Usmena izlaganja

Oral Presentations

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FARMAKOTERAPIJSKI PROBLEMI I INTERVENCIJE FARMACEUTA U BOLNICI ZA MEDICINSKU REHABILITACIJU

Gordana Ljubojević

Zavod za fizikalnu medicinu i rehabilitaciju „Dr Miroslav Zotović", Banja Luka (Bosna i Hercegovina)

Aktivnosti bolničkih farmaceuta značajno su se promijenile u poslednjih 30 godina, sa većim naglaskom na klinički rad i farmaceutsku zdravstvenu zaštitu. Cilj ovog istraživanja bio je ustanoviti farmakoterapijske i logističke probleme, farmaceutske intervencije i ishode tih intervencija tokom svakodnevnog rutinskog rada farmaceuta u bolnici za medicinsku rehabilitaciju.

Sistematično, prospektivno, opservaciono istraživanje provedeno je tokom 2,5 godine u Zavodu za fizikalnu medicinu i rehabilitaciju, Banjaluka, Bosna i Hercegovina, sa 594 bolnička kreveta. Tri bolnička farmaceuta pružala su konsultacije u vezi sa farmakoterapijskim i/ili logističkim problemima, a na lični ili telefonski upit doktora, medicinskih sestara/tehničara, fizioterapeuta i pacijenata. Glavne mjere ishoda bile su vrsta farmakoterapijskog ili logističkog problema, pokretač konsultacije, ishod i vrsta farmaceutske intervencije, te vrijeme utrošeno za rješavanje problema. Farmaceuti su imali pristup medicinskoj dokumentaciji, premda nisu bili rutinskih prisutni na odjeljenjima. Od 1515 farmaceutskih intervencija, 48,8% odnosilo se na rješavanje farmakoterapijskih problema, od kojih su najzastupljeniji bili preporuka za izbor ili doziranje lijeka i potreba za dodatnim informacijama o lijekovima. Cijena i mogućnost nabavke lijeka bili su najčešći logistički problemi. Više su vremena iziskivale farmakoterapijske konsultacije, koje su najčešće inicirali doktori (Mann–Whitney U test, $p \leq 0{,}001$), nego rješavanje logističkih problema. Intervencije na rješavanju farmakoterapijskih problema bile su slabije prihvaćene (83,7%) u odnosu na logističke intervencije (95,2%; $p \leq 0{,}00$). Prosječan broj identifikovanih farmakoterapijskih problema po pacijentu (1,37) niži je u poređenju sa rezultatima sličnih istraživanja (2,6-6,5), a kako farmaceuti (0.„51/100 bolničkih kreveta) nisu rutinski radili reviziju farmakoterapije to može biti obrazloženje za samo 19% farmakoterapijskih problema identifikovanih od strane farmaceuta.

Bolnički farmaceuti su se tokom rutinskog rada bavili približno istim brojem farmakoterapijskih i logističkih problema. Ukupna stopa prihvaćenih farmaceutskih intervencija bila je visoka, te naši rezultati ukazuju na potrebu za većim angažmanom farmaceuta u kliničkim aktivnostima, ali i za većim brojem bolničkih farmaceuta u Bosni i Hercegovini.

DRUG RELATED PROBLEMS AND INTERVENTIONS OF PHARMACISTS IN A PHYSICAL REHABILITATION HOSPITAL

Gordana Ljubojević

Institute for the Physical Medicine and Rehabilitation „Dr Miroslav Zotovic", Banja Luka (Bosnia and Herzegovina)

In the last 30 years, activities of hospital pharmacists have gone through significant changes and pharmacists are increasingly involved in patient care. The aim of this study was to explore drug-related and logistic problems, interventions, and outcomes during routine work of pharmacists in a physical rehabilitation hospital. During the 2.5 years a systematic, prospective observational study was performed in the 594-bed Institute for physical medicine and rehabilitation, Banjaluka, Bosnia and Herzegovina. Medical doctors, nurses, physiotherapists, and patients addressed three pharmacists, face-to-face or by telephone, with drug-related problems (DRPs) and/or logistic issues. Type of DRP or logistic issue, intervention, outcome, initiator and time spent for solving the problem were documented for each consultation as the main outcome measures. Pharmacists had access to electronic medical records of patients but they were not ward based. Out of 1515 interventions, 48.8% were aimed at solving DRPs. The most common DRPs were the recommendation of a drug or dose and need for additional information about drugs. Drug price and supply were the most prevalent logistic issues. DRPs were more frequently initiated by doctors and required more time to solve the problem compared to logistic issues (Mann–Whitney U test, $p \leq 0.001$). The acceptance rate of interventions to solve DRPs (83.7%) was lower compared to logistic issues (95.2%; $p \leq 0.001$). The average number of DRPs/patient (1.37) was lower compared to other studies in hospital settings (2.6-6.5). Pharmacists (0.51/100 beds) did not perform medication reviews routinely which could explain the low level of clinical DRPs identified by pharmacists (19%).

Hospital pharmacists were faced with an approximately equal number of DRPs and logistic issues during routine work. The overall acceptance rate of pharmacists' interventions was high, and our results indicate that hospital pharmacists in Bosnia and Herzegovina should be more involved in clinical activities and more pharmacists are clearly needed.

POTENCIJALNE INTERACIJE IZMEĐU LEKOVA U TERAPIJI NA OTPUSTU KOD GERIJATRIJSKIH PACIJENATA

Ivana Baralić, Vesna Janković, Tatjana Savković, Mirjana Stanojlović, Višnja Glišić, Goran Marković, Sonja Simić

Kliničko-bolnički centar „Zvezdara", Beograd (Srbija)

Interakcije između lekova mogu dovesti do neželjenih događaja i zdravstvenih problema koji se mogu sprečiti. Interakcije su važan faktor, posebno kod gerijatrijske populacije, gde je primena većeg broja lekova uobičajena. Cilj ovog istraživanja je bio da se identifikuju potencijalne interakcije između lekova u terapiji koja je propisana gerijatrijskim pacijentima na otpustu iz Kliničko-bolničkog centra "Zvezdara". Ova retrospektivna studija je sprovedena pregledom otpusnih lista pacijenata koji su bili hospitalizovani na Kliničkom odeljenju za gerijatriju u Kliničko-bolničkom centru „Zvezdara" u periodu od januara do aprila 2018. godine. Epocrates aplikacija je korišćena za utvrđivanje potencijalnih interakcija izmedu lekova. Identifikovane interakcije su prema nivou opasnosti podeljene u 4 grupe: kontraindikovane, izbegavati/koristiti alternative, modifikovati/pratiti i savetuje se oprez. Studija je obuhvatila 70 pacijenata. Srednja starost ispitanika je bila 79,8±6,87 godina. Ukupan broj propisanih lekova je bio 525, dok je presečan broj lekova po pacijentu bio 7,5 ±2,83. Šezdeset četiri (91,43%) pacijenta uzima 5 i više lekova. Ukupno 430 interakcija je identifikovano u terapiji 65 pacijenata. Kontraindikovane kombinacije lekova su uočene kod samo 2 pacijenta (2,86%). Trideset devet (9,07%) interakcija izbegavati/koristiti alternative je pronađeno u terapiji 22 pacijenta. Trista trideset četiri (77,67%) interakcije tipa modifikovati/pratiti je uočeno u terapiji 59 pacijenata. Pedeset i pet (12,79%) interakcija kod kojih se savetuje oprez detektovano je u terapiji 32 pacijenta.

Polifarmacija i starija populacija su dokazani faktori rizika za veću učestalost interakcija između lekova. Rezultati ove studije su pokazale visoku učestalost interakcija izmedu lekova u terapiji koja je propisana gerijatrijskim pacijentima nakon hospitalizacije. Ipak, pokazana je niska učestalost kontraindikovanih kombinacija, dok je najčešće uočena interakcija bila tipa „modifikovati/pratiti". Na osnovu dobijenih rezultata, bilo bi od koristi definisati sistem praćenja i optimizacije upotrebe lekova od strane farmaceuta, da bi se negativne posledice interakcija između lekova izbegle i svele na najmanju moguću meru.

POTENTIAL DRUG-DRUG INTERACTION IN GERIATRIC PATIENTS AT DISCHARGE

Ivana Baralić, Vesna Janković, Tatjana Savković, Mirjana Stanojlović, Višnja Glišić, Goran Marković, Sonja Simić

Zvezdara University Medical Center, Belgrade (Serbia)

Drug-drug interactions (DDIs) may often lead to preventable adverse drug events and health damage. This may be an important factor, particularly in geriatric population, as multiple drug therapy is common. The aim of the present study was to identify potential DDIs between drugs prescribed to the patients at discharge from the Zvezdara University Medical Center. A retrospective study was conducted by reviewing discharge lists of hospitalized patients in geriatric clinical ward in Zvezdara University Medical Center, Belgrade, Serbia, from January to April 2018. Epocrates drug interaction checker was used for screening potential DDIs. The identified DDIs were categorized by level of severity into 4 groups: contraindicated, avoid/use alternative, modify/monitor and caution advised. The study included 70 patients. The mean age of patients was 79.8±6.87 years. Total number of drugs prescribed was 525 and average number of drugs per patient was 7.5±2.83. Sixty four patients (91.43%) received 5 and more drugs. Total 430 DDIs were identified in therapy prescribed to 65 out of 70 patients. Contraindicated DDIs were recorded only in two patients (2.86%). Thirty nine (9.07%) avoid/use alternative interactions were found in 22 patients. Three hundred thirty four (77.67%) modify/monitor interactions were identified in 59 patients. Fifty five (12.79 %) interactions where caution is advised were detected in 32 patients.

Polypharmacy and older age are proven risk factors to potential drug interactions. The findings of the present study showed high prevalence of DDIs in therapy prescribed to the geriatric patients. However, we found low rate of contraindicated interactions, while the most prevalent type of interaction was type modify/monitor. Based on these findings, it could be helpful to established clinical pharmacy system to monitor and optimize medication use, in order to avoid and minimize negative outcomes of drug interactions.

UNAPREĐENJE KOMPETENCIJA STUDENATA FARMACIJE

Dragana Jocić[1], Ljiljana Tasić[2], Andrijana Milošević Georgijev[2], Dušanka Krajnović[2], Valentina Marinković[2]

[1]ZU Apoteka BENU, [2]Katedra za socijalnu farmaciju i farmaceutsko zakonodavstvo, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Profesionalne i lične kompetencije farmaceuta predstavljaju podršku stručnim i organizacionim kompetencijama i neophodne su u uslovima savremene farmaceutske prakse. Potrebno je ove kompetencije razvijati tokom studija u akademskom okruženju, kao i u nastavnim bazama, kako bi studenti bili pripremljeni za realno radno okruženje. Cilj ovog rada je unapređenje profesionalnih i ličnih kompetencija studenata farmacije neophodnih u uslovima savremene farmaceutske prakse.

Projekat „Profesionalni razvoj studenata farmacije" realizovan je u saradnji ZU Apoteke BENU i Centra za razvoj farmaceutske i biohemijske prakse Univerziteta u Beogradu. Projekat je organizovan kroz tri radionice i odbranu projektnog zadatka i trajao je od 15.2.2018. do 15.6.2018. godine. Teme projektnih zadataka bile su: izgled apoteke; kartica poverenja; facebook/instagram u cilju unapređenja eksterne komunikacije ka pacijentima i kupcima; unapređenje komunikacije farmaceut - lekar u cilju dobrobiti pacijenta; procesi koji će povećati prodaju OTC proizvoda i savetovanje pacijenata; e-karton kao platforma za unapređenje kvaliteta života i optimizaciju nege pacijenta.

U projektu je učestvovalo 70 studenata farmacije. Projekat je realizovan kroz tri modula sa fokusom na profesionalni razvoj i unapređenje kompetencija studenata upoznavanjem sa operativnim procesima u apoteci, kvalitetu radnih procesa, upravljanje i marketing različitih kategorija proizvoda u uslovima savremene farmaceutske prakse. Nakon završenih modula studenti su kroz 6 mini projekata implementirali stečene veštine. Projekat je uspešno odbranilo 48 studenata farmacije. Evaluacija postignuća je sprovedena postavljanjem pitanja od strane mentora tokom odbrane projekata. Sistematski pristup unapređenju kompetencija studenata farmacije organizacijom projekata sa fokusom na profesionalni razvoj studenata i sticanje dodatnih znanja i veština potrebnih za rad u realnom radnom okruženju može doprineti unapređenju profesionalnih i ličnih kompetencija studenata farmacije kao značajnoj potpori stručnih kompetencija koje se razvijaju u akademskom okruženju, kao i njihovoj boljoj pripremljenosti za realno radno okruženje.

Povezivanje procesa u akademskom okruženju sa procesima u realnom radnom okruženju može doprineti unapređenju profesionalnih i ličnih kompetencija farmaceuta i unapređenju farmaceutske prakse.

IMPROVING THE COMPETENCIES OF PHARMACY STUDENTS

Dragana Jocić[1], Ljiljana Tasić[2], Andrijana Milošević Georgijev[2], Dušanka Krajnović[2], Valentina Marinković[2]

[1]BENU Pharmacy, [2]Department of Social Pharmacy and Pharmaceutical Legislation, University of Belgrade - Faculty of Pharmacy (Serbia)

Professional and personal competences of pharmacists represent support for professional and organizational competences and are necessary in the conditions of modern pharmaceutical practice. These competencies need to be developed during studies in the academic environment in order to prepare students for a real working environment. The aim is to improve the professional and personal competencies of pharmacy students that are necessary in the conditions of modern pharmaceutical practice.

Project „Professional development of students of pharmacy" was realized in cooperation with BENU Pharmacy and Center for Development of Pharmaceutical and Biochemical Practice of the University of Belgrade. The project was organized through three workshops and project presentation task. Project lasted from 15.2.2018. to 15.6.2018. The themes of the project tasks were: pharmacy layout, loyalty card, facebook/instagram in order to improve external communication to patients and customers, improve communication between pharmacist and physician in order to benefit the patient, processes that will increase the sale of OTC products and patient counseling, e-card as a platform for improving the quality of life and optimizing patient care.

The project was attended by 70 students of pharmacy. The project was realized through three modules focusing on professional development and improvement of students' competence by familiarizing with the operational processes in pharmacy, quality, management and marketing in the conditions of modern pharmacy practice. After the completed modules, students implemented the acquired skills through 6 mini projects. The project was successfully presented by 48 students of pharmacy. Evaluation of the project was done by asking questions from a mentor during project presentation. A systematic approach to improving the competence of pharmacy students by organizing projects with a focus on professional development of students and acquiring additional knowledge and skills are necessary for working in a real working environment. That can contribute to the improvement of the professional and personal competences of pharmacy students as a significant support of professional competences that are developed in the academic environment, as well as their better preparedness for a real working environment.

Linking processes in the academic environment with processes in a real work environment can contribute to the improvement of professional and personal competencies of pharmacists and the advancement of pharmacy practice.

B.CELL: INTERAKTIVNA EDUKACIJA I EDUKATIVNA INTERAKCIJA

Neda Trivić, Milica Puđa, Tamara Kovačević

Nacionalna asocijacija studenata farmacije – NAPSer (Srbija)

Onkologija i biotehnologija, sfere izuzetnih dostignuća i primeri najdinamičnijih oblasti medicine, sa konstantnim povećanjem incidence malignih oboljenja zahtevaju proporcionalan porast u broju stručnjaka i inovativnosti u prevenciji i terapiji. Tim povodom susretom farmacije, medicine i informacionih tehnologija na navedenim poljima formirana je B.Cell platforma, u vidu aplikacije i veb sajta. Namenjena je studentima biomedicinskih usmerenja i stažerima, upravo jer predstavlja brz, jednostavan, savremen i besplatan način preuzimanja informacija, podizanja svesti i upotpunjavanja stečenog znanja kako studenata tako i mladih stručnjaka u navedenim sferama.

Platforma nudi mogućnost elektronskog učenja i pruža relevantne, praktično primenljive i najnovije naučno zasnovane vesti sa fokusom na onkologiju. Korisnici imaju pristup edukativnim materijalima, kao što su naučne publikacije, online časopisi, predavanja i kursevi. Specifičnost ponuđene edukacije se oslikava u tome što pored dinamičnog informisanja, B.Cell motiviše korisnike da za svoje angažovanje na samoj platformi budu nagrađeni i viđeni od strane fakulteta, kompanija, budućih poslodavaca i poslovnih partnera. Korisnici rešavanjem kvizova znanja i informisanosti, mini kliničkih studija, diskusijama i volontiranjem sakupljaju „Super ćelije", koje mogu da iskoriste na različite načine, kao što su posete farmaceutskim kompanijama, prisustva stručnim predavanjima, seminarima, treninzima, radionicama ili pak ostvarivanje prava na stručne prakse. Za uspešnu realizaciju ovih programa oslonac su partneri B.Cell-a, društveno odgovorne kompanije, kao i nastavnici Medicinskog i Farmaceutskog fakulteta Univerziteta u Beogradu koji svojom stručnošću podržavaju kredibilitet platforme.

B.CELL: INTERACTIVE EDUCATION & EDUCATIVE INTERACTION

Neda Trivić, Milica Puđa, Tamara Kovačević

National Association of Pharmacy Students – NAPSer (Serbia)

Oncology and biotechnology, the spheres of exceptional achievements and examples of the most dynamic areas of medicine, with a constant increase in the incidence of malignancies, require proportional increase in the number of experts and innovations in prevention and therapy. On that basis, combining pharmacy, medicine and information technologies, B.Cell platform was formed, as an application and a web site. It is intended for students and interns of biomedical professions because it represents a fast, simple, modern and cost effective way of acquiring information, raising awareness and knowledge improvement of students and young professionals.

The platform offers the possibility of e-learning and provides relevant, practically applicable and latest scientifically based news with a focus on oncology. Users have access to educational materials, such as scientific publications, online journals, lectures and courses. Apart from dynamic information that platform provides, specificity is reflected in the fact that B.Cell motivates users to be rewarded and seen by faculties, companies, future employers and partners for their engagement on the platform itself. The users collect „Super Cells" by solving knowledge quizzes, mini-business and clinical studies, by discussing on various cases or volunteering, which then can be used in different ways, such as visits to pharmaceutical companies, attendance at expert lectures, seminars, trainings, workshops or the opportunity for professional practice placements.

B.Cell is connected with its partners - socially responsible companies, as well as academic staff from the University of Belgrade - Faculty of Medicine and Faculty of Pharmacy which, by their expertise, support the credibility of the platform.

UTICAJ PRAVILNIKA KOJIM SE REGULIŠU MAKSIMALNE VELEPRODAJNE CIJENE LIJEKOVA NA CIJENE LIJEKOVA U BOSNI I HERCEGOVINI

Biljana Tubić, Jelena Aničić, Tijana Spasojević, Ana Cvijanović, Aleksandar Zolak

Agencija za lijekove i medicinska sredstva Bosne i Hercegovine (Bosna i Hercegovina)

Bosna i Hercegovina je u 2017. godini prvi put implementirala podzakonski akt kojim se reguluše nivo maksimalnih veleprodajnih cijena lijekova. Cilj rada je ocjeniti prve rezultate uticaja Pravilnika na nivo veleprodajnih cijena lijekova na tržištu Bosne i Hercegovine.

Upoređene su veleprodajne cijene lijekova za 2016. godinu kada Pravilnik nije postojao u odnosu na 2017. godinu kada je Pravilnik prvi put implementiran. Izvori veleprodajnih cijena lijekova bili su podaci dobijeni od velprometnika za godišnje izvještaje o potrošnji lijekova koje naša agencija publikuje svake godine na svojoj internet prezentaciji www.almbih.gov.ba.

Ukupna sredstva izdvojena za lijekove u 2017. godini niža su u odnosu na 2016. godinu. Takođe, veleprodajne cijene lijekova koji se izdaju na recept ljekara niže su u 2017. godini u odnosu na 2016. godinu. S druge strane, može se vidjeti da su veleprodajne cijene lijekova koji se izdaju bez ljekarskog recepta (OTC lijekovi) više u 2017. u odnosu na iste u 2016. Međutim, ovi bezreceptni lijekovi čine samo 15 % tržišta lijekova, tako da to navedeno nije imalo uticaj na ukupna finansijska sredstva izdvojena na lijekove u 2017. godini u Bosni i Hercegovini. Implementacija Pravilnika i uvođenje sistema maksimalnih veleprodajnih cijena lijekova ima pozitivan uticaj na budžet fondova zdravstvenog osiguranja u Bosni i Hercegovini.

INFLUENCE OF THE RULEBOOK FOR REGULATING MAXIMUM WHOLESALE PRICES ON MEDICINE COST IN BOSNIA AND HERCEGOVINA

Biljana Tubić, Jelena Aničić, Tijana Spasojević, Ana Cvijanović, Aleksandar Zolak

Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina (Bosnia and Herzegovina)

Bosnia and Herzegovina have implemented rulebook for regulating maximum wholesale prices at the first time in 2017. The aim of this study was to assess the first results of the influence of the rulebook on the level of wholesale prices of medicines on the market of Bosnia and Herzegovina.

Medicine prices in the years 2017 and 2016 were analyzed. The level of wholesale prices in 2016, when rulebook has not existed, were compared with wholesale prices of medicines in 2017 when rulebook was implemented for the first time. The wholesale prices of medicines were data obtained from wholesalers which we collect every year for Annual reports about the distribution of medicines in Bosnia and Herzegovina and which are published on website www.almbih.gov.ba by our agency.

The total financial expenses for medicines were reduced in 2017 compared to 2016. Also, it was shown that the wholesale prices of Rx medicines are decreased compared with 2016. On the other side, it could be seen that OTC medicines have increased prices in 2017 as compared with the year 2016. But, OTC medicines make 15% of the whole market of medicines and this increase did not have the influence on financial cost in all. Implementation of the Rulebook and system of maximal wholesale prices of Rx medicines has positive influence on budget of fonds for healthcare insurance in Bosnia and Herzegovina.

OD TRADICIONALNE MEDICINE DO RACIONALNE FITOTERAPIJE – 50 GODINA FARMACEUTSKE SLUŽBE U OKVIRU BILJNE APOTEKE INSTITUTA ZA PROUČAVANJE LEKOVITOG BILJA „DR JOSIF PANČIĆ"

Nebojša Menković

Institut za proučavanje lekovitog bilja „Dr Josif Pančić", Beograd (Srbija)

Značaj lekovitih biljaka i pripravaka od biljnih droga, iz godine u godinu ima tendenciju porasta. Tako je i u našoj zemlji i u svetu, a posebno u razvijenim zemljama. Potražnju lekovitih i aromatičnih biljaka stimulišu i potkrepljuju pozitivna iskustva tradicionalne medicine koja su i dalje osnov za moderna naučna istraživanja i, paralelno sa sveobuhvatnim istraživanjima savremenim laboratorijskim metodama, doprinose razvoju novih biljnih lekova. Ovakav pristup razvoja je i ideja vodilja Instituta za proučavanje lekovitog bilja „Dr Josif Pančić". Ove godine Institut slavi 70 godina postojanja i rada, kao i 50 godina rada Biljne Apoteke, u okviru Instituta.

Biljna apoteka Instituta je svojevrsni centar fitoterapije gde su prethodne i današnje generacije pronalazile rešenje za mnoge zdravstvene tegobe. Savetovalište za fitoterapiju i lekovito bilje osnovano je u okviru Biljne Apoteke. Njime prvenstveno želimo da unapredimo kontakt sa pacijentima i ponudimo dodatni podsticaj za korišćenje proizvoda na bazi lekovitog bilja na racionalni način (promocija racionalnih fitofarmaka standardizovanih na aktivne ili preovlađujuće materije, proizvedenih u definisanim uslovima u institutskim farmaceutskim pogonima i laboratorijama kao i „ex tempore"). Sa druge strane, razgovor sa pacijentima i njihova iskustva u korišćenu lekovitog bilja su značajan izvor informacija za istraživače Instituta.

Od velikog značaja je i sakupljanje terenskih informacija o upotrebi poznatih i manje poznatih lekovitih biljaka koje se u narodu koriste za različite bolesti i simptome. Čitav taj sistem prikupljanja informacija, omogućava da se na kvalitetan način razvije formulacija i postpak izrade racionalnog fitofarmaka.

U ovom radu predstavljamo naša iskustva kroz rad: Savetovališta, Botaničke bašte lekovitog bilja „Akademik Jovan Tucakov" u Valjevu, kao i terenskih i drugih istraživanja u okviru Instituta.

FROM TRADITIONAL MEDICINE TO RATIONAL PHYTOTHERAPY -50 YEARS OF PHARMACEUTICAL PRACTICE WITHIN THE HERBAL PHARMACY OF THE INSTITUTE FOR MEDICINAL PLANTS RESEARCH „DR JOSIF PANČIĆ"

Nebojša Menković

Institute for Medicinal Plants Research „Dr Josif Pančić" (Serbia)

The importance of medicinal plants and herbal remedies, from year to year, has a tendency to increase. This is the situation in our country as well as in the world, especially in developed countries.

