, isolated from C57BL/6 mice embryos, and human SH-SY5Y neuroblastoma cells simultaneously exposed to toxic amyloid beta oligomers during 24 hours. Various assays (MTT, Muse, Promega) were used to determine cell viability and underlying mechanisms, while GraphPad Prism was used to interpret the obtained results. Results: Our results demonstrated that DHEA and DHEAS exert neuroprotective actions on primary mouse neurons and SH-SY5Y cells exposed to amyloid beta oligomers, probably via anti-apoptotic mechanisms.
Conclusions: These findings suggest that DHEA and DHEAS may have therapeutic effects against amyloid beta toxicity. DHEA(S) could potentially represent novel preventive and/or therapeutic agents for AD in the future. This study needs to be confirmed and extended by further in vitro research and studies using animal models and human samples.

P2 02

OVER-DOSE CAFFEINE TOXICITY IN RATS AND TRETMENT WITH STABLE GASTRIC PENTADECAPEPTIDE BPC 157

Vukovic V (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Sablic M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Krezic I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Antagonist of adenosine A2A receptors, caffeine, during overdosing, manifests convulsions, arrhythmias, muscle spasms, urination etc. In this study, we administered caffeine to the rats at doses close to LD50 and above LD50 (i.e. LD50 for Wistar rats 367 mg/kg (Adamson RH. Regul Toxicol Pharmacol. 2016 Oct;80:274-6. doi: 10.1016/j.yrtph.2016.07.011.)). We observed the effect of stable gastric pentadecapeptide BPC 157 on mitigation of caffeine overdose.
Materials and methods: We used male Wistar rats, weighing 250 g. Caffeine was administered in the solution, intraperitoneally (two groups; the first group - below LD50 (200 mg/kg), the second group - above LD50 (400 mg/kg)). Therapy (BPC 157 (10 ng/kg) or saline (5 ml/kg)) was given intraperitoneally immediately after caffeine. We monitored survival duration of animals, ECG and blood pressures in: inferior caval vein, portal vein, abdominal aorta and superior sagittal sinus as described before (Biomedicines. 2022;10(7):1462).
Results: Before fatal outcome, without therapy, caffeine intoxicated rats exhibited severe brain swelling, portal hypertension, caval hypertension, increased intracranial pressure and aortic hypotension and severe supraventricular arrhythmias and extrasystoles, known to be characteristic for the vascular and multiorgan failure-induced occlusion/occlusion like syndromes recently described following major vessel occlusion and alike noxious procedures (Biomedicines. 2022;10(7):1462). These noxious effects were counteracted in the BPC 157 caffeine rats.
Conclusions: We found beneficial effects of BPC 157 in the treatment of caffeine overdose.

P2 03

THE ASSOCIATION OF PLATELET SEROTONIN (5-HT) AND 5HT2A GENE POLYMORPHISMS WITH ASTHMA

Marcela Konjevod (Ruder Boskovic Institute, Division of Molecular Medicine, Zagreb, Croatia), Katherina Sreter (Department of Clinical Immunology, Pulmonology and Rheumatology, University Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia), Sanja Popovic-Grle (Clinic for Lung Diseases Jordanovac, University Hospital Centre Zagreb, Zagreb, Croatia; School of Medicine, University of Zagreb, Zagreb, Croatia), Marina Lampalo (Clinic for Lung Diseases Jordanovac, University Hospital Centre Zagreb, Zagreb, Croatia), Irena Jukic (Croatian Institute of Transfusion Medicine, Zagreb, Croatia; Josip Juraj Strossmayer University of Osijek, Faculty of Medicine, Osijek, Croatia), Jasna Bingulac-Popovic (Croatian Institute of Transfusion Medicine, Zagreb, Croatia), Hana Safic Stanic (Croatian Institute of Transfusion Medicine, Zagreb, Croatia), Jasenka Markeljevic (Department of Clinical Immunology, Pulmonology and Rheumatology, University Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia; School of Medicine, University of Zagreb, Zagreb, Croatia), Nela Pivac (Ruder Boskovic Institute, Division of Molecular Medicine, Zagreb, Croatia), Dubravka Svob Strac (Ruder Boskovic Institute, Division of Molecular Medicine, Zagreb, Croatia)

Introduction: Asthma is a common, chronic inflammatory disease of the respiratory airways, characterized by an increased contractility of the bronchial smooth muscle cells, mucus hyperproduction and airway hyperresponsiveness. Several studies reported involvement of serotonin (5-HT) and different 5-HT receptors, particularly 5-HT2A receptors in asthma.
The aim of this study was to investigate the association of platelet 5-HT concentrations and 5HT2A gene polymorphisms with asthma.
Materials and methods: This study enrolled 120 asthma patients and 120 healthy subjects. Platelet 5-HT concentrations were determined using the spectrofluorometric method, while genomic DNA was isolated from the peripheral blood by a salting out method. DNA samples were genotyped for the 5HT2A (rs6314 and rs6313) polymorphisms using real-time polymerase chain reaction.
Results: The platelet 5-HT concentrations were significantly decreased in asthma patients compared to healthy subjects. The frequency of 5HT2A rs6314 genotypes, alleles and A vs. GG carriers, as well as frequency of 5HT2A rs6313 genotypes, A vs. GG carriers and G vs. AA carriers were significantly different between asthma patients and healthy subjects. There were no significant differences in the platelet 5-HT concentration and the distribution of 5HT2A rs6314 and rs6313 genotypes, alleles and carriers between patients with different asthma phenotypes (non-severe vs. severe, T2- high vs. T2-low; non-allergic vs. allergic; non-eosinophilic vs. eosinophilic; non-AERD vs. AERD).
Conclusions: Our study demonstrated that asthma patients have lower 5-HT concentration than healthy subjects, whereas 5HT2A gene polymorphisms are associated with asthma. These findings suggest possible involvement of serotonergic system in asthma pathophysiology; however further research is needed.

P2 04

THE EFFECTS OF PHLORIDZIN, A SODIUM-GLUCOSE COTRANSPORTER INHIBITOR IN AN ORAL GALACTOSE-TREATED RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE

Ana Babić Perhoč (Laboratory for molecular neuropharmacology, Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine), Jan Homolak (Laboratory for molecular neuropharmacology, Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine), Ana Knezović (Laboratory for molecular neuropharmacology, Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine), Jelena Osmanović Barilar (Laboratory for molecular neuropharmacology, Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine), Davor Virag (Laboratory for molecular neuropharmacology, Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine), Melita Šalković-Petrišić (Laboratory for molecular neuropharmacology, Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine)

Introduction: A shared pathomechanism is postulated for sporadic Alzheimer's disease (sAD) and metabolic dysfunction in type 2 diabetes mellitus and drugs available for treatment of diabetes are being studied as possible sAD therapy.
Therefore, we aimed to research whether phloridzin, a non-selective sodium-glucose cotransporter inhibitor (SGLTI), may influence metabolic and cognitive parameters in a galactose-treated rat model of sAD.
Materials and methods: 4 groups (N=10) of 3-month-old Wistar rats were randomized to controls (CTR), sAD model induced by intracerebroventricular (icv) administration of streptozotocin (STZ; 3 mg/kg divided in two doses), CTR+SGLTI and STZ+SGLTI. In 2 groups, SGLTI treatment by oral gavage (10 mg/kg) was initiated 1 month after STZ-icv and lasted two months, along with galactose treatment (200 mg/kg in drinking water) in all 4 groups. PET-scan with [18F]-fluorodeoxyglucose and cognitive tests were performed post-treatment and prior to sacrification.
Results: SGLTI treatment failed to correct the cognitive deficit induced by STZ-icv or induce any significant changes in the measured metabolic parameters, including intraperitoneal glucose tolerance test, plasma and CSF glucose, insulin, glucagon-like peptide 1 or glucose-dependent insulinotropic polypeptide levels. However, PET-scans showed increased glucose uptake in galactose-treated STZ-icv rats, which was lowered by SGLTI treatment, at the level of the whole brain, and in the hippocampus and several cortical regions. SGLTI-induced decrements were evident in cerebellum, midbrain, medulla and auditory and visual cortex.
Conclusions: SGLTI treatment in STZ-icv rats on oral galactose does not induce changes in cognitive dysfunction or plasma and CSF metabolic parameters, but alters brain glucose uptake.
This research is co-financed by the Croatian Science foundation (HRZZ-IP-2018-01-8938) and the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxicischemic damage in perinatal and adult brain"; GA KK01.1.1.01.0007 funded by the European Union through the European Regional Development Fund).

P2 05

ANTISTEATOTIC EFFECT OF LIRAGLUTIDE IS MEDIATED THROUGH ACSL1 and SREBP-1c SIGNALING PATHWAY IN A CELL CULTURE MODEL OF TAMOXIFEN-INDUCED STEATOSIS

Tea Omanović Kolarić (University of Osijek, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia and University of Osijek, Faculty of Medicine Osijek, Osijek, Croatia), Vjera Ninčević (University of Osijek, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia), Tomislav Kizivat (University of Osijek, Faculty of Medicine Osijek, Osijek, Croatia and University Hospital Center Osijek, Osijek, Croatia), Lucija Kuna (University of Osijek, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia), Milorad Zjalić (Faculty of Medicine Rijeka, Rijeka, Croatia), Ines Bilić-Ćurčić (University of Osijek, Faculty of Medicine Osijek, Osijek, Croatia and University Hospital Center Osijek, Osijek, Croatia), Robert Smolić (University of Osijek, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia), Hrvoje Roguljić (University of Osijek, Faculty of Medicine Osijek, Osijek, Croatia and University Hospital Center Osijek, Osijek, Croatia), Ana Petrović (University of Osijek, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia), Aleksandar Včev (University of Osijek, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia), George Wu (University of Connecticut Health Center, Farmington, CT, USA), Martina Smolić (University of Osijek, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia and University of Osijek, Faculty of Medicine Osijek, Osijek, Croatia)

Introduction: Nonalcoholic fatty liver disease (NAFLD) has become one of the global health problems. Drugs, such as tamoxifen, may trigger or exacerbate pre-existing NAFLD. The aim of our study was to establish a reliable cell culture model of tamoxifen-induced steatosis (TIS) and to investigate a possible antisteatotic effect of the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide in this model.

Materials and methods: The cell culture model of drug-induced hepatic steatosis was established by incubating Huh7 cells, a human liver cell line expressing the GLP-1 receptor, with 2 µM tamoxifen for 24 hours. Cells were co-treated with 5 nM to 20 nM liraglutide. Cell survival was measured by the erythrosin B staining exclusion assay, and changes in cell shape and the extent of hepatosteatosis were assessed by fluorescence microscopy with Oil-Red-O (ORO) and DAPI staining, respectively. The expression of various lipogenic genes and signals was assessed by RT-PCR.

Results: Tamoxifen significantly decreased cell survival in the TIS model ($p < 0,05$), and concurrent treatment with liraglutide had no significant effect. A 5-fold increase in lipid accumulation was observed by ORO staining in the TIS model ($p < 0,001$), which was due to the significant increase in the number of lipid droplets. However, liraglutide reversed this effect and significantly decreased the number of lipid droplets ($p < 0,05$). Liraglutide co-treatment significantly ameliorated the lipogenic ACSL1 and SREBP-1c gene expression signaling pathways, which were increased in the TIS model ($p < 0,001$).

Conclusions: Liraglutide ameliorates microsteatotic changes observed in TIS model by downregulation of ACSL1 and SREBP-1c gene pathways.

P2 06

IS VASCULAR RESPONSIVENESS OF THE ISOLATED RAT AORTA AFFECTED BY 4 WEEKS OF MODERATE STANDARD AND MACERATED WHITE WINE CONSUMPTION?

Marin Mornar (Department of Basic and Clinical Pharmacology University of Split School of Medicine), Natalija Filipović (Department of Anatomy, University of Split School of Medicine), Marko Grahovac (Department of Basic and Clinical Pharmacology University of Split School of Medicine), Diana Gujinović (Department of Basic and Clinical Pharmacology University of Split School of Medicine), Ana Marija Dželalija (Department of Basic and Clinical Pharmacology University of Split School of Medicine), Ivica Grković (Department of Anatomy, University of Split School of Medicine), Mladen Boban (Department of Basic and Clinical Pharmacology University of Split School of Medicine), Ivana Mudnić (Department of Basic and Clinical Pharmacology University of Split School of Medicine)

Introduction
Biological effects of white, amber-colored macerated white wines rich in polyphenolic content, are rarely investigated.
Therefore, we examined and compared the effects of standard and macerated white wine consumption on rats' vascular responsiveness.
Materials and methods
Male Sprague Dawley rats (N=45) were randomized into 3 groups and subjected to a 4-week consumption protocol: the C group consumed only water, the SW, standard, and the MW, macerated white wine. Following consumption period, the thoracic aortas were isolated, and the vascular rings prepared (N = 107). The C, SW and MW rings were exposed to dose - response vasodilatory or vasoconstriction protocol. Acetylcholine or noradrenaline were applied cumulatively to final concentrations from 1 nM to 10 µM. Maximal vasodilation and vasoconstriction effect (Emax) and the concentration of noradrenaline and acetylcholine that produced 50% of maximal effect (EC50) were evaluated.
Results
Vasodilatory efficacy of acetylcholine was highest in the aortic rings from animals that consumed macerated white wine (Emax in MW 105,2±3,8%) relative to SW (Emax 99,7±3,3%) and C (97,4± 1,6%). Similarly, the potency of acetylcholine was the highest in MW, slightly lower in SW, and the lowest in the C group, with EC50 values of 43 nM, 57 nM and 70 nM, respectively. Noradrenaline-induced vasoconstriction did not differ between the groups.
Conclusion
Moderate consumption of macerated white wine for four weeks resulted in improved vasodilatory capacity of the rat aorta, as evidenced by enhanced endothelium-dependent vasodilatory response to acetylcholine.

P2 07

AWARENESS AND ATTITUDES OF NURSES ABOUT DIET THERAPY AND NUTRITIONAL SUPPORT OF PERSONS WHIT CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN HOSPITAL ENVIROMENT

Zora Kocić (Pharmacy Pablo, Rijeka, Croatia), Tea Fistonić (University of Rijeka, Faculty of Health Studies Rijeka, Croatia), Željko Jovanović (University of Rijeka, Faculty of Health Studies Rijeka, Croatia)

Introduction
In patients with COPD, the quality of care in the area of nutritional support is of particular importance, as it significantly influences treatment outcomes and quality of life. The aim of this study was to investigate nurses' knowledge of nutritional support for people with COPD.
Material and methods
A descriptive cross-sectional survey with 175 respondents conducted in an anonymous survey from November 2020 to April 2021. A hi-squared test was used to check whether the obtained/observed frequencies of respondents' answers to the survey questions differed from the theoretical frequencies that would be expected per case.
Results
The knowledge of the nurses surveyed was below average and 44.6% of them were rated negatively. Mostly they know what kind of diet is recommended for COPD patients, they are not familiar with the composition and effect of the adapted enteral preparation, nor with the differentiation of metabolism, CO_2 production during macronutrient metabolism and the influence on the course, especially in the phase of exacerbation of the disease. Only two subjects consider themselves fully educated about diet therapy and clinical nutrition, 44 (25.1%) consider themselves somewhat educated, and as many as 39 (22.3%) consider themselves totally in need. Subjects are interested in additional education, but indicate that there are currently no ongoing educational programmes within the hospital system for nutritional support for COPD patients.
Conclusion
Knowledge of nutritional support is below average, suggesting that additional education of nurses on diet therapy and nutritional support is needed, both during training and within health facilities through lifelong education and training, which should include dietitians and pharmacists in addition to physicians.