The demand for medicinal and aromatic plants is stimulated and supported by positive experiences of traditional medicine which are still the basis for modern scientific research and, along with comprehensive research with modern laboratory methods, contribute to the development of new herbal remedies. This type of approach is also the leading idea for the development of the Institute for Medicinal Plants Research „Dr Josif Pančić". This year, the Institute celebrates 70 years of existence and work, as well as 50 years of work of the Herbal Pharmacy, within the Institute.

Herbal Pharmacy of the Institute is a kind of phytotherapy center where the previous and present generations who worked in the Institute have found a solution for many health problems. Counseling center for phytotherapy and medicinal herbs was established within the Herbal Pharmacy. We primarily want to improve contact with patients and offer additional incentives for the use of medicinal products in a rational manner (promotion of rational phytopharmaceuticals standardized on active or predominant compounds produced in defined conditions in Institutes production sector, laboratories as well as „ex tempore"). On the other hand, talking with patients and their experiences in the use of medicinal herbs are of significant importance for the researchers of the Institute.

Collection of terrain information on the use of well-known or less well-known medicinal plants that are used by the people for various diseases and symptoms are of great importance as well. All this information gathering enables us to make the formulation and production of rational phytopharmaceuticals in a quality way.

In this paper we present our experiences through the work of Counseling center, Botanical Garden of medicinal herbs „Akademik Jovan Tucakov" in Valjevo, as well as terrain and other research within the Institute.

APOTEKAR I JAVNO-ZDRAVSTVENI PROSVETITELJ MR PH MILIVOJE MOLJAC: PEČAT U VREMENU

Stevan Vukov

Apoteka „Sent Andreja", Zrenjanin (Srbija)

Ovaj rad ima za cilj da prikaže sveukupni doprinos apotekara Milivoja Moljca i na taj način otrgne od zaborava njegov lik i delo. Korišćeni su primarni i sekundarni izvori za istorijsku analizu, kako biografskih podataka o životu Moljca, tako i hronoloških podataka o njegovom radu.

Milivoje Moljac (1890 - 1979) bio je farmaceut po obrazovanju, i apotekarski poziv obavljao je tokom celog profesionalnog života. Od kako je 1919. godine dobio koncesiju za otvaranje šeste po redu apoteke „Kod Svetog Jovana" u ondašnjem Velikom Bečkereku (današnji Zrenjanin), pa sve do prisilnog otkupa apoteka 1949. godine aktivno je učestvovao na različitim poljima, ne samo stručne već i kulturno-prosvetne delatnosti. Bio je vlasnik i urednik apotekarskih časopisa, učestvovao u izradi Jugoslovenske farmakopeje (1933), bio u upravnom odboru veledrogerije „Slavija", učestvovao u organizaciji Sveslovenskog kongresa apotekara (1939). Istovremeno, obavljao je značajne dužnosti u Crvenom krstu, Sokolskom društvu, Narodnoj odbrani, kao i Jadranskoj straži. Kao istaknuti član Demokratske stranke aktivno je učestvovao u političkom životu. Tokom Drugog svetskog rata pripadao je neformalnoj organizaciji građanskih intelektualaca koja je prikupljala hranu, lekove i novac, ne samo za hiljade izbeglica, već i za članove pokreta otpora. Posle rata nastavlja sa radom u sopstvenoj apoteci, pod budnim okom novih vlasti. Tokom 1949. godine, njegova apoteka je prešla u državnu svojinu. Sve do odlaska u penziju ostao je na mestu upravnika nekad svoje, a potom Treće narodne apoteke. Njegovi potomci, ćerka Vukosava i sin Slobodan, nastavili su očevim stopama i ostali verni apotekarskom pozivu. U zaključku, možemo naglasiti da se Moljčev doprinos kao receptariusa nesumnjivo osećao i izvan okvira apoteke, te da je on ostavio pečat u kulturnom i političkom razvoju grada. S druge strane, njegov doprinos farmaceutskoj profesiji je daleko prevazišao lokalni karakter i može se reći da je rad apotekara Moljca bio od velike važnosti za razvoj farmacije u Jugoslaviji između dva svetska rata.

PHARMACIST AND PUBLIC HEALTH EDUCATOR MILIVOJE MOLJAC: SEAL IN TIME

Stevan Vukov

Pharmacy „Sent Andreja" Zrenjanin (Serbia)

The aim of this work is to show overall contribution of pharmacist Milivoje Moljac, and turn away from forgetting his character and working. Primary and secondary sources, biographical data about life and activities of Moljac have been used for historical analysis.

Milivoje Moljac (1890-1979) was a pharmacist, and he was engaged in pharmacy practice through entire his professional life. Since he received a concession to open the sixth consecutive pharmacy „St. John", in 1919, in Veliki Beckerek, until the forcible acquisition in 1949, he actively participated in various fields, not only professional, but also cultural and educational activities. He was the owner and editor of pharmaceutical journals, also he participated in the development of the Yugoslav Pharmacopoeia (1933), he was member of the board of the wholesaler „Slavija" and participated in the organization of the all Slovenian Congress of Pharmacists (1939). At the same time, he performed important duties in the Red Cross, the Sokol Society, the National Defense, and the Adriatic Guard. During the Second World War he belonged to the non-formal organization of civil intellectuals who collected food, medicine and money, not only for thousands of refugees, but also for members of the resistance movement. After the war, he continues to work in his own pharmacy, under the watchful eye of new authorities. During 1949, his pharmacy has passed into the State ownership. Until his retirement he remained the manager of what was formerly his own, and later the Third People's Pharmacy. In conclusion, we can emphasize that Moljac`s contribution as a receptarius was extended beyond the pharmaceutical area, and he left a mark on the cultural and political development of the city. On the other hand, his contribution to the pharmaceutical profession has overcome the local character and it can be said that the work of Moljac was of great importance for the development of pharmacy in Yugoslavia between the two World Wars.

HOMEOPATHY 222 YEARS AFTER – THE HISTORICAL KNOWLEDGE AND VIEWS OF SAMUEL HAHNEMANN IN CONTEXT OF HIS WRITINGS

Łukasz Komsta

Medical University of Lublin (Poland)

Homeopathy is one of the few trends in alternative medicine that have survived to our times and have not gone away since its beginning. Despite the lack of convincing scientific evidence, it still has many followers. As almost all literature sources are subjective and present the point of view of an enthusiast or a hater. Therefore, there is a general need to look with a distance and see the original motivations that led Hahnemann to think in the homeopathic way.

The point-by-point reading of original Organon is the best way to see what Hahnemann thought and how he perceived the nature in his times. It allows to understand the neglected and forgotten details of medical knowledge and to verify many views in today's knowledge of the etiology of diseases and classical pharmacology. It is also beneficial to see Organon in context of Hahnemann's contemporary philosophical views, to sort in a chronological manner scientific milestones and to understand the placement of Hahneman's life around the most important nineteenth century chemical discoveries.

In current scientific methodology, the „similia similibus curantur" paradigm cannot be even called a theory and it is a great example of a priori deduction. The contemporary philosophical arguments an example of another paradigm and a scientific troublesome. The only paradigm of treatment are the laws of nature, which do not depend on the adopted philosophical view and one has to understand the lack of the knowledge in Hahnemann's times.

It is very hard to perceive the homeopathy in any scientific way. It should be perceived only as a historical curiosity without any unneeded emotional background. If there is any undiscovered medical mechanism beyond any homeopathic drug, it surely cannot be derived from „similia…" principle.

KRATAK ISTORIJSKI PRIKAZ MAGISTRALNIH LEKOVA KOJI SE PRIMENJUJU KOD OPSTIPACIJE

Ilinka Vuković[1], Mirjana Gajdaš[2], Dušanka Krajnović[3]

[1]Srpsko lekarsko društvo, [2]Apoteka Beograd, [3]Katedra za socijalnu farmaciju i farmaceutsko zakonodavstvo, Univerzitet u Beogradu–Farmaceutski fakultet (Srbija)

Izrada magistralnih lekova pominje se još u prvim recepturnim priručnicima lekaro-apotekara, a i značajni nacionalni istorijski izvori prvog reda, poput Hilandarskog medicinskog kodeksa, na više mesta se bave sredstvima za čišćenje na bazi šljive, aloje, belog duda i drugih biljnih droga. U savremenoj terapiji magistralni lekovi zauzimaju značajno mesto, a njihova izrada podržana je i Rezolucijom Evropske komisije (Resolution CM/ResAP, 2011), odobrenom od Saveta Evrope. U Evropskoj farmakopeji postoji monografija o preparatima ex tempore, što odgovara magistralnim lekovima. Među onima koji se koriste u terapiji bolesti organa za varenje nalazimo veći broj lekova koji se preporučuju kod opstipacije, čiji uzroci mogu biti brojni, funkcionalni ili organski kao posledica neke bolesti, a lečenje je kompleksno i zavisi od uzroka. Iako je opstipacija češća kod starih osoba, mogu je imati i deca, trudnice, ili može biti posledica uzimanja lekova (analgetici, antacidi, opioidi, antiparkinsonici, antibiotici...).

U radu je analizirano 38 preskripcija za magistralne lekove koji se primenjuju kod opstipacije, preuzetih iz nekoliko izvora: 8 magistralnih lekova iz Sveske magistralnih lekova dr Miloša Todorova (1894-1969), privatna ordinacija somborskog lekara, 4 iz Formulae magistrales et reagentia FM II (1966), 6 lekova iz FM III (1979), 12 preskripcija iz Farmakoterapije Dragutina Tomića (1989) i 8 monografija iz važećih propisa Magistralne formule (2008). Prisutno je više farmaceutskih oblika lekova, a najviše preskripcija se odnosi na podeljene praškove (12), pilule (6), supozitorije (6), oralne emulzije (6) i čajne mešavine (3). U pogledu sastava prisutno je preko 60 aktivnih komponenti i ekscipijenasa, a dominiraju droge biljnog porekla. U zaključku možemo reći da su analizirane preskripcije magistralnih lekova za opstipaciju, prisutne u više farmaceutskih oblika, primenjivane peroralno i rektalno, pružale mogućnost, uz druge mere lečenja, za prilagođavanje terapije prema individualnim potrebama pacijenta.

SHORT HISTORICAL OVERVIEW OF EXTEMPORANEOUSLY COMPOUNDED MEDICINES FOR CONSTIPATION

Ilinka Vuković[1], Mirjana Gajdaš[2], Dušanka Krajnović[3]

[1]Serbian Medical Society, [2]Pharmacy Beograd, [3]Department of Social Pharmacy and Pharmaceutical Legislation, University of Belgrade - Faculty of Pharmacy (Serbia)

Pharmaceutical compounding can be traced back to early practitioner-pharmacists' prescription manuals, including prominent national historical sources such as The Hilandar Medical Codex, which contains several references to treatments for defecation, based on plum, aloe, white mulberry and other plants. Extemporaneously compounded medicines are relevant in contemporary treatment and their preparation is supported by European Committee Resolution (Resolution CM/ResAP, 2011), approved by The European Council, while The European Pharmacopoeia includes a monograph on ex tempore products which correspond to extemporaneously compounded medicines. Amongst medications used in treating digestive disorders, many are recommended for constipation. Its causes are either functional or organic, or a result of another illness, the treatment is complex, and it depends on the exact cause. Even though it often affects the elderly, it might occur in children, during pregnancy or as a consequence of taking other prescription drugs (analgesics, antacids, opioids, antiparkinsonics, antibiotics…).

Our analysis includes a total of 38 prescriptions for extemporaneously compounded medicines used for treating constipation, from several sources: 8 extemporaneously compounded medicines from the Extemporaneously Compounded Medicines Notebook by a physician Miloš Todorov (1894-1969), private physician's practice in Sombor, Serbia, 4 from Formulae magistrales et reagentia FM II (1966), 6 extemporaneously compounded medicines from FM III (1979), 12 prescriptions from Pharmacotherapy by Dragutin Tomić (1989), and 8 monographs from contemporary regulations Formulae Magistrales (2008). We found several pharmaceutical dosage forms, and the majority prescriptions are for divided powders (12), pills (6), suppositories (6), oral emulsions (6), and tea concoctions (3). In terms of ingredients there are over 60 active substances and excipients, with plant-based drugs being dominant. We can conclude that analysed prescriptions for extemporaneously compounded medicines for constipation, which existed in several pharmaceutical dosage forms, and were administered either orally or rectally, facilitated the adjustment of therapy to individual needs of the patient, in addition to other ways of treatment.

FALSIFIKOVANI LEKOVI - IZAZOVI REGULATIVE U SPROVOĐENJU I PROMOCIJI BEZBEDNE UPOTREBE LEKOVA

Pavle Zelić, Saša Jaćović

Agencija za lekove i medicinska sredstva Srbije (Srbija)

Rad ima za cilj da predstavi razvoj legislative u oblasti falsifikovanih lekova i trenutno stanje u pogledu terminologije, pravnih akata, smernica i ostalih relevantnih dokumenata na nacionalnom i međunarodnom planu koji se tiču lažnih lekova i medicinskih sredstava. Na ovaj način bi se pokazala određena disjunktnost i neusaglašenost između organa zaduženih za regulativu i sprovođenje mera u svrhu minimizacije javno-zdravstvenih rizika od ovih ilegalnih medicinskih proizvoda. Upoređivana su pravna akta na nivou Saveta Evrope, Evropske Unije, Svetske zdravstvene organizacije, Internacionalne konferencije o harmonizaciji i drugih međunarodnih aktera, kao i nevladinih organizacija koje se bave borbom i podizanjem svesti o problematici falsifikovanih medicinskih proizvoda. Ova saznanja su komparirana i na nacionalnom nivou, kako u pogledu zakona i podzakonskih akata u Republici Srbiji, ali i regionu i ključnim državama Evrope i sveta kao što su SAD, Ruska federacija, Japan, Australija, Kina, Indija, Švajcarska i Kanada. Takođe je pravljeno poređenje kako farmaceutske, ali i legislative u pogledu zaštite prava intelektualne svojine i konačno, praktične implikacije svih ovih dokumenata u stvarnom životu.

Utvrđena su značajna odstupanja počev od samog pojma lažnog odnosno falsifikovanog leka, preko njegove definicije u užem i širem smislu, do daljih elaborata o pristupu ovom problemu i njegovom rešavanju kroz operativne i kaznene odredbe. Nedovoljan broj radova na ovu temu ukazuje da se ova važna oblast nije na adekvatan način obrađivala u naučne svrhe, niti postoji uzajamno razumevanje između ključnih činilaca koji bi, uz određeno usmeravanje, morali da obezbede objedinjen i sveobuhvatan pristup problematici, bez dupliranja posla, a naročito nejasnoća u pogledu pravne utemeljenosti koja podržava akcije na terenu. Za regulatorne autoritete u Srbiji i drugim zemljama, neophodno je da se pronađu pravi modaliteti i primeri koji bi olakšali kako donošenje propisa, ali i njihovu primenu uz određeni naučni osnov svih aktivnosti.

FALSIFIED MEDICINES – REGULATORY CHALLENGES IN SAFE DRUG USE AND ITS PROMOTION

Pavle Zelić, Saša Jaćović

Medicines and Medical Devices Agency of Serbia (Serbia)

The paper aims to present the development of legislation for falsified medicines and medical devices and current situation regarding terminology, legal acts, guidelines and other relevant documents on the national and international level. Certain disagreement between the regulatory authorities and the implementation of measures will be demonstrated in order to minimize the public health risks of illegal medicinal products. Legal acts from the Council of Europe, the European Union, the World Health Organization, the International Conference on Harmonization and other international actors, and non-governmental organizations fighting and raising awareness about the problem of falsified medical products were compared. This is comparable on national level, in terms of laws and by-laws in the Republic of Serbia, but also in the region and key countries of Europe and the world - United States, the Russian Federation, Japan, Australia, China, India, Switzerland and Canada. Further comparison was made of both pharmaceutical and legislative with regard to the protection of intellectual property rights and, practical implications of all these documents in real life.

Significant deviations were identified, starting from the notion of a false or falsified drug, through its definition in broader sense, to further studies on access to this problem and its resolution through operational and penal provisions. Insufficient number of papers on this topic indicate this important area has not been adequately addressed for scientific purposes, nor there is a mutual understanding between key factors that, with a certain direction, should provide a unified and comprehensive approach to the problem, without duplication of work, and especially uncertainty in terms of legal basis that supports action on the ground. For regulatory authorities in Serbia and other countries, it's necessary to find real modalities and examples that would facilitate both the adoption of regulations and their application, along with a certain scientific basis for all activities.

DEFEKT KVALITETA LEKA - REGULATORNI ZAHTEVI I SAVREMENI TRENDOVI

Svjetlana Mihaljica, Žarko Jović, Boris Bojić, Marija Malešević, Gordana Pejović

Agencija za lekove i medicinska sredstva Srbije (Srbija)

Defekt kvaliteta lekova ima veliki značaj u post-marketinškom praćenju kvaliteta lekova. Defekt kvaliteta lekova može da dovede do povlačenja serija koje odstupaju od standarda kvaliteta i do suspenzije ili zabrane njihovog prometa. Regulatorna očekivanja za rukovanje reklamacijama i povlačenje proizvoda se zasnivaju na GMP/EU-EudraLex Vol.4 Part I (Medicinal Product), Chapter 8 and Part II (Active Substance used as Starting Materials), Section 15. U radu će biti dat pregled svih propisa koji su u vezi sa defektom kvaliteta/procesom povlačenja u zemljama EU i Republici Srbiji i odgovornostima svih uključenih učesnika u ovom postupku.

Sve reklamacije i druge informacije koje su u vezi sa mogućim proizvodima koji odstupaju od standarda kvaliteta moraju biti pažljivo pregledane u skladu sa pisanom procedurom. Treba da postoji sistem koji omogućava brzo i efikasno povlačenje poznatih proizvoda ili onih za koje postoji sumnja da odstupaju od standarda kvaliteta iz prometa, ako je potrebno. Postoji spisak kategorija odstupanja za klasifikaciju defekta proizvoda (kroskontaminacija, neusaglašenost sa dozvolom za lek, FDA Warning Letter, OOS, test stabilnosti…). Inicijalne akcije trebaju da budu preduzete kao rezultat preliminarne istrage za defekt kvaliteta (Rapid Alert, povlačenje). Povlačenja serije za defekt kvaliteta su klasifikovana zavisno od moguće ugroženosti po život i rizika po zdravlje.

Koji su sledeći koraci istrage: Glavni uzrok defekta je određen? CAPA su analizirane i implementirane? U skladu sa Aneksom 16 GMP, QP je odgovoran da obezbedi da je svaka pojedinačna serija proizvedena u skladu sa zahtevima dozvole za lek i sa GMP. Dodatno, QP je odgovoran da obezbedi da sve reklamacije koje su u toku, istrage ili povlačenja budu prepoznate za sertifikaciju predmetne serije. Postoji veliki značaj za implementaciju regulative za defekt kvaliteta, kao i potrebe za jačanje sistema za efikasno povlačenje lekova koji odstupaju od kvaliteta u cilju da se obezbedi kvalitet, efikasnost i bezbednost lekova u prometu.

MEDICINE QUALITY DEFECT - REGULATORY REQUIREMENTS AND CURRENT TRENDS

Svjetlana Mihaljica, Žarko Jović, Boris Bojić, Marija Malešević, Gordana Pejović

Medicines and Medical Devices Agency of Serbia (Serbia)

Medicines quality defect is of increasing importance in post-marketing medicines quality monitoring, as it can lead to the recall of a defected batch and potential suspension or prohibition on the market. Regulatory expectations for complaint handling and product recall are based on GMP/ EU-EudraLex Vol.4 Part I (Medicinal Product), Chapter 8 and Part II (Active Substance used as Starting Materials), Section 15. Review of regulation related to the quality defect/recall process in EU countries and Republic of Serbia and responsibilities of all participants involved in this procedure has been performed.

All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. A system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market. There is a list of categories of deficiencies to classify product defects (cross-contamination, deviation from MA, FDA Warning Letter, OOS, stability testing…). Initial actions should be taken as a result of preliminary investigation for quality defect (rapid alert, recall). Batch recalls for quality defects are classified depending on potentially life-threatening and risk to health.

What are the next steps of investigation: Root Cause is determined? CAPA are analysed and implemented? In line with Annex 16 GMP, the QP is resposonsible for ensuring that each individual batch has been manufactured in accordance with the MA and GMP requirements. Additionally, QP has responsibility to ensure that any on-going complaint, investigation or recall does not negate the conditions for certification of the batch in question. There is a great importance for the implementation of quality defect regulations, as well as for strengthening the system for effective recall of the defective medicines in order to achieve quality, efficacy and safety of medicines on the market.

SPECIFIČNOSTI FARMAKOVIGILANCE BIOTEHNOLOŠKIH LEKOVA

Milena Miljković[1], Cvijeta Bielen[2], Aleksandra Pajić[2]

[1]PrimeVigilance, Beograd (Srbija), [2]PrimeVigilance, Zagreb (Hrvatska)

Tokom poslednje dve decenije upotreba biotehnoloških lekova u medicini stalno se povećavala. Otkrivanje monoklonskih antitela i njihovo uvođenje posebno u terapiju autoimunskih/inflamatornih i malignih bolesti, smatra se jednim od najvećih napredaka biotehnologije do sada. Cilj ovog rada je da rezimira specifičnosti farmakovigilance visoko sofisticiranih biotehnoloških lekova.

Proučeni su relevantni pregledi, smernice i preporuke, objavljene u medicinskoj literaturi i preko regulatornih agencija tokom poslednjih pet godina, uključujući i odobrene proizvode.

Biotehnološki lekovi su biološki proizvodi dobijeni korišćenjem biotehnoloških metoda i bioloških sistema za njihovo stvaranje ili modifikaciju. Biološki slični lekovi su skoro identične kopije originalnih biotehnoloških proizvoda, sa kojima su veoma slični, ali ne i identični. Postoje određeni aspekti farmakovigilance biotehnoloških lekova koji zahtevaju posebnu pažnju. Značajna karakteristika bezbednosti biotehnoloških lekova je njihov kapacitet da indukuju imunogenost. Svi biološki lekovi proteinske strukture pokreću imunski odgovor, a kao rezultat nastaju anti-lek antitela. Brojni faktori vezani za sam lek, pacijenta ili način davanja leka mogu da utiču na imunogenost. U pojedinim slučajevima, razvoj imunskog odgovora na biotehnološki lek može smanjiti njegovu efikasnost, uz blage neželjene efekte, dok u drugim slučajevima imunski odgovori mogu dovesti do ozbiljnih, a ponekad i fatalnih neželjenih efekata. Dodatno, pri primeni biotehnoloških lekova mogu se pojaviti i infuzijske reakcije. One mogu biti anafilaktičke (IgE-posredovane) i anafilaktoidne (nisu IgE-posredovane). Ove reakcije javljaju se već u toku davanja infuzije ili u okviru jednog sata od njenog završetka i mogu imati širok spektar neželjenih efekata, ponekad i nespecifičnih. Kod biotehnoloških proizvoda, predmet većine regulatornih bezbednosnih mera bile su reakcije na mestu primene leka, infekcije, neoplazme i poremećaji imunološkog sistema.

U postmarketinškom periodu, biotehnološki lekovi zahtevaju pažljivo praćenje imunološki posredovanih neželjenih efekata i infuzijskih reakcija, dok za imunomodulatorne lekove treba pažljivo pratiti razvoj oportunističkih infekcija i sekundarnih neoplazmi.

SPECIFICITIES OF PHARMACOVIGILANCE OF BIOTECHNOLOGICAL MEDICINES

Milena Miljković[1], Cvijeta Bielen[2], Aleksandra Pajić[2]

[1]PrimeVigilance, Belgrade (Serbia), [2]PrimeVigilance, Zagreb (Croatia)

Over the past two decades, the use of biopharmaceuticals in medicine was constantly increasing. The discovery of monoclonal antibodies and particulary their introduction in the therapy of autoimmune/inflamatory and malignant diseases, are considered as one of the greatest advances in the field of biotechnology so far. The aim of this work is to summarize specificities of pharmacovigilance of highly sophisticated biopharmaceuticals.

Relevant reviews, guidelines and recommendations published in the medical literature and through regulatory agencies during the last five years, including approved products, have been examined.