P2 08

PREVALENCE OF ANXIOLYTICS USE BY HEALTH PROFESSIONALS

Željko Jovanović (University of Rijeka, Faculty of Health Studies Rijeka, Croatia and Josip Juraj Strossmayer University of Osijek, Faculty of Medicine, Osijek, Croatia), Sara Pešut (Josip Juraj Strossmayer University of Osijek, Faculty of Medicine, Osijek, Croatia), Zora Kocić (Pharmacy Pablo, Rijeka, Croatia)

Introduction
Stress at work is an important health problem. No less than 44.6% of workers are exposed to risk factors that have a negative impact on health. In order to better tolerate stressful situations, many take anxiolytics. The aim is to determine the extent of stress, the conditions that exacerbate it, the means of prevention, and the prevalence of anxiolytic use by health professionals.
Materials and Methods
Quantitative, descriptive cross-sectional study with a sample of 159 health professionals from the General Hospital, Health Center, and Department of Emergency Medicine in Slavonski Brod.
Results
The majority of health professionals surveyed were satisfied with their lives, but 80.5% found their work stressful, 9.4% sought help due to stress, and 25.8% took anxiolytics to relieve stress, with 43.9% taking anxiolytics several times a month and 5% daily. During work hours, 36.6% of respondents took anxiolytics, and 17.1% felt that it improved the quality of their work that day. 75.6% said that taking anxiolytics helped them to do their work normally.
Conclusions
Healthcare professionals belong to a profession that is exposed to high levels of stress. Contributing to this stress are shift and night work, a tight work schedule and staff shortages, which is why many work overtime, emergencies, caring for the seriously ill and dying, conflicts, and poor work organization. For all these reasons, one in four occasionally takes anxiolytics to function normally at work. It is necessary to provide adequate psychological support to all who need it.

P2 09

PATIENTS ATTITUDES TOWARDS ANTIPSYCHOTIC MEDICATION: A CROSS-SECTIONAL STUDY

Josipa Bukic (University of Split School of Medicine), Doris Rusic (University of Split School of Medicine), Dario Leskur (University of Split School of Medicine), Ana Šešelja Perisin (University of Split School of Medicine), Dora Herceg (University of Zagreb School of Medicine), Tin Cohadzic (University of Split School of Medicine), Darko Modun (University of Split School of Medicine), Miroslav Herceg (University of Zagreb School of Medicine)

lntroduction: Schizophrenia is a serious mental illness that requires the use of pharmacotherapy. Antipsychotics, as a firstline schizophrenia treatment, can often lead to a variety of adverse drug reactions, which can affect patient adherence.
Therefore, the aim of this study was to examine the satisfaction with treatment in patients with schizophrenia and the frequency of drug adverse reactions.
Materials and methods: The study was organised as a cross-sectional, and the sample consisted of patients from the Institute for Psychotic Disorders of Women, Clinic for Psychiatry Vrapče. We used Drug Attitude Inventory (DAI-10) scale to assess patients attitudes towards their medication.
Results: In total, 55 women participated in our study. Their mean age was 49 Years, with standard deviation of 10 Years.
Half of the study participants used first Generation antipsychotic drug and 47.2 % of all participants experienced adverse drug reaction. Only one participant, which accounts for 1.9%, reported the experienced adverse drug reaction to the authority. Patients attitudes mean score was 6.79 (1.47) which reflects positive attitude towards pharmacotherapy.
Conclusions: Our results showed positive attitudes of schizophrenic patients towards the use of antipsychotics. However, frequency of adverse drug reaction reporting practice is very low in this group of patients and health care professionals should address this concern.

P2 10

DO FINAL-YEAR MEDICAL STUDENTS IN CROATIA FEEL SUFFICIENTLY PREPARED TO PRESCRIBE ANTIMICROBIALS PRUDENTLY? – COMPARISON BETWEEN FOUR CROATIAN MEDICAL SCHOOLS

Andrej Belančić (Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, Rijeka, Croatia and University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Dora Palčevski (Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Clinical Hospital Centre Rijeka, Rijeka, Croatia and University of Rijeka, Faculty of Medicine, Rijeka, Croatia), Robert Likić (Division of Clinical Pharmacology, Department of Internal Medicine, Clinical Hospital Centre Zagreb, Zagreb, Croatia and University of Zagreb, School of Medicine, Zagreb, Croatia), Vera Vlahović- Palčevski (Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, Rijeka, Croatia and University of Rijeka, Faculty of Medicine, Rijeka, Croatia and Department of Basic Medical Sciences, Faculty of Health Studies, University of Rijeka, Rijeka, Croatia)

Introduction: Studies have shown that medical graduates feel unprepared for their future antibiotic prescribing task. The aim of this study was to compare self-reported preparedness on responsible antibiotic use of medical graduates in four Croatian medical schools in 2019.
Materials and methods: All final-year medical students (2019 yr. graduates) were eligible to participate in this crosssectional study. For the survey a 47-item questionnaire developed by ESGAP Student-PREPARE Working Group was used. It included questions on demographics, self-reported preparedness on prudent antimicrobial use, perceptions of the usefulness of teaching methods and perceived need for further education.
Results: We received a total of 159 responses. Response rates varied by medical school from 15.71% to 31.33%. Global preparedness scores (GPS; self-reported preparedness regarding prudent antimicrobial use) for Osijek, Zagreb, Rijeka and Split medical schools were: 48.82%, 53.56%, 57.14% and 66.28%, respectively. The average GPS for Croatia in 2019 was 56.45%, with no statistically significant difference compared to 2015 (62.66%). Statistically significant difference was observed for 3/27 curriculum topics on prudent antimicrobial use, all in favor of Split medical students.
Most students (73.68%-100%) reported the need for more/further education on antimicrobial use. Higher self-reported availability/usefulness of interactive teaching methods was reported for Split Medical School.
Conclusions: Croatian medical students, who are about to start prescribing antimicrobials on their own, generally do not feel sufficiently prepared to do so. No noticeable interregional differences were found in self-reported preparedness on prudent antimicrobial use, while greater differences were observed in perceived usefulness of teaching methods between medical schools.
Keywords: antibiotics, antimicrobial stewardship, drug prescribing, education, medical students

P2 11

EFFECTS OF LOW DOSE TETANUS TOXIN INJECTIONS INTO THE RAT MOTOR CORTEX AND BASAL GANGLIA ON MOTOR PERFORMANCE

Patrik Meglić (Department of Pharmacology, School of Medicine, University of Zagreb, Croatia), Petra Šoštarić (Department of Pharmacology, School of Medicine, University of Zagreb, Croatia), Davor Virag (Department of Pharmacology, School of Medicine, University of Zagreb, Croatia), Ivica Matak (Department of Pharmacology, School of Medicine, University of Zagreb, Croatia)

Introduction: Abnormalities in the motor cortex (Mc) and basal ganglia excitability play a central role in movement disorders such as dystonias and parkinsonism. Tetanus neurotoxin (TeNT) prevents the inhibitory neurotransmission in central synapses. The aim of the experiments was to examine the behavioral effect of neuronal disinhibition in mentioned brain regions induced by low, non-convulsive doses of TeNT.
Materials and methods: In the first experiment rats were unilaterally injected into the caudate putamen (CPu) or Mc with 0.5 ng TeNT. The injections were repeated into the contralateral motor regions after 2 weeks, and the effect of TeNT was assessed for another 2 weeks. In the another preliminary experiment, rats were unulateraly injected with 0.5 ng of TeNT into the globus pallidus internus (GPi) and substantia nigra (SN), or SN alone. Different behavioral tests were performed repeatedly to assess the effect of TeNT induced disinhibition on motor performance, as well as to exclude possible epileptogenic action of TeNT.
Results: The Mc or CPu disinhibition with TeNT induces subtle motor impairment during the narrow beam crossing in 50% of treated animals, without signs of epileptogenic action. Animals injected into the GPi and SN, or SN alone, showed ipsilateral circling tendency in open field (50%) and swimming tests (100%).
Conclusion: TeNT injected into defined motor regions can induce motor impairments of different modalities, depending on the site of injection. While subtle motor impairment after CPu and MC disinhibition require aggravation by contralateral regional disinhibition, unilateral GPi od SN disinhibition induced more prominent motor impairment.

P2 12

EXPERIMENTAL FOCAL MUSCLE HYPERTONIA OFFERS NOVEL INSIGHTS INTO MOTOR EFFECTS OF BOTULINUM TOXIN TYPE A

Ivica Matak (Department of Pharmacology, University of Zagreb School of Medicine, Croatia), Patrik Meglić (Department of Pharmacology, University of Zagreb School of Medicine, Croatia), Petra Šoštarić (Department of Pharmacology, University of Zagreb School of Medicine, Croatia)

Introduction: Transient and reversible synaptic silencing by botulinum toxin type A (BoNT-A) is the basis of its therapeutic efficacy and safe use in movement disorders. Based on timing of BoNT-A actions and importance of appropriate muscle targeting, neuromuscular paralysis is considered its main therapeutic effect. Preclinical models have mostly focused on measurement of BoNT-A neuroparalytic effects in normal animals, in contrast to the possibly more relevant models of sustained or intermittent muscle hyperactivity. Moreover, clinical and experimental studies suggested that therapeutic effects of BoNT-A are not entirely explainable by peripheral neuromuscular site of action, suggesting the need for models of muscle hyperactivity.
Results: In a series of experiments, we employed tetanus toxin (TeNT) as an elegant way to disinhibit the motoneuronal activity and evoke focal muscle hypertonia. We found that BoNT-A induces simultaneous and non-mutually exclusive antispastic activity at both peripheral muscular and central spinal level. When separated from muscular action, central trans-synaptic toxin action alone was effective in reducing the experimental muscle spasm. The central antispastic effect is masked by the toxin's peripheral action in the early period post injection, and becomes more prominent as the neuromuscular effect starts to weaken (2 months post BoNT-A). The toxin's activity at peripheral and central sites, as well as the duration of its beneficial antispastic action, was found to be dose-dependent.
Conclusion: Preclinical models recapitulating some of the neurophysiological mechanisms of spastic and hyperkinetic movement disorders may be more helpful at explaining the factors and mechanisms of the BoNT-A’s long term clinical actions.

P2 13

TETANUS NEUROTOXIN ACTS AT THE NEUROMUSCULAR JUNCTION AND ON BRAINSTEM CENTERS THAT CONTROL MUSCLE MOVEMENT, RESPIRATION AND SWALLOWING IN A MURINE MODEL OF CEPHALIC TETANUS

Fabris F (Department of Biomedical Sciences, University of Padua), Varani S (Department of Biomedical Sciences, University of Padua), Tonellato M (Department of Biomedical Sciences, University of Padua), Matak I (Department of Pharmacology, School of Medicine, University of Zagreb), Šostaric P (Department of Pharmacology, School of Medicine, University of Zagreb), Meglic P (Department of Pharmacology, School of Medicine, University of Zagreb), Simonato M (Department of Biomedical Sciences, University of Padua), Rubini A (Department of Biomedical Sciences, University of Padua), Caleo M (Department of Biomedical Sciences, University of Padua), Megighian A (Department of Biomedical Sciences, University of Padua and Padua Neuroscience Center, University of Padua), Rossetto O (Padua Neuroscience Center, University of Padua; Institute of Neuroscience, Italian Research Council, University of Padua and Interdepartmental Research Center of Myology CIR Myo, University of Padua), Montecucco C (Department of Biomedical Sciences, University of Padua and Institute of Neuroscience, Italian Research Council, University of Padua), Pirazzini M (Department of Biomedical Sciences, University of Padua and Interdepartmental Research Center of Myology CIR Myo, University of Padua)

Introduction: Tetanus is a neuroparalytic syndrome caused by Tetanus Neurotoxin (TeNT), the protein exotoxin produced by Clostridium tetani. The toxin enters in the cytosol of peripheral nerves to be then retrotransported to the central nervous system, where it enters inhibitory interneurons to cleave its target VAMP, thus preventing neurotransmission and leading to spastic paralysis.
One of the most dangerous and less understood form of tetanus is cephalic tetanus (CT), that begins with an unusual facial palsy, and then evolves in the canonical spastic paralysis of facial muscles, dysphagia and a rapid failure of ventilation. The contrasting symptoms often postpone the correct diagnosis, making the prognosis poor. The molecular pathogenesis of these contrasting symptoms and why CT rapidly evolves into respiratory failure remain unresolved.
Materials and Methods: We developed a CT model with local injections of TeNT in different muscles of mouse's head. We then evaluated CT molecular pathophysiology by immunofluorescence and functional analyses (whisking, ventilation).
Results: We report the unexpected finding that CT facial palsy is caused by VAMP proteolysis at the neuromuscular junction. This effect shadows the canonical central effect of TeNT, which however rapidly spreads to brainstem areas controlling critical functions, including mastication, deglutition and respiration.
Conclusions: In addition to elucidating the molecular bases behind the unusual CT facial palsy, we unraveled why CT can rapidly evolve in a life-threatening form of tetanus and suggest that patients presenting to the emergency room with facial nerve palsy of unknown origin should be considered for CT and immediately hospitalized.

P2 14

CALCIUM CHLORIDE-INDUCED RAT MODEL OF ABDOMINAL AORTIC ANEURYSM AND THE EFFECT OF PENTADECAPEPTIDE BPC 157

Zizek H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Diagnostic and Interventional Radiology, Sisters of Charity University Hospital, Zagreb, Croatia) Sjekavica I (Department of Diagnostic and Interventional Radiology, Sisters of Charity University Hospital, Zagreb, Croatia), Smoday I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Oroz K (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Boban Blagaic A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Abdominal aortic aneurysm (AAA) is characterised by dilation of an abdominal aortic (AA) segment ≥1.5 times more than adjacent, normal segment, which is caused by an inflammatory process that leads degrades elastin and collagen fibers within the vessel wall. We investigated the effect of pentadecapeptide BPC 157 therapy in an experimental rat model of AAA.
Materials and methods: An established calcium chloride-induced rat model of AAA was used. Rats were divided in two groups, BPC 157 treated group (10 ng/kg perorally) and control group, and evaluated 4 and 8 weeks after AAA induction. AAA macroscopic presentation was recorded using USB microcamera and AAA diameter measurement using imageJ software was performed before AAA induction and at both time periods. Diameter ratios (DR) were calculated as follows DR=(largest diameter/start diameter)x100. Histopathological examination of AAA specimens was performed at 8 weeks time period.
Results: Rats treated with BPC 157 showed slower and lower increase in AAA diameters in contrast to the control rats. DRs were as follows, control group: 162±4 at 4 weeks, and 186±4 at 8 weeks; and treated group: 110±2 at 4 weeks, and 117±3 at 8 weeks. Histopathological examination of AAA specimens at 8 weeks revealed linear lamina elastica interna, thinning of tunica media with areas of detachment and leukocyte aggregates in control gorup, whereas treated group showed undular lamina elastica interna, no thinning or detachments in tunica media, and few solitary leukocytes.
Conclusions: BPC 157 therapy slows the progression of AAA in rats.