Biotechnology-derived medicines are biologicals manufactured by biotechnological methods and biological systems to create or modify products. Biosimilars are almost identical copies of original biotechnological medicines, with which they are highly similar but not identical. There are certain aspects of pharmacovigilance of biopharmaceuticals that require special attention. An important feature of biopharmaceuticals safety is their capacity to induce immunogenicity. All biopharmaceuticals trigger an immune response, and as a result, anti-drug antibodies are produced. Numerous factors associated with the medicine itself, the patient, or the method of administration may affect immunogenicity. In some cases, development of immune response to biopharmaceuticals can decrease their efficacy with only mild adverse effects, while in other cases, immune responses can lead to serious, and sometimes fatal, adverse events. Additionaly, infusion related reactions can occur with biopharmaceuticals. These reactions can be anaphylactic (IgE-mediated) or anaphylactoid (non-IgE-mediated). They appear already during infusion or within one hour of its completion, can be broad, and at times non-specific. Administration site reactions, infections, neoplasms, and immune system disorders were the subject of most safety-related regulatory actions for biopharmaceuticals.

In the post-marketing period, biopharmaceuticals require careful monitoring of immune-mediated adverse events and infusion related reactions, while for immunomodulatory agents careful surveillance for development of opportunistic infections and secondary malignancies is needed.

ULOGA FARMAKOGENETIKE U PERSONALIZOVANOJ TERAPIJI KOD PACIJENATA SA TRANSPLANTIRANIM BUBREGOM NA TAKROLIMUS-BAZIRANOJ IMUNOSUPRESIJI

Nikola Stefanović[1], Radmila Veličković-Radovanović[1], Katarina Dinić[2], Tatjana Cvetković[3]

[1]Katedra za farmaciju, Univerzitet u Nišu-Medicinski fakultet, [2]Univerzitet u Nišu-Medicinski fakultet, [3]Katedra za Biohemiju, Univerzitet u Nišu-Medicinski fakultet (Srbija)

Kliničku primenu takrolimusa komplikuje izražena interindividualna varijabilnost u farmakokinetici i hronična nefrotoksičnost leka. Glavni cilj ovog istraživanja bila je procena potencijalnog uticaja citohrom P450 3A5 (CYP3A5) 6986A>G i ABCB1 3435C>T genskih polimorfizama na dozom-prilagođenu koncentraciju takrolimusa (C0/D) u toku 36 meseci nakon transplantacije bubrega (RTx). Dodatno, istražili smo da li ispitivani polimorfizmi mogu ispoljiti negativan uticaj na bubrežnu funkciju u posmatranom post-transplantacionom periodu.

Studija je uključila 93 pacijenta sa transplantiranim bubregom na takrolimus-baziranoj imunosupresiji. Njima je određen CYP3A5 i ABCB1 genotip (kodira P-glikoprotein) korišćenjem alel-specifične PCR metodologije. C0/D (ng/mL/mg) je izračunat kao količnik predozne koncentracije i odgovarajuće doze takrolimusa. Procenjena brzina glomerularne filtracije (mL/min/1.73m^2, eGFR) je izračunata korišćenjem MDRD formule.

Pacijenti su genotipizirani na CYP3A5 (12,9% CYP3A5*1/*3; 87,1% CYP3A5*3/*3) i ABCB1 (25,8% CC; 47,3% CT; 26,9% TT) genski polimorfizam. Nosioci CYP3A5*1/*3 imali su niže vrednosti C0/D takrolimusa u poređenju sa nosiocima CYP3A5*3/*3 nakon 1, 6, 12, 24 i 36 meseci post-transplantacionog perioda (0,91±0,38 vs. 1,35±0,54, p=0,008; 1,17±0,69 vs. 2,02±1,14, p=0,011; 1,35±0,56 vs. 2,41±1,57; p=0,015; 1,50±0,71 vs. 2,28±1,45, p=0,046; 1,86±1,22 vs. 2,44±1,14, p=0,041, respektivno). Nije bilo razlike u C0/D takrolimusa u odnosu na ABCB1 genotip. Multivarijantna regresiona analiza potvrdila je da CYP3A5 predstavlja nezavisan prediktor C0/D u toku posmatranog perioda. Nosioci CYP3A5*1/*3 imali su nižu eGFR u poređenju sa pacijantima sa CYP3A5*3/*3 genotipom nakon 24 i 36 meseci post-transplantacionog perioda (37,62±12,70 vs. 51,89±15,97, p=0,022; 37,25±16,48 vs. 50,99±16,74, p=0,023; respektivno).

CYP3A5 genotip doprinosi interindividualnoj varijabilnosti u dozi takrolimusa neophodnoj da održi optimalnu imunosupresiju, ne samo u ranom, već i kasnijem periodu nakon RTx. Smanjenje bubrežne funkcije može biti izraženije kod pacijenata sa CYP3A5*1/*3 genotipom u dugoročnom periodu nakon RTx. Uvođenje CYP3A5 genotipizacije zajedno sa terapijskim monitoringom takrolimusa može obezbediti personalizovanu terapiju kod pacijenata sa transplantiranim bubregom.

THE ROLE OF PHARMACOGENETICS IN PERSONALIZED THERAPY OF RENAL TRANSPLANT RECIPIENTS ON TACROLIMUS-BASED IMMUNOSUPPRESSION

Nikola Stefanović[1], Radmila Veličković-Radovanović[1], Katarina Dinić[2], Tatjana Cvetković[3]

[1]Department of Pharmacy, University of Niš-Faculty of Medicine, [2]University of Niš - Faculty of Medicine, [3]Department of Biochemistry, University of Niš - Faculty of Medicine (Serbia)

The clinical use of tacrolimus is complicated by marked inter-individual variability in its pharmacokinetics and chronic nephrotoxicity. The main goal of this study was to evaluate potential influence of cytochrome P450 3A5 (CYP3A5) 6986A>G and ABCB1 3435C>T gene polymorphisms on tacrolimus dose–adjusted trough concentrations (C0/D) up to 36 months after renal transplantation (RTx). Additionally, we aimed to investigate whether tested polymorphisms might have negatively affected renal function or not, in the observed post–transplant period.

The study enrolled 93 renal transplant recipients on tacrolimus-based immunosuppression, who were genotyped for CYP3A5 and ABCB1 (encoding P-glycoprotein) using allele–specific PCR method. We calculated C0/D (ng/mL/mg) as trough concentration divided by corresponding tacrolimus dose. Estimated glomerular filtration rate (mL/min/1.73m2, eGFR) was calculated by MDRD formula.

We genotyped patients for CYP3A5 (12.9% CYP3A5*1/*3; 87.1% CYP3A5*3/*3) and ABCB1 (25.8% CC; 47.3% CT; 26.9% TT) gene polymorphism. CYP3A5*1/*3 carriers had lower tacrolimus C0/D than CYP3A5*3/*3 carriers after 1, 6, 12, 24 and 36 months of post-transplant period (0.91±0.38 vs. 1.35±0.54, p=0.008; 1.17±0.69 vs. 2.02±1.14, p=0.011; 1.35±0.56 vs. 2.41±1.57; p=0.015; 1.50±0.71 vs. 2.28±1.45, p=0.046; 1.86±1.22 vs. 2.44±1.14, p=0.041; respectively). There was no difference in tacrolimus C0/D with respect to ABCB1 genotype. Multivariate regression analysis confirmed that CYP3A5 gene polymorphism was an independent predictor of C0/D within observed period. The carriers of CYP3A5*1/*3 genotype had lower eGFR compared to patients with CYP3A5*3/*3 genotype after 24 and 36 months of post-transplant period (37.62±12.70 vs. 51.89±15.97, p=0.022; 37.25±16.48 vs. 50.99±16.74, p=0.023; respectively).

CYP3A5 genotype contributes to the inter–individual variability in tacrolimus dose requirements in order to maintain optimal immunosuppression, not only in the early, but as well in the late period after RTx. Renal function decline may be more pronounced in patients with CYP3A5*1/*3 genotype in long–term periods after RTx. The introduction of CYP3A5 genotyping alongside therapeutic monitoring of tacrolimus may provide personalized therapy in renal transplant recipients.

ULOGA I ZNAČAJ MITOHONDRIJALNIH MARKERA APOPTOZE U TERAPIJI KARCINOMA KOLONA

Ivana Damnjanović[1], Gordana Kocić[2], Stevo Najman[3], Sanja Stojanović[3], Andrej Veljković[2], Srđan Pešić[4]

[1]Katedra za farmaciju, Univerzitet u Nišu - Medicinski fakultet, [2]Institut za biohemiju, Univerzitet u Nišu - Medicinski fakultet, [3]Institut za biologiju i humanu genetiku, Univerzitet u Nišu - Medicinski fakultet, [4]Katedra za farmakologiju, Univerzitet u Nišu - Medicinski fakultet (Srbija)

Mnoge komponente mitohondrijalnog puta apoptoze su deregulisane u ćelijama karcinoma. Članovi Bcl-2 familije proteina predstavljaju važne markere ćelijske apoptotične funkcije, igrajući važnu ulogu u unutrašnjoj, mitohondrijalnoj kaskadi apoptoze. Cilj ovog istraživanja bio je ispitati efekat alfa-liponske kiseline (ALA) same ili u kombinaciji sa cisplatinom (CP) i 5-fluorouracilom (FU) na proliferaciju i Bcl-2/Bax ekspresiju u kulturi Caco-2 ćelija, humanih ćelija karcinoma kolona.

Ispitivan je efekat različitih koncentracija ALA, same ili u kombinaciji sa CP i FU na proliferaciju Caco-2 ćelija MTT testom. Kvantitativna ekspresija Bcl-2 i Bax proteina u kulturi Caco-2 ćelija takođe je ispitivana. Podaci su analizirani SPSS programom, verzija 17.0, Čikago, USA. Rezultati su prikazani kao srednja vrednost absorbance ± SD.

ALA pokazuje citotoksični i antiproliferativni efekat u kulturi Caco-2 ćelija. Ispitivane supstance pokazuju tendenciju smanjenja Bcl-2 i povećanja nivoa Bax ekpresije u poređenju sa kontrolnim uzorcima. ALA dovodi do signifikantne inhibicije ekspresije Bcl-2 proteina u koncentraciji od 1000 μM. Odnos Bax/Bcl-2 proteina može uticati na osetljivost ćelije na apoptozu, kao i progresiju i agresivnost karcinoma, dok povećana ekspresija antiapoptotičkih proteina, ne samo da doprinosi progresiji karcinoma, vec potpomaže razvoju rezistence na primenjeni terapijski protokol.

Prema našim rezultatima, alfa-lipoinska kiselina se može smatrati obećavajućim agensom u borbi protiv karcinoma kolona uzimajući u obzir njenu efiksanost i značajni uticaj na mitohondrijalni put apoptoze. ALA dovodi do smanjenja ekspresije Bcl-2 i povećanja ekspresije Bax proteina kao važnih regulatornih činioca apoptoze. Fokusiranje na mitohondrijalne proteine kao dela apoptotičnog puta može biti atraktivan koncept za pronalaženje novih antikancerskih lekova, međutim još uvek postoje veliki izazovi koje treba prevazići.

Istraživanje je podržano od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije (projekat br. TR 31060 i projekat br. III41017).

THE ROLE AND SIGNIFICANCE OF MITOCHONDRIAL MARKERS OF APOPTOSIS IN COLON CANCER TREATMENT

Ivana Damnjanović[1], Gordana Kocić[2], Stevo Najman[3], Sanja Stojanović[3], Andrej Veljković[2], Srđan Pešić[4]

[1]Department of Pharmacy, University of Niš - Faculty of Medicine, [2]Institute of Biochemistry, University of Niš - Faculty of Medicine, [3]Institute of Biology and Human Genetics, University of Niš - Faculty of Medicine, Serbia, [4]Department of Pharmacology, University of Niš - Faculty of Medicine (Serbia)

Many components of the mitochondrial apoptosis pathway are deregulated in cancer cells. Members of Bcl-2 family proteins are important markers of cell apoptotic function and they play a major role in the intrinsic mitochondrial apoptotic cascade. The aim of this study was to examine the effects of both pure alpha-lipoic acid (ALA)/ALA combined with cisplatin (CP) and 5-fluorouracil (FU) on the proliferation and Bcl-2/Bax quantitative expression in human colon cancer Caco-2 cell line.

We examined the effect of different concentrations of both pure ALA or combined with CP and FU on proliferation of Caco-2 by MTT test. Bcl-2 and Bax quantitative expression were also performed. The data were analyzed by SPSS (v. 17.0). The results were in the range of the average value of absorbance ± SD.

The research results show that ALA exerts cytotoxic and antiproliferative effects on Caco-2 cells. The tested compounds tended to decrease Bcl-2 and increase Bax expression levels, compared with control samples. It was found that ALA exerts a significant inhibitory effect on Bcl-2 expression at the concentration of 1000 μM. Bax/Bcl-2 ratio can act as a rheostat which determines cell susceptibility to apoptosis and affects tumor progression and aggressiveness as well. However, an over expression of prosurvival proteins not only contributes to the progression of cancer, but also confers resistance to the therapeutic treatments.

According to our results, alpha-lipoic acid may be considered a promising agent in the battle against colon cancer due to its efficiency and significant impact on mitochondrial apoptosis pathway. This way ALA inhibits Bcl-2 or activates Bax apoptotic checkpoints and regulators. Targeting of Bcl-2 family proteins as a part of apoptotic pathway may be an attractive concept to finding new anticancer therapies, although there are still huge challenges to meet.

The study was supported by the Ministry of Science and Technological Development of the Republic of Serbia (project no. TR 31060 and project no. III 41017).

INTERAKCIJE ERLOTINIBA U TERAPIJI ONKOLOŠKIH BOLESNIKA NA KLINICI ZA PLUĆNE BOLESTI

Tijana Kovačević[1], Branislava Miljković[2], Sandra Vezmar-Kovačević[2], Mirko Stanetić[3], Peđa Kovačević[4]

[1]Klinička apoteka, Univerzitetski Klinički Centar Republike Srpske, [2]Katedra za farmakokinetiku i kliničku farmaciju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija), [3]Klinika za plućne bolesti, Univerzitetski Klinički Centar Republike Srpske, [4]Klinika intenzivne medicine za nehirurške grane, Univerzitetski Klinički Centar Republike Srpske (Bosna i Hercegovina)

Karcinom pluća predstavlja najčešći uzrok smrti od malignog oboljenja, odmah nakon karcinoma prostate kod muškaraca i karcinoma dojke kod žena. Erlotinib je inhibitor tirozin kinaze indikovan za liječenje nemikrocelularnog karcinom pluća sa aktiviranom mutacijom receptora epidermalnog faktora rasta. Erlotinib ulazi u klinički značajne interakcije sa drugim lijekovima što za posljedicu ima promjenu serumske koncentracije erlotiniba.

Cilj rada je da se pokaže da učešće kliničkog farmaceuta u onkološkom konzilijumu na klinici za plućne bolesti značajno smanjuje broj interakcija u liječenju oboljelih od nemikrocelularnog karcinom pluća ciljanom terapijom erlotinibom.

Grupa od 44 bolesnika označena je kao intervencijska grupa i podaci o njima su prikupljeni prospektivno u vremenskom periodu od 01.01.2017.-01.05.2018. godine za vrijeme učešća na redovnom onkološkom konzilijumu. Kontrolnu grupu sačinjavalo je 44 od ukupno 110 bolesnika koji su liječeni lijekom erlotinib od kada je dostupan u Univerzitetskom Kliničkom Centru republike Srpske (UKC RS) izabranih uparivanjem sa ispitanicima iz intervencijske grupe (*matched pair* analiza), a prije uključivanja kliničkog farmaceuta u rad onkološkog konzilijuma na Klinici za plućne bolesti UKC RS.

Klinički značajne interakcije identifikovane su kod čak dvije trećine ispitanika u studiji (57 od 88). U najvećem broju interakcija, čak 38%, dolazi do smanjenja serumske koncentracije erlotiniba. Klinički farmaceut je dao sugestije za 32 od 44 (72.,72%) ispitanika od kojih je većina prihvaćena od strane ljekara. U intervencijskoj grupi bilo je statistički značajno manje klinički značajnih interakcija u odnosu na kontrolnu grupu (10 *vs* 24, p = 0,044).

Značajno manji broj klinički značajnih interakcija sa erlotinibom u intervencijskoj grupi pacijenata ukazuje na doprinos kliničkog farmaceuta u sprovođenju racionalne terapije pacijenata sa karcinomom pluća.

INTERACTIONS OF ERLOTINIB IN THE TREATMENT OF ONCOLOGIC PATIENTS AT THE LUNG DISEASE CLINIC

Tijana Kovačević[1], Branislava Miljković[2], Sandra Vezmar-Kovačević[2], Mirko Stanetić[3], Peđa Kovačević[4]

[1]Pharmacy Department, University Clinical Centre of the Republic of Srpska, [2]Department of Pharmakocinetics and Clinical Pharmacy, University of Belgrade - Faculty of Pharmacy (Serbia), [3]Lung Disease Clinic, University Clinical Centre of the Republic of Srpska, [4]Clinic for nonsurgical intensive care medicine, University Clinical Centre of the Republic of Srpska (Bosnia and Herzegovina)

Lung cancer is the most common cause of death from malignancy, immediately after prostate cancer in men and breast cancer in women. Erlotinib is a tyrosine kinase inhibitor indicated for treating non-small cell lung cancer with an activated epidermal growth factor receptor mutation. Erlotinib interacts with other medicinal products, which results in a change of erlotinib serum concentration.

The aim of the study was to demonstrate that clinical pharmacist, as a member of oncology consilium at the lung disease clinic, significantly reduces the number of erlotinib interactions in the treatment of non-small cell lung cancer patients.

A group of 44 patients was labeled as intervention group and they were analysed prospectively in the period from 01.01.2017. - 01.05.2018. during clinical pharmacist's participation in the regular oncology consilium. The control group consisted of 44 out of 110 patients treated with erlotinib since it was available in University Clinical Centre of the Republic of Srpska, match paired with patients in intervention group, and before the involvement of a clinical pharmacist in the oncology consilium at the University Clinical Centre of the Republic of Srpska lung diseases clinic. Clinically significant interactions were identified in two-thirds of studied patients (57 out of 88). Most drug interactions, 38%, reduce serum concentration of erlotinib. Clinical pharmacist gave suggestions for 32 out of 44 (72.72%) patients, most of which were accepted by doctors. In the intervention group there were statistically significantly less clinically significant interactions compared to the control group (10 vs 24, $p = 0.044$). A significantly lower number of clinically significant erlotinib interactions in the intervention group of patients advocates the contribution of a clinical pharmacist in the implementation of rational therapy for lung cancer patients.

POTENCIJALNE INTERAKCIJE LEKOVA KOD PACIJENATA SA HIPERTENZIJOM

Zorica Cvetković[1], Aneta Perić[2], Ana Udilović[3]

[1]Vojna apoteka „Slavija", Centralna apoteka, [2]Sektor za farmaciju, Vojnomedicinska akademija, Medicinski fakultet Vojnomedicinske akademije, Univerzitet odbrane, [3]Medicinski fakultet Vojnomedicinske akademije, Univerzitet odbrane (Srbija)

Interakcije lek-lek (DDI) predstavljaju ozbiljan problem među hipertenzivnim pacijentima koji u terapiji koriste veći broj lekova (polifarmacija). Poznavanje potencijalnih DDI-a (pDDI) može pomoći lekarima da minimiziraju štetne efekte pažljivim kombinovanjem upotrebljenih lekova. Cilj naše studije je bio identifikovanje najčešćih pDDI među hipertenzivnim pacijentima i procena mehanizama nastanka i ozbiljnosti interakcija.

Prospektivna, opservaciona studija je sprovedena među hipertenzivnim ambulantnim pacijentima lečenim na Vojnomedicinskoj akademiji u periodu od mesec dana. Studijom su obuhvaćeni pacijenti oba pola stariji od 18 godina koji su u terapiji koristili dva ili više leka. Softver za kontrolu interakcije lekova *Medscape* korišćen je za identifikaciju i analizu pDDI. Deskriptivna statistika i višestruka analiza linearne regresije sprovedena je upotrebom PASW 18.0 (SPSS Inc, Chicago, Illinois).

Od 350 pacijenata u starosnoj grupi od 36 do 98 godina (prosečno 75 ± 11), bilo je neznatno više žena (51,4%). Kod 72,6% pacijenata identifikovane su pDDI od kojih je 18,29% imalo ozbiljne, 65,71% značajne i 28,86% beznačajne pDDI. Utvrđena je pozitivna korelacija između broja propisanih lekova i pDDI ($r = 0,709$; $p < 0,001$). Upotreba digoksina, nesteroidnih antiinflamatornih lekova, antikoagulantnih lekova i statina pozitivan je prediktor za ozbiljne pDDI. Broj značajnih interakcija je niži u poređenju sa drugim studijama u kojima se broj kretao u rasponu od 71,29% do 95,42%. Utvrđena je pozitivna korelacija između pDDI i broja propisanih recepata ($r= 0,788$, $p<0,001$).

Studija je istakla podložnost hipertenzivnih pacijenata na pDDI i posledično pojavu neželjenih reakcija na lekove. Pacijenti na terapiji sa više lekova su skloniji lek-lek interakcijama.

POTENTIAL DRUG INTERACTIONS IN HYPERTENSIVE PATIENTS

Zorica Cvetković[1], Aneta Perić[2], Ana Udilović[3]

[1]Military Pharmacy „Slavija", Central Department for Pharmacy Service, [2]Sector for Pharmacy, Military Medical Academy, Medical Faculty of the Military Medical Academy, University of Defense, [3]Medical Faculty of the Military Medical Academy, University of Defense (Serbia)

Drug-drug interactions (DDIs) are a serious concern among hypertensive patients receiving multidrug therapy. Knowing the potential DDIs (pDDIs) may help physicians minimize adverse effects by careful combining the drugs that are used. Purpose of our study was to identify the most common pDDIs among hypertensive patients and evaluate the mechanism and severity of such interactions.

A prospective, observational study was conducted among the hypertensive outpatients treated at the Military Medical Academy over the period of one month. Patients of both genders over the age of 18 taking two or more drugs were included in the study. Medscape drug interaction checker software was used to identify and analyze the pattern of pDDIs. Descriptive statistics and multiple linear regression analysis were performed using PASW 18.0 (SPSS Inc, Chicago, Illinois).

Among 350 patients in the age group of 36 to 98 years (average 75±11), most were female (51.4%). There were 72.6% patients with pDDIs of which 18.29% patients had serious, 65.71% significant and 28.86% minor pDDIs. A positive correlation was observed between the number of drugs prescribed and pDDIs ($r=0.709$; $p<0.001$). Use of digoxin, nonsteroidal anti-inflammatory drugs, anticoagulant drugs and statins was found to be a positive predictor for serious pDDIs. The number of significant interactions was lower compared to other studies in which the number ranged from 71.29% to 95.42%. A positive correlation between pDDI and the number of prescribed recipes was determined ($r = 0.788$, $p <0.001$).

The study highlighted the susceptability of hypertensive patients to DDIs and therefore adverse drug reactions. Patients on multidrug therapy are more prone to these interactions.

POVRATAK U BUDUĆNOST: KAKO RACIONALIZOVATI BOLNIČKU POTROŠNJU ANTIBIOTIKA?

Aneta Perić[1,2], Bojana Milenković[1], Jelena Brusić-Renaud[1], Mirjana Antunović[1,2], Vesna Šuljagić[2,3]

[1]Služba za farmaceutsku delatnost, Vojnomedicinska akademija, [2]Medicinski fakultet Vojnomedicinske akademije, Univerzitet odbrane, [3]Odsek za prevenciju i kontrolu bolničkih infekcija, Vojnomedicinska akademija (Srbija)

Antibiotici su najčešće korišćeni lekovi u bolničkim uslovima. Praćenje i predviđanje potrošnje antibiotika u bolnicama je značajno za optimizaciju terapije. Prognoza vremenskih serija je metoda koja se koristi za predviđanje buduće potrošnje, a bazira se na analizi trendova potrošnje u proteklom, dužem vremenskom periodu.

Cilj ove studije je da se proceni potrošnja antibiotika u Vojnomedicinskoj akademiji (VMA), posebno cefalosporina i karbapenema, i da se predvidi potrošnja u narednom petogodišnjem periodu.

Retrospektivna studija je sprovedena u periodu od 2001-2017. godine u VMA, tercijernoj, univerzitetskoj bolnici, sa 1200 kreveta. Analizirani su antibiotici za sistemsku primenu (Anatomsko-terapijsko-hemijska (ATC) klasifikacija - J01-antibiotici za sistemsku primenu). Korišćeni su podaci o potrošnji antibiotika iz bolničkog informacionog sistema, a potrošnja je izražena kao Definisana dnevna doza na 100 bolničkih dana (DDD/100 BD), korišćenjem ATC/DDD indeksa za 2017. godinu. Podaci o potrošnji su prikazani kao srednja vrednost ± standardna devijacija. Prognoza vremenskih serija je sprovedena korišćenjem srednjih vrednosti podataka za svaku grupu antibiotika, za svaku analiziranu godinu. Na osnovu trenda srednjih vrednosti predvideli smo buduću potrošnju u odabranom petogodišnjem vremenskom periodu (2018-2022. godine) pomoću ARIMA predikcionog modela.

Prosečna potošnja antibiotika je bila 51,3±7,9 DDD/100 BD. Najčešće korišćeni su bili cefalosporini (15,1±2,8 DDD/100 BD), a zatim karbapenemi (2,9±1,6 DDD/100 BD). Trendovi potrošnje pokazali su da bi očekivano povećanje bilo 0,2 DDD/100 BD godišnje za cefalosporine i 0,3 DDD/100 BD za karbapeneme. Njihova potencijalna prekomerna upotreba će dovesti do visoke stope rezistencije Gram-negativnih bakterija i porasta broja gljivičnih infekcija. Procenjeno je da je antibiotska hirurška profilaksa bila razlog velike potrošnje cefalosporina. Pokazano očekivano povećanje potrošnje antibiotika u bolničkim uslovima lečenja naglašava potrebu za pažljivim praćenjem korišćenja ovih lekova.

BACK TO THE FUTURE: HOW TO OPTIMIZE HOSPITAL ANTIBIOTIC CONSUMPTION?

Aneta Perić[1,2], Bojana Milenković[1], Jelena Brusić-Renaud[1], Mirjana Antunović[1,2], Vesna Šuljagić[2,3]

[1]Department of Pharmacy, Military Medical Academy, [2]Faculty of Medicine of the Military Medical Academy, University of Defence, [3]Department of Infection Control, Military Medical Academy (Serbia)

Antibiotics are the most frequently used drugs in hospitalized patients. Investigating, monitoring and predicting the consumption of antibiotics in hospital is necessary in order to encourage prudent use of these drugs. Forecasting analysis is the process of making predictors of the future based on past and present data and analysis of trends. The aim of this study was to evaluate the antibiotic consumption in the Military Medical Academy (MMA), especially cephalosporins and carbapenems, and to predict future consumption in a five-year period.

The retrospective study was conducted from 2001 to 2017 in MMA, Belgrade, a tertiary, university hospital, with 1200 beds. Antibacterials for systemic use (Anatomical Therapeutic Chemical (ATC) code J01) were included in this study. Data regarding the use of antibiotics were extracted from hospital computer system and expressed as Defined Daily Dose per 100 bed days (DDD/100 BD), using the 2017 version of the ATC/DDD index. Results are expressed as mean value ± standard deviation. Forecasting analysis was performed on mean values of all data for each group of antibiotics in a single year. Based on mean value trend we predicted how this variable is likely to behave in the future, using ARIMA prediction model in a selected time horizon (2018-2022).

The average antibiotic consumption was 51.3±7.9 DDD/100 BD. The most frequently used were cephalosporins (15.1±2.8 DDD/100 BD), followed by carbapenems (2.9±1.6 DDD/100 BD). Trends of consumption showed that the expected increase would be 0.2 and 0.3 DDD/100 BD per year for cephalosporins and carbapenems, respectively. Potential overuse will lead to the high rate of both Gram-negative bacteria resistance and fungal infections. It is estimated that surgical antibiotic prophylaxis is the reason for high levels of cephalosporin consumption. Demonstrated expected increase in antibiotic consumption highlights the need for careful drug use monitoring.

TROVANJA OLANZAPINOM U NACIONALNOM CENTRU ZA KONTROLU TROVANJA SRBIJE U 2017. GODINI

Snežana Đorđević[1], Vesna Kilibarda[1], Gordana Brajković[2], Nataša Perković Vukčević[1], Gordana Vuković Ercegović[1], Jasmina Jović Stošić[1], Slavica Vučinić[1]

[1]Vojnomedicinska akademija - Medicinski fakultet, Univerzitet Odbrane, Beograd, [2]Nacionalni centar za kontrolu trovanja, Beograd (Srbija)

Olanzapin je lek koji pripada novoj generaciji antipsihotika. Koristi se za lečenje šizofrenije i bipolarnog poremećaja ličnosti. Efekti nastaju verovatno kao rezultat blokiranja ili antagonizovanja dopaminskih D2 receptora. Kao i drugi netipični antipsihotici olanzapin je jak antagonista 5-HT2A serotoninskih receptora. Akutna trovanja olanzapinom su retka. Simptomi trovanja podrazumevaju dublji ili fluktuirajući poremećaj stanja svesti sa hipersalivacijom i miozom. Visoke doze mogu da uzokuju komu i smrt. Terapijske koncentracije olanzapina u krvi su u opsegu od 0,01-0,05 mg/L. Letalan ishod može nastati pri koncentracijama olanzapina u plazmi većim od 1 mg/L.

Cilj ovog rada je da prikaže slučajeve akutnih trovanja olanzapinom u Nacionalnom centru za kontrolu trovanja (NCKT) Srbije u 2017. godini.

Prema podacima NCKT registrovan je 31 pacijent (26 žena i 6 muškaraca) zbog sumnje na trovanje olanzapinom. Svi pacijenti su imali olanzapin u svojoj redovnoj terapiji. Određivanje koncentracije olanzapina vršeno je validiranom metodom tečne hromatografije sa masenom spektrometrijom (LC-MS).

Rezultati pokazuju da je 15 pacijenata (10 žena i 5 muškaraca) imalo terapijske koncentracije olanzapina u krvi, a kod 16 pacijenata (15 žena i 1 muškarac) su registrovane toksične i čak letalne koncentracije olanzapina. Jedna pacijentkinja je zbog pokušaja suicida bila hospitalizovana 2 puta u toku tri meseca. Koncentracije olanzapina na prijemu od 1,75 mg/L i 2,44 mg/L su u oba slučaja bile letalne. Ona je imala karakterističnu kliničku sliku trovanja olanzapinom. Hospitalizacija je trajala više od jedne nedelje, ali je bila sa povoljnim ishodom.

Trovanja olanzapinom su retka i uglavnom lakšeg stepena. Međutim, u izvesnim slučajevima visoke koncentracije mogu da izazovu ozbiljna trovanja. S obzirom da ne postoji antidot kod trovanja olanzapinom, primena adekvatne simptomatske i suportivne terapije dovodi do povoljnog terapijskog ishoda čak i u slučajevima trovanja sa visokim koncentracijama olanzapina.

OLANZAPINE INTOXICATIONS IN NATIONAL POISON CONTROL CENTER SERBIA IN 2017

Snežana Đorđević[1], Vesna Kilibarda[1], Gordana Brajković[2], Nataša Perković Vukčević[1], Gordana Vuković Ercegović[1], Jasmina Jović Stošić[1], Slavica Vučinić[1]

[1]Medical Faculty Military Medical Academy, University of Defense, Belgrade,
[2]National Poison Control Centre, Belgrade (Serbia)

Olanzapine is the drug that belongs to the group of new generation of antipsychotics. It is used for treating of schizophrenia and bipolar disorder. The effects are probably result of blocking or antagonizing of dopamine D2 receptors. Like other atypical antipsychotics, olanzapine also strongly antagonizes the 5-HT2A serotonin receptor. Acute poisonings with olanzapine are rare. Symptoms of an overdose include deeper or fluctuating disorder of consciousness with hypersalivation and miosis. High doses can cause coma and death. Therapeutic blood concentration of olanzapine is in the range of 0.01-0.05 mg/L. Fatalities generally have occurred with olanzapine plasma concentrations greater than 1 mg/L.

The aim of this work is to present cases of acute poisonings with olanzapine in National Poison Control Centre (NPCC) Serbia in 2017.

According to NPCC data, there were 31 patients (26 female and 6 male) under suspicion of olanzapine intoxication. All of the patients had olanzapine in their regular therapy. Determination of olanzapine was done by validated liquid chromatographic mass spectrometric (LC-MS) method.

Results showed that 15 patients (10 female and 5 male) had olanzapine concentration in the therapeutic range, and 16 in toxic and even lethal range (15 female and 1 male). One of the patients with a suicide attempt has been hospitalized two times during the three months period. Olanzapine concentrations of 1.75 mg/L and 2.44 mg/L after reception in both cases were in the fatal range. She had characteristic clinical picture for acute olanzapine poisoning. Hospitalization lasted more than one week, but with favorable outcome.

Olanzapine intoxications are rare and mostly with mild degree. But in some cases, high concentration can cause severe intoxication. Since there is not antidote for olanzapine poisoning, applying of adequate symptomatic and supportive therapy lead to favorable outcome even in cases with high olanzapine concentration.

EFIKASNOST OMEGA-3 MASNIH KISELINA U PREVENCIJI KARDIOVASKULARNIH BOLESTI: DOKAZI I PREPORUKE

Silva Dobrić

Univerzitet odbrane - Medicinski fakultet Vojnomedicinske akademije, Institut za naučne informacije, Beograd (Srbija)

Veći broj opservacionih studija ukazao je na povezanost redovnog konzumiranja ribe bogate omega-3 masnim kiselinama (omega-3 MK) sa smanjenim rizikom od smrti zbog kardiovaskulanih bolesti (KVB). Ova zapažanja rezultirala su povećanim interesom za primenu dijetetskih suplemenata sa omega-3 MK u prevenciji KVB. Međutim, kliničke studije, u kojima je ispitivana njihova protektivna efikasnost kod osoba sa povećanim rizikom od KVB, dale su kontradiktorne rezultate. Stoga je cilj ovog rada bio da se kritički analiziraju rezultati studija objavljeni u poslednjih 10 godina kako bi se sagledala uloga i mesto suplemenata sa omega-3 MK u smanjenju fatalnih i nefatalnih kardiovaskularnih događaja kod osoba sa povišenim rizikom od KVB.

Analizom su bili obuhvaćeni rezultati kontrolisanih kliničkih studija i meta-analiza o upotrebi suplemenata sa omega-3 MK u prevenciji KVB objavljeni u časopisma indeksiranim u bazi *PubMed/MEDLINE* u periodu 2008-2018.

Rezultati analiziranih kliničkih studija, većinom dvostruko-slepih i kontrolisanih placebom, pokazali su da redovno uzimanje suplemenata sa omega-3 MK u dozi 0,5-2 g/dan nije dovelo do značajnog smanjenja neželjenih kardiovaskularnih događaja kod osoba sa povišenim rizikom od KVB. Ovi nalazi ne podupiru preporuke koje sugerišu upotrebu otprilike 1 g/dan omega-3 MK kod osoba sa istorijom ishemijske bolesti srca. Trenutno je u toku nekoliko velikih studija, u koje je uključeno blizu 55000 osoba sa rizikom od razvoja velikih kardiovaskularnih događaja, u kojima se ispituje protektivna efikasnost omega-3 MK, primenjenih u dozama od 3-4 g/dan. Rezultati ovih studija treba da pokažu da li će više doze omega-3 MK, od trenutno preporučenih, imati značajan efekat na smanjenje rizika od neželjenih kardiovaskularnih događaja.

Rezultati novijih kliničkih studija pokazuju da upotreba suplemenata sa omega-3 MK nema značajan efekat u prevenciji fatalnih i nefatalnih vaskularnih događaja kod osoba sa povišenim rizikom od KVB.

EFFECTIVENESS OF OMEGA-3 FATTY ACIDS IN PREVENTION OF CARDIOVASCULAR DISEASES: EVIDENCE AND RECOMMENDATIONS

Silva Dobrić

University of Defense - Faculty of Medicine of the Military Medical Academy, Institute for Scientific Information, Belgrade (Serbia)

A number of observational studies have highlighted the association of regular consumption of fish rich in omega-3 fatty acid (omega-3 FA), with a reduced risk of death from cardiovascular disease (CVD). These observations have resulted in increased interest in the use of omega-3 FA supplements in the prevention of CVD. However, clinical studies, in which their protective effectiveness was investigated in people with an increased risk of CVD, gave contradictory results. Therefore, the aim of this paper was to critically analyze the results of clinical studies published over the past 10 years to look at the role and place of omega-3 FA supplements in reducing unwanted cardiovascular events in people at high risk of CVD.

The analysis included results of controlled clinical studies and meta-analyses on the use of omega-3 supplements in the prevention of CVD, published in journals indexed at the PubMed/MEDLINE database in the period 2008-2018.

Results of analyzed studies showed that regular use of omega-3 FA (0.5-2 g/ day) failed to significantly reduce fatal and non-fatal cardiovascular events in people with high risk of CVD. These findings do not support recommendations suggesting the use of approximately 1 g/day omega-3 FA in people with ischemic heart disease. Several ongoing large trials, involving almost 55000 people at risk of developing major cardiovascular events, in which the protective effectiveness of 3-4 g/day omega-3 FA is tested, will provide evidence whether higher doses of omega-3 FA than currently recommended may have a significant effect on reducing the risk of unwanted cardiovascular events.

The results of recent clinical studies show that the use of omega-3 FA supplements has no significant effect in the prevention of fatal and non-fatal vascular events in people at high risk of CVD.

KORISTI I RIZICI UPOTREBE DIJETETSKIH SUPLEMENATA

Davor J. Korčok, Bogdan Mitić

Abela Pharm d.o.o., Beograd (Srbija)

Dijetetski suplementi kao farmaceutski dozirani oblici se mogu naći u slobodnoj prodaji u apotekama na internetu, drogerijama i drugim objektima i važno je pravilno proceniti njihove koristi kao i rizike. Cilj ovog rada jeste procena koristi i bezbednosnih rizika upotrebe dijetetskih suplemenata u zdravstvene svrhe kod ljudi pregledom kliničkih studija i naučnih radova.

Urađena je pretraga baza podataka na PUBMED-u i Google Scholar website-u za radove koji su objavljeni periodu od 2011 do 2018. godine. Procena studija je urađena od strane autora rada. Da bi bili uključeni u rad, studije su morale da sadrže bezbednosne aspekte i korist upotrebe dijetetskih suplemenata kod ljudi.

Pregledom velikog broja radova koji su dobijeni unosom sledećih pojmova, uz njihovu kombinaciju u pretragu: „safety", „efficiency", „dietary supplements" i „food supplements", odabrano je 10 radova u kojima su praćeni pozitivni ishodi suplementacije dijetetskim suplementima kao što su: smanjenje rizika od nastanka određene bolesti, poboljšanje opšteg zdravstvenog stanja i drugi. Podaci o dijetetskim suplementima koji su sadržali sledeće supstance su razmatrani: vitamin D, kalcijum, probiotici, glukozamin, hondroitin, S-adenozilmetionin, folati, karnitin, cimet, vitamin C i druge. Rezultati su pokazali da su se dijetetski suplementi koristili u cilju poboljšanja opšteg zdravlja pojedinca ili u cilju poboljšanja određenog stanja bez dodatnih rizika po njihovo zdravlje.

Dokazi pokazuju da korist upotrebe dijetetskih suplemenata prevazilazi njihove bezbednosne rizike po zdravlje ljudi, i da se njihova upotreba generalno može preporučivati, međutim, potrebno je uraditi još istraživanja i proceniti u kojim situacijama primena suplementa neće izazvati neželjene događaje i iskazati efikasnost.

BENEFITS AND RISKS OF DIETARY SUPPLEMENTS USE

Davor J. Korčok, Bogdan Mitić

Abela Pharm d.o.o., Belgrade (Serbia)

Dietary supplements as pharmaceutical dosage forms can be marketed and sold in pharmacies, on the Internet, in drugstores and other facilities, so it is important to properly assess their benefits and risks. The aim of this paper is to evaluate the benefits and safety risks of dietary supplements use for health purposes in humans by review of clinical studies and scientific papers.

Database search on PubMed and Google Scholar has been completed for the research papers published in the time period from 2011 until 2018. The evaluation of the studies was performed by the authors of this paper. In order to be included, the studies had to include the safety aspects and the benefits of dietary supplements use in humans.

After the performed review of large number of scientific papers that were found using the key words: „safety", „efficiency", „dietary supplements" and „food supplements", 10 of them were included in this overview, and the positive outcomes of a supplementation with dietary supplements were analyzed such as: risk reduction for the development of certain disease, improvement of general health of the individuals, and others. Data on dietary supplements containing the following supplements were assessed: vitamin D, calcium, probiotics, glucosamine, chondroitin, S-adenosyl methionine, folate, carnitine, cinnamon, vitamin C and others. The results showed that dietary supplements were generally used to improve general health of an individual or to improve a certain health condition without additional risks to their health.

Evidence suggests that the benefits of dietary supplements use outweigh their safety risks for human health, and that their use can generally be recommended. However, further research is needed to assess the situations when the supplement use would not cause side effects and demonstrate complete efficacy.

DIJETETSKI SUPLEMENTI SA VITAMINIMA I MINERALIMA NA TRŽIŠTU SRBIJE

Bojana Vidović, Mirko Lazović, Lana Kostić, Slađana Šobajić

Katedra za bromatologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Vitamini i mineralne materije, kao esencijalni nutrijenti, ubrajaju se u najčešće aktivne sastojke dijetetskih suplemenata. Cilj rada bio je da se dobije uvid u zastupljenost, karakteristike sastava i hemijske oblike vitamina i minerala u dijetetskim suplementima na tržištu Srbije.

Istraživanje je sprovedeno prikupljanjem i analizom deklaracija dijetetskih suplemenata sa vitaminima i mineralima koji se nalaze na našem tržištu.

Od ukupno 705 dijetetskih suplemenata koji sadrže vitamine i/ili minerale, 19,43% je proizvedeno u Srbiji, a ostali su iz uvoza. Monokomponentnih dijetetskih suplemenata je bilo 36,4%. Od ukupnog broja polikomponentnih proizvoda, 35,8% sadrži samo vitamine, 4,1% samo minerale, dok ostatak čine kombinacije vitamina i minerala, sa i bez dodatka drugih biološki aktivnih sastojaka. Vitamin C je najzastupljeniji vitamin (u 59,4% proizvoda), slede vitamini B grupe, dok je vitamin K prisutan u svega 6,4% dijetetskih suplemenata. Najzastupljeniji makroelementi su magnezijum (41,7%) i kalcijum (35,6%), a od mikroelemenata cink (36,9%) i selen (26,7%). Najčešće korišćene organske soli kao izvori minerala su citrati i glukonati, a od neorganskih izvora: karbonati, oksidi i sulfati. Prirodni izvori vitamina zastupljeni su u 6,2% dijetetskih suplemenata. Upoređivanjem dnevnih doza vitamina i minerala (na osnovu predviđenog načina upotrebe navedenog na deklaraciji) sa njihovim nutritivnim referentnim vrednostima (NRV), utvrđeno je da veliki broj dijetetskih suplemenata sadrži vitamine i minerale u količinama većim od 150% NRV.

Na tržištu se nalazi veliki broj dijetetskih suplemenata sa vitaminima i/ili mineralima, uključujući i one čijom se primenom u organizam unose količine vitamina i minerala koje su višestruko veće od 100% NRV. U cilju racionalne i bezbedne upotrebe ovih proizvoda veoma je značajna savetodavna uloga zdravstvenih radnika, prvenstveno farmaceuta.

VITAMIN AND MINERAL SUPPLEMENTS ON THE SERBIAN MARKET

Bojana Vidović, Mirko Lazović, Lana Kostić, Slađana Šobajić

Department of Bromatology, University of Belgrade - Faculty of Pharmacy (Serbia)

Vitamins and minerals, as essentials nutrients, are the most common active compounds in dietary supplements. The aims of this work were to investigate the presence, sources, and amounts of vitamins and minerals in the dietary supplements on Serbian market.

The research was conducted by analyzing the declarations of dietary supplements from Serbian market.

During the survey, it was established that 705 dietary supplements contained vitamins and/or minerals. In Serbia 137 dietary supplements (19.43%) have been produced, and the rest was imported. There were 36.4% mono-component products. Among the multicomponent, 35.8% contain only vitamins, 4.1% contain only minerals, and the rest was the combination of vitamins and minerals with or without the addition of other bioactive components. The most common vitamin was vitamin C (59.5%), followed by B-vitamins group while the least frequent vitamin K was present in only 6.4% of the products. The most common macroelements were magnesium (41.7%) and calcium (35.6%). Zinc and selenium were the most common microelements present in 36.9% and 26.7% of dietary supplements, respectively. The most common organic salts of minerals were citrates and gluconates; among inorganic sources, these were carbonates, oxides, and sulfates. Natural vitamin sources were present in 6.2% of the dietary supplements. The recommended daily dosage vitamins and minerals have been compared with the reference doses for nutrition labeling (NRV) and a large number of dietary supplements have exceeded the value of 150% NRV.

On the market, there is a large number of dietary supplements with the content of vitamins and minerals higher than NRV values. In order to improve rational and safe use of dietary supplements, the consumers before use need to consult with pharmacists or other health professionals.

ISPITIVANJE BRZINE RASTVARANJA RESVERATROLA IZ DIJETETSKIH SUPLEMENATA

Mira Mikulić, Ljilja Torović, Milica Atanacković Krstonošić, Veljko Ćućuz, Jelena Hogervorst

Katedra za farmaciju, Univerzitet u Novom Sadu - Medicinski fakultet (Srbija)

Resveratrol (*trans*-3,5,4′-trihidroksistilben) je fitoaleksin koji pripada grupi stilbena - fenolnih jedinjenja prisutnih u različitim biljnim vrstama. Njegovi najpoznatiji prirodni izvori su crveno vino, grožđe, kikiriki i borovnice. Na tržištu raste broj dijetetskih suplemenata koji sadrže ovo jedinjenje, jer se smatra da može imati značajnu ulogu u prevenciji kardiovaskularnih i malignih oboljenja, pre svega zbog svoje antioksidativne i antiinflamatorne aktivnosti. Cilj ovog rada je određivanje brzine rastvaranja resveratrola iz komercijalno dostupnih dijetetskih suplemenata koji sadrže resveratrol ili ekstrakt grožđa.

Ispitivano je 12 različitih dijetetskih suplemenata koji sadrže resveratrol (7 uzoraka, F6-F12) ili neku vrstu ekstrakta grožđa (5 uzoraka, F1-F5). Test brzine rastvaranja rađen je na ERWEKA DT800 aparatu u acetatnom puferu pH 4,5, a uzorkovanje je vršeno nakon 45 minuta. Identifikacija i kvantifikacija resveratrola je izvedena na Agilent 1100 Series tečnom hromatografu uz upotrebu Poroshell 120 EC-C18 kolone, UV detekciju na 305 nm i gradijentnu eluciju.

Od 12 testiranih suplemenata, resveratrol je kvantifikovan u samo 4 suplementa (F6, F7, F8, F12) koji su svi imali deklarisan sadržaj ove komponente. Među njima, jedino je kod dve kapsule suplementa F7utvrđeno rastvaranje više od 75% u odnosu na deklarisani sadržaj. U ostalim uzorcima količina rastvorenog resveratrola nije prelazila 33%. U uzorcima na bazi ekstrakta grožđa, resveratrol nije detektovan. Dobijeni rezultati mogu biti posledica slabe rastvoljivosti resveratrola, neadekvatne formulacije, ali i niskog sadržaja u samim suplementima.

Budući da nijedan od testiranih suplemenata nije pokazao zadovoljavajuću brzinu oslobađanja resveratrola, potrebno je posebno obratiti pažnju na ovu vrstu komercijalno dostupnih preparata. Svakako, ovakvi rezultati dovode u pitanje i potencijalnu efikasnost ovih preparata u ljudskom organizmu.

ANALYSIS OF RESVERATROL DISSOLUTION FROM DIETARY SUPPLEMENTS

Mira Mikulić, Ljilja Torović, Milica Atanacković Krstonošić, Veljko Ćućuz, Jelena Hogervorst

Department of Pharmacy, University of Novi Sad - Faculty of Medicine (Serbia)

Resveratrol (*trans*-3,5,4′-trihydroxystilbene) is a phytoalexin from group of stilbenes – phenolic compounds present in various plant species. Natural sources rich in resveratrol include red wine, grapes, peanuts and blueberries. Number of dietary supplements containing resveratrol on the market is rising, mainly because of its potential role in the prevention of cardiovascular and malignant diseases as well as antiaging properties. It has been shown that this component possesses antioxidant and anti-inflammatory activity. Therefore, the aim of this study was assessment of dissolution of dietary supplements containing resveratrol or grape extract.

Twelve different dietary supplements with declared resveratrol (7 samples, F6-F12) or grape extract content (5 samples F1-F5) were analyzed. Dissolution test was performed on ERWEKA DT800 apparatus in acetate buffer pH 4.5, and sampling was done after 45 minutes. Identification and quantification of resveratrol was performed on Agilent 1100 Series liquid chromatograph with Poroshell 120 EC-C18 column, UV detection on 305 nm and gradient elution.