P2 15

BRAIN EDEMA AND BLOOD PRESSURE DISTURBANCES INDUCED BY ACUTE WATER INTOXICATION IN A RAT MODEL AND THE EFFECT OF PENTADECAPAPTIDE BPC 157

Yago H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Neuropsychiatric Hospital "Dr Ivan Barbot", Popovača, Croatia), Zizek H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia) Smoday IM (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia) Durasin T (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Acute water intoxication causes cellular brain edema accompanied with increased intracranial pressure, which was established in a rat model. Recent studies showed that pentadecapeptide BPC 157 mitigates brain edema and superior saggital sinus (SSS) hypertension caused by major blood vessel occlusion.
Materials and methods: Medication (/kg) (BPC 157 (10ng)(treated group) or saline (5mL)(control group)) was applied subcutaneously in male Wistar rats weighing 200-220 g, immediately after 20% of rats body weight of destilled water was applied intraperitoneally. 30min and 1h after medication application rats were deeply anaesthetised, laparatomised and intravascular cannulation of portal vein (PV), inferior vena cava (IVC) and abdominal aorta (AA) was performed in order to obtain blood pressure values. Craniotomy was also performed to cannulate SSS and evaluate brain edema using USB microcamera recordings at 30 min and 1h after medication application. Brain volume (V) ratios were measured using ImageJ software area (A) measurement option and areas were put into ratios after square-cube law equation was introduced: $V_{con}/V_{BPC157} = (\sqrt{\frac{A_{con}}{A_{1BPC157}}})^3$.
Results: Control rats exhibited SSS, PV and IVC hypertension, aortic hypotension (mmHg) (30min: 6±1SSS, 15±2PV, 14±2IVC, 63±3AA; 1h: 10±1SSS, 14±1PV, 25±3IVC, 80±4AA). Treated rats showed improved pressure values (30min: -10±2SSS, 4±1PV, 11±2IVC, 82±3AA; 1h: -5±1SSS, 6±1PV, 8±2IVC, 90±4AA). Control group exhibited greater brain volumes than treated group at both 30 min V_{con}/V_{BPC157}=1.05±0.01 and 1h V_{con}/V_{BPC157}=1.16±0.01.
Conclusions: BPC 157 counteracts SSS, PV and IVC hypertension and AA hypotension, as well as an increase in brain volume in a rat model of acute water intoxication.

P2 16

TREATMENT OF ULCER, INTRACRANIAL, PORTAL AND CAVAL HYPERTENSION AND AORTAL HYPOTENSION WITH BPC 157 AFTER STOMACH PERFORATION

Vranes H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Kalogjera L (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Chiddenton MH (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Buric S (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Stomach perforation with a 5-mm diameter metal needle on the ventral side in the prepyloric area induced a defect that doesn't heal. Rapidly, these rats developed superior sagittal sinus, portal and caval hypertension and aortal hypotension. Previously, stable gastric pentadecapeptide BPC 157 significantly reduced or even eliminated the portal and caval hypertension and aortal hypotension in Budd-Chiari syndrome in rats. Here, we examined the therapy of BPC 157 in rats with stomach perforation.
Materials and methods: In deeply anesthetized randomly assigned rats, the stomach perforation was performed. Medication (BPC 157 (10 µg /kg, 10 ng /kg 1mL) or saline (5 ml/kg)) was given intraperitoneally at 5 min after stomach perforation. At 10 min after stomach perforation, we measured the pressures in the superior sagittal sinus, portal vein, inferior vena cava and abdominal aorta as described before (Biomedicines. 2022 Jun 1;10(6):1299. doi: 10.3390/biomedicines10061299).
Results: In the control groups, intracranial hypertension, portal and caval hypertension and aortal hypotension had a rapid onset whereas BPC 157 quickly normalises the increased pressure in the superior sagittal sinus, portal and caval hypertension and aortal hypotension. Finally, BPC 157 entirely healed the stomach defect.
Conclusion: BPC 157 showed an anti-ulcer effect and also counteracted intracranial hypertension, portal and caval hypertension and aortal hypotension in both groups of treated animals.

P2 17

STABLE GASTRIC PENTADECAPEPTIDE BPC 157 THERAPY EFFECT ON REPERFUSION FOLLOWING MAINTAINED INTRA-ABDOMINAL HYPERTENSION, GRADE III AND IV

Tepes M (Department of Surgery, General Hospital Nasice, Nasice, Croatia; Department of Clinical Medicine, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia; PhD Program Translational Research in Biomedicine—TRIBE, School of Medicine, University of Split, Split, Croatia and Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Madzar Z (Clinical Department of Surgery, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia) Miskic B (Department of Clinical Medicine, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia) Miskic S (Department of Nursing and Palliative Medicine, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia), Duzel A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia) Sever M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia) Dretar V

Introduction: We focused on the effect of the BPC 157 therapy on reperfusion following maintained intra-abdominal hypertension, grade III and IV. Recently, by activating particular collateral pathways, BPC 157 counteracted major vessel occlusion syndromes, induced by either direct occlusion (ligation) of peripheral and/or central vessel, or maintained intra-abdominal hypertension. BPC 157 therapy activated azygos vein via the inferior-superior caval vein rescue pathway, promptly and definitively reduced intracranial (superior sagittal sinus), portal and caval hypertension and aortal hypotension. There were, reduced gross and microscopic organs lesions, congestion and hemorrhage (brain, heart (subendocardial infarct), lung, liver, kidney and gastrointestinal tract), and antagonized severe ECG disturbances. Previously congested inferior caval and superior mesenteric veins were reversed to the normal vessel presentation, and previously collapsed azygos vein made fully functioning, and almost eliminated thrombosis as prove of the eliminated general stasis and reorganized blood flow.
Materials and methods: After maintained IAH (25 mmHg (60 min), 30 mmHg (30 min), 40 mmHg (20 min)), and then, laparotomy and calvariectomy, the reperfusion assessment was carried out at 60 min (25 mmHg-IAH), 30 min (30 mmHg-IAH), and 20 min (40 mmHg-IAH) of reperfusion, therapy (BPC 157 10 µg/kg, 10 ng/kg ip) at 1 min-reperfusion time.
Results: Along with reperfusion-organ lesions and ECG-disturbances reduction, providing that body cavities interact with each other, and BPC 157 therapy compensatory and counteracting potential, illustrative for decompression/reperfusion are marked pressure disturbances, all markedly attenuated/eliminated.
Conclusions: BPC 157 therapy may be used in reperfusion therapy following maintained IAH, grade III and IV.

P2 18

BPC 157 IN PSORIASIS MODEL

Šola M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Dermatology and Venereology, University Hospital Osijek, Osijek, Croatia), Skroza N (Dermatology Unit "D. Innocenzi", Sapienza University of Rome, Polo Pontino, Italy and Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy), Mangino G (Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy), Boban Blagaic A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Pentadekapeptide BPC 157 is a peptide with proven cytoprotective and organ protective properties used in numerous laboratory models. In therapies of different wound types, its use leads to complete tissue restitution. Psoriasis is an immune-mediated chronic skin disease. The model of psoriasis is easily feasible in laboratory animals using 5% imiquimod creme topically.
Materials and methods: The experiment was done on male Wistar Albino rats. „Psoriasis-like" lesions were induced in all animals by applying 5% imiquimod cream topically on shaved skin on their backs for 2, 4, 6, and 7 consecutive days. Every day 3 hours after applying imiquimod creme, BPC 157 in cream (conc. 1µg/g neutral cream) was applied in BPC 157 treated group or only neutral cream (Belobaza) in the control group. Animals were treated and observed daily. The severity of lesions was measured clinically using a modified PASI score. Animals were sacrificed according to the schedule. Statistical analysis of the results was done.
Results: In the BPC 157 treated group antagonizing effect of the BPC 157 was achieved. "Psoriasis-like" lesions were not developed completely like in the control group.
Conclusions: Since the use of BPC 157 antagonized the effect of the 5% imiquimod cream in the psoriasis model and it is known that BPC 157 has no lethal dose and there are no side effects of its use BPC 157 offers the potential for further research in treating psoriasis.

P2 19

THERAPEUTIC EFFECT OF BPC 157 ON MANDIBULAR FRACTURE HEALING

Suman O (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Staresinic M (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Kocman I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Jadrijevic S (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb)

Introduction: Despite the advances in maxillofacial surgery, impaired mandibular bone healing still remains a concern for surgical teams. The aim of this study is to evaluate effect of pentadecapeptide BPC 157 on fracture healing of mandible in rats. The effect of BPC 157 on tissue healing is described in many studies. It enhances wound healing in burns, mucous fistulas, muscle, tendon and ligament injuries and has beneficial role in bone healing.

Matherials and methods: A mandibular fracture was performed in in deeply anesthesized Wistar albino rats that were random divided in treated (BPC 157 applied both in fracture and applied orally) and control group (saline applied). We directly examined the hematoma formation after the fracture and in the next 6 weeks measured bone healing and functional recovery. Differences were clinically, radiologically and pathohistologically observed. Animals were grouped and sacrificed 6 weeks after fracture was performed. After thesacrifice, rats mandibles were scanned by Computer tomograph (CT) and fracture samples were taken for pathohistological examination.

Results In treated group, we found hematoma formation inside the fracture gap, better fracture healing and functional outcome. These clinical findings were observed in better weight gain in BPC 157 group, less swelling and better function. CT scans showed better bone remodeling and better callus formation. Results were confirmed along with pathohistology.

Conclusion BPC 157 therapy improved bone healing process of mandibular fracture.

P2 20

PENTADECAPEPTIDE BPC 157 AS THERAPY OF THE INFERIOR CAVAL VEIN EMBOLIZATION POST-EMBOLIZATION SYNDROME WITH SODIUM LAURATE IN RATS

Smoday IM (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Kalogjera L (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Sara Buric (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Vranes H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

The therapy of the inferior caval vein embolization post-embolization syndrome (sodium laurate 10 mg/kg, 15, 30, 60 min) might correspond to the stable gastric pentadecapeptide BPC 157 therapy (10 µg, 10 ng ip or po) particular effect (i.e. activation of the collateral pathways, “bypassing vascular key”) in the recovery of the multiorgan failure syndrome in the rats with the vascular failure induced by multicausal pathology, either by major vessel(s) occlusion or with other noxious procedures. As rapidly acting Virchow triad circumstances, likely shared in the rats with the vascular failure and in the post-embolization syndrome, there were the occluded many major vessels, artery or vein, artery and vein, peripherally or centrally, as occlusion-syndromes. Likewise, as vascular failure, peripherally and centrally, there were the absolute alcohol intragastric instillation, lithium-overdose, isoprenaline-myocardial infarction, bile duct occlusion acute pancreatitis, maintained intra-abdominal hypertension as occlusion-like syndrome. Thus, we revealed that the post-embolization syndrome and the BPC 157 therapy particular effect might correspond to the rapidly shared multiorgan failure, and vessel failure, the intracranial (superior sagittal sinus) hypertension, portal and caval hypertension, aortal hypotension, progressing venous and arterial thrombosis peripherally and centrally, congested and/or failed major veins, and ECG disturbances. Whatever the cause, there were the brain, heart, lung, liver, kidney and gastrointestinal tract lesions and with progressing venous and arterial thrombosis progressing stasis, peripherally and centrally, all counteracted by BPC 157 therapy application, along with the ECG disturbances, intracranial (superior sagittal sinus) hypertension, portal and caval hypertension, and aortal hypotension eliminated/attenuated.

P2 21

THERAPY EFFECT OF THE PENTADECAPEPTIDE BPC 157 ON DEVELOPMENT OF ABDOMINAL AORTIC ANEURYSM AND VASCULAR FAILURE SYNDROME CAUSED BY CIPROFLOXACIN

Ivan Škorak (Department of Vascular surgery, University Hospital Center Zagreb, Zagreb, Croatia), Ivan Brižić (Department of Vascular surgery, University Hospital Center Zagreb, Zagreb, Croatia), Klaudija Hriberski (Department of Vascular surgery, University Hospital Center Zagreb, Zagreb, Croatia), Ivan Krezić (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Helena Žižek (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Ivan Maria Smoday (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Tomislav Meštrović (Department of Vascular surgery, University Hospital Center Zagreb, Zagreb, Croatia), Predrag Pavić (Department of Vascular surgery, University Hospital Center Zagreb, Zagreb, Croatia), Predrag Sikirić (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Rupture of the aneurysm of abdominal aorta (AAA) is a catastrophic event with extremely high mortality. Ciprofloxacin, a frequently used fluoroquinolone antibiotic, is associated with AAA development, and known model of AAA. As novel point, we described ciprofloxacin induced aortic wall damage at 5 minutes after application along with a general occlusion like syndrome, the multiorgan failure, and vessel failure, the intracranial (superior sagittal sinus) hypertension, portal and caval hypertension, aortal hypotension, progressing venous and arterial thrombosis peripherally and centrally, congested and/or failed major veins, and ECG disturbances, as previously with major vessel occlusion, or various major procedures. Whatever the cause, along with maintained aortal integrity, there were the brain, heart, lung, liver, kidney and gastrointestinal tract lesions and with progressing venous and arterial thrombosis progressing stasis, peripherally and centrally, all counteracted by BPC 157 therapy application, along with the ECG disturbances, intracranial (superior sagittal sinus) hypertension, portal and caval hypertension, and aortal hypotension eliminated/attenuated. Materials and methods. In deep anesthesia randomly assigned, male Albino Wistar rats abdominal aorta was exposed, and ciprofloxacin (400 mg/kg i.p.) given as a bath and BPC 157 10 µg or 10 ng/kg intragastrically at 15 min thereafter, and effects assessed as described Biomedicines 2022 ,10(6):1299, Front. Pharmacol 2021, 12:718147.
Results. As mentioned above, the BPC 157 therapy effect with both regimens appeared since very beginning. Conclusions. Practical value of BPC 157 beneficial effect might be further seen in regular AAA therapy.