From total of 12 analyzed supplements, resveratrol was quantified only in 4 (F6, F7, F8, F12) which all had declared resveratrol content. Among them, more than 75% of the declared content was dissolved only from two capsules of supplement F7. In the rest of the samples, amount of dissolved resveratrol did not exceed 33% of the declared content. In 5 dietary supplements with grape extracts, resveratrol was not detected. Obtained results can be consequence of different factors, including low solubility of resveratrol, inadequate formulation as well as its low content in analyzed samples.

Since none of the tested supplements has shown optimal dissolution properties, there is a need for more detailed analysis of resveratrol supplements present on the market. Additionally, these results indicate that potential efficacy of this type of preparations in humans should be further studied.

ISPITIVANJE ANTIMIKROBNOG POTENCIJALA ETARSKOG ULJA HERBE CRVENOG ZDRAVCA (*GERANIUM ROBERTIANUM* L.)

Jelena Antić Stanković[1], Nikola Krstić[1], Nikola Jakovljević[1], Dubravka Bigović[2]

[1]Katedra za mikrobiologiju i imunologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Institut za proučavanje lekovitog bilja „Dr Josif Pančić" (Srbija)

Imajući u vidu sve češću pojavu rezistencije mikroorganizama prema konvencionalnim antibioticima, jedan od ciljeva istraživačkih timova širom sveta je ispitivanje antimikrobnog potencijala jedinjenja biljnog porekla i definisanje hemijskih sastojaka koji ispoljavaju antimikrobnu aktivnost. Cilj ovog rada je bio određivanje antimikrobne aktivnosti etarskog ulja crvenog zdravca, *Geranium robertianum* L., dobijenog destilacijom nadzemnog dela biljke u cvetu, prema standardnim sojevima *Staphyloccocus aureus* i *Escherichia coli,* kao i efekat kombinovane primene etarskog ulja sa amoksicilinom.

Za ispitivanje antimikrobne aktivnosti, korišćena je agar mikrodiluciona metoda. Inokulum je pripremljen u skladu sa smernicama Instituta za kliničke i laboratorijske standarde (CLSI). Sveže pripremljene kolonije vrsta *S. aureus* (ATCC 25923), *E. coli* (ATCC25922) (18-24h) su suspendovane u određenoj zapremini fiziološkog rastvora da bi se postigao turbiditet vrednosti 0,5 koja prema McFarland standardu odgovara 1-2x10^8 CFU/ml. U hranljivom bujonu je od pripremljene suspenzije napravljeno razblaženje 1:10 (10^7 CFU/ml bakterija). Za inokulaciju na površinu agara u bazenu mikrotitracione ploče korišćeno je 5 µl ovako pripremljene bakterijske suspenzije. Temperatura Mueller-Hinton bujona je bila 55±5˚C, kako bi medijum bio tečan pre inkorporiranja odgovarajućih koncentracija etarskog ulja i/ili amoksicilina.

Agar mikrodilucionom metodom utvrđeno je da minimalna inhibitorna koncentracija (MIK) etarskog ulja *G. robertianum* iznosi 2,39 mg/ml prema testiranim mikroorganizmima. Poređenja radi, disk difuzionom metodom, efekat testiranog etarskog ulja uočen je pri koncentraciji koja je nekoliko puta veća. Na osnovu vrednosti indeksa frakcione inhibitorne koncentracije (FICI), zaključeno je da testirano etarsko ulje pokazuje sinergistički efekat sa amoksicilinom prema *S. aureus*, a indiferentan u kombinaciji sa amoksicilinom prema *E.coli*.

Agar mikrodiluciona metoda se pokazala kao pogodna za *in vitro* ispitivanje antimikrobne aktivnosti etarskog ulja, a izdvaja se od ostalih prema ekonomičnosti, jednostavnosti i smanjenju pojave razdvajanja hidrofobnog etarskog ulja i hidrofilnog medijuma.

EXPLORATION OF ANTIMICROBIAL POTENTIAL OF THE ESSENTIAL OIL FROM AERIAL PARTS OF *GERANIUM ROBERTIANUM* L.

Jelena Antić Stanković[1], Nikola Krstić[1], Nikola Jakovljević[1], Dubravka Bigović[2]

[1]Department of Microbiology and Immunology, University of Belgrade - Faculty of Pharmacy, [2]Institute for Medicinal Plant Research „Dr Josif Pančić" (Serbia)

Bearing in mind the increasingly frequent occurrence of microbial resistance to conventional antibiotics, one of the goals of research teams around the world is investigation of the antimicrobial potential of compounds of plant origin and identification of chemical ingredients that exhibit antimicrobial activity. The aim of this work was investigation of antibacterial activity of essential oil obtained by distillation of the aerial parts of *Geranium robertianum* L. during the flowering period, against standard bacterial strains *Staphylococcus aureus* and *Escherichia coli.* Also, effect of essential oil in combination with amoxycillin was investigated.

An inoculum was prepared according to the Clinical and Laboratory Standards Institute methods (CLSI). Briefly, fresh (18–24 h) bacterial colonies of *S. aureus* (ATCC 25923) and *E. coli* (ATCC 25922) were suspended in Mueller-Hinton broth to achieve a turbidity of 0,5 McFarland standard corresponding to approx. 1–2 x 10^8 colony-forming units (CFU). Next, 0,5 McFarland suspensions were diluted 1:10 in fresh Mueller-Hinton broth to obtain a concentration of 10^7 CFU/ml and then 5 ml of prepared bacterial suspension was applied to the surface of agar in each well of the microplate.

During the experiment, the Miller-Hinton agar temperature of 55±5°C was maintained, so that the agar was liquid prior to mixing with essential oil or/and antibiotic solution.

Agar microdilution method showed that the minimal inhibitory concentration (MIC) of *G. robertianum* essential oil against the tested microorganisms is 2.39 mg/ml. For comparison, using the disc diffusion method, the effect of the tested essential oil was observed at a several times higher concentration. Based on the values of fractional inhibitory concentration index (FICI), it was concluded that the tested essential oil exhibits a synergistic effect with amoxicillin against *S. aureus*, and is indifferent in combination with amoxicillin according to *E. coli.*

The agar microdilution method proved to be suitable for *in vitro* testing of antimicrobial activity of essential oil, and it distinguishes itself from others in terms of economy, simplicity and reduction in the occurrence of separation of hydrophobic essential oil and hydrophilic medium.

EFFECT OF EXENATIDE LAR IN TYPE-2 DIABETIC PATIENTS WITH VS. WITHOUT ELEVATED ADIPO-INFLAMMATORY RISK SCORE AT BASELINE: AN 8-MONTH PROSPECTIVE INTERVENTION STUDY

Dragana Nikolic[1], Roberta Chianetta[1], Giuseppa Castellino[1], Jelena Vekic[2], Aleksandra Zeljkovic[2], Vesna Spasojevic-Kalimanovska[2], Manfredi Rizzo[1]

[1]University of Palermo (Italy), [2]University of Belgrade – Faculty of Pharmacy (Serbia)

The effect of exenatide once-weekly (long-acting release, LAR) on cardiovascular risk may be mediated by the modulation of several cytokines involved in inflammatory process and endothelial function. We evaluated different cytokines associated with inflammation at the endothelial level and glycemic decompensation in subjects with type 2 diabetes (T2DM), in order to make a new adipo-inflammatory risk score. The effect of exenatide LAR was then assessed in such T2DM patients in relation to the presence of elevated adipo -inflammatory risk score at baseline.

Sixty subjects with T2DM (41 men and 19 women) naïve to incretin-based therapies were treated with exenatide LAR as add-on to metformin (from 1500 up to 3000 mg/day) for 8 months. Elevated cardiometabolic risk score at baseline was defined by the combination of the following 5 cytokines: adiponectin, leptin, resistin, monocyte chemotactic protein 1, plasminogen activator inhibitor-1, E-Selectin, and soluble intercellular adhesion molecule. The median value of each cytokine was used as cut-off for defining the „abnormal value" of each cytokine, and the cohort of patients was then subdivided in 2 groups: with elevated adipo-inflammatory risk score at baseline (n=28) and without elevated adipo-inflammatory risk score at baseline (n=32). Carotid intima media thickness (cIMT) was assessed by B-mode real-time ultrasound, while endothelial function by flow mediated dilation (FMD) of the brachial artery.

We found improvements in most of the investigated cardio-metabolic parameters among subjects with and without elevated adipo-inflammatory risk score at baseline, and did not find any significant difference among the two subgroups of patients.

This study showed that exenatide LAR similarly improved cardio-metabolic parameters in T2DM subjects with vs. without elevated adipo-inflammatory risk score at baseline. Our data somewhat extend previous findings of anti-inflammatory effects of exenatide in animal models.

POVEZANOST IZMEĐU OBRAZACA HOMEOSTAZE HOLESTEROLA I KONCENTRACIJA NE-HDL HOLESTEROLA KOD ZDRAVIH OSOBA I PACIJENATA SA ISHEMIJSKOM BOLEŠĆU SRCA KOJI NISU NA TERAPIJI STATINIMA

Tamara Gojković, Sandra Vladimirov, Vesna Spasojević-Kalimanovska, Aleksandra Zeljković, Jelena Vekić, Zorana Jelić-Ivanović

Katedra za medicinsku biohemiju, Univerzitet u Beogradu – Farmaceutski fakultet (Srbija)

Homeostaza holesterola predstavlja ravnotežu između sinteze i apsorpcije holesterola. Određivanjene holesterolskih sterola (NHS) kao markera sinteze i apsorpcije holesterola, može ukazivati na rani razvoj dislipidemije i predvideti odgovor na terapiju statinima. Ne-HDL holesterol (ne-HDL-h) je bolji prediktor rizika za ishemijsku bolest srca (IBS) od LDL holesterola.

Studija je obuhvatala 47 IBS pacijenata bez terapije statinima i 31 zdravog ispitanika (KG). Koncentracije NHS-a su kvantifikovane metodom gasne hromatografije sa plamenojonizacijonom detekcijom (GC-FID). Koncentracije ukupnog holesterola i HDL-holesterola, merene su rutinskim metodama na Ilab 300+ analizatoru.

Obrasci homeostaze holesterola su dobijeni na osnovu medijalnih vrednosti latosterola i β-sitosterola (L/β). U KG, učesnici sa većim nivoima sinteze imali su veće vrednosti ne-HDL-h u odnosu na podgrupu sa manjom sintezom ($p<0,05$). Nivoi apsorpcije u obe podgrupe su bili isti. Pacijenti bez terapije statinima sa povećanom sintezom holesterola, bez obzira na apsorpciju, imali su povećane nivoe ne-HDL-C u poređenju sa podgrupama sa slabom sintezom i slabom apsorpcijom ($p<0.01$, za oba poređenja).

Odnos L/β može biti korisna alatka za procenu individualnih obrazaca homeostaze holesterola, a samim tim i rano otkrivanje dislipidemije i predviđanje odgovora na terapiju statinima.

ASSOCIATION BETWEEN CHOLESTEROL HOMEOSTASIS PATTERNS AND NON-HDL CHOLESTEROL IN HEALTHY PEOPLE AND NON-STATIN TREATED CORONARY ARTERY DISEASE PATIENTS

Tamara Gojković, Sandra Vladimirov, Vesna Spasojević-Kalimanovska, Aleksandra Zeljković, Jelena Vekić, Zorana Jelić-Ivanović

Department of Medical Biochemistry, University of Belgrade - Faculty of Pharmacy (Serbia)

Cholesterol homeostasis represents the balance between cholesterol synthesis and absorption. Evaluation of non-cholesterol sterols (NCSs) as synthesis and absorption markers may indicate the dyslipidemia early development and predict statin response. Non-HDL cholesterol (non-HDL-C) is a better predictor of coronary artery disease (CAD) risk than LDL cholesterol. This study investigates associations of different cholesterol homeostasis patterns with non-HDL-C concentration.

We enrolled 47 statin-untreated CAD patients and 31 controls (CG). NCSs concentrations were quantified using gas chromatography-flame ionization detection (GC-FID). Concentrations of total cholesterol (TC) and HDL-cholesterol (HDL-C) were measured by routine methods on an ILab 300+ analyzer.

Cholesterol homeostasis patterns were obtained according to lathosterol and β-sitosterol median values (L/β). CG participants with same absorption levels, but elevated cholesterol synthesis had higher non-HDL-C concentration compared to those with reduced synthesis ($p<0.05$). Statin-untreated patients with increased cholesterol synthesis, regardless of absorption, had increased levels of non-HDL-C compared to subgroups with poor synthesis and poor absorption ($p<0.01$, for both).

L/β ratio could be a useful tool for estimating individual cholesterol homeostasis patterns, and consequently dyslipidemia early development and statin therapy response.

LONG TERM EFFECTS OF LIRAGLUTIDE ON GLYCO-METABOLIC PARAMETERS AND cIMT IN PATIENTS WITH TYPE-2 DIABETES: 5 YEARS PROSPECTIVE REAL-WORLD STUDY

Giuseppa Castellino[1], Dragana Nikolic[1], Roberta Chianetta[1], Jelena Vekic[2], Aleksandra Zeljkovic[2], Vesna Spasojevic-Kalimanovska[2], Manfredi Rizzo[1]

[1]University of Palermo, (Italy), [2]University of Belgrade – Faculty of Pharmacy (Serbia)

Non-glycemic effects of liraglutide in subjects with type-2 diabetes (T2DM) including carotid intima-media thickness (cIMT), a recognized marker of subclinical atherosclerosis, are well established. Furthermore, the LEADER study determined its beneficial cardiovascular (CV) effect. However, the long-term effects of liraglutide on CV risk markers, including cIMT, in real-world setting are still limited. Here we investigated whether the reduction in glycemic and metabolic parameters, with particular focus on cIMT, could be maintained in T2DM subjects under routine clinical practice.

Thirty one T2DM subjects (19 men and 12 women; mean age: 60±17 years) without prior history of a major CV event were included in this prospective 5 years real-world study. All of them were naïve to incretin-based therapies and treated with metformin only. Liraglutide (1.2 mg/day) was added to stabile dose of metformin (1500-3000 mg/day). cIMT was measured by B-mode real-time ultrasound.

As expected, there was a significant reduction in fasting glycemia, HbA1c, total- and LDL- cholesterol over the time. Of interest, also cIMT significantly reduced during the 5 years follow-up. Yet, changes in cIMT did not correlate with changes in any other variable studied.

Long-term liraglutide treatment in real world settings effectively maintained the reduction of several glyco-metabolic parameters in T2DM subjects. The main finding of the present study, a reduction of cIMT over the time with the use of liraglutide is in accordance with its CV actions. Our data together with the results from the LEADER study, support the fact that liraglutide's effect could be translated into an effective CV prevention independently of its effect on plasma glucose and/or lipids.

INTERAKCIJA REZISTINA I CAP-1 RECEPTORA SA HDL-HOLESTEROLOM KOD PACIJENATA SA KOLOREKTALNIM KANCEROM

Marija Mihajlović, Ana Ninić, Miron Sopić, Milica Miljković, Aleksandra Stefanović, Vesna Spasojević-Kalimanovska, Aleksandra Zeljković

Katedra za medicinsku biohemiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Rezistin se može smatrati adipocitokinom od interesa u kolorektalnom karcinomu (CRC), s obzirom da su njegove koncentracije povećane kod ovih pacijenata u odnosu na zdrave, asimptomatske osobe. Razvoj CRC je takođe povezan sa poremećajima u lipidnom statusu; stoga je cilj naše studije bio da se ispita veza koja postoji između rezistina i njegovog receptora, proteina udruženog sa adenilat ciklazom (CAP1) kao inflamatorne komponente i koncentracije HDL-holesterola (HDL-H) kao lipidnog markera i jednog od nosilaca antiinflamatornog statusa.

Naša studija je uključila 100 pacijenata sa CRC i 109 zdravih osoba. Koncentracija rezistina u plazmi je određena ELISA metodom. Rutinsko laboratorijsko određivanje je primenjeno za HDL-H. Određivanje nivoa iRNK rezistina i CAP1 iz mononuklearnih ćelija periferne krvi (MĆPK) je sprovedeno qRT-PCR metodom.

Naša studija je pokazala povišen nivo iRNK CAP1 ($p<0,05$) i snižen nivo iRNK rezistina ($p<0,001$), više vrednosti koncentracije rezistina ($p<0,001$) i sniženu koncentraciju HDL-H ($p<0,001$), kod pacijenata u odnosu na kontrolu. Značajna negativna korelacija je uočena između HDL-H i koncentracije rezistina u CRC ($\rho=-0,250$; $p<0,05$). Koncentracija rezistina (OR=1,074; $p<0,001$) i HDL-H (OR=0,210; $p<0,001$) su izdvojene kao značajne determinante povećanog rizika za razvoj CRC.

Naši rezultati su ukazali na značajnu povezanost između rezistina i HDL-H, kao i značajan prediktivni potencijal oba markera za razvoj CRC. S obzirom da se ovi markeri nalaze na suprotstavljenim stranama na inflamatornom raskršću, njihove međusobne interakcije treba dalje istraživati u CRC.

INTERACTION OF RESISTIN AND CAP1 RECEPTOR WITH HDL-CHOLESTEROL IN COLORECTAL CANCER PATIENTS

Marija Mihajlović, Ana Ninić, Miron Sopić, Milica Miljković, Aleksandra Stefanović, Vesna Spasojević-Kalimanovska, Aleksandra Zeljković

Department of Medical Biochemistry, University of Belgrade - Faculty of Pharmacy (Serbia)

Different types of meta analyses revealed resistin as an adipocytokine of interest in colorectal cancer (CRC), since its concentrations were generally higher when compared with healthy asymptomatic individuals. CRC is also associated with lipid status disorders; therefore the aim of our study was to investigate the link between resistin and its receptor adenylate cyclase-associated protein 1 (CAP1), as inflammatory components and HDL cholesterol (HDL-C), as a lipid marker and one of the anti-inflammatory status carriers.

Our study included 100 colorectal cancer patients and 109 healthy controls. Plasma resistin concentration was measured by ELISA method. Routine laboratory method was applied for HDL-C determination. Resistin and CAP1 mRNA levels from peripheral blood mononuclear cells (PBMC) were measured using qRT-PCR method.

Our study showed increased CAP1 mRNA levels ($p<0.05$) and lower resistin mRNA levels ($p<0.001$), higher values of resistin protein concentration ($p<0.001$) and lower HDL-C concentration ($p<0.001$) in CRC patients relative to control group. Significant negative correlation was observed between HDL-C and resistin in CRC ($\rho=-0.250$; $p<0.05$). Univariate logistic analysis showed that both resistin (OR=1.074; $p<0.001$) and HDL-C (OR=0.210; $p<0.001$) are significant determinants of increased risks for CRC development.

Our results indicated significant associations between resistin and HDL-C, as well as notable predictive potential of both individual markers for CRC development. Since these markers represent opponents at the inflammatory crossroads, their mutual relationship in CRC should be further explored.

POTENCIJALNI RAZLOZI ZA SMANJENJE ANTIOKSIDATIVNE AKTIVNOSTI HDL ČESTICA KOD PACIJENATA NA HEMODIJALIZI

Milica Miljković[1], Aleksandra Stefanović[1], Jelena Vekić[1], Sanja Simić-Ogrizović[2], Vesna Spasojević-Kalimanovska[1], Jelena Kotur-Stevuljević[1]

[1]Katedra za medicinsku biohemiju, Univerzitet u Beogradu – Farmaceutski fakultet, [2]Klinika za nefrologiju, Klinički Centar Srbije; Univerzitet u Beogradu - Medicinski fakultet (Srbija)

Paraoksonaza1 (PON1) predstavlja glavni antioksidativni enzim na HDL česticama. Dislipidemija, oksidativni stres i inflamacija kod pacijenata na hemodijalizi mogu dovesti do promena u strukturi apoA-I, što može uticati na aktivnost PON1. Oksidativna modifikacija apoA-I u HDL česticama, kao posledica smanjene aktivnosti PON1 može dovesti do formiranja proaterogenih HDL čestica. Cilj ove studije je bio da se ispita povezanost između koncentracije apoA-I i aktivnosti PON1 kod pacijenata na hemodijalizi.

U studiju je uključeno 57 pacijenata na hemodijalizi i 20 zdravih kontrola, Koncentracija apoA-I je izmerena imunoturbidimetrijski, dok je arilesterazna aktivnost PON1 određena korišćenjem fenilacetata kao supstrata.

Dobijene vrednosti koncentracija apoA-I i aktivnosti PON1 su bile značajno niže kod pacijenata na hemodijalizi u odnosu na zdrave ispitanike ($p<0,01$). Pronađena je i jaka pozitivna korelacija između koncentracije apoA-I i aktivnosti PON1 ($\rho=0,649$, $p<0,01$) što potencijalno ukazuje da strukturne promene u apoA-I koje nastaju kao posledica povišenog oksidativnog stresa i inflamacije, mogu uticati na aktivnost PON1.

Ispitivanje strukture i funkcije HDL čestica merenjem koncentracije apoA-I i aktivnosti PON1 omogućava bolju procenu antiaterogenog potencijala ovih čestica.

POTENTIAL REASONS FOR DECREASED ANTIOXIDATIVE ACTIVITY OF HDL PARTICLES IN HEMODIALYSIS PATIENTS

Milica Miljković[1], Aleksandra Stefanović[1], Jelena Vekić[1], Sanja Simić-Ogrizović[2], Vesna Spasojević-Kalimanovska[1], Jelena Kotur-Stevuljević[1]

[1]Department of Medical Biochemistry, University of Belgrade – Faculty of Pharmacy, [2]Clinic for Nephrology, Clinical Center of Serbia; University of Belgrade - Faculty of Medicine (Serbia)

Paraoxonase1 (PON1) presents the most important antioxidative enzyme at HDL particles. Dyslipidemia, oxidative stress and inflammation in hemodialysis patients can change apoA-I structure and influence PON1 activity. Oxidative modification of apoA-I in HDL particles as a consequence of decreased PON1 activity could lead to formation of proatherogenic HDL particles. The aim of the present study was to examine association between apoA-I concentration and PON1 activity in hemodialysis patients.

This study included 57 hemodialysis patients and 20 healthy controls. apoA-I concentration was measured by immunoturbidimetric method, while arylesterase activity of PON1 was determined kinetically using phenylacetate as substrate.

The concentration of apoA-I and PON1 activity showed significantly lower values in hemodialysis patients compared to healthy subjects ($p < 0.01$). A strong positive correlation was found between apoA-I concentration and PON1 activity ($\rho = 0.649$, $p < 0.01$), which potentially indicates that structural changes in apoA-I as a result of increased oxidative stress and inflammation can affect PON1 activity.

Examination of the structure and function of HDL particles by measuring concentration of apoA-I and PON1 activity enables a better estimation of antiatherogenic potential of these particles.

METABOLIČKI ZDRAVA GOJAZNOST I RIZIK ZA RAZVOJ KARDIOVASKULARNIH BOLESTI

Sanja Vujčić[1], Jelena Vekić[1], Aleksandra Zeljković[1], Lidija Memon[2], Nataša Bogavac-Stanojević[1], Vesna Spasojević-Kalimanovska[1]

[1]Katedra za medicinsku biohemiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Kliničko-bolnički centar „Bežanijska kosa", Beograd (Srbija)

Gojaznost je epidemija modernog doba i faktor rizika za razvoj kardiovaskularnih bolesti (KVB). Međutim, neke gojazne osobe su metabolički zdrave, dok normalno uhranjene mogu imati metaboličke poremećaje. Cilj rada je bio ispitivanje uticaja metaboličkog statusa na rizik od razvoja KVB, kod normalno uhranjenih osoba i kod osoba prekomerne telesne mase.

U ispitivanje su uključene 164 zdrave osobe i 163 pacijenta sa KVB. Na osnovu indeksa telesne mase (ITM) svi ispitanici su najpre razvrstani na normalno uhranjene (ITM<27 kg/m^2) i one sa prekomernom telesnom masom (ITM≥27 kg/m^2). Metabolički status je procenjen na osnovu prisustva sledećih faktora rizika: hipertenzija, povišen obim struka, hipertrigliceridemija, snižen HDL-holesterol, hiperglikemija. Ispitanici sa ≤ 2 faktora rizika su označeni kao metabolički zdrave osobe.

Ispitanici sa prekomernom telesnom masom su imali značajno viši rizik za razvoj KVB od normalno uhranjenih osoba (OR: 2,36; 95% CI: 1,51-3,68; P<0,001). Rizik za razvoj KVB je bio 11 puta veći kod metabolički nezdravih nego kod metabolički zdravih osoba (OR: 10,93; 95% CI: 6,54-18,28; P<0,001). U grupi ispitanika sa povišenom telesnom masom, metabolički nezdrave osobe su imale značajno viši rizik od metabolički zdravih (OR: 9,37; 95% CI: 4,49-19,53; P<0,001). Slično, u grupi normalno uhranjenih osoba, rizik za KVB je bio značajno viši kod metabolički nezdravih nego kod metabolički zdravih (OR: 12,38; 95% CI: 5,40-28,40; P<0,001). Sa druge strane, u poređenju sa normalno uhranjenim metabolički zdravim osobama, metabolički zdravi ispitanici sa prekomernom telesnom masom nisu imali povišen rizik za KVB (OR: 1,23; 95% CI: 0,59-2,57; P=0,585).