P2 22

THE EFFECT OF PENTADECAPEPTIDE BPC 157 ON ALCOHOL- INDUCED LESIONS OF BREAST AND SOURROUNDING TISSUE IN RATS

Samara M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb), Zic R (Clinic for Plastic, Reconstructive and Aestehtic Surgery, Clinical Hospital Dubrava, Zagreb, Croatia), Sikiric P (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Robert's concept of cytoprotection describes the effect of direct application of alcohol (nociceptive agent) on the gastric mucosa, and the antagonism of lesion by mediators of cytoprotection. We used intramammary administration of alcohol in rats to create a basis for the application of cytoprotective agents in mammary lesions. The stable gastric pentadecapeptide BPC 157 has been shown to be a new mediator of cytoprotection, wich has a therapeutic BPC 157 therapeutic effect should be demonstrated in alcohol-induced mammary lesions in rats.
Materials and methods: In deeply anesthesized rats, 0.1 ml of 96% ethanol was applied intramammary with a 30G insulin needle (30 seconds after the application, the needle is carefully pulled out). Immediately after pulling out the needle, 0.9% NaCl 5 ml/kg (control) and BPC 157 (10 ng/kg) were administered intraperitoneally. The evaluation was done using the macroscopic score - where the total score was made up of the change in the diameter of the lesion, the presence of edema (yes/no) and redness (yes/no).
Results: Compared to control groups of animals, groups treated with pentadecapeptide BPC 157, had significantly less pronounced redness, swelling and a smaller change in the diameter.
Conclusion: Using intramammary application of alcohol, we createded a basis for the use of cytoprotective agents and their effectiveness in breast tissue damage. In addition, the positive effect of the pentadecapeptide BPC 157 on the healing of alcohol-induced breast lesions and the reduction of inflammation caused by it has been proven.

P2 23

„OCCLUSION-LIKE“ SYNDROME IN RAT LOWER LEG FRACTURE AND THE THERAPEUTIC EFFECT OF PENTADECAPEPTIDE BPC 157.

Prtoric A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Dobric I (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia) Jurjevic I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Durasin T (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: The effect of stable pentadecapeptide BPC 157 on tissue healing is described in many studies including its cytoprotective effect and benefits in inflammatory bowel diseases. It enhances wound healing in burns, mucous fistulas, muscle, tendon and ligament injuries and benefits bone healing. It has a therapeutic effect in cases of occlusion of superior mesenteric artery, superior sagittal sinus and vena cava inferior, but also counteracts the *Occlusion-like* syndrome characterized by ECG disturbances, multiorgan failure and lesions, intracranial, portal and caval hypertension and aortal hypotension. We have demonstrated the *Occlusion-like* syndrome and the therapeutic effect of BPC 157 after lower leg fracture in rats.
Materials and methods: A tibia and fibula fracture was induced in male Wistar albino rats that were randomized divided in treated (BPC 157 applied at the fracture site and orally) and control group (saline applied). We directly examined the hematoma formation after the fracture and in the next 30 days measured bone healing and functional recovery. In addition, we examined the onset of *Occlusion-like* syndrome in lower-leg fracture, with or without BPC 157 therapy.
Results: In treated group we found hematoma formation inside the fracture gap, better fracture healing and functional outcome. After the lower leg fracture the onset of *Occlusion-like* syndrome arose in control group, but was absent in the treated group.
Conclusions: *Occlusion-like* syndrome is a result of lower leg fracture in rats, and is counteracted by pentadecapeptide BPC 157, which also leads to better fracture healing and functional outcome.

P2 24

SOTALOL-INDUCED GENERAL OCCLUSION-LIKE SYNDROME AND QTC PROLONGATION IN RATS ARE COUNTERACTED BY PENTADECAPEPTIDE BPC 157

Premuzic Mestrovic I (Department of Internal Medicine, Merkur Clinical Hospital, Zagreb, Croatia) Smoday IM (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Mestrovic T (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Skorak I (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Haluzan D (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Figl J (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia) Brizic I (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Staresinic M (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Pavic P (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Pentadecapeptide BPC 157, apart from general cytoprotective and organ-protective properties, has already been demonstrated to exert beneficial antiarrhythmic effects that counteract digoxin, bupivacaine, potassium-overdose, succinylcholine and lidocaine cardiotoxicity. In this study we examined the effect of BPC 157 on sotalol, a class III antiarrhythmic with non-selective beta-blocking activity-induced a general occlusion-like syndrome, multiorgan and vessel failure, intracranial (superior sagittal sinus) hypertension, portal and caval hypertension, aortal hypotension, progressing venous/arterial thrombosis/stasis peripherally and centrally, congested and/or failed major veins, and ECG disturbances, as previously reported with major vessel occlusion, or various major procedures.
Materials and methods: Albino Wistar rats received sotalol and afterwards were treated with saline or BPC 157. In particular, QT intervals were analyzed on the ECG recordings at baseline, after application of sotalol; and in different time intervals after the application of sotalol. Corrected QT intervals (QTc) were calculated by using Fridericia formula.
Results: Sotalol caused QTc prolongation, organ lesions (i.e. brain, heart, lung, liver, kidney and gastrointestinal tract) and hemodynamic changes (an increase in superior sagittal sinus pressure, portal vein and posterior caval vein pressures, as well as a decrease in abdominal aortic pressure) in treated rats. All the before mentioned effects of sotalol were mitigated by BPC 157.
Conclusions: These results consistently support the property of BPC 157 as a rapid-acting cytoprotective, organ-protective, and especially cardioprotective, agent.

P2 25

PROTECTIVE EFFECTS OF PENTADECAPEPTIDE BPC 157 ON CAUSTIC LESIONS OF THE ESOPHAGUS IN RATS

Peklic M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Krezic I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Boban Blagaic A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Vranes H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Smoday IM (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Ingestion of a caustic substance causes severe damage of the gastrointestinal tract, mainly of esophagus and stomach, and can therefore be a cause of serious morbidity. We examined cytoprotective effect of pentadecapeptide BPC 157 on caustic lesions of the esophagus in rats.
Materials and methods: Male Albino Wistar rats were randomly assigned to control and treated group. Caustic lesions were induced by intraesophageal administration of 0.5 mL of 10% NaOH or 20% HCl at the proximal part of the rat esophagus. Immediately thereafter, 1.0 mL of pentadecapeptide BPC 157, in the dose of 10μg/kgBW (treatment group) or equivolume of 0.9% NaCl (control group) was administered intraperitoneally.The time between administration of the irritants and sacrifice was 1, 5 and 10 minutes respectively. Right after sacrificing, esophagus was removed and lesions were evaluated macro-and microscopically. In tissue samples oxidative stress was determined by measuring malondialdehyde, and also the determination of NO was done in tissue samples.
Results: In treated groups, in both caustics, a significant reduction of the lesions was found both macroscopically and microscopically in all investigated time intervals, in contrast to control groups. We also showed a significant reduction of MDA and NO in esophageal tissue samples of treated groups.
Conclusions: Until now, no study of cytoprotective effect of pentadecapeptide BPC 157 on caustic lesions of the esophagus by direct application of the irritans was conducted, and this study confirmed its cytoprotective effect. These results open the possibilities for further studies on chronic caustic lesions and a potentially new pharmacologic treatment of esophageal caustic lesions.

P2 26

TOURNIQUET-INDUCED COMPARTMENT SYNDROME OF RATS' LIMB AND ITS COUNTERACTION WITH PENTADECAPEPTIDE BPC 157 THERAPY

Oroz K (Department of Pharmacology, University of Zagreb, School of Medicine), Coric L (Department of Pharmacology, University of Zagreb, School of Medicine), Dretar V (Department of Pharmacology, University of Zagreb, School of Medicine)

INTRODUCTION: This study aimed to investigate tourniquet-induced compartment syndrome of limb, consequential development of multiple organ dysfunction syndrome, and its counteraction with pentadecapeptide BPC 157 therapy.
MATERIALS AND METHODS: Rubber-band tourniquet was placed on the left knee of anesthetized rats to induce 20 minutes long ischemia. Injection of either saline (5 ml/kg b.w.) or BPC 157 (2 µg/kg b.w.) was intraperitoneally administered at 10 to 20 seconds post-inducing ischemia. Changes in volume and color of both legs were recorded with a USB microcamera pre- and post-inducing ischemia and after removing the tourniquet. After 20 minutes of reperfusion, the internal organs, vessels, and brains of rats were recorded. Furthermore, blood pressure was measured via intravascular cannulation. The walking and function failure was also observed in the control and treated groups.
RESULTS: In the rats with rubber band-induced compartment syndrome, there were progressing leg swelling and congestion, huge noxious syndrome, and multiorgan failure. There were, peripherally and centrally, progressing thrombosis, intracranial, portal and caval hypertension, and aortal hypotension. Function recovery and walking were impaired in the control group. Rats treated with BPC 157 had slower progression of leg swelling and congestion and after 15 minutes of reperfusion, normal leg presentation. BPC 157 also counteracted changes in blood pressure, and reduced brain swelling and congestion of internal organs. The treated rats didn't show walking failure.
CONCLUSION: The application of BPC 157 at the beginning of tourniquet-induced compartment syndrome reduces leg swelling and congestion, as well as the systemic effects of compartment syndrome.

P2 27

BPC 157 COUNTERACTS RADIATION-INDUCED ORAL MUCOSITIS IN RATS

Milatic K (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia), Alajbeg I (Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia), Sobat H (Radiation Oncology Department, University Hospital for Tumors, "Sestre milosrdnice" University Hospital Center, Zagreb, Croatia), Andabak-Rogulj A (Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia), Reić T (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Radiation-induced oral mucositis (RIOM) is a common side effect and a limiting factor in radiotherapy of head and neck cancer, with significant clinical and economic consequences, for which there is still no effective treatment. As a potential agent to counteract RIOM in a rat model, BPC 157, an antiulcer peptide with cytoprotective effect, was used.
Materials and methods: To establish a RIOM model, we used a gynaecological brachytherapy probe to modify a previously used method of rat's tongue irradiation as presented before (Acta stomatol Croat. 2019;53(3):280-292.). Gynaecological brachytherapy probe (diameter 6mm, radionuclide Cs-137) was inserted in male Wistar Albino rats (200-250 g bw) into oral cavity to the depth of 25 mm from incisors to pharynx. Area of the insertion (lips, oral mucosa, tongue, oral cavity) was then exposed to a single dose of 30 Gy (exposure time 3480 s). Rats were randomly assigned to groups for particular treatment and period of evaluation of the effect of BPC 157. BPC 157 was applied as pretreatment intraperitoneally or posttreatment in drinking water till sacrifice. Assessment in any given period included edema, erythema and ulcerations of the lips, oral mucosa, tongue and pharynx, scored accordingly. Histological analysis of lesions was performed as well.
Results: BPC 157 had strong beneficial effect. BPC 157 counteracted edema, erythema and ulcerations of the irradiated area, as well as the paresis of the lip directly exposed to irradiation and hair loss from the snout.
Conclusion: BPC 157 is a cytoprotective agent that has effect in counteracting RIOM in a rat model.

P2 28

CYTOPROTECTIVE EFFECTS OF BPC 157 ON MULTIORGAN DAMAGE CAUSED BY HIGH DOSES OF MEGESTROL ACETATE IN RATS

Krtalic B (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Koprivanac A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Kalogjera L (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Oroz K (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Durasin T (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

INTRODUCTION: Megestrol Acetate (MA), a synthetic progestogen commonly used to treat anorexic patients suffering from cancer or AIDS, has been linked with an increased risk of thromboembolic incidents in certain studies, some studies even suggest a dose-dependent effect. Previously, studies on rats have shown that various substances (e.g. alcohol, lithium, isoprenaline) can, among other pathologies, cause a syndrome that includes aortic hypotension, caval and portal hypertension, widespread veinous and arterial thrombosis, intracranial hypertension, end-organ damage etc. Thus, we propose that high doses of MA in rats might lead to similar consequences. The forementioned syndrome in rats has been shown to be attenuated or negated with the application of pentadecapeptide BPC 157 isolated from human gastric juice. Therefore, the aim is to observe whether the same cytoprotective effect will occur in rats that receive high doses of MA.
MATERIALS AND METHODS: Anesthetized (thiopenthal 40 mg/kg and diazepam 10 mg/kg) 4-month-old female Wistar rats (200-250g) were injected with 80 mg/kg of MA in their inferior vena cava. Control group received saline (0,9%) via peritoneum, while the treated groups received BPC 157 (10 mcg/kg). 1 hour later the rats were sacrificed, and the pathohistology of the brain, heart, lungs and visceral organs were obtained.
RESULTS: Pathohistological findings in the brains of the rats in control groups showed more pronounced congestion/edema in comparison with the treated group. Congestion was also more pronounced in the lungs, hearts, kidneys and the stomach of the control group. Also, their lungs had signs of bleeding and the livers exhibited dilatation.
CONCLUSION: Pathohistological findings suggest that high doses of MA cause multiorgan damage in rats, with a cytoprotective effect of BPC 157 applied immediately afterwards. Further research is required.

P2 29

NEUROPROTECTIVE EFFECT OF PENTADEKAPEPTIDE BPC 157 ON 3-NITRO PROPRIONIC ACID-INDUCED MODEL OF HUNTINGTONS DISEASE

Krezic I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Jurjevic I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Chiddenton HM (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Huntingtons disease (HD) is an autosomal neurodegenerative disease associated with severe degeneration of basal ganglia neurons, especially the striatum, and characterized by motor, cognitive, and psychiatric disorders and has no existing cure for the disease. Stable gastric pentadecapeptide BPC 157 has been proven as a potent cytoprotective agent at healing of different injuries. Its neuroprotective effects were shown in models of Parkinson disease and multiple sclerosis as well as in model of spinal cord injury. We wanted to demonstrate the neuroprotective effect of pentadecapeptide BPC 157 on a model of 3-nitro proprionic acid (3-NP) induced model of HD in rats.
Materials and methods: Female Albino Wistar rats was administered 3-NPK (20 mg/kg body mass, by intraperitoneal injection) once a day for 3 days; and BPC 157 (10 µg/mL or 10ng/mL) was given intraperitoneally before (pretreatment) or after (treatment) with 3-NPK. After third application, functional tests (gait abnormalities), and neurological scoring, will be used to determine the degree of damage.
Results: 3-NP resulted in a marked locomotion activity and deterioration of the neurological status. BPC 157 application significantly alleviated (treatment regime) or prevent the occurrence (pretreatment regime) of neurological and motor deficit.
Conclusions: In this study, we demonstrated the protective effect of BPC 157 on preventing and reducing damage (measured by functional and neurological scores) in the animal model of 3-NPK-induced HD and its potential for clinical use in HD to halt disease progression.

P2 30

EFFECT OF PENTADECAPEPTIDE BPC 157 ON LUNG REEXPANSION IN RIGHT-SIDED PNEUMOTHORAX IN RATS WITH PENETRATING CHEST INJURY

Koprivanac A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Krtalic I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Zizek H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Boban Blagaic A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Oroz K (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Coric L (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: It has been experimentally proven that the pentadecapeptide BPC 157, affects accelerated healing of a number of organ systems and tissues as it has strong angiogenic potential by activation of the VEGFR2-Akt-eNOS signaling pathway. BPC 157 application allows normalization of blood flow through the damaged organ system, which is a fundamental prerequisite for the preservation of organic function and subsequent structural restitution. This study shows therapeutic efficacy of pentadecapeptide BPC 157 applied by intraperitoneal injection on effective lung reexpansion in right - sided pneumothorax in rats after penetrating chest injury and its positive hemodynamic effect as in other congestive conditions described in previous BPC 157 studies.
Materials and methods: Male Wistar rats with iatrogenic induced right-sided pneumothorax are objectified under deep anesthesia by: multi-slice CT, macroscopic measurement (microcamera), monitoring of hemodynamic parameters and pathohistological analysis of lung, heart, brain, liver and kidney samples. Therapy (BPC 157 10 ug/kg or 10 ng/kg, control group 0.9% NaCl 5ml/kg) is applied immediately after induction or 1 hour after induction.
Results: All rats with induced right-sided pneumothorax that received BPC 157 exhibited faster lung reexpansion (after 24 h), maintained hemodynamic stability, and reduced severe ECG disturbances. BPC 157 application largely counteracted potential negative changes at the microscopic level, including reduced lung congestion and severe intraalveolar hemorrhage, heart and liver congestion, renal hemorrhage and brain edema.
Conclusions: Application of BPC 157 causes rapid activation of collateral vascular pathways that allows efficient reversal of congestive states with hemostatic action, what ultimately affects faster lung reexpansion.

P2 31

STABLE GASTRIC PENTADECAPEPTIDE BPC 157 THERAPY EFFECT ON REPERFUSION FOLLOWING OCCLUSION OF SUPERIOR MESENTERIC ARTERY, SUPERIOR MESENTERIC VEIN, AND SUPERIOR MESENTERIC ARTERY AND VEIN

Knezevic M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Knezevic T (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia) Kolak T (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Prtoric A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Sever M (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia) Giljanovic A (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia) Gojkovic S (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Muzinic D (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia) Boban Balagaic A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: We demonstrated the rescue effect of the stable gastric pentadecapeptide BPC 157 therapy by activating particular collateral pathways reliant on vascular injury. BPC 157 therapy counteracted the severe ischemia-injuries triggered in different vessels tributaries with permanently occluded superior sagittal sinus, superior mesenteric artery and/or vein, infrarenal and suprahepatic inferior caval vein, and portal triad; as well as major intoxication (alcohol, lithium) and maintained intra-abdominal hypertension, grade III and IV).
Materials and methods. Therapy (BPC 157 10 µg/kg, 10 ng/kg ip) was given at 1 min reperfusion time after occlusion removal in rats which had 30 min-occlusion of the superior mesenteric artery and/or vein; assessment at 30 min-reperfusion time, provided the similar therapy effect in reperfusion as well.
Results: Beneficial effect in reperfusion of BPC 157 therapy included also the counteraction/attenuation of the consequent adverse effects that would appear as shared severe ischemic syndrome. BPC 157 counteracted the reported brain swelling and lesions, heart dysfunction, lung lesions, liver and kidney failure, and gastrointestinal lesions. Congested were inferior caval vein and superior mesenteric vein and failed azygos vein. Widespread were arterial and venous thrombosis. Without therapy, as in ischemia, these rats exhibited in reperfusion severe intracranial (superior sagittal sinus), portal and caval hypertension and aortal hypotension, eliminated/attenuated by BPC 157 therapy
Conclusions: BPC 157 therapy may be reperfusion therapy after occlusion of the superior mesenteric vessels.

P2 32

PENTADECAPEPTIDE BPC 157 AS THERAPY OF THE AIR EMBOLIZATION AND POST-EMBOLIZATION SYNDROME IN RATS

Kalogjera L (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Smoday I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Chiddenton HM (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Sara Buric (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Coric L (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

The therapy of the air embolization induced post-embolization syndrome (0.1 ml air/rat in inferior caval vein, assessed at 15, 30, 60 min) might correspond to the stable gastric pentadecapeptide BPC 157 therapy (10 µg, 10 ng ip or ig) particular effect (i.e. activation of the collateral pathways, “bypassing vascular key”) in the recovery of the multiorgan failure syndrome in the rats with the vascular failure induced by multicausal pathology, either by major vessel(s) occlusion or with other noxious procedures (i.e. absolute alcohol intragastric instillation, lithium-overdose, isoprenaline-myocardial infarction, bile duct occlusion acute pancreatitis, maintained intra-abdominal hypertension). Thus, we revealed the rapidly shared multiorgan failure, and vessel failure, the intracranial (superior sagittal sinus) hypertension, portal and caval hypertension, aortal hypotension, progressing venous and arterial thrombosis peripherally and centrally, congested and/or failed major veins, and ECG disturbances that were as the post-embolization syndrome attenuated by the BPC 157 therapy particular effect. Whatever the cause, there were the brain, heart, lung, liver, kidney and gastrointestinal tract lesions and with progressing venous and arterial thrombosis progressing stasis, peripherally and centrally, all counteracted by BPC 157 therapy application, along with the ECG disturbances, intracranial (superior sagittal sinus) hypertension, portal and caval hypertension, and aortal hypotension eliminated/attenuated.

P2 33

EFFECT OF PENTADECAPEPTIDE BPC 157 ON APICAL PERIODONTITIS CAUSED BY PULP EXPOSURE IN RATS

Juzbasic M (Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia and Department of Pharmacology Medical Faculty, University of Zagreb, Zagreb, Croatia), Talapko J (Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia), Krezic I (Department of Pharmacology Medical Faculty, University of Zagreb, Zagreb, Croatia), Zizek H (Department of Pharmacology Medical Faculty, University of Zagreb, Zagreb, Croatia), Tomas M (Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia)

Introduction: Apical periodontitis is one of the most common inflammatory conditions of the teeth. Despite the frequent failure of mechanical cleaning as the gold standard, there is still no alternative therapy that would reduce the damage caused by the opening of the pulp and preserve the tooth. The pentadecapeptide BPC 157 has shown great healing potential in various animal studies in many experimental models to date. This study aimed to analyze the effect of BPC 157 on a model of apical periodontitis.
Materials and methods: Trepanation of the rat's first right maxillary molar was performed on the mesial side of the tooth occlusal surface. The treated groups in the therapy received BPC 157 (10ng/kg or 10µg/kg) per os, while the control group drank water during the experiment. Saliva samples and swabs of the oral cavity were collected for microbiological analysis. The damaged tooth and the surrounding tissue were analyzed histologically and molecularly, while the whole experiment was monitored macroscopically and radiologically.
Results: Macroscopic observation showed that the remaining coronal part of the tooth tissue around the trepanation opening is more prone to cracking in the non-treated group. Microbiological analysis showed the same count of colonies and bacterial species in all rats. The area of radiographic periapical bone loss and furcation defect was significantly smaller in rats that were taken BPC 157. This was also confirmed by the histological analysis.
Conclusion: This positive effect of BPC 157 opens up opportunities for further research and a novel approach to apical periodontitis treatment.

P2 34

SYNDROME ARISING AFTER CATALEPTOGENIC DOSE OF L-NAME APPLICATION IN RATS AND THE EFFECT OF PENTADECAPEPTIDE BPC 157

Jurca I (Department of Diagnostic and Interventional Radiology, University Hospital Centre, Zagreb, Croatia and Departments of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Zizek H (Department of Diagnostic and Interventional Radiology, University Hospital Centre, Zagreb, Croatia and Departments of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Sjekavica I (Department of Diagnostic and Interventional Radiology, Sisters of Charity University Hospital, Zagreb, Croatia) Coric L (Departments of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: L-NAME causes catalepsy if administered in high doses, but syndrome occuring before, parallel and after clinical signs of catalepsy remains unexplored. We investigated pathophysiological changes leading to and following L-NAME-induced catalepsy and the effect of BPC 157 on these changes.
Materials and methods: Male Wistar rats were divided in 6 rats/group/time interval (30 minutes, 1 day and 3 days). Control ratsats were intraperotonelly administered with only L-NAME (40 mg/kg) and treated rats were afterwards adiministered BPC 157 10ng/kg intraperitoneally. Analysis of brain volume ratios was performed after craniotomy, via USB microcamera recordings, as well as presure measurement in superior saggital sinus (SSS), vena cava inferior (IVC), portal vein (PV) and abdominal aorta (AA) via intravascular cannulation. Brain volume (V) ratios were calculated using ImageJ software area (A) measurement uand square-cube law equation: $V_{con}/V_{BPC157} = (\sqrt{\frac{A_{con}}{A_{1BPC157}}})^3$.Venography was performed using 1mL of iodine contrast after infrarenal segment of IVC was cannulated, immediately after medication application.
Results: Control rats exhibited SSS, PV and IVC hypertension, AA hypotension (mmHg) (30min: 8±1SSS, 10±2PV, 19±2IVC, 62±4AA; 1day: 15±1SSS, 17±2PV, 20±2IVC, 90±4AA; 3days: 11±1SSS, 10±1PV, 18±2IVC, 50±3AA). Treated rats showed improved pressure values (30min: -3±1SSS, 6±1PV, 7±1IVC, 80±2AA; 1day: -12±1SSS, 7±1PV, 13±2IVC, 90±3AA; 3days: -17±2SSS, 8±1PV, 5±1IVC, 86±3AA). Control group exhibited greater brain volumes than treated group at all intervals: 30min-V_{con}/V_{BPC157}=1.52±0.02, 1day-V_{con}/V_{BPC157}=1.48±0.03, 3days-V_{con}/V_{BPC157}=1.22±0.02. Venography showed IVC dilation without opacification of visceral branches of AA in control rats, whereas in treated rats IVC wasn't dilated, visceral branches were opacified, along witd supraaortic branches of thoracic aorta.
Conclusions: BPC counteracts syndrome leading to and following L-NAME-induced catalepsy.

P2 35

THERAPEUTIC EFFECT OF PENTADECAPEPTIDE BPC157 ON KREON INDUCED MODEL OF ABDOMINAL AORTA ANEURYSM IN RATS

Hriberski K (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Brizic I Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Skorak I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Haluzan D, Figl J, Pavic P (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia), Mestrovic T (Department of Surgery, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: We showed the therapy effect of the stable gastric pentadecapeptide BPC 157 on Kreon (mixture of pancreatic enzymes) induced aneurysm of abdominal aorta in rats through activation of the collateral vascular pathways, mainly the azygos vein. Furthermore, we reveled the therapy's positive effect on vascular failure syndrome (intracranial, portal and caval hypertension, aortal hypotension, peripheral and central thrombosis). We used novel approach to cause damage to the aortic wall by using Kreon, mixture of pancreatic enzymes and applying it intravenously, without clamping the blood vessel unlike in previous models.
Materials and methods: We used male albino Wistar rats that were randomized in control and treated groups. The application-sacrifice period was 0-15 min. At the time period, we documented macroscopic appearance of the aorta, ECG changes, pressure in superior sagittalis sinus, portal vein, inferior vena cava and abdominal aorta. After sacrifice we evaluated the blood vessels for presence of thrombus and evaluated them as described before Biomedicines 2022 ,10(6):1299, Front. Pharmacol 2021, 12:718147.
Results: In all animals the application Kreon lead to the formation of aneurysm, while BPC 157 counteracted changes to the vessel wall as well as development of the vascular failure syndrome.
Conclusions: Therapy effect of the stable gastric pentadecapeptide BPC 157 should be further evaluated for the regular therapy of the aneurysm of the abdominal aorta.

P2 36

OCCLUSION OF SUPERIOR SINUS SAGITTAL SINUS IN RATS AND THERAPY WITH THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157, L-NAME AND L-ARGININE

Gojkovic S (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Dretar V (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Krezic I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: The aim of this study is to resolve the consequences of the permanently occluded superior sagittal sinus (SSS) and central venous occlusion in rats (i.e., multiorgan failure syndrome). The resolving focus was on the stable gastric pentadecapeptide BPC 157, its therapy effect shown to overwhelm peripheral venous occlusion syndromes.
Materials and methods: This study was conducted with 12-week-old, 200 g body weight, male albino Wistar rats, randomly assigned at 6 rats/group/interval. We administered the BPC 157, L-NAME, L-Arginine and combination of the latter two agents. For the rats euthanized at 24 h ligation-time, medication was given at 1 min ligation-time, 10 µg/kg BPC 157, 10 ng/kg BPC 157, or 5 mL/kg saline. We analyzed the mean blood pressure, ECGs and tissue specimens from internal organs at the predetermined intervals. On being euthanized major vessels were evaluated for clots. The presentation of the brain, and peripheral veins (azygos, superior mesenteric and inferior caval) was recorded in deeply anaesthetized rats, with a USB microscope.
Results: We observed rapid brain swelling in rats and peripheral vessels failure. Addition of L-NAME, L-arginine and the combination of these agents showed L-NAME reducing the effects, L-arginine aggravating the effects and the combination having a similar tied effect. Ligation of the SSS immediately overwhelms normal (negative) pressure and induces the increased (positive) pressure, along with the severe portal and caval hypertension (portal hypertension exceeding caval hypertension), and aortal hypotension, persisting throughout the entire experimental period. Thrombosis rapidly appeared.
Conclusions: BPC 157 fully counteracted observed disturbances in rat model of superior sinus sagittal sinus occlusion.

P2 37

FOURIER TRANSFORM INFRARED SPECTROSCOPY MEASUREMENTS OF INFLUENCE OF THE STABLE GASTRIC PENTADECAPEPTIDE BPC 157 ON RAT THORACIC AORTA

Gamulin O (Department of Physics and Biophysics, School of Medicine, University of Zagreb, Zagreb, Croatia), Maria Krajacic M (Department of Physics and Biophysics, School of Medicine, University of Zagreb, Zagreb, Croatia), Skrabic M (Department of Physics and Biophysics, School of Medicine, University of Zagreb, Zagreb, Croatia), Oroz K (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Coric H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Recently, confronted with major vessel occlusion and vascular failure, stable gastric pentadecapeptide BPC 157 therapy might rapidly upgrade minor vessel to take over the function of the disable major vessel, reorganize blood flow, and compensate failed vessel function.
Materials and Methods: We focused on the BPC 157 therapy effect given 10 ng/kg ip in rats at 5 min before sacrifice and on the rat thoracic aorta assessed with Fourier transform infrared spectroscopy (FTIR) at 90 min thereafter. We applied principal component analysis (PCA). PCA model showed, with a clear distinction mostly due to the PC1 score, difference between spectra of BPC 157- and saline-treated rats. Comparison of the averaged spectra of these two groups with their differential spectrum and PC loadings identified the parts of FTIR spectra that contributed the most to the spectral separation two observed groups.
Results: PC1 loadings and differential spectrum showed that the main bands affecting the separation were amid I band around 1650 cm^{-1}, amid II band around 1540 cm^{-1} and vibrational band around 1744 cm^{-1}. Fitting the spectral range between 1450 and 1800 cm^{-1} showed changes in protein conformation and confirms appearance of the vibrational band at 1744 cm^{-1}. Controls had the vibrational band at 1744 cm^{-1} substantially more intense. These might show the cells from saline-treated (control) rats in the early stage of the cell death while the samples from BPC 157-rats were protected.
Conclusions: Thus, BPC 157 therapy changed the lipid content and protein secondary structure conformation, rapid effect on vessels, within a short time upon application.