Naši rezultati su potvrdili da gojaznost značajno doprinosi razvoju KVB. Takođe, utvrdili smo da metabolički zdrave osobe prekomerne telesne mase nisu pod većim rizikom za razvoj KVB u odnosu na metabolički zdrave, normalno uhranjene osobe, što ukazuje na potencijalni značaj otkrivanja metabolički zdravog fenotipa gojaznosti za prevenciju nastanka KVB.

METABOLICALLY HEALTHY OBESITY AND CARDIOVASCULAR DISEASE RISK

Sanja Vujčić[1], Jelena Vekić[1], Aleksandra Zeljković[1], Lidija Memon[2], Nataša Bogavac-Stanojević[1], Vesna Spasojević-Kalimanovska[1]

[1]Department of Medicinal Biochemistry, University of Belgrade - Faculty of Pharmacy, [2]Clinical Centre Bezanijska Kosa, Belgrade (Serbia)

Obesity has epidemic proportion and it is an important risk factor for developing cardiovascular disease (CVD). However, some people are metabolically healthy despite being obese, while normal weight people may exhibit metabolic disorders. The aim of this study was to examine the influence of the metabolic status on the risk for developing CVD in normal weight and overweight individuals.

The study included 164 healthy individuals and 163 patients with CVD. According to body mass index (BMI), the subjects were classified as normal weight (BMI <27kg/m^2) and overweight (BMI ≥27 kg/m^2). The metabolic status was assessed on the basis of the presence of the following risk factors: hypertension, large waist circumference, hypertriglyceridemia, decreased HDL-cholesterol, hyperglycemia. Subjects with ≤ 2 risk factors were categorized as metabolically healthy (MH).

Overweight individuals were at significantly higher risk of developing CVD compared to normal weight individuals (OR: 2.36; 95% CI: 1.51-3.68; P<0.001). Metabolically unhealthy (MU) individuals had 11 fold higher CVD risk compared to MH subjects (OR: 10.93; 95% CI: 6.54-18.28; P<0.001). Among overweight subjects MU individuals had significantly higher CVD risk than their MH counterparts (OR: 9.37; 95% CI: 4.49-19.53; P<0.001). Similarly, among normal weight subjects, MU had higher risk compared to MH individuals (OR: 12.38; 95% CI: 5.40-28.40; P<0.001). When compared to MH normal weight subjects, the risk for development of CVD in MH overweight subjects was not significant (OR: 1.23; 95% CI: 0.59-2.57; P=0.585).

Obesity significantly contributes to the development of cardiovascular disease. Also, we found that MH overweight status is not associated with increased CVD risk, as compared to MH normal weight individuals, indicating the potential significance of detecting a metabolically healthy obese phenotype in prevention of CVD.

ISPITIVANJA NA PACOVSKOM VALPROATNOM MODELU AUTIZMA OTKRIVAJU POZITIVNU MODULACIJU ALFA5GABAA RECEPTORA KAO MOGUĆI NOVI TERAPIJSKI PRISTUP

Anja Santrač[1], Marija Banićević[1], Jovana Aranđelović[1], Bojan Marković[2], Guanguan Li[3], James Cook[3], Miroslav Savić[1]

[1]Katedra za farmakologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za farmaceutsku hemiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija), [3]Univerzitet u Viskonsin-Milvokiju, Milvoki (SAD)

Spektar autističnih poremećaja (ASD) je spektar stanja koje karakterišu problemi u socijalnoj komunikaciji i interakciji, i restriktivni, repetitivni obrasci ponašanja, interesovanja i aktivnosti.

Cilj je bio da ispitamo uticaj pozitivne modulacije alfa5GABAA receptora na repetitivno i restriktivno ponašanje u pacovskom valproatnom (VPA) modelu ASD.

Sprovedena je farmakokinetička studija da bi se ustanovile doze pozitivnog modulatora alfa5GABAA receptora, MP-III-022, koje izazivaju blag i umeren selektivan odgovor. Trudne Wistar ženke su primile VPA ili fiziološki rastvor (SAL). Od 21. do 27. postnatalnog dana njihovo potomstvo oba pola je dnevno primalo rastvarač (SOL) ili MP-III-022 u dozama 0,3 (MP0,3) ili 1 mg/kg (MP1). Nakon toga, sprovedeni su test spontane lokomotorne aktivnosti (SLA) i reverzni Morisov vodeni lavirint (rMWM).

Tokom SLA, VPA-SOL su bili više vremena aktivni, i napravili više rotacija, posebno nadesno, u poređenju sa SAL-SOL pacovima. Primenjen VPA mužjacima, MP0,3 je smanjio hiperaktivnost i rotacije nadesno, i imao tendenciju da smanji ukupne rotacije. Dat SAL mužjacima, MP0,3 ih je učinio hiperaktivnim, sa sklonošću da poveća njihove rotacije. Slično, MP1 je pogoršao sva triparametra u SAL, sa tendencijom da smanji rotacije nadesno kod VPA mužjaka. Kod ženki, MP1 je pokazao trend da smanji hiperaktivnost kod VPA, ali poveća je kod SAL, i slično, smanjio rotacije nadesno kod VPA, a povećao rotacije kod kontrole.

U rMWM, VPA-SOL životinje su imale manju efikasnost puta sa tendencijom da ulaze više puta u prethodnu ciljnu zonu. MP0,3 je poboljšao oba parametra kod VPA mužjaka; MP1 je pokazao isti trend za drugi parametar kod oba pola.

MP-III-022 je pokazao tendenciju da normalizuje praćene bihejvioralne parametre kod VPA, ali da ih pogorša kod SAL životinja. Efekat doze je polno zavisan: MP0,3 ima veći uticaj na mužjake, MP1 na ženke.

Pozitivna modulacija alfa5GABAA receptora poboljšava repetitivno i restriktivno ponašanje u pacovskom modelu ASD.

THE VALPROATE RAT MODEL REVEALS POSITIVE MODULATION OF ALPHA5GABAA RECEPTORS AS A NOVEL TARGET FOR TREATMENT OF AUTISM SPECTRUM DISORDER

Anja Santrač[1], Marija Banićević[1], Jovana Aranđelović[1], Bojan Marković[2], Guanguan Li[3], James Cook[3], Miroslav Savić[1]

[1]Department of Pharmacology, University of Belgrade - Faculty of Pharmacy, [2]Department of Pharmaceutical Chemistry, University of Belgrade - Faculty of Pharmacy (Serbia), [3]University of Wisconsin-Milwaukee, Milwaukee (USA)

Autism spectrum disorder (ASD) is a range of conditions characterized with problems in social communication and interaction, and restricted, repetitive patterns of behavior, interests or activities. We aimed to determine the influence of a positive modulation of alpha5GABAA receptors on repetitive and restricted behavior in the rat valproate (VPA) model of ASD.

Pharmacokinetic study was performed to determine doses of a positive modulator of alpha5GABAA receptors, MP-III-022, that elicit a mild and a moderate selective response. Pregnant Wistar females were given VPA or saline (SAL). On postnatal days 21-27, the respective offspring of both sexes received daily doses of solvent (SOL) or MP-III-022, at 0.3 (MP0.3) or 1 mg/kg (MP1). Afterwards, spontaneous locomotor activity test (SLA) and reverse Morris water maze (rMWM) were performed.

In SLA, VPA-SOL spent more time in activity, making more rotations, especially clockwise, compared to SAL-SOL rats. Administered to VPA males, MP0.3 lowered hyperactivity, decreased clockwise rotations and tended to decrease overall rotations. MP0.3 made SAL males hyperactive, with a propensity to increase their rotations. Similarly, MP1 exacerbated all three parameters in SAL, while tended to decrease clockwise rotations in VPA males. In females, MP1 revealed a trend to lower hyperactivity in VPA, but increase it in SAL, and, similarly, to decrease clockwise rotations in VPA, while increase rotations in controls.

In rMWM, VPA-SOL animals had lower path efficiency with a tendency to visit more times the previous target zone. MP0.3 improved both parameters in VPA males; MP1 exerted the same trend for the second parameter in both sexes.

MP-III-022 tended to normalize the performance of VPA, but worsen it in SAL animals. The effect of the dose is sex-dependent: MP0.3 has a greater influence on males, MP1 on females. Positive modulation of alpha5GABAA receptors ameliorates repetitive and restricted behavior in the rat model of ASD.

DISULFIRAM – POTENCIJALNE TERAPIJSKE PRIMENE STAROG LEKA

Ana Đurić, Mirjana M. Đukić

Katedra za toksikologiju „Akademik Danilo Soldatović", Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Disulfiram (DSF) se koristi u averzivnoj terapiji alkoholizma više od 60 godina. Do danas su se mnoge studije bavile različitim terapijskim primenama DSF. Disulfiram i njegovi glavni metaboliti ditiokarbamati (DTCs) se predlažu za korišćenje: u tretmanima nekih gljivičnih, bakterijski i virusnih infekcija; kod inflamacije; u terapiji trovanja niklom i bakrom (Cu); u eksperimentalnim tretmanima AIDS-a; kao dodatak hemioterapiji; kod kokainske i udružene kokainske i alkoholne zavisnosti. Helirajući esencijalne metale (Cu i/ili druge esencijalne metale) DTCs inhibiraju aktivnosti nekoliko Cu-zavisnih enzima: dopamin-β-hidroksilaze, karboksiesteraze i holin-esteraze. Smatra se da poznato Cu-helatno dejstvo indukuje inhibiciju proteazoma i posledičnu apoptozu ćelija kancera, što kandiduje DSF za korišćenje u antikancerskoj terapiji. Kako bismo ispitali uticaj DSF na redoks, metalni i androgeni status u testisima nakon i tokom izlaganja kadmijumu (Cd), sproveli smo studiju na Wistar pacovima.

Naši rezultati ukazuju da primena DSF nakon i tokom izlaganja Cd pokazuje protektivno dejstvo na narušen oksidativni status u testisima tretiranih pacova. Ovaj fenomen se može objasniti jakim helirajućim kapacitetom DSF kao i antioksidativnim kapacitetom DTC/DSF redoks para koji deluje slično kao endogeni redoks par redukovani glutation/oksidovani glutation. Vezujući toksične jone Cd DSF onemogućava ovaj metal da ostvari svoje štetne prooksidativne efekte na tkivo testisa. Takođe smo pokazali da DSF ne može popraviti smanjenu proizvodnju testosterona ni morfološke promene testisa nastale usled izlaganja pacova Cd. Iako je DSF pokazao značajan antioksidativni potencijal, on nije uspeo da ukloni štetne efekte izazvane izlaganjem Cd koji se odnose na proizvodnju testosterona i morfološke promene testisa pacova.

DISULFIRAM – POTENTIAL THERAPEUTIC APPLICATIONS OF AN OLD DRUG

Ana Djurić, Mirjana M. Djukić

Department of Toxicology „Akademik Danilo Soldatović", University of Belgrade - Faculty of Pharmacy (Serbia)

Disulfiram (DSF) has been used in the aversive therapy of alcoholism for more than 60 years. To date, many studies have dealt with different therapeutic applications of DSF. Disulfiram and its main metabolites dithiocarbamates (DTCs) are suggested for the treatment of some fungal, bacterial and viral infections; inflammation; nickel and copper (Cu) poisoning therapy; experimental treatment of AIDS; as an adjuncts for chemotherapy; and cocaine dependence alone or co-morbid cocaine and alcohol dependence. By chelating essential metals (Cu and/or other essential metals) DTCs inhibit activities of a few Cu-dependent enzymes: dopamine-β-hydroxylase, carboxylesterase and cholinesterase. This same Cu-chelating action is thought to induce proteasome inhibition and subsequent cancer cell apoptosis, leading to the proposal that DSF could serve as an anticancer therapy. We conducted an animal study on Wistar rats to examine the influence of DSF on red-ox, metal and androgen status in testes after and during the exposure to cadmium (Cd).

Our results have indicated that application of DSF after and during Cd exposure, has shown beneficial effect on impaired oxidative status in the testes of treated rats. This phenomenon can be explained by strong chelating capacity of DSF and antioxidant capacity of DTC/DSF red-ox couple similar to endogenous reduced glutathione/oxidized glutathione redox couple. Binding toxic Cd ions DSF disables this metal to achieve its harmful pro-oxidant effects on testicular tissue. Also, we showed that DSF cannot repair the decreased production of testosterone and morphological changes of testes caused by exposure of rats to Cd. Although DSF showed significant antioxidant potential, it failed to remove the deleterious effects of Cd exposure on testosterone production and morphological changes in rat testes.

UTICAJ VINIFIKACIJE NA SADRŽAJ FENOLNIH KISELINA I ANTIOKSIDATIVNE OSOBINE VINA OD ARONIJE

Uroš Čakar[1], Aleksandar Petrović[2], Vlatka Vajs[3], Brižita Đorđević[1]

[1]Katedra za bromatologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Institut za prehrambenu tehnologiju i biohemiju, Univerzitet u Beogradu - Poljoprivredni fakultet, [3]Centar za hemiju, Institut za hemiju tehnologiju i metalurgiju, Univerzitet u Beogradu (Srbija)

Aronija (*Aronia melanocarpa* Heynh.) je biljka koja je autohtona za severne krajeve Evrope i Azije. Zbog njenog pozitivnog zdravstvenog efekta na ljudski organizam aronija se uspešno danas gaji širom sveta, pa i u Srbiji. Vino predstavlja jedan od proizvoda koji se može dobiti preradom ovog voća.

Vino od aronije je proizvedeno postupkom mikrovinifikacije. Kontrolisano vrenje aronije je sprovedeno uz pomoć dve različite čiste kulture kvasca. Pored toga, primenjeni su šećer i enzim koji su dodati u neke od uzoraka pre fermentacije, da bi se povećao sadržaj fenolnih jedinjnja u krajnjem proizvodu. Sadržaj fenolnih jedinjenja je određen UPLC TQ-MS/MS. Takođe je primenjena i Folin-Ciocalteu metoda za određivanje ukupnog sadržaja polifenola (USP). Antiradikalska aktivnost je određena uz pomoć DPPH radikala, a takođe je primenjena i FRAP metoda.

Rezultati ukazuju da postupak vinifikacije značajno utiče na sadržaj izabranih polifenolnih jedinjenja i antioksidativne osobine. Vinifikacije u kojima je dodat šećer i enzim pre početka fermentacije dale su vino od aronije sa najvišim sadržajem izabranih fenolnih jedinjnja kao i najboljim antioksidativnim osobinama. Kontrola koja je proizvedena bez dodatka šećera i enzima pokazala je najniže antioksidativne osobine kao i sadržaj izabranih polifenolnih jedinjnja. Posebno se ističe sadržaj fenolnih kiselina i to derivata hidroksicimetne, među kojima su se istakle kafeinska, p-kumarinska, sinapinska i hlorogena. Sadržaj ukupnih polifenola u analiziranim voćnim vinima je bio od 2271,4 do 2477,6 mg GAE/L, dok su vrednosti za FRAP bile od 67,2 do 83,5 mmol/L Fe^{2+}. Antiradikalska aktivnost određena DPPH testom predstavljena je IC50 vrednostima koje su bile od 1,23 do 1,50%. Rezultati ukazuju da vino od aronije predstavlja proizvod sa pozitivnim zdravstvenim efektom na ljudski organizam koji ima mnogućnost „hvatanja" slobodnih radikala.

Dobijeni rezultati ukazuju da je vino od aronije bogat izvor derivata hidroksicimetne kiseline koji predstavljaju samo mali deo ostalih jedinjenja koja su odgovorna za jake antioksidativne i antiradikalske osobine ovog vina.

VINIFICATION INFLUENCE ON PHENOLIC ACID CONTENT AND ANTIOXIDANT PROPERTIES OF BLACK CHOKEBERRY WINE

Uroš Čakar[1], Aleksandar Petrović[2], Vlatka Vajs[3], Brižita Đorđević[1]

[1]Department of Bromatology, University of Belgrade - Faculty of Pharmacy, [2]Institute of Food Technology and Biochemistry, University of Belgrade - Faculty of Agriculture, [3]Center for Chemistry, Institute for Chemistry, Technology and Metallurgy, University of Belgrade (Serbia)

Black chokeberry (*Aronia melanocarpa* Heynh.) is plant autochthonous for the northern parts of Europe and Asia. Due to their beneficial health effects on human organism black chokeberry is successfully introduced in Serbia and all around the world. Fruit wine is one product which can be derived from this fruit.

Black chokeberry wine was produced in micro-vinification procedure. The fermentation of black chokeberry must was conducted by using two different pure selected yeast cultures. Beside, in some samples enzyme and sugar were added to increase content of phenolic compounds in the final product. Phenolic profile was analyzed by UPLC TQ-MS/MS. Also, Folin-Ciocalteu method was used for determination of total phenolic content (TPC). Antiradical activity was investigated by DPPH radical while FRAP method was conducted too.

The results indicate that vinification process have significant influence on selected phenolic profile and antioxidant properties. Vinification process in which sugar and enzyme were added before fermentation resulted in black chokeberry wine with the highest content of selected phenolic compounds and the best antioxidant properties. The control produced without addition of enzyme and sugar showed the lowest antioxidant properties and content of selected phenolic compounds. Phenolic acids, such as hydroxycinnamic acid derivatives (caffeic, *p*-coumaric, sinapinic and chlorogenic acids) were the most abundant in analyzed samples. The TPC for fruit wine samples was in the range from 2271.4 to 2477.6 mg GAE/L while FRAP values were from 67.2 to 83.5 mmol/L Fe^{2+}. Antiradical DPPH activity was presented with IC_{50} values which were in the range from 1.23 to 1.50%. The findings indicate that black chokeberry wine represents product with beneficial health effects and ability in free radical scavenging.

Obtained results indicate that black chokeberry wine is a rich source of hydrohycinnamic acid derivatives which are only small part of many other compounds responsible for potent antioxidant and antiradical properties of this wine.

ISPITIVANJE RETENCIONOG PONAŠANJA ODABRANIH LIGANADA IMIDAZOLINSKIH RECEPTORA U REVERZNO-FAZNOJ I TEČNOJ HROMATOGRAFIJI HIDROFILNIH INTERAKCIJA

Darija Obradović, Slavica Oljačić, Danica Agbaba

Katedra za farmaceutsku hemiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Primena *mixed-mode* HILIC/RP kolona omogućava analizu velikog broja strukturno različitih jedinjenja pri RP (*reversed-phase*) i HILIC (*hydrophilic interaction liquid chromatography*) hromatografskim uslovima koji se postižu adekvatnim odabirom mobilne faze. Cilj rada je bio da se ispita primenljivost particionog modela u opisivanju retencionog ponašanja liganada imidazolinskih receptora, da se odrede volumenske frakcije vodene faze pri kojima dolazi do smene RP i HILIC hromatografskih sistema (φ_{min}) i izdvoje najznačajniji molekulski deskriptori koji utiču na njihovu interkonverziju.

Retenciono ponašanje 17 liganada imidazolinskih receptora ispitano je na *mixed-mode* HILIC stacionarnoj fazi korišćenjem smeše acetonitrila i vodenog rastvora 20 mM amonijumacetata (pH 6) u širokom opsegu zapreminskih frakcija vodene faze (φ). Višestruka linearna regresija je korišćena za izdvajanje najznačajnijih Abrahamovih deskriptora koji utiču na φ_{min} kao i korelaciju φ_{min} sa lipofilnošću ispitivanih jedinjenja.

Volumenska frakcija pufera pri kojoj dolazi do smene između retencionih RP i HILIC uslova izračunata je korišćenjem nelinearne relacije logk vs φ. U sledećem koraku za svako pojedinačno jedinjenje, definisani HILIC i RP regioni su opisani linearnom relacijom između logaritma retencionih faktora i zapremine modifikatora mobilne faze. Dobro slaganje retencionih podataka za korišćeni hromatografski model potvrđeno je dobijenim visokim koeficijentima korelacije, $r>0,86$. Pronađeno je da lipofilnost ispitivanih jedinjenja (AClogP) značajno utiče na minimalnu vrednost vodene frakcije pufera pri kojoj dolazi do smene retencionih uslova ($r=0,90$). Pored toga, značajna korelacija je ostvarena i u modelu u kojem su izdvojene sledeće molekulske osobine: stepen jonizacije (Di), kiselost jedinjenja (Ai), i McGowan-ova zapremina (Vi) ($r=0,86$).

Utvrđena je primenljivost particionog modela u opisivanju retencije u HILIC/RP sistemima odabranih jedinjenja. Izračunavanjem odabranih molekulskih deskriptora moguće je na brz i jednostavan način predvideti prevojnu tačku pri kojoj dolazi do smene između HILIC i RP retencionog mehanizma.

INVESTIGATION OF RETENTION BEHAVIOUR OF SELECTED IMIDAZOLINE RECEPTOR LIGANDS IN REVERSED-PHASE AND HYDROPHILIC INTERACTION LIQUID CHROMATOGRAPHY

Darija Obradović, Slavica Oljačić, Danica Agbaba

Department of Pharmaceutical Chemistry, University of Belgrade - Faculty of Pharmacy (Serbia)

The use of mixed-mode HILIC/RP stationary phases allows the analysis of structurally different pharmaceutical compounds in the RP (*reversed-phase*) and HILIC (*hydrophilic interaction liquid chromatography*) systems. The aim of this study was to investigate applicability of the partition model in description of the retention behavior of the imidazoline-related compounds within the HILIC and RP systems, determination of the aqueous phase volume fraction when the turning point between the RP and HILIC mode occurs (φ_{min}), and selection of the most important physico-chemical properties which influence this interconversion.

Retention behaviour of 17 imidazoline receptor ligands was investigated on the mixed-mode HILIC stationary phase by using acetonitrile and the 20 mM aqueous ammonium acetate (pH=6) as a mobile phase in a wide range of volume fractions of the buffered eluent (φ). Stepwise multiple linear regression was used to select the Abraham descriptors which influence the φ_{min} value. Correlation between φ_{min} and lipophilicity of the investigated compounds was also examined.

Parameter φ_{min} was calculated from the non-linear relation logk vs φ. For each compound, the HILIC and RP regions were established from linear relation between logk and the mobile phase modifier. A good fit of the retention data was obtained for the employed retention model ($r>0.86$). It was found that lipophilicity (AClogP) ($r=0.90$), as well as degree of ionization (Di), hydrogen bond acidity (Ai) and McGowan volume (Vi) ($r=0.86$) reflect molecular properties of the investigated compounds which affect the turning point between the two retention mechanisms in a given chromatographic system.

Applicability of the assumed retention model in description of the RP and HILIC retention behaviour was successfully demonstrated. Calculation of selected molecular descriptors enables fast and easy prediction of the turning points between the RP and HILIC systems.

PRAĆENJE NIVOA OLOPATADINA U HUMANIM SUZAMA HILIC-ESI/MS/MS METODOM

Jelena Maksić[1], Ana Stajić[2], Miroslav Knežević[3], Bojana Dačić Krnjaja[3], Biljana Jančić-Stojanović[2], Mirjana Medenica[4]

[1]Odeljenje za ispitivanje i kontrolu lekova, Služba za farmaceutsku delatnost, Vojnomedicinska akademija, [2]Katedra za analitiku lekova, Univerzitet u Beogradu-Farmaceutski fakultet, [3]Klinika za očne bolesti, Klinički centar Srbije, [4]Katedra za fizičku hemiju i instrumentalne metode, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Cilj rada bio je određivanje malih koncentracija olopatadina u humanim suzama i procena njegovog farmakokinetičkog ponašanja u oku. Za praćenje nivoa olopatadina upotrebljena je prethodno optimizirana i validirana metoda tečne hromatografije hidrofilnih interakcija (HILIC) u kombinaciji s tandem masenom spektrometrijom (MS/MS).

Hromatografska separacija izvršena je u UPLC Acquity BEH amidnoj koloni (2,1 mm x 100 mm, 1,7μm veličina čestica) koristeći 0,1% mravlju kiselinu u vodi i acetonitril kao mobilnu fazu. Kvantifikacija je izvedena pozitivnom elektrosprej jonizacijom (ESI) u MRM modu. Prekursor-proizvod jon tranzicije praćene za kvantitativnu analizu i strukturnu karakterizaciju bile su 338→165 i 338→247 m/z za olopatadin, odnosno 265→91 i 265→208 m/z za interni standard mianserin.