P2 38

INFLUENCE OF PENTADECAPEPTIDE BPC 157 ON THE HEALING OF COLON-COLONIC ANASTOMOSIS UNDER VENOUS CONGESTION CONDITIONS IN RATS

Duzel A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Artukovic B (Department of Veterinary Pathology, Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia), Rakic M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Kolovrat M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia),Begovic A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Andabak M (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Sabic A (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Intestinal anastomosis dehiscence is a major problem in abdominal surgery, especially under venous congestion conditions, as one of the most important factors of anastomosis healing is adequate intestinal blood supply. BPC 157 helps the healing process by stimulating granulation tissue creation, reducing the edema and stimulating angiogenesis. Additionaly, BPC 157 activates collateral circulation during vessel obstruction.
Material and methods: Total od 105 male Wistar rats were used, bodyweight 200-220 g, aged 8-10 weeks, divided into 15 groups and 5 time intervals (3,5,7,15, or 30 days post-op). For each time interval there was one control group and two treated groups (10µg/ kg or 10 ng/kg of BPC 157 i.p.). In deeply anesthetized rats, median laparotomy was performed and caudal mesenteric vein was ligated. Then transection of the colon descendens was done, after which terminoterminal colon-colonic anastomosis was created. Treated animals then received BPC 157, and control animals recieved 1 mL saline i.p. At each time interval various changes were examined: anastomosis dehiscence, adhesions, anastomosis passability, and vasa recta branching presentation, as well as histopathological study.
Results: Anastomosis dehiscence was evidenced in 31.42% control animals and in 2.85% treated animals. Adhesions and intestinal obstruction of the anastomosis were mitigated in treated groups. Anastomosis testing revealed better anastomosis solidity in treated animals and improved branching of the vasa recta sorrounding the anastomosis was evidenced. Histopathological analysis showed less edema and necrosis, earlier formation of granulation tissue, and better anastomosis epithelisation in treated animals.
Conclusions: Pentadecapeptide BPC 157 enhances colon-colonic anastomosis healing under venous congestion conditions.

P2 39

THE EFFECT OF PENTADECAPEPTIDE BPC 157 ON GLYCEROL INDUCED ACUTE KIDNEY INJURY

Dretar V (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Durasin T (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Vranes H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Rhabdomyolysis is a common clinical disorder in which 10 to 50% of patients develop some degree of acute kidney injury. Here we investigate the effect of stable gastric pentadecapeptide BPC157 on glycerol-induced rhabdomyolysis causing acute kidney injury.
Materials and methods: 14 Wistar rats were divided into 2 groups treated with 1mL/100g solution of 50% v/v glycerol in distilled water and injected intramuscularly into one thigh. After injection, one group received 1mL of a 10ng/kg solution of BPC 157 intraperitoneal injection followed by the same solution per os ad libitum for 24 hours, while the other group received 1 mL of saline followed by per os ad libitum for 24 hours. After treatment, blood pressure was measured by the non-invasive tail cuff method at minute 0, 15, 45, 90, 135, 180 and at the 24th hour when blood samples were collected. Serum urea and creatinine levels were measured to assess renal function and its injury.
Results: Blood pressure increased in both groups (highest value was 143/100mmHg at 90th minute in control group), but less in the BPC157-treated group (133/92mmHg at 90th minute). In the glycerol-injected saline-treated rats, serum urea (42 mmol/L) and creatinine (316 µmol/L) levels were elevated, indicating significant tubular and glomerular injury, whereas in the BPC157-treated rats, both serum urea (21 mmol/L) and creatinine (168 µmol/L) levels were lower and renal injury was less severe.
Conclusion: This result suggests that the pentadecapeptide BPC157 may have nephroprotective effects in glycerol-induced acute kidney injury in a 24-hour model.

P2 40

THE EFFECT OF BPC-157 ON SURGICALLY INDUCED LUMBAR SPINE INSTABILITY IN A RAT MODEL

Dokuzovic S (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia and Department of Spine surgery, Clinic for traumatology, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia), Krezic I (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Smoday IM (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Durasin T (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Dretar V (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: The aim of this study is to demonstrate the applicability of the therapeutic effects of BPC 157 (as earlier described for muscle, tendon, ligament, cartilage and bone) to a combination of these tissues (as in the spinal dynamic segment) in surgically induced lumbar spine instability in the rat.
Materials and methods: Upon performance of an interlaminectomy and bilateral facetectomy at the L3/4 level in deeply anesthesized female Wistar rats, aged 4 months, pentadecapeptide BPC 157 is applied perorally in drinking water (10mcg/kg/day and 10ng/kg/day, whereas controls drink only water 12ml/day/rat). Gait analysis, radiological and histological analysis is to be performed at 1, 2, 4, 6, and 12 montsh after surgery.
Results: Treated animals consistently demonstate better clinical performance as determined through gait analysis, less lumbar kyphotic deformity progression (clinically and radiographically), as well as better paravertebral muscle regeneration and intervertebral disk status histologically.
Conclusions: Our goal is to demonstrate that BPC 157 can be applicable as a pharmacological means for treating lumbar spinal instability.

P2 41

PILOCARPINE AND LITHIUM STATUS EPILEPTICUS IN RATS AND PENTADECAPEPTIDE BPC 157, L-NAME, AND L-ARGININE THERAPY EFFECT

Chiddenton HM (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Buric S (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Kalogjera L (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Vranes H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

As particular point of the BPC-157 activities (i.e. BPC-157 counteracted lidocaine-arrhythmias, local anesthetic effect, and convulsions). It might be that BPC 157 activities might approach and modulate the long-ago suggested antiarrhythmic agents potential throughout myocardial ischemia-arrhythmia-local anesthetic-anti-convulsion potential (for review see i.e. Am. J. Physiol. 1950, 163, 505-516.). Illustratively, in addition to the lidocaine-induced convulsion antagonization, BPC-157 might counteract standard convulsants (i.e. picrotoxine, strychnine, bicuculline, metrazole)-induced seizures, as well as the insulin-, paracetamol-, alcohol withdrawal- and serotonin-syndrome-induced convulsion. Recently, we reported the BPC 157 particular therapy effect in the neuroleptic or L-NAME-induced catalepsy, lithium intoxication and in the schizophrenia positive and negative symptoms, through particular interaction with NO-system. Here, we reported the effect of the BPC-157 (10 µg/kg, 10 ng/kg), L-NAME (5 mg/kg), L-arginine (100 mg/kg), given intraperitoneally alone and/or combined, on the status-epilepticus in rats induced by pilocarpine 60, 80, 120 mg/kg and lithium 127 mg/kg by intraperitoneal application. The effects were assessed throughout 3 h. BPC-157 application consistently counteracted pilocarpine/lithium convulsions. L-NAME consistently aggravated the pilocarpine/lithium convulsion presentation and was associated with fatal outcome before the end of the observation period. Interestingly, L-arginine also consistently aggravated the pilocarpine/lithium convulsion presentation. Given together, these aggravating effects did not counteract each other. These aggravating effects were consistently attenuated by the BPC-157 application. Thus, with BPC-157 involvement, the pilocarpine/lithium convulsions have a particular NO-relation, L-NAME aggravating potential, and L-arginine-aggravating potential. Since these parallel effects might not counteract each other effect, the other non-NO-system might be also involved.

P2 42

THERAPEUTIC EFFECT OF PENTADECAPEPTIDE BPC 157 IN RATS WITH ISCHEMIAREPERFUSION INJURY AFTER OCCLUSION OF THE INFRARENAL ABDOMINAL AORTA

Ivan Brižić (MEF Zagreb), Ivan Škorak (Mef Zagreb), Klaudija Hriberski (Mef Zagreb), Predrag Pavić (KBC Zagreb), Tomislav Meštrović (KBC Zagreb), Ivan Krezić (MEF Zagrb), Helena Žižak (Mef Zagreb), Predrag Sikirić (Mef Zagreb)

Introduction

During every vascular operation surgery on arteries, ischemia-reperfusion (IR) injury occurs, Therefore it is extremely important to discover new therapeutics in treatment. We demonstrated the therapeutic effect of the pentadecapeptide BPC 157 (10 µg/kg, 10 ng/kg ig or po) in rats with ischemia-reperfusion injury after occlusion of the infrarenal abdominal aorta.

Materials and methods

An established model of infrarenal abdominal aorta clamping was used, in which one hour ischemia is achieved by placing a vascular clamp directly infrarenal in a previously laparotomized rat. Immediately after releasing the vascular clamp, the rats were treated with intraperitoneal or intragastric administration of BPC 157 in a dose of 10 ng/kg. We observed the animals, recorded them with a microcamera, analyzed heart rhythm, heart pressure, analyzed PHD samples and organ function according to previously described research in 3 intervals from the release of the clamp (15 min, 1 hour, 24 hours).

Results

In all groups treated with BPC 157, suppression of the early adverse effects of occlusion-like syndrome and immediate vascular failure was evident. Untreated compared to treated animals usually had intracranial (superior sagittal sinus), portal and caval hypertension and aortic hypotension, massive brain swelling, bleeding and lesions, cardiac dysfunction, pulmonary lesions, liver and kidney failure and gastrointestinal lesions, severe arterial and venous thrombosis, peripheral and central.

Conclusion

Considering the mechanisms by which it achieves its effects and the effects of BPC 157 itself, the application of BPC 157 directly post-ischemic will have a favorable effect on the suppression of vascular failure and occlusion-like syndrome, as well as organ dysfunction and injury after infrarenal aortic clamping from the macroscopic to the molecular level.

P2 43

SEVERE ULCERATIVE COLITIS AND PENTADECAPEPTIDE BPC 157 THERAPY

Bekic D (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Kalogjera L (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Vranes H (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Severe ulcerative colitis leads to the development of systemic syndrome with secondary repercussions on pressure in blood vessels. That causes injuries in intraabdominal, intrathoracic organs and brain. The protective effect of BPC 157 in lesions in the gastrointestinal tract has been described, but the systemic effect of severe ulcerative colitis and the effect of BPC 157 in it has not been described. Previous large blood vessel occlusion studies in rats have described that pentadecapeptide 157 activates collateral circulation, thereby antagonizing the hemodynamic effect of vascular occlusion and reducing secondary parenchymal organ damage.
Materials and Methods: In our study, we induced severe ulcerative colitis by intrarectal injection of 1 ml (9%) of acetic acid, and we proved the systemic effect by invasive hemodynamic measurements.
Results: We showed that severe ulcerative colitis causes systemic syndrome characterized with systemic hypotension, intracaval, intraportal and intracranial hypertension. Pentadecapeptide BPC 157 was given intraperitoneally in defined time intervals (1 minute, 15minutes, 30 minutes, 60 min and 12 hours) counteracted severe colitis development. In addition, all systemic effects were reversed by BPC 157.
Conclusions. We revealed that BPC 157 antagonizes systemic effects caused by severe ulcerative colitis.

P2 44

THE EFFECT OF BPC-157 ON THE SISTEMIC EFFFECTS OF INDUCED OPEN ANGLE GLAUCOMA IN RAT MODEL

Sablic M (Department of anatomy and neuroscience, Medical faculty Osijek and Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Vukovic V (Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia), Kokot A (Department of anatomy and neuroscience, Medical faculty Osijek and Department of Pharmacology, School of Medicine, University of Zagreb, Zagreb, Croatia)

Introduction: Using rat open-angle glaucoma model (cauterization of the three of the four episcleral veins), we demonstrated a particular beneficial effect of BPC 157 therapy on the glaucomatous eye injury (Biomedicines. 2021;10(1):89). Per-oral, intraperitoneal and local eye therapy with stable gastric pentadecapeptide BPC 157 regimens immediately normalized intraocular pressure, and at the end, preserved ganglion cells with normal fundus, retinal and choroidal blood vessel and optic nerve presentation. With the evidence that the upgraded minor vessel may take over the function of the failed major vessel, and reorganize blood flow, we combined this anti-glaucomatous effect in the rat eye with the recovery of the other vascular and multiorgan failures-induced various occlusion/occlusion like syndromes induced with major occlusion and other alike noxious procedures. Now, we focused the beneficial effects of BPC 157 on rat glaucoma as vascular failure and multiorgan failure-induced occlusion/occlusion like syndrome, and therapy as whole.
Materials and methods/Results: In the glaucomatous rats (Biomedicines. 2021;10(1):89.), using assessment previously described (Biomedicines. 2022;10(7):1462), BPC 157 therapy (intragastrically, two drops in each eye, subcutaneously) counteracted the noxious course of the occlusion/occlusion like syndrome as whole given at 15 min, or latter (1, 24, 48h after cauterization). In addition to the rapid normalization of intraocular pressure, counteracted were specifically the intracranial (superior sagittal sinus) hypertension, portal hypertension, aortal hypotension, thrombosis and the organs lesions (i.e. post-injury brain swelling was instantly reversed) as described in the therapy of the other occlusion/occlusion like syndromes.
Conclusion. These findings favor further BPC 157 anti-glaucomatous therapy.

Poster session 3 with organized discussion Students section "HDF youth programme"

Chairpersons: Petra Dolenec (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Jelena Osmanović Barilar (Department of Pharmacology and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia)

P3 01

THE EFFECT OF MUSIC AND SOUNDS ON ANXIETY AND STRESS LEVELS

Nora Bacelj (2nd year student of graduate study of Experimental Biology, University of Zagreb Faculty of Science, Zagreb, Croatia), Lucija Tudor (Laboratory for Molecular Neuropsychiatry, Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, Croatia)

INTRODUCTION: Stress and anxiety are becoming inevitable part of everyday life, especially in younger population, which can lead to numerous psychophysical changes. Lately, it has been shown that relaxation music, auditory beat stimulation (bineural beats) in theta frequency range and pink noise could lower the cortisol levels, heart beat and blood pressure and promote sleep stability which could lead to better cognitive performance.
MATERIALS AND METHODS: The study included total of 34 students of both sex from Music Academy and Rochester Institute of Technology in Zagreb, that were divided in groups who listened to classical music, pink noise and combination of pink noise and bineural beats (4Hz – 8Hz) for 20 minutes. All subjects completed the State-Trait Anxiety Inventory (STAI) and Relaxation Scale State (RSS) before and after listening to music or sounds. The change in anxiety and relaxation levels between students who listened different tapes was analyzed using ANOVA or t-test for repeated measures.
RESULTS: All students had significantly lower scores on STAI state scale after listening to tape, independent of the type of sound they were listening to, although there was a trend showing that music had the highest effect on lowering the anxiety levels, especially in students from music academy. The increased RSS scores after listening to tape were observed in most subjects, but it failed to reach significance levels.
CONCLUSIONS: This study showed that listening to music and auditory beat stimulation could lower the anxiety levels in students and could offer alternative strategies in coping with stress.