U prospektivnoj kliničkoj studiji ispitivani su uzorci suza dobijeni od 30 ambulantnih pacijenata nakon bilateralne primene 0,1% kapi za oči olopatadin-hidrohlorida. Suze su uzorkovane indirektnom tehnikom pomoću Širmerovih test traka. Precipitacija proteina s acetonitrilom kao agensom za denaturisanje definisana je kao pogodna procedura pripreme uzoraka. Jednoprostorni matematički model prvog reda primenjen je u cilju izračunavanja značajnih okularnih farmakokinetičkih parametara. Dobijeni rezultati omogućili su uvid u dužinu prisustva ispitivanog leka u očnoj vodici i u proces njegove eliminacije iz tkivnih struktura oka. Na taj način, opravdana je učestalost predloženog režima doziranja oftalmološkog rastvora olopatadina, kao i njegova efikasnost i bezbednost u terapiji alergijskog konjuktivitisa. Potvrđena je primenljivost novorazvijene, veoma osetljive i selektivne HILIC metode sa MS/MS detekcijom za pouzdanu i brzu kvantifikaciju olopatadina u ograničenim zapreminama humanih suza za vreme kliničke prakse. Takođe, postignuto je precizno predviđanje okularne farmakokinetike olopatadina.

MONITORING OF OLOPATADINE LEVEL IN HUMAN TEARS BY HILIC-ESI/MS/MS METHOD

Jelena Maksić[1], Ana Stajić[2], Miroslav Knežević[3], Bojana Dačić Krnjaja[3], Biljana Jančić-Stojanović[2], Mirjana Medenica[4]

[1]Department of Drug Control and Examination, Service for Pharmaceutical Activity, Military Medical Academy, [2]Department of Drug Analysis, University of Belgrade-Faculty of Pharmacy, [3]Clinic for Eye Diseases, Clinical Center of Serbia, [4]Department of Physical Chemistry and Instrumental Methods, University of Belgrade-Faculty of Pharmacy (Serbia)

The objective of the paper was the determination of olopatadine small concentrations in human tears as well as the assessment of its pharmacokinetic behavior in the eye. For the monitoring of olopatadine level, previously optimized and validated Hydrophilic Interaction Liquid Chromatography (HILIC) method coupled with tandem mass spectrometry (MS/MS) was used.

The chromatographic separation was carried out on UPLC Acquity BEH amide column (2.1 mm x 100 mm, 1.7 μm particle size) using 0.1% formic acid in water and acetonitrile as the mobile phase. The quantification was performed by positive ion electrospray ionization (ESI) in the multiplereaction monitoring (MRM) mode. The precursor-product ion transitions followed for the quantitative analysis and the structure characterization were 338→165 and338→247 m/z for olopatadine as well as 265→91 and 265→208 m/z for the internal standard mianserin.

In the prospective clinical study, the tear samples obtained from 30 outpatients were investigated following bilateral administration of 0.1% olopatadine hydrochloride eye drops. The tears were sampled by an indirect technique using the Schirmer test strips. The protein precipitation with acetonitrile as a denaturation agent was defined as a suitable sample preparation procedure. The one compartment first-order mathematical model was applied for calculating the significant ocular pharmacokinetic parameters. The obtained results provided insight into the length of presence of the examined drug in aqueous humor and also in its elimination process from the eye tissue structures. In that manner, the frequency of the proposed dosage regimen of the olopatadine ophthalmic solution has been justified as well as its efficacy and safety in treatment of allergic conjunctivitis.

The applicability of a newly developed, highly sensitive and selective HILIC method with MS/MS detection for reliable and rapid quantification of olopatadine in limited volumes of human tears during clinical practice was confirmed. Additionally, a precise prediction of olopatadine ocular pharmacokinetics was achieved.

PRIMENA HPLC METODE U ODREĐIVANJU KONSTANTI STABILNOSTI KOMPLEKSA β-CIKLODEKSTRINA SA ODABRANIM ANTIPSIHOTICIMA

Nevena Maljurić, Biljana Otašević, Jovana Krmar, Mira Zečević, Ana Protić

Katedra za analitiku lekova, Univerzitet u Beogradu-Farmaceutski fakultet (Srbija)

Ciklodekstrini grade inkluzione komplekse sa velikim brojem različitih organskih jedinjenja. Na taj način menjaju fizičko-hemijske osobine kompleksiranih lekova, smanjujući njihova neželjena dejstva, povećavajući rastvorljivost i biološku raspoloživost. Kao aditivi mobilne faze, omogućavaju povećanje udela vodene, a smanjenje udela organske faze uz istovremeno smanjenje retencije analita. Zbog značajnosti primene, proces formiranja kompleksa, kao i njihova stabilnost su uvek aktuelne teme. Cilj rada je ispitivanje mogućnosti primene hromatografskog pristupa za izračunavanje konstanti stabilnosti kompleksa (K) β-ciklodekstrina sa odabranim antipsihoticima i njihovim nečistoćama.

K je izračunata na osnovu formule: $1/k = 1/k0 + K\,[\beta\text{-CD}]x/k0$, gde je k retencioni faktor, k0 retencioni faktor bez β-ciklodekstrina u mobilnoj fazi, [β-CD] koncentracija β-ciklodekstrina, a x stehiometrija kompleksa. Retencioni faktori su dobijeni HPLC metodom na Thermo Scientific, Dionex 3000 Ultra, dok je stehiometrija kompleksa određena pomoću ESI-MS na Thermo Scientific TSQ Quantum Access Max.

β-ciklodekstrin modifikovani RP-HPLC sistemi su složeniji od regularnih zbog raspodele supstance između stacionarne, mobilne faze i rastvorenog β-ciklodekstrina. Ako je pH vrednost mobilne faze ispod 3, silanolne grupe su u neutralnom obliku, što za posledicu ima smanjenje interakcija sa stacionarnom fazom, pa su na pH 2 K za risperidon, nečistoću 1, nečistoću 2, nečistoću 3, olanzapin, nečistoću B i nečistoću C iznosile 185,52 M-1, 105,39 M-1, 423,89 M-1, 187,68 M-1, 20,24 M-1, 93,01 M-1 i 17,16 M-1, redom. Pri pH 3,5 i 5,0, sa porastom koncentracije β-ciklodekstrina u mobilnoj fazi retenciona vremena su se produžavala, zbog dominantnih interakcija sa stacionarnom fazom. Posledično, hromatografski pristup nije bio odgovarajući za određivanje K, izuzev u slučaju nečistoće B, koja se nalazi u neutralnom obliku pri ispitivanom pH opsegu i ceo molekul učestvuje u građenju inkluzionog kompleksa sa β-ciklodekstrinom.

Hromatografski pristup ima potencijal da bude upotrebljen za izračunavanje K u uslovima u kojima je retencija predvođena interakcijama analita sa β-ciklodekstrinom.

APPLICATION OF HPLC METHOD IN DETERMINING THE COMPLEX STABILITY CONSTANTS BETWEEN β-CYCLODEXTRIN AND SELECTED ANTIPSYCHOTICS

Nevena Maljurić, Biljana Otašević, Jovana Krmar, Mira Zečević, Ana Protić

Department of Drug Analysis, University of Belgrade-Faculty of Pharmacy (Serbia)

Cyclodextrins form inclusion complexes with variety of organic compounds. Therefore, physico-chemical characteristics of complexed drugs are affected, reducing their side effects and improving solubility and bioavailability. As mobile phase additives, they allow increase of water and decrease of organic solvent content with simultaneous reduction of analyte's retention. Due to inherent usefulness, the complex formation process and stability is always a challenging topic. The aim was to investigate the possibility to apply chromatographic approach for determination of complex stability constants (K) between β-cyclodextrin and selected antipsychotics and their impurities.

K was calculated according to formula: $1/k = 1/k0 + K [\beta\text{-CD}]x/k0$, where k is retention factor, k0 is retention factor without β-cyclodextrin in mobile phase, [β-CD] β-cyclodextrin concentration and x is the complex stoichiometry. Retention factors were determined by HPLC method on Thermo Scientific, Dionex 3000, while the stoichiometry was determined by ESI-MS on Thermo Scientific TSQ Quantum Access Max.

β-cyclodextrin modified RP-HPLC systems are more complicated than regular, since solute is distributed between stationary, mobile phase and dissolved β-cyclodextrin. If mobile phase pH is under 3, silanol groups are non-ionized, minimizing the solute's interactions with stationary phase, so at pH = 2 K for risperidone, impurity 1, impurity 2, impurity 3, olanzapine, impurity B and impurity C was 185.52 M-1, 105.39 M-1, 423.89 M-1, 187.68 M-1, 20.24 M-1, 93.01 M-1 i 17.16 M-1, respectively. If pH=3.5 or 5, retention times were prolonged with increasing β-cyclodextrin concentration due to stationary phase interactions. Consequently, the chromatographic approach appeared unsuitable for K determination, except in case of impurity B, which is non-ionized across the investigated pH range and whole molecule participates in inclusion complex formation with β-cyclodextrin.

Chromatographic approach could be used for K determination if the retention is governed by solutes interactions with dissolved β-cyclodextrin.

KVANTIFIKOVANJE VEZE STRUKTURE ARIPIPRAZOLA I SRODNIH NEČISTOĆA SA GENERISANIM ESI ODGOVOROM PRIMENOM METODA MAŠINSKOG UČENJA

Jovana Krmar[1], Ljiljana Tolić[2], Tatjana Đurkić[3], Ana Protić[1], Nevena Maljurić[1], Mira Zečević[1], Biljana Otašević[1]

[1]Katedra za analitiku lekova, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Inovacioni centar Tehnološko-Metalurškog fakulteta, [3]Katedra za inženjerstvo zaštite životne sredine, Univerzitet u Beogradu - Tehnološko-metalurški fakultet (Srbija)

Elektrosprej jonizacija (ESI) predstavlja najčešće korišćenu tehniku jonizacije u LC/MS analizi polarnih i umereno polarnih analita. Nedovoljno rasvetljeni mehanizmi generisanja ESI jona uslovljavaju dugotrajnu optimizaciju odgovora sistema, zasnovanu na primeni pristupa pokušaja-i-greške. Upotreba metodologije kvantifikovanja veze strukture analita sa osobinom od interesa (QSPR), odnosno, ESI signalom može da dâ doprinos razumevanju procesa jonizacije, utemeljen na fizičko-hemijskom značenju uvrštenih molekulskih deskriptora. Cilj rada bio je modelovanje ESI odgovora test supstanci – atipičnog antipsihotika aripiprazola i srodnih nečistoća primenom QSPR pristupa, radi sticanja uvida u faktore koji kontrolišu efikasnost jonizacije i sledstvene mogućnosti sistematičnog pospešivanja osetljivosti metode.

LC/ESI-MS analize izvedene su na hibridnom Dionex UltiMate 3000® LC–LTQ XL linearnom jon trap sistemu (Thermo Fisher Scientific), koristeći fenil-heksil kolonu (100 mm × 4,6 mm, 2,6 μm; Phenomenex). Promene površina pikova praćene su variranjem udela metanola (60–75%, v/v), pH vodene komponente mobilne faze (3,0–8,2), protoka mobilne faze (400–500 μl/min), napona raspršivanja (2,5–5,0 kV), temperature kapilare (200–400 °C), pritiska nebulizirajućeg gasa (12–52 AU) i pritiska desolvatacionog gasa (3–21 AU) prema Box-Behnken dizajnu eksperimenata. Molekulski deskriptori izračunati su za sve supstance u odgovarajućoj jonizovanoj/nejonizovanoj formi primenom Dragon 6.0.7 softvera (Talete srl). QSPR modeli sagrađeni su tehnikom veštačkih neuronskih mreža i metodom potpornih vektora (RapidMiner Studio 6.5.002, RapidMiner, Inc.).

Prediktivna moć dobijenih modela procenjena je korišćenjem ukrštene validacije sa 10 odeljaka. Konstruisani modeli postigli su zadovoljavajuće performanse – niske vrednosti kvadratnog korena srednje vrednosti sume kvadrata greške i visoke vrednosti validacionog regresionog faktora, odnosno, koeficijenta determinacije.

Rezultati studije ukazali su na prikladnost korišćenog pristupa u proučavanju analitičkog problema. Računanje velikog broja deskriptora doprinelo je uspostavljanju sveobuhvatnijeg QSPR modela u odnosu na do sada razvijene. Ipak, shodno relativno malom broju ispitivanih struktura, predloženi mehanizmi jonizacije generalizovani su na nivo ispitivanog sistema.

QUANTITATIVE STRUCTURE – PROPERTY RELATIONSHIP MODELING OF ESI RESPONSE OF ARIPIPRAZOLE AND ITS IMPURITIES USING MACHINE LEARNING METHODS

Jovana Krmar[1], Ljiljana Tolić[2], Tatjana Đurkić[3], Ana Protić[1], Nevena Maljurić[1], Mira Zečević[1], Biljana Otašević[1]

[1]Department of Drug Analysis, University of Belgrade - Faculty of Pharmacy, [2]Innovation Center of the Faculty of Technology and Metallurgy, [3]Department of Environmental Engineering, University of Belgrade - Faculty of Technology and Metallurgy (Serbia)

Electrospray ionization, ESI represents the most widespread ionization technique in LC-MS analysis of (moderately) polar analytes. Insufficiently elucidated mechanisms of ions' formation induce the time-consuming optimization of system's response. Quantitative Structure Property Relationship, QSPR study of ESI responsiveness may add to the understanding of the ionization process, based on physicochemical meaning of involved molecular descriptors. The aim was to model the ESI response of the aripiprazole and related impurities using QSPR approach, in order to optimize factors that control ionization efficiency.

LC/ESI-MS analysis were performed on the Dionex UltiMate 3000® LC–LTQ XL linear ion trap system (Thermo Fisher Scientific), using a Phenyl-Hexyl column (100 mm × 4.6 mm, 2.6 μm). The changes in peaks' areas were observed by varying the methanol content (60-75%, v/v), the pH of the aqueous component of mobile phase (3.0-8.2), the flow rate (400-500 μl/min), the spray voltage (2.5-5.0 kV), capillary temperature (200-400 °C), nebulizer gas pressure (12-52 AU) and desolvation gas pressure (3-21 AU) according to the Box-Behnken experimental design. Molecular descriptors were calculated for all substances in appropriate ionized/non-ionized form using the Dragon 6.0.7 (Talete srl). QSPR models were built using ANN and SVR (RapidMiner Studio 6.5.002, RapidMiner, Inc.).

The predictive power of the obtained models was estimated using a 10-fold cross-validation. Constructed models have achieved satisfactory performance in terms of low root mean square errors (RMSE) and the high values of the (cross-validated) coefficients of determination (R^2 and Q^2).

The results indicated the appropriateness of the utilized approach for studying the ESI ionization. Calculating a large number of descriptors has contributed to the establishment of more comprehensive QSPR models in comparison with the so far developed. According to the relatively small number of employed structures, generalization of proposed ionization mechanisms was precluded.

SIMULACIJE MOLEKULSKE DINAMIKE I VIRTUAL SCREENING STUDIJA INHIBITORA SIRTUINA 2

Nemanja Đoković[1], Katarina Nikolić[1], Danica Agbaba[1], Maija Lahtela-Kakkonen[2]

[1]Katedra za Farmaceutsku hemiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija), [2]School of Pharmacy (Pharmaceutical Chemistry) University of Eastern Finland (Finska)

Modulacija aktivnosti epigenetičkog brisača, NAD-zavisne protein deacetilaze sirtuina 2 (SIRT2), poslednjih godina se pokazala kao obećavajuća strategija u lečenju Parkinsonove bolesti, depresije, određenih tipova kancera, ishemijsko-reperfuzionih povreda itd. Nasuprot terapijskom potencijalu, još uvek nijedan predstavnik ove grupe farmakološki aktivnih supstanci nije našao svoje mesto na tržištu. Najčešći problemi sa dosada opisanim SIRT2 inhibitorima predstavljaju niska potentnost, loša selektivnost, kao i loše farmakokinetičke osobine što dalje opravdava razvoj novih predstavnika.

Cilj ovog rada je bio ispitivanje konformacionih promena SIRT2 u prisustvu inhibitora i dalje poboljšanje dostupnih kristalografskih modela u cilju razvoja efikasnijeg protokola virtual screening-a.

Polazeći od 5 različitih kristalografskih struktura SIRT2-inhibitor kompleksa, ukupno 1,5 μs simulacija molekulske dinamike u eksplicitnom solventu je izvedeno. 3D deskriptori zasnovani na GRID-u i linearna diskriminantna analiza su korišćeni za virtual screening (VS) studiju.

Konformaciona fleksibilnost SIRT2-inhibitor kompleksa zabeležena tokom simulacija ukazuje na značajnu fleksibilnost aktivnog mesta i posledično na multiple vezivne modove inhibitora. Nakon procedure klasterovanja trajektorije, nekoliko relevantnih modela kompleksa je izdvojeno i uključeno u dalju VS studiju. VS modeli generisani pomoću tri relevantna kompleksa dobijena studijom molekulske dinamike su pokazali značajno bolje performanse u poređenju sa modelima dobijenim pomoću do danas opisanih kristalografskih struktura. Performanse generisanog VS protokola su značajno poboljšane i u odnosu na do danas publikovane protokole. Rezultati ove studije jasno ukazuju na značaj uračunavanja fleksibilnosti aktivnog mesta u racionalni dizajn SIRT2 inhibitora. Novi hemotipovi potenijalnih inhibitora SIRT2 su izdvojeni iz baza komercijalno dostupnih jedinjenja primenom generisanih VS modela.

U ovoj studiji formirani su realističniji modeli aktivnog mesta sirtuina 2 kojima su značajno poboljšane performanse virtual screening-a u odnosu na do danas publikovane studije. Rezultati ove studije, uključujući i opisane konformacione promene doprinose sveobuhvatnom razumevanju odnosa strukture i aktivnosti SIRT2 inhibitora i dodatno racionalizuju dizajn selektivnijih i potentnijih inhibitora.

MOLECULAR DYNAMICS-BASED VIRTUAL SCREENING OF SIRTUIN 2 INHIBITORS

Nemanja Đoković[1], Katarina Nikolić[1], Danica Agbaba[1], Maija Lahtela-Kakkonen[2]

[1]Department of Pharmaceutical Chemistry, University of Belgrade - Faculty of Pharmacy (Serbia), [2]School of Pharmacy (Pharmaceutical Chemistry) University of Eastern Finland (Finland)

Modulation of activity of epigenetic eraser, NAD-dependent protein deacetylase sirtuin 2 (SIRT2), recently emerged as promising therapeutic strategy for the treatment of many diseases, including Parkinson's disease, depression, some types of cancers, necrotic injuries (ischemic stroke, myocardial infarction) etc. Contrary to therapeutic potential, none of SIRT2 inhibitors reported to date has been approved for the market. Some of the most common problems with current SIRT2 inhibitors include poor potency, selectivity and pharmacokinetic properties which justify further development of novel inhibitors.

The Aim of this study was to explore conformational space of sirtuin2-inhibitor complexes and further refinement of available crystallographic structures in order to develop more efficient virtual screening (VS) protocol.

Starting from five different crystallographic structures of SIRT2 co-crystalized with inhibitors, total of 1.5 μs of molecular dynamics (MD) simulations in explicit solvent has been performed. GRID-based 3D descriptors and linear discriminant analysis were used for virtual screening.

Significant conformational flexibility of SIRT2-inhibitor complexes was observed during simulations indicating overall binding site flexibility and multiple binding modes of inhibitors. Several atomistic models of SIRT2-inhibitor complexes were extracted and used for structure-based VS study. VS models generated from three extracted SIRT2-inhibitor complexes were significantly better compared to VS models generated from available crystallographic structures. Generated VS protocol was also better in performance compared to published virtual screening studies. These results clearly indicate importance of considering flexibility of binding site in rational design of SIRT2 inhibitors. Obtained models were used for screening of commercial databases of compounds. Several chemotypes of potential novel SIRT2 inhibitors have been identified.

Refined atomistic models of SIRT2-inhibitor complexes have been generated and significant improvement of virtual screening performance has been achieved. These results further rationalize design of SIRT2 inhibitors with improved selectivity and potency.

ISPITIVANJE FIZIČKO–HEMIJSKIH SVOJSTAVA SMEŠA POLIMERA I POVRŠINSKI AKTIVNIH MATERIJA KAO POTENCIJALNIH NOSAČA LEKOVA

Maja Milanović, Veljko Krstonošić, Milica Atanacković Krstonošić

Katedra za farmaciju, Univerzitet u Novom Sadu - Medicinski fakultet (Srbija)

Polimeri i površinski aktivne materije (PAM) ulaze u sastav brojnih farmaceutskih formulacija u cilju povećanja stabilnosti ili predstavljaju nosioce formulacije. Prisustvo interakcija između polimera i PAM, može značajno uticati na osobine ovih sistema u zavisnosti od njihove prirode, koncentracije i naelektrisanja. Poznavanje fizičko–hemijskih svojstava smeša polimer–PAM neophodno je u cilju razvoja farmaceutskih formulacija unapređenih osobina. Cilj istraživanja je određivanje prisustva i mehanizma interakcije između anjonskog polimera–ksantan gume i nejonske PAM–Tween 80 primenom infracrvene spektroskopije sa Fourierovom transformacijom (FT–IR) i tenziometrije.

Nakon FT–IR analize strukture ksantan gume i Tween 80, u opsegu talasnih brojeva od 4000 do 600 cm^{-1} (pri rezoluciji od 4 cm^{-1}), površinski napon smeša ksantan guma–Tween 80 određen je metodom prstena po *du Noüy-u* na 25ºC ± 0,1. Analizom FT-IR spektara može se pretpostaviti da osim hidrofobnih interakcija, ksantan guma međudejstvo sa Tween 80 ostvaruje i formiranjem vodoničnih mostova.

Krive zavisnosti površinskog napona od koncentracije Tween 80, pre i posle dodatka konstantne koncentracije ksantan gume, se razlikuju usled prisustva polimer–PAM interakcija. Formiranjem kompleksa ksantan guma–Tween 80 u unutrašnjosti rastvora smanjuje se količina monomera PAM na granici faza voda–vazduh što rezultuje višim vrednostima površinskog napona smeše u odnosu na rastvor čiste PAM, iste koncentracije. Nakon zasićenja lanaca ksantan gume molekulima Tween 80, površinski napon smeše je konstantan i odgovara vrednostima rastvora čiste PAM. Dobijeni rezultati potvrđuju postojanje interakcija između ksantan gume i Tween 80. Ponašanje Tween 80 u prisustvu ksantan gume na granici faza voda–vazduh upućuje da su formirani kompleksi rezultat hidrofilnih i hidrofobnih interakcija.

PHYSICO–CHEMICAL EVALUATION OF POLYMER-SURFACTANT MIXTURES AS POTENTIAL DRUG DELIVERY SYSTEMS

Maja Milanović, Veljko Krstonošić, Milica Atanacković Krstonošić

Department of Pharmacy, University of Novi Sad - Faculty of Medicine (Serbia)

Polymer and surfactants could be found in many drug delivery systems due to their individual properties. However, the characteristics of these systems may be influenced by the occurrence of interactions between polymer and surfactant which depend on nature, concentration, and net charge of both of them. Hence, the understanding of physico-chemical properties of polymer-surfactant mixtures is necessary in order to create appropriate and efficient drug delivery vehicles. The aim of this work was to determine the occurrence and possible mechanism of interactions between anionic polymer–xanthan gum and nonionic surfactant–Tween 80 using Fourier transform infrared spectrometry (FT–IR) and tensiometry.

After FT–IR analysis of pure substances that was performed in the wave number range 4000 to 600 cm^{-1} (resolution of 4 cm^{-1}), the surface tension measurements of xanthan gum–Tween 80 mixtures were done at 25ºC ± 0.1using a du Noüy ring method. The obtained FT–IR spectra imply that complexes between xanthan gum and Tween 80 could occur through hydrophobic interactions as well as hydrogen bonding.

The differences in the shape of curves with and without constant xanthan gum concentration, on the surface tension versus Tween 80 concentration plot, could be ascribed to the occurrence of polymer– surfactant interactions. The xanthan gum–Tween 80 complexes occurred in the bulk, and thus the amount of free surfactant monomer was decreased at the air–water interface resulting in the higher surface tension value of mixtures in compare to the pure surfactant solution of the same concentration. After the saturation of xanthan gum chains with Tween 80, the obtained surface tension values for mixtures corresponded to the values for pure Tween 80.

The obtained results confirmed the occurrence of xanthan gum–Tween 80 interactions. Based on the mixture behavior at air–water interface, xanthan gum and Tween 80 mainly form complexes through hydrophobic and hydrophilic association.