P3 02

SAFETY PROFILE OF JAK INHIBITORS BASED ON THE RECEIVED REPORTS OF SUSPECTED SIDE EFFECTS

Lora Pavlinovic (5th year student of the Study of Pharmacy, University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Nikica Mirošević Skvrce (Agency for Medicinal Products and Medical Devices of Croatia, Zagreb, Croatia)

INTRODUCTION: EMA's safety committee, PRAC, has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders. JAK inhibitors are categorized as synthetic disease-modifying antirheumatic drugs (tsDMARDs) which suppress multiple cytokine and growth factor receptor signaling pathways. At present, 5 medicines are approved by EMA - tofacitinib, abrocitinib, baricitinib, upadacitinib and filgotinib. The review was prompted by the final results from a clinical trial with tofacitinib that showed that patients at risk of heart disease were more likely to experience a major cardiovascular problem, cancer, venous thromboembolism, infections and death than those treated with TNF-alpha inhibitors.
MATERIALS AND METHODS: Aim of this study was to analyze reported ADRs available in HALMED's database by 01.06.2022. in relation to the total number, age and sex of the patient, seriousness of reactions and reported reactions by MedDRA organic classification (Medical Dictionary for Regulatory Affairs).
RESULTS: A total of 153 reports of suspected side effects of JAK inhibitors were received. Most reports were received for patients aged 45 to 64 years. Regarding gender, majority (72%) of reports refer to female patients. Considering MedDRA organic classification, largest number of side effects refer to following organ systems: General disorders and administration site conditions, Infections and infestations, Investigations, Gastrointestinal disorders and Skin and subcutaneous tissue disorders. Majority of received reports, 59.5%, refer to non-serious side effects and the rest, 40.5%, refer to serious side effects. Most of the 62 serious side effects led to other medically significant conditions and only a few caused or prolonged hospitalization.
CONSLUSIONS: JAK inhibitors have shown good efficacy and rapid response, but nevertheless, their safety profile and various reports of suspected side effects indicates that monitoring of therapy and caution is necessary.

P3 03

ATTITUDES TOWARDS USE OF SUPPLEMENTS DURING COVID- 19 PANDEMICS

Ana Matijević (6th year student of the Study of Medicine, J.J. Strossmayer University of Osijek School of Medicine, Osijek, Croatia), Suzana Mimica (Clinic for Internal Diseases, Clinical Hospital Centre Osijek, Osijek, Croatia)

INTRODUCTION: The popularity of complementary and alternative therapy is increasing. COVID-19 pandemic has led to a global increase in the consumption of diet supplements to boost immunity. Patients often do not have a diet rich in vitamins and minerals, hence they use diet supplements to replace the nutrients. There is no robust evidence that any supplement could lead to COVID cure.
MATERIALS AND METHODS: 753 adults of all ages were included in the study. The survey was conducted anonymously, online (700) and in family physicians' clinics (53). The questionnaire covered demographic and socioeconomic determinants and questions were designed to evaluate the knowledge on food supplement terminology, proper use, possible side effects and contraindications.
RESULTS: Supplements were used by most subjects, most commonly vitamins B, C and D, zinc and magnesium. One-third of subjects started using supplements during the pandemic, mostly on their own initiative. Generally, supplements were mostly used by subjects between 25 and 45 years of age and were used less frequently by the elderly. Family practitioners were generally not aware of the patient's use of supplements. Also, supplements were used more by subjects higher vocational education. Most subjects claimed to know the exact purpose of using each supplement and were well acquainted with possible side effects and interactions.
CONCLUSION: 80% of respondents used to or were using supplements, half of whom started during the pandemic. The subjects partially understood important data on supplement use, side effects, and interactions with other drugs. As diet supplements are regulated by the Food Act and are not a subject to medicines regulation, a great caution and rationalization of use is required.

P3 04

THE EFFECT OF ORAL GALACTOSE ON THE INSULIN SIGNALLING PATHWAY IN THE PARIETAL CORTEX OF A TRANSGENIC MICE MODEL OF ALZHEIMER'S DISEASE

Anna Ipša (5th year student of the Study of Pharmacy, University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Ana Babić Perhoč (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia)

INTRODUCTION: Tg2576 is a widely used strain of familial Alzheimer's disease (fAD) transgenic models. In the present research, we aimed to further characterize several aspects of this model and analyse its response to oral galactose, which was previously shown to prevent/normalize cognitive and metabolic deficit in a model of sporadic AD characterized by dysfunction of the insulin receptor pathway and insulin-resistant brain state.
MATERIALS AND METHODS: A total of 48 male Tg2576 transgenic mice (TG) and matching wild-type controls (WT) aged 5 and 10 months were used. Oral galactose (200 mg/kg/day; +GAL) or tap water as a drink was administered for two months. At 7 and 12 months, respectively, mice were sacrificed and their parietal cortices were withdrawn and fresh-frozen. Insulin receptor (IR), phosphorylated/total protein kinase B (pAKT/AKT) and glycogen synthase kinase 3β (pGSK-3β/GSK-3β) levels were measured by Western blot.
RESULTS: Compared to WT, 7-month-old TG mice showed significantly increased levels of IR (+31% vs WT), with no effect by GAL, whereas GAL exposure significantly increased the pAKT/AKT ratio (+64,36% vs TG) in TG mice. No such effects were observed in 12-months-old TG and WT mice in either measured protein expression. Furthermore, no significant changes were noted in the pGSK-3β/GSK-3β ratio in either group at both ages.
CONCLUSIONS: Changes in the parietal cortex insulin receptor signalisation and alteration by oral GAL administration were found to only occur in the presymptomatic phase of fAD (7-month-old Tg2576 mice), with the observed effects being lost in the mild fAD model (12-months-old mice).

P3 05

USE OF CANNABIS FOR MEDICINAL PURPOSES

Frane Valković (6th year student of the Study of Medicine, University of Rijeka Faculty of Medicine, Rijeka, Croatia), Jasenka Mršić-Pelčić (Department of Basic and Clinical Pharmacology and Toxicology, University of Rijeka Faculty of Medicine, Rijeka, Croatia)

INTRODUCTION: Cannabis sativa has been the subject of research for medicinal use for decades. A number of active compounds have the potential to be used in medicine, such as tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN), etc.
MATERIAL AND METHODS: A review of the available literature was conducted using PubMed database and sources on the official websites of HALMED, EMA, and WHO to search clinical studies related to medicinal use, as well as the legal framework for the medicinal use of cannabis in the Republic of Croatia and worldwide.
RESULTS: Numerous therapeutic effects of cannabis have been demonstrated in clinical research, and the medical use of cannabis and cannabinoid-based medicines has been established in most of the countries studied, including the Republic of Croatia. The main indications are the treatment of nausea and vomiting in patients with malignant diseases, receiving emetogenic therapy, resistant epileptic seizures in Dravet syndrome, cachexia and anorexia in HIV/AIDS patients, spasticity in multiple sclerosis, and chronic pain in patients with malignancies. Approved indications may vary from country to country. Medications based on cannabis and cannabinoids are used as adjunct therapy to other medically indicated conditions.
CONCLUSION: The medical use of cannabis and cannabinoid-based medications continues to be the subject of numerous clinical trials. There are several approved indications, as well as therapeutic potential in a number of other diseases, but the results of the effects in a large number of patients and the analysis of the dosage are needed to allow further indications.

P3 06

REDOX HOMEOSTASIS PRESERVATION ALONG THE GASTROINTESTINAL TRACT OF THE RAT BRAIN-FIRST 6-HYDROXYDOPAMINE MODEL OF PARKINSON'S DISEASE

Gracia Grabarić (5th year student of the Study of Medicine, University of Zagreb School of Medicine, Zagreb, Croatia) Jan Homolak (Laboratory for Molecular Neuropharmacology, Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia), Melita Šalković-Petrišić (Laboratory for Molecular Neuropharmacology, Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia)

INTRODUCTION: Parkinson's disease (PD) is a neurodegenerative disorder often accompanied by gastrointestinal changes that precede central neuropathology. Oxidative stress is an important etiopathogenetic factor, however, the relationship between gastrointestinal alterations and redox dyshomeostasis in PD is not well understood. We aimed to study gut redox homeostasis in the brain-first rat model of PD[1] to elucidate whether central changes may promote gastrointestinal oxidative stress.
MATERIALS AND METHODS: Brain-first model of PD was generated by bilateral intrastriatal 6-hydroxydopamine (n=14; 8µg in 2µl 0.02% ascorbic acid/striatum;6OH). Untreated (n=9;CTR) and vehicle-treated animals (n=14;CIS) were used as controls. Motor deficits were assessed with the rotarod test. Redox biomarkers (thiobarbituric acid reactive substances, nitrocellulose redox permanganometry, catalase/peroxidases, low molecular weight thiols (LMWT) and protein sulfhydryls, and Cu/Zn and Mn superoxide dismutase activities) were measured in duodenum, ileum, and colon. The ethics approval was granted by the Croatian Ministry of Agriculture (EP 186 /2018) and the UZSM Ethical Committee (380-59-10106-18-111/173).
RESULTS: The 6OH group developed pronounced motor deficits. Analysis of redox biomarkers revealed no pronounced alterations of the overall redox homeostasis. Lipid peroxidation was decreased in the duodenum and ileum of the CIS and 6OH tissue.LMWTs were increased in the colon of the CIS group. [2]
CONCLUSIONS: The 6-OH brain-first model of PD is characterized by motor deficits that are not accompanied by gut redox dyshomeostasis.

P3 07

ADHERENCE TO CHRONIC THERAPY DURING COVID-19 PANDEMICS

Ivan Balić (student of the Study of Medicine, J.J. Strossmayer University of Osijek School of Medicine, Osijek, Croatia), Suzana Mimica (University hospital center Osijek, Department of Clinical Pharmacology and Faculty of Medicine Osijek, Department of Internal Medicine and History of Medicine, Osijek, Croatia)

INTRODUCTION: Adherence to medication is the patient's willingness to comply with time, dose and the frequency of taking that medicine. According to data from the World Health Organization, around 50% patients in developed countries is adherent to their therapy. Adherence is particularly important in treatment of chronic diseases as higher degree of adherence leads to better health outcome and lower treatment costs.
MATERIALS AND METHODS: A survey questionnaire was use in our reseach and it included a series questions on demographic, socioeconomic and specific indicators that determined adherence to chronic therapy in the last year. Also, a validated adherence assessment questionnaire (Morisky Medication Adherence Scale, MMAS) was also used. The survey was conducted among 173 adults patients with one or more chronic diseases in the family medicine offices in Health Centre Osijek in April 2022.
RESULTS: High adherence (a score up to one point according to MMAS) was observed in one third of the patients in this study. Demographic and socioeconomic indicators did not influence the adherence. Indicators that significantly influenced adherence in this study was availability of city transport, adherence to therapeutic scheme obtained by doctors and habits of picking up medicines in local pharmacies. COVID status and availability of doctors during the pandemic did not affect the adherence. No significant difference was found in adherence with regard to the type of chronic disease.
CONCLUSION: The COVID-19 pandemic had no effect on adherence to chronic therapy in this study. For most patients, the family doctor was available and they could maintain their chronic therapy. Habits and mobility of the patient affect the adherence and should represent the basis of adherence strengthening. Our research also proved the importance of interprofessional cooperation between doctors and pharmacists.

P3 08

INTESTINAL REDOX PARAMETERS IN THE ALZHEIMER'S DISEASE RATS RECEIVING ORAL D-GALACTOSE

Mihovil Joja (6th year student of the Study of Medicine, University of Zagreb School of Medicine, Zagreb, Croatia), Jan Homolak (Laboratory for Molecular Neuropharmacology, Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia), Melita Šalković-Petrišić (Laboratory for Molecular Neuropharmacology, Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia)

INTRODUCTION: Intracerebroventricular administration of streptozotocin (STZ-icv) to rats causes cognitive deficits with accompanying pathological changes reminiscent of those found in sporadic Alzheimer's disease (1). Interestingly, chronic oral D-galactose administration prevented cognitive impairment in STZ-icv rats (2). However, chronic parenteral administration of D-galactose accelerates cognitive decline in aging rodents via an increase in oxidative stress (3). Therefore, we aimed to access the effect of oral D-galactose on redox parameters along the intestinal tract in control and STZ-icv rats.
METHODS: Three-month-old male Wistar rats (N=40) were split into two groups treated bilaterally by intracerebroventricular injection of either streptozotocin (STZ-icv,3 mg/kg) or vehicle (CTR). Animals were further assigned into a group receiving daily oral galactose solution (200 mg/kg) or vehicle (tap water). After two months, rats were euthanized and proximal duodenum, distal ileum, and distal colons (N = 20) were dissected and stored at -80°C. Lipid peroxidation was assessed by thiobarbituric acid reactive substances (TBARS), catalase activity was assessed indirectly by quantification of the carbonato-cobaltate (III) complex, low molecular weight thiols (LMWT) and total protein sulfhydryls (SH) were measured with 5,5'-dithio-bis(2-nitrobenzoate). Total antioxidant capacity (TAC) was evaluated by nitrocellulose redox permanganometry (4) (NRP) and ABTS assay.
RESULTS: In the duodenum, LMWT and SH were decreased in groups receiving galactose, and catalase was decreased in STZ-icv animals. In the ileum, the only noticeable change was a decrease in TBARS in STZ-icv group receiving galactose. In the colon, D-galactose reduced CAT and TBARS levels, with TAC and SH levels decreased only in the galactose-treated STZ-icv group.
CONCLUSION: The effect of oral D-galactose administration on redox parameters differs in between parts of the intestine, with a slight shift in the colon and no prominent effect in the ileum and duodenum. STZ-icv animals might have a different response to D-galactose.
This work was funded by the Croatian Science Foundation (IP 2018 01 8938 and Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxic ischemic damage in perinatal and adult brain" GA KK 01 1 1 01 0007 funded by the European Union through the European Regional Development Fund).

P3 09

ASSESSMENT OF PATIENTS ON ORAL ANTITHROMBOTIC THERAPY REFERRED TO THE DEPARTMENT OF ORAL SURGERY FOR SIMPLE TOOTH EXTRACTION – A PRELIMINARY REPORT

Monika Burja Vladić (6th year student of the Study of Dental Mmedicine, University of Zagreb School of Dental Medicine, Zagreb, Croatia), Ivan Salarić (University of Zagreb School of Dental Medicine, Department of Maxillofacial and Oral Surgery, University Hospital Dubrava, Zagreb, Croatia), Ena Zdunić (University of Zagreb School of Dental Medicine, Department of Maxillofacial and Oral Surgery, University Hospital Dubrava, Zagreb, Croatia), Berislav Perić (University of Zagreb School of Dental Medicine, Department of Maxillofacial and Oral Surgery, University Hospital Dubrava, Zagreb, Croatia), Lea Vuletić (Department of Physiology, University of Zagreb, School of Dental Medicine, Zagreb, Croatia)

INTRODUCTION: This study aims to assess the necessity of the referral of patients on oral antithrombotic therapy to the University Hospital Dubrava Department of Oral Surgery in Zagreb for simple tooth extraction.

PARTICIPANTS AND METHODS: Thirty patients were recruited into the study from June to August 2022. Patients referred to the Department of Oral Surgery for an uncomplicated tooth extraction using any kind of oral antithrombotic therapy met eligibility criteria. Other patient information (age, general health, medication use, allergies to drugs, etc.) were collected using a questionnaire. Oral surgeons assessed if the procedure could have been performed in general dental practice.

RESULTS: Most commonly used antithrombotic agent was acetylsalicylic acid. Seven patients were taking warfarin and four used NOACs. General dental or medical practitioner advised the patient to stop their antithrombotic therapy 1-3 days prior to dental procedure in 14 cases. Oral surgeons estimated that the indicated procedure could have been safely performed in primary dental care for 22 patients, given that the clinician has the relevant training and self-confidence.

CONCLUSIONS: Referral of patients to oral surgery departments for simple extractions is not uncommon, likely to ensure patients' safety. However, a number of these patients may be provided service safely in general dental practice as well. Preliminary data of the study show that dentists still tend to advise patients to discontinue their antithrombotic therapy prior to simple tooth extraction which is not in line with the contemporary guidelines for managing dental patients receiving antithrombotic treatment.

P3 10

COMPLEX MECHANISMS OF BOTULINUM TOXIN TYPE A ACTION ON EXPERIMENTAL PAIN - TIME TO LOOK BEYOND THE FIRST SYNAPSE

Matej Mustapić (4th year students of the study of Medical Biochemistry, University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Marijana Skenderović (4th year students of the study of Medical Biochemistry, University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Dalia Vađunec (Department of Pharmacology, University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia), Lidija Bach-Rojecky (Department of Pharmacology, University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia)

INTRODUCTION: Botulinum neurotoxin type A (BoNT-A) cleaves SNAP-25, a part of cellular machinery that mediates neurotransmitters exocytosis. Its antinociceptive effect, demonstrated in various experimental pain models, is mediated by complex mechanisms in the central nervous system, possibly at the level of the first synapse. This study aimed to investigate possible transcytosis of BoNT/A after its peripheral application.
MATERIALS AND METHODS: BoNT-A (7 IU/kg) was unilaterally applied in the facial vibrissae of Wistar rats one day before intracisternal administration of antitoxin against BoNT-A (5 IU/10µL). After seven days, formalin (2.5%) was injected into both facial vibrissae. The time rats spent rubbing the application sites was measured for 45 minutes. Immunohistochemical analyses of c-Fos (a marker of neural activation) and cleaved SNAP-25 (a marker of BoNT-A activity) were performed in the sections of the trigeminal nucleus caudalis (TNC). Experiments were approved by the Ethical Committee of the University of Zagreb School of Medicine.
RESULTS: Peripheral application of BoNT-A reduced the time that rats spent rubbing the injected area, while antitoxin prevented this effect. Immunohistochemical data showed that BoNT-A reduced the expression of c-Fos positive neurons at the ipsilateral side of TNC and, to a lesser extent, on the contralateral side, while the applied antitoxin significantly reduced this effect. Similarly, antitoxin reduced the BoNT-A associated expression of cleaved SNAP-25 at both sides of the TNC.
CONCLUSIONS: Here we show that BoNT-A decreases the pain intensity, especially at the beginning of the inflammatory phase, and suggest its possible transcytosis within TNC in the brainstem.
This research is supported by Croatian Science Foundation (project no. HRZZ-UIP-2019-04-8277).

P3 11

BIOCHEMICAL PROPERTIES OF RAT FECAL PELLETS ACCOMPANYING THE DEVELOPMENT OF MOTOR DEFICITS IN A 6-HYDROXYDOPAMINE-INDUCED RAT MODEL OF PARKINSON'S DISEASE

Pavel Marković (5th year student of the Study of Medicine, University of Zagreb, School of Medicine), Ana Babić Perhoč (Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia)

INTRODUCTION: Gastrointestinal alterations precede the development of motor symptoms of Parkinson's disease (PD) and accumulating evidence suggests a possible causal relationship. Consequently, the gastrointestinal tract may be an important pharmacological target for the prevention of disease development and feces may serve as a valuable source of biomarkers for early diagnosis. The present aim was to assess biochemical profiles of fecal pellets accompanying the development of motor deficits in the 6-hydroxydopamine-induced rat model of PD.
MATERIALS AND METHODS: Intrastriatal administration of 6-hydroxydopamine (8µg/2µl/striatum in 0.02% ascorbic acid) was performed in 20 rats, while 10 animals received vehicle only (CTR). Motor performance was assessed using the rotarod performance test, and 24-hour fecal pellets were collected at 3-time points during the 9 weeks. Pellets were analyzed morphometrically in the context of motor performance trajectory and then subjected to biochemical analysis of lipids (Sudan black lipid blot[1]), redox homeostasis (nitrocellulose redox permanganometry[2], 2,2'-Azinobis(3-Ethylbenzthiazoline-6-Sulfonate)[3], catalase/peroxidase), and mucin content (Alcian blue). The ethics approval was granted by the Croatian Ministry of Agriculture (EP 186 /2018) and the UZSM Ethical Committee (380-59-10106-18-111/173).
RESULTS: The 6-hydroxydopamine-treated rats demonstrated variable susceptibility to the development of motor deficits. Highly susceptible animals had lower fecal antioxidant capacity and mucin content and increased fecal lipid concentration. The animals with low susceptibility to 6-hydroxydopamine-induced motor impairment produced more fecal pellets and had higher stool water content.
CONCLUSIONS: The biochemical composition of feces may predict the development of motor deficits in the 6-hydroxydopamine model and may provide valuable insights into the pathogenesis of PD.
This work was funded by the Croatian Science Foundation (IP-09-2014-4639 and IP-2018-01-8938) and the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain"; GA KK01.1.1.01.0007 funded by the European Union through the European Regional Development Fund).

P3 12

THE NEUROPROTECTIVE POTENTIAL OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN AN *IN VITRO* MODEL OF ALZHEIMER'S DISEASE

Robert Pendelić (2nd year of graduate study of Molecular Biology, University of Zagreb Faculty of Science, Zagreb, Croatia), Gordana Nedić Erjavec (Division of Molecular Medicine, Ruđer Bošković Institute, Zagreb, Croatia)

INTRODUCTION: Alzheimer's disease (AD) is the most common cause of dementia manifested through memory loss and decline of other cognitive functions caused by neuronal and synaptic loss in the brain, associated with amyloid beta (Aβ) accumulation. To this date, the disease has no cure and this represents a major challenge for scientists all over the world. However, brain derived neurotrophic factor (BDNF), involved in the promotion and survival of neurons and the growth and differentiation of new neurons and synapses, shows potential in AD prevention. The aim of this study was to observe the potential neuroprotective effect of BDNF treatment in an *in vitro* model of AD.
MATERIALS AND METHODS: Cortical neurons, isolated from C57BL/6 mice embryos* and exposed to Aβ42 oligomers, were used as an *in vitro* model of AD. After the treatment with BDNF, neuronal viability and underlying mechanisms were tested using MTT, Promega apoptosis assays and Muse viability and apoptosis assays. GraphPad Prism was used to interpret the obtained results.
RESULTS: The results of the study confirm the neuroprotective effect of BDNF and suggest that it reduces apoptotic activity in an *in vitro* model of AD.
CONCLUSIONS: Although our findings imply potential therapeutic effects of BDNF against amyloid beta toxicity in AD, further extensive studies, including animal and human studies, are needed to confirm the obtained results.
**In accordance with Directive 2010/63/EU by European Parliament and the Council for the protection of animals used for scientific purposes, the Animal Protection Act NN 102/17, 32/19, and the Ordinance for the Protection of Animals Used in scientific purposes NN 55/13, and its amendments NN 39/17, procedures on sacrificed animals for the purpose of organ isolation for the purpose of obtaining primary cell cultures are not considered experiments and do not require a permit from the Ethics Committee.*
Funding source: Project 'Therapeutic potential of neurosteroids and neurotrophins in dementia' (HRZZ-IP-2019-04-6100), PI Dubravka Švob Štrac

P3 13

ANTIBIOTIC THERAPY IN THE COVID-19 PANDEMIC: RETROSPECTIVE COHORT STUDY OF PATIENTS HOSPITALIZED AT THE UNIVERSITY HOSPITAL OF SPLIT

Starčević D (6th year student of the Study of Dental Medicine, University of Split School of Medicine, Split, Croatia) Pranić S (Department of Research in Biomedicine and Health, University of Split School of Medicine, Split, Croatia) Pinjatela J (Department of Internal Medicine University Hospital of Split, Split, Croatia) Skelin M (Department of Basic and Clinical Pharmacology with Toxicology, University of Rijeka Faculty of Medicine, Rijeka, Croatia) Mudnić I (Department of Basic and Clinical Pharmacology University of Split School of Medicine, Split, Croatia)

INTRODUCTION: During the COVID-19 pandemic, the frequency of antibiotic use has increased globally. Our primary objective was to determine the frequency of use and type of antibiotic therapy for COVID-19 patients hospitalized at the University Hospital of Split. The secondary objective was to show the association of the use of antibiotic therapy with comorbidities, selected laboratory findings and death.
SUBJECTS AND METHODS: The retrospective study is part of a larger multicenter study and was conducted on a cohort of 285 patients hospitalized at the Clinic for Infectious Diseases in Split during October and November 2020. Following variables were analysed: age, gender, number of days spent in hospital, data on previous illness, antibiotic therapy, diagnosed pneumonia, systolic and diastolic blood pressure, and laboratory findings: value of peripheral blood oxygen saturation, concentration of urea, creatinine, total bilirubin, D dimer and proportion of neutrophils and lymphocytes.
RESULTS: Data on the use of antibiotic therapy refer to 266 subjects. The majority of subjects were treated with antibiotics (N=239 (84 %)). Patients on antibiotic therapy had more comorbidities compared to those non-treated (P=0.008). The antibiotic of choice was azithromycin in 141 (59%), followed by amoxicillin with clavulanic acid, used in 117 (49%) patients. Ceftriaxone was used in 51 (21%) patients, and only one patient was treated with doxycycline (0.4%).
CONCLUSION: Antibiotic treatment of COVID-19 patients requires individual clinical judgment for each patient and should be carried out in accordance with existing guidelines. In the presented cohort antibiotic therapy was not associated with a fatal outcome.

P3 14

EXPLORATION OF THE ANTIOXIDATIVE AND ANTI-INFLAMMATORY EFFECTS OF ARONIA MELANOCARPA EXTRACT IN AN *IN VITRO* MODEL OF PARKINSON'S DISEASE

Tomislav Glavan (Integrated Undergraduate and Graduate University Study of Medicine, 5th year, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Anja Harej Hrkać (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia), Kristina Pilipović (Department of Basic and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia)

Introduction: Numerous studies have suggested that astrocytes are involved in the pathophysiology of Parkinson's disease (PD), but most of the research on the therapeutic options in PD have been focused on the effects of potential treatments on the neurons. We have previously found that pretreatment of primary mouse astrocytes exposed to mitochondrial toxin 6-hydroxydopamine (6-OHDA) with Aronia melanocarpa (chokeberry) extract had protective effects. In this study, we aimed to explore if the protection of astrocytes in this in vitro model of PD was related to the antioxidant and anti-inflammatory effects of chokeberry.
Materials and methods: Primary mouse astrocytes were grown on 6-well plates until confluent. Cells were either not treated or pretreated for 24 h with chokeberry extract (100 µg/mL), and 6-OHDA (120 µM) was added to the cell culture medium during the next 72 h at which point cell samples were prepared for the western blot analyses. Non-treated, non-injured cells were used as the control.
Results: In this preliminary study, we found no significant effects of 6-OHDA application or chokeberry extract pretreatment on the expressions of antioxidant enzymes SOD-1 and GPX-1, as well as on the activation of the NFκB pathway.
Conclusions: In our experimental conditions, we found no evidence on the mechanism of the observed protective effect of chokeberry extract in the used in vitro model of PD as this still needs to be the subject of further research.

P3 15

TESTING THE POSSIBILITY OF LOADING AND SUBSEQUENT RELEASE OF FLUORIDE IONS FROM BIOACTIVE DENTAL MATERIALS AFTER COATING WITH HIGHLY CONCENTRATED FLUORIDE GEL

Marija Kelić (4th year students of the Study of Dental Medicine, University of Zagreb School of Dental Medicine, Zagreb, Croatia), Domagoj Kilić (4th year students of the Study of Dental Medicine, University of Zagreb School of Dental Medicine, Zagreb, Croatia), Kristina Peroš (Department of Pharmacology, University of Zagreb School of Dental Medicine, Zagreb, Croatia)

INTRODUCTION: The purpose of this study was to determine the possibility of recharge of restorative materials and a degree of re-release of fluoride after topical treatment with fluoride gel.
MATERIALS AND METHODS: Three bioactive materials (Fuji IX Extra, Beautifil II, Cention), an adhesion system (G-aenial ™ Bond) and a glass-ionomer coating (GC Fuji Coat LC) were used. Each of the materials was divided into two subgroups of 6 samples (one subgroup was coated and the other was not). Masses of samples were measured. The samples were treated with Miradent Mirafluor gel and then rinsed out. Fluoride ion release was measured every 24 hours in the interval of 1, 2, 3, 4, 5, 6, 7, and 14 days with an ion selective electrode.
RESULTS: The cumulative fluoride ion concentrations for samples without dentinal adhesion system / coating differed in the following order: Cention> Beautifil II> Fuji IX Extra ($p < 0.05$). The concentrations of re-released fluoride ions for samples coated with dentin adhesion system / coating differed: Cention G-aenial> Beautifil G-aenial> Fuji IX Extra Coat LC ($p < 0.05$). There was no statistically significant change of the mass.
CONCLUSION: The tested bioactive dental materials show the possibility of refilling and subsequent release of fluoride ions. Adhesion systems / glass ionomer coatings interfere with the refilling process of restorative materials.

AUTHOR INDEX

N

O

S

Pridružite se zajednici čitatelja Pharmaca sada i putem nove mrežne stranice

www.e-pharmaca.com

Pretplatnicima uz pristup svim objavljenim brojevima Pharmaca nudimo i dodatne sadržaje:

- Edukacijski materijali
- Terapijske smjernice
- Podcast
- Forum za pretplatnike

Na našem blogu čitajte novosti iz farmakoterapije, osvrte na objavljene članke i druge aktualnosti iz područja farmakologije, ali i drugih područja medicine.
Besplatno se prijavite na naš popis primatelja novosti i obavijesti.

Nudimo i mogućnost direktne pretplate na Pharmaca putem mrežne stranice.

Nadamo se da ćemo objavljivanjem naše mrežne stranice doprinijeti većem dosegu Pharmaca i olakšanom pristupu neovisnim i objektivnim informacijama o lijekovima za naše čitatelje.

Vaše mišljenje nam je važno! Javite nam se s primjedbama i prijedlozima.

Srdačan pozdrav,

Ksenija Makar- Aušperger
glavna urednica

Viktorija Erdeljić Turk
tajnica uredništva

SPONSORS, DONORS AND EXHIBITORS

GOLD SPONSORS

MSD INVENTING FOR LIFE

novo nordisk®

AstraZeneca

SILVER SPONSORS

Lilly

RECORDATI RARE DISEASES GROUP

BRONZE SPONSORS

BIOMARIN

Selvita

jgl

NOVARTIS

SPONSORS

ALKALOID Health above all

abbvie

ewo pharma since 1959

DONORS

Swixx BioPharma Modern Medicines for All

LJEKARNA ZUBOVIĆ

LJEKARNA Nives Miloš

SUPORTED BY

KEFO

Pfizer

Takeda

TURISTIČKA ZAJEDNICA KVARNERA Raznolikost je ljepša

OPATIJA OPATIJSKA RIVIJERA TURISTIČKA ZAJEDNICA GRADA OPATIJA

MINISTARSTVO ZNANOSTI I OBRAZOVANJA REPUBLIKE HRVATSKE

EPHAR THE FEDERATION OF EUROPEAN PHARMACOLOGICAL SOCIETIES