ACE I α-GLUKOZIDAZNA INHIBITORNA AKTIVNOST METANOLNOG EKSTRAKTA *ALCHEMILLA VIRIDIFLORA* ROTHM. (ROSACEAE)

Jelena Radović[1], Nađa Grozdanić[2], Tatjana Stanojković[2], Relja Suručić[3], Tatjana Kundaković-Vasović[1]

[1]Katedra za farmakognoziju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Institut za onkologiju i radiologiju Srbije, Beograd (Srbija), [3]Katedra za farmakognoziju, Univerzitet u Banjoj Luci - Medicinski fakultet, Republika Srpska (Bosna i Hercegovina)

Tanini, polifenolni biljni metaboliti, značajno smanjuju postprandijalnu hiperglikemiju inhibicijom α-glukozidaze, i stoga mogu biti efikasna strategija u kontroli dijabetesa tipa 2. Takođe, dokazano je i da nespecifično inhibiraju aktivnost angiotenzin-konvertujućeg enzima (ACE). Kako su tanini identifikovani samo u vrsti *Alchemilla vulgaris* L., cilj ovog istraživanja je da se odredi sadržaj tanina u do sada neistraženoj vrsti *A. viridiflora* Rothm. (Rosaceae), kao i inhibitorni uticaj na aktivnost ACE i α-glukozidaze.

Ukupni sadržaj tanina u metanolnom ekstraktu *A. viridiflora* određen je prema propisu Ph. Eur. 9.0. Suvi metanolni ekstrakt, enzimski rastvor (400 mU/ml α-glukozidaze u 0,1 M fosfatnom puferu) i supstrat, p-nitrofenil α-D-glukopiranozid korišćeni su za kolorimetrijski test inhibitorne aktivnosti α-glukozidaze. Kao pozitivna kontrola korišćena je akarboza. ACE inhibitorna aktivnost metanolnog ekstrakta ispitana je korišćenjem komercijalnog testa *ACE Kit- WST* (Dojindo Inc., Japan) prema uputstvu proizvođača. Procenat inhibicije enzima je izračunata IC_{50} vrednost, tj. procenjena koncentracija ekstrakta koja je izazvala 50% inhibicije aktivnosti enzima, koristeći linearnu regresionu analizu.

IC_{50} vrednost metanolnog ekstrakta *A. viridiflora*, očitana sa dozno-zavisne krive iznosi 2,6±0,5 μg/ml, i ekstrakt pokazuje bolju anti-α-glukozidaznu aktivnost od standarda akarboze (IC_{50}=74,2±3,3 μg/ml). Takođe, ispitivani ekstrakt pokazuje dozno-zavisnu inhibiciju ACE pri IC_{50} 2 μg/ml. Dobijeni rezultati su u korelaciji sa visokim sadržajem tanina u metanolnom ekstraktu *A. viridiflora* (3,74 %).

Pokazane inhibicije angiotenzin-konvertujućeg enzima i α-glukozidaze čine metanolni ekstrakt vrste *A. viridiflora* pogodnim za dalje istraživanje u cilju pronalaženja novih prirodnih proizvoda značajnih za terapiju kardiovaskularnih bolesti i dijabetesa.

Istraživanje je podržano od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije (Projekat ON 173021).

ACE AND α-GLUCOSIDASE INHIBITORY ACTIVITY OF METHANOL EXTRACT OF *ALCHEMILLA VIRIDIFLORA* ROTHM. (ROSACEAE)

Jelena Radović[1], Nađa Grozdanić[2], Tatjana Stanojković[2], Relja Suručić[3], Tatjana Kundaković-Vasović[1]

[1]Department of Pharmacognosy, University of Belgrade-Faculty of Pharmacy, [2]Institute of Oncology and Radiology of Serbia, Belgrade (Serbia), [3]Department of Pharmacognosy, University of Banja Luka - Faculty of Medicine, Republic of Srpska (Bosnia and Herzegovina)

Tannins, polyphenolic plant metabolites, significantly reduce postprandial hyperglycemia by inhibiting α-glucosidase, and therefore can be an effective strategy for controlling type 2 diabetes. It has also been proven that they are non-specific inhibitors of the activity of angiotensin-converting enzyme (ACE). As tannins were identified only in the species *Alchemilla vulgaris* L., the aim of this study is to determine the content of tannins in the unexplored *A. viridiflora* Rothm. (Rosaceae), as well as the inhibitory effect on the activity of angiotensin-converting enzyme and α-glucosidase.

The content of tannins in methanol extract of *A. viridiflora* was determined according to the Ph. Eur. 9.0. Dry methanol extract, enzyme solution (400 mU/ml of α-glucosidase in 0.1 M phosphate buffer) and substrate, p-nitrophenyl α-D-glucopyranoside were used for colorimetric α-glucosidase inhibitory activity test. Acarbose was used as a positive control. The ACE inhibitory activity of the methanol extract was tested using the commercial *ACE Kit-WST* (Dojindo Inc., Japan) according to the manufacturer's instructions. The percentage of enzyme inhibition is the calculated IC_{50} value, i.e. estimated concentration of the extract that caused 50% inhibition of enzyme activity using linear regression analysis.

The IC_{50} of *A. viridiflora* methanol extract, read from the dose-dependent curve, was 2.6±0.5 μg/mL, and this extract demonstrated better anti-α-glucosidase activity than standard acarbose (IC_{50}=74.2±3.3 μg/mL). In addition, the examined extract shows a dose-dependent inhibition of ACE with IC_{50} 2 μg/mL. Obtained results were in correlation with high level of tannins in methanol extract of *A. viridiflora* (3.74%).

The proven inhibitions of ACE and α-glucosidase make the methanol extract of *A. viridiflora* suitable for further scientific research in order to find a new natural product for the treatment of cardiovascular diseases and diabetes.

The study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project ON 173021).

PROCENA BEZBEDNOSNOG PROFILA ETARSKIH ULJA TAKSONA RODA *HERACLEUM* L. (APIACEAE) U ODNOSU NA UTVRĐENI SADRŽAJ FURANOKUMARINA

Ljuboš Ušjak, Silvana Petrović

Katedra za farmakognoziju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Za etarska ulja izolovana iz različitih biljnih organa osam taksona roda *Heracleum* L. (*H. sphondylium* L., *H. sibiricum* L., *H. montanum* Schleich. ex Gaudin, *H. ternatum* Velen., *H. pyrenaicum* subsp. *pollinianum* (Bertol.) F. Pedrotti & Pignatti, *H. pyrenaicum* subsp. *orsinii* (Guss.) F. Pedrotti & Pignatti, *H. verticillatum* Pančić i *H. orphanidis* Boiss.), u prethodnim ispitivanjima pokazana je antimikrobna, citotoksična i antioksidantna aktivnost. S obzirom da je u pojedinim od ovih etarskih ulja utvrđeno prisustvo potencijalno fototoksičnih furanokumarina (bergaptena, izobergaptena, pimpinelina i/ili izopimpinelina), cilj rada bio je da se izvrši kvantifikacija ukupnih furanokumarina i ustanovi maksimalni dozvoljeni dnevni unos ispitivanih ulja u skladu sa preporukama u odgovarajućem dokumentu Evropske agencije za lekove (Doc. Ref. EMEA/HMPC/317913/2006).

Furanokumarini su kvantifikovani gasnom hromatografijom, metodom eksternog standarda, na osnovu površina pikova detektovanih plameno-jonizacionim detektorom (FID). U skladu sa preporukom EMA, sadržaj ukupnih furanokumarina izražen je kao ksantotoksin (8-metoksipsoralen, 8-MOP).

Prema navedenom dokumentu EMA, smatra se da dnevni unos 1,5 mg furanokumarina izraženih kao 8-MOP putem biljnih lekovitih proizvoda ne doprinosi značajno ukupnom riziku, a da dnevni unos 15 μg ne predstavlja nikakav rizik. U skladu sa tim, dnevni unos ispitivanih etarskih ulja koji ne doprinosi značajno ukupnom riziku kreće se u opsegu 1,94-5,23 mL za 15 etarskih ulja korena, 5,23-15,68 mL za 14 ulja plodova i 2,90-15,68 mL za tri ulja listova ili cvasti, a unos koji ne predstavlja nikakav rizik kreće se u opsegu 0,02-0,05 mL za navedena etarska ulja korena, 0,05-0,16 mL za ulja plodova i 0,03-0,16 mL za ulja listova ili cvasti. U četiri ulja plodova i 24 ulja listova ili cvasti ispitivanih taksona roda *Heracleum* furanokumarini nisu detektovani.

Ovaj rad demonstrira praktičnu primenu aktuelnih preporuka EMA koje se odnose na maksimalni dozvoljeni dnevni unos furanokumarina u cilju utvrđivanja bezbednosnog profila biljnih preparata u kojima su ovi sastojci detektovani.

Istraživanje je podržano od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije (Projekat ON 173021).

EVALUATION OF SAFETY PROFILE OF THE ESSENTIAL OILS OF *HERACLEUM* L. TAXA (APIACEAE) RELATED TO DETERMINED FURANOCOUMARIN CONTENT

Ljuboš Ušjak, Silvana Petrović

Department of Pharmacognosy, University of Belgrade - Faculty of Pharmacy (Serbia)

Essential oils of different plant parts of eight *Heracleum* L. taxa (*H. sphondylium* L., *H. sibiricum* L., *H. montanum* Schleich. ex Gaudin, *H. ternatum* Velen., *H. pyrenaicum* subsp. *pollinianum* (Bertol.) F. Pedrotti & Pignatti, *H. pyrenaicum* subsp. *orsinii* (Guss.) F. Pedrotti & Pignatti, *H. verticillatum* Pančić and *H. orphanidis* Boiss.) previously exhibited antimicrobial, cytotoxic and antioxidant activities. Considering that in some of these oils potentially phototoxic furanocoumarins were detected (bergapten, isobergapten, pimpinellin and/or isopimpinellin), the aim of this work was to quantify total furanocoumarins and estimate maximum daily intake of investigated oils, according to recommendations in corresponding document of European Medicines Agency (Doc. Ref. EMEA/HMPC/317913/2006).

Furanocoumarins were quantified using gas chromatography, by external standard method, based on peak areas obtained by flame ionization detector (FID). As proposed by EMA, the sum of furanocoumarins equivalent to xanthotoxin (8-methoxypsoralen, 8-MOP) was calculated.

According to noted EMA document, daily exposure of 1.5 mg furanocoumarins expressed as 8-MOP through herbal medicinal products is not considered to contribute significantly to overall risk, and the intake of 15 μg is not considered to pose any unacceptable risk. Thus, daily intake of investigated essential oils, not contributing significantly to overall risk is in the range of 1.94-5.23 mL for 15 root essential oils, 5.23-15.68 mL for 14 fruit oils and 2.90-15.68 mL for three leaf or flower oils, and the intake, not posing any unacceptable risk is in the range of 0.02-0.05 mL for mentioned root oils, 0.05-0.16 mL for fruit oils and 0.03-0.16 mL for leaf or flower oils. In four fruit, and 24 leaf or flower oils of investigated *Heracleum* taxa furanocoumarins were not detected.

This work demonstrates practical application of current EMA recommendations, which refer to maximum daily intake of furanocoumarins in order to establish safety profile of herbal preparations containing these compounds.

The study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project ON 173021).

ISPITIVANJE POGODNOSTI GRANULATA OBLOŽENOG TOPLJENJEM ZA KOMPRIMOVANJE U TABLETE DEFINISANE DEBLJINE

Ana Milanović[1,2], Marija Bujišić[1], Katarina Drezgić[1], Jovana Drobnjak[1], Ivana Aleksić[1], Sandra Cvijić[1]

[1]Agencija za lekove i medicinska sredstva Srbije, [2]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Oblaganje topljenjem podrazumeva oblaganje biokompatibilnim lipidnim supstancama, bez primene rastvarača. Pored ostalog, dobijena lipidna obloga može uticati na tabletabilna svojstva dobijenog proizvoda (npr. granulata). Cilj ovog rada je da se ispitaju tabletabilna svojstva granula sa paracetamolom obloženih glicerol distearatom (Precirol® ATO 5) metodom topljenja, pri komprimovanju do zadate debljine tablete.

Granule sa paracetamolom (15 uzoraka obloženih topljenjem u modifikovanom uređaju tipa fluidizirajućeg sistema (Mycrolab, Huttlin, Nemačka) pod različitim procesnim uslovima), neobloženi granulat i smeša komponenti granulata komprimovani su pomoću uređaja Gamlen D serije (Gamlen Instruments Ltd, Velika Britanija), pri uslovima zadate debljine tablete (3 mm). Pritisak kompresije, rad kompresije, elastični oporavak i ejekcioni stres su obračunati na osnovu podataka koje generiše uređaj. Zatezna čvrstina je izračunata na osnovu čvrstine tableta određene pomoću uređaja Erweka TBH125D (Erweka GmbH, Nemačka). Sva merenja su urađena u triplikatu. Pri kompresiji neobloženog granulata do zadate debljine tablete primenjena je veća sila kompresije i veći rad (ukupni, neto, rad elastične sile) u odnosu na obložene granulate. Zatezna čvrstina komprimata izrađenih od neobloženog granulata (0,92 MPa) takođe je veća u odnosu na komprimate obloženih uzoraka (0,53-0,83 MPa), sa izraženom varijabilnošću između neobloženih uzoraka. Zbog lubrikantnog svojstva lipidne obloge, ejekcioni stres komprimata obloženih granula smanjen je više od tri puta u odnosu na neobložene uzorke. Fizička smeša je pokazala najveći elastični oporavak, slabu kompaktibilnost i nedovoljnu čvrstinu dobijenih tableta (tablete su se lomile pre ispitivanja).

Tablete dobijene kompresijom obloženih granulata, pod uslovima zadate debljine, pokazale su prihvatljivu zateznu čvrstinu i nizak ejekcioni stres, ukazujući na dobre tabletabilne osobine uzoraka obloženih topljenjem. Tabletabilna svojstva neobloženog granulata su lošija, dok fizička smeša nije pogodna za komprimovanje u tablete zadate debljine.

ASSESSING THE ABILITY OF HOT MELT COATED GRANULES TO PRODUCE TABLETS OF CONTROLLED THICKNESS

Ana Milanović[1,2], Marija Bujišić[1], Katarina Drezgić[1], Jovana Drobnjak[1], Ivana Aleksić[1], Sandra Cvijić[1]

[1]Medicines and Medical Devices Agency of Serbia, [2]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia)

Hot-melt coating (HMC) refers to a solvent-free coating technique using biocompatible lipid materials. Among other properties, lipid coating can influence tableting properties of HMC product (e.g. granules). The aim of this study was to investigate tableting properties of paracetamol granules coated with glycerol distearate (Precirol® ATO5), when tablets are compressed to predetermined thickness.

HMC paracetamol granules (15 samples obtained in a modified fluid-bed apparatus (Mycrolab, Hüttlin, Germany) under different process parameters setups), uncoated granules and mixture of granules ingredients were compressed using Gamlen D series (Gamlen Instruments Ltd, UK) under fixed thickness (3 mm) operating mode. Compaction pressure, work of compaction, elastic recovery and ejection stress were calculated from the instrument generated data. Tensile strength was calculated from tablets hardness tested using Erweka TBH125D tester (Erweka GmbH, Germany). All measurements were done in triplicate. Fixed thickness compression of uncoated granules resulted in higher compression force and higher work of compaction (total, plastic, elastic) in comparison to HMC granules. Tensile strength of tablets obtained from uncoated samples (0.92 MPa) was also higher than for HMC granules (0.53-0.83 MPa), with notable variability between uncoated samples. Lubricating effect of lipid coating decreased ejection stress of tablets obtained from HMC granules more than three times, compared to uncoated samples. Physical mixture of ingredients showed the highest elastic recovery, poor compactibility and insufficient tablets hardness (tablets broke even before testing).

The assessment of HMC granules to produce tablets of controlled thickness indicated acceptable tablets tensile strength and low ejection force, demonstrating good tableting properties of all HMC samples. Tableting properties of uncoated granules were less favourable, while the tested physical mixture was not suitable for tableting under the target thickness.

FORMULACIJA I OPTIMIZACIJA ORALNO-DISPERZIBILNIH TABLETA IZRAĐENIH DIREKTNOM KOMPRESIJOM SA VISOKIM UDELOM AKTIVNE SUPSTANCE

Milica Drašković, Erna Turković, Jelena Đuriš, Jelena Parojčić

Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu-Farmaceutski fakultet (Srbija)

Najveći izazov u razvoju formulacije oralno-disperzibilnih tableta (ODT) je postizanje kratkog vremena raspadanja uz održavanje prihvatljivih mehaničkih karakteristika. Ovo se može postići primenom sistemskog pristupa formulaciji uz detaljnu analizu uticaja faktora formulacije i procesnih parametara na kritična svojstva kvaliteta tableta. Cilj ovog rada je razvoj i optimizacija formulacije ODT sa visokim udelom aktivne supstance namenjene direktnoj kompresiji koja poseduje prihvatljiva mehanička svojstva i kratko vreme raspadanja.

ODT su izrađene direktnom kompresijom smeše aktivne supstance (ibuprofen, odnosno kofein primenjeni u masenom udelu 10-90%) i različitih komercijalno dostupnih koprocesovanih ekscipijenasa (Ludiflash®, Parteck® ODT, Disintequik™ ODT i Pharmaburst® 500). Odgovarajućim metodama ispitana je zatezna čvrstina i raspadljivost uzoraka, nakon čega je primenom teorije perkolacije određen maksimalan udeo aktivne supstance u formulaciji. Kako bi se procenio efekat procesnih parametara na kritična svojstva kvaliteta odabranih formulacija, kao i uticaj visokog udela aktivne supstance na kompakciona svojstva koprocesovanih ekscipijenasa primenjena je dinamička analiza kompakcije.

Primenom teorije perkolacije uočeno je da raspadljivost predstavlja osetljiviji parametar kvaliteta ODT, u poređenju sa zateznom čvrstinom i da je najveći udeo aktivnih supstanci moguće inkorporirati u uzorke sa Disintequik™ ODT i Pharmaburst® 500. Pomenuti uzorci su pokazali i najkraće vreme raspadanja uz optimalnu zateznu čvrstinu (> 1 MPa). Brzina kompresije je pokazala neznatan uticaj na ispitivana svojstva kvaliteta odabranih formulacija. Inkorporiranje aktivne supstance smanjilo je kompresibilnost koprocesovanih ekscipijenasa, međutim, pozitivno je uticalo na kompaktibilnost i tabletabilnost kod svih formulacija izuzev kod ODT sa Pharmaburst® 500 i ibuprofenom. Međutim, jedino kod pomenute formulacije povećanje pritiska kompresije nije značajno usporilo raspadanje, ukazujući na mogućnost primene nešto veće sile kompresije, kako bi se postigla prihvatljiva mehanička otpornost. Odabirom pogodnih koprocesovanih ekscipijenasa moguće je inkorporirati visok udeo aktivne supstance u formulaciju ODT, bez narušavanja njihovih kompakcionih svojstava i uz postizanje kratkog vremena raspadanja i optimalne mehaničke otpornosti.

FORMULATION AND OPTIMIZATION OF ORODISPERSIBLE TABLETS CONTAINING HIGH DRUG LOAD PREPARED BY DIRECT COMPRESSION

Milica Drašković, Erna Turković, Jelena Đuriš, Jelena Parojčić

Department of Pharmaceutical Technology and Cosmetology, University of Belgrade-Faculty of Pharmacy (Serbia)

The greatest challenge in orally disintegrating tablet (ODT) formulation development is achievement of fast disintegration, while maintaining the acceptable mechanical properties. Considering systematic approach to formulation development, it is necessary to gain knowledge about impact of formulation factors and process parameters on product quality. The aim of this study is formulation and optimization of ODT with high drug load, short disintegration time and acceptable tensile strength.

Samples are prepared by direct compression of tablet mixtures containing model drug (caffeine or ibuprofen in the range of 10-90%) and commercially available co-processed excipients (Ludiflash®, Parteck® ODT, Disintequik™ ODT and Pharmaburst® 500). After evaluation of tensile strength and disintegration time, percolation theory was applied to determine maximum drug load that can be incorporated in ODT formulation. Dynamic compaction analysis was used in order to assess effect of process parameters on ODT critical quality attributes, as well as influence of high drug load on compaction properties of co-processed excipients.

Based on the results obtained by percolation theory application, it can be assumed that disintegration is more critical ODT quality parameter than tensile strength. The highest drug load can be incorporated in samples containing Disintequik™ ODT and Pharmaburst® 500. Those samples have the shortest disintegration time and optimal mechanical properties. Compression speed did not influence evaluated critical quality attributes. Drug inclusion affected negatively compressibility, while compactibility and tabletability in all formulations, except one containing Pharmaburst® 500 and ibuprofen, were improved. However, only in the mentioned formulation increase in compression pressure did not significantly prolong disintegration time, indicating to possibility of applying somewhat greater compression force in order to achieve acceptable mechanical characteristics. By selection of suitable co-processed excipient, it is possible to incorporate high drug load in ODT formulation, without disrupting compaction properties, and achieve optimal tensile strength followed by fast disintegration.

SUPERKRITIČNA IMPREGNACIJA TABLETA MIKROKRISTALNE CELULOZE IBUPROFENOM

Jovana Potpara[1], Jasna Ivanović[2], Svetlana Ibrić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za organsku hemijsku tehnologiju, Univerzitet u Beogradu - Tehnološko-metalurški fakultet (Srbija)

Bioaktivne komponente (antiinflamatorne, antimikrobne, antiseptične, itd.) se, u zavisnosti od svoje biološke uloge, mogu impregnirati u čvrste materijale različitim metodama. Jedna od takvih metoda je i superkritična impregnacija, koja podrazumijeva rastvaranje aktivne supstance u superkritičnom fluidu, pri čemu nastali rastvor dolazi u kontakt sa čvrstim matriksom (najčešće polimernim materijalom) koji će se impregnirati. Cilj rada je bio ispitivanje mogućnosti korišćenja mikrokristalne celuloze dobijene iz prirodnih sirovina, u formi tableta, kao nosača za aktivnu supstancu ibuprofen, metodom superkritične impregnacije uz pomoć ugljen-dioksida.

Mikrokristalna celuloza je iz pšeničkih ostataka dobijena metodom kisele hidrolize, koristeći 64% rastvor sumporne kiseline. Tablete mikrokristalne celuloze (mase 70 mg i prečnika 6 mm) su izrađene metodom direktne kompresije pod opterećenjem od 100 kg, pomoću laboratorijskog simulatora kompakcije Gamlen Tablet Press-a (Gamlen Tableting Ltd, Velika Britanija). Impregnacija ibuprofena u izrađene tablete mikrokristalne celuloze pomoću superkritičnog ugljen-dioksida je izvršena u ćeliji za rad pod visokim pritiscima (Eurotechnica GmbH, Njemačka). Superkritična impregnacija je izvedena pri pritisku od 10 MPa i temperaturi od 40˚C, u trajanju od 2h, a masa impregniranog ibuprofena je određena gravimetrijski. Tablete mikrokristalne celuloze, dobijene iz pšeničnih ostataka, su uspješno impregnirane ibuprofenom pomoću superkritičnog ugljen-dioksida, pri odabranim uslovima (10 MPa, 40˚C), pri čemu nisu pokazale znakove oštećenja. Iz razlike mase čvrstog nosača prije i posle impregnacije izračunat je prinos impregnacije ibuprofena, koji je iznosio 2,9%. U daljim eksperimentima neophodno je optimizovati uslove impregnacije, pri čemu bi se postigla bolja rastvorljivost ibuprofena u superkritičnom ugljen-dioksidu, kao i razmotriti korišćenje mikrokristalne celuloze u vidu praška umjesto tableta, sa ciljem dobijanja većih prinosa impregnacije.

SUPERCRITICAL IMPREGNATION OF MICROCRYSTALLINE CELLULOSE TABLETS WITH IBUPROFEN

Jovana Potpara[1], Jasna Ivanovic[2], Svetlana Ibric[1]

[1]Department od Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]Department od Organic Chemical Technology, University of Belgrade - Faculty of Technology and Metallurgy (Serbia)

Bioactive components (anti-inflammatory, antimicrobial, antiseptic, etc.), depending on their biological role, can be impregnated into solid materials by different methods. One of these methods is supercritical impregnation, which involves the penetration of supercritical fluid with a dissolved active substance into a solid matrix (usually polymer material) enabling distribution of the active substance through the whole material. The aim of this work was to investigate the possibility of using microcrystalline cellulose (MCC), obtained from natural raw materials, in the form of tablets as a carrier for the active substance ibuprofen by the method of supercritical impregnation with carbon dioxide.

MCC is obtained from wheat straw by acid hydrolysis method using 64% sulfuric acid solution. MCC tablets (70 mg weight and 6 mm diameter) were made using a direct compression method at a load of 100 kg, using the Gamlen tablet press laboratory simulator (Gamlen Tableting Ltd, UK). Impregnation of ibuprofen into manufactured MCC tablets was performed in a high pressure cell (Eurotechnica GmbH, Germany) using supercritical carbon dioxide. Supercritical impregnation was performed at a pressure of 10 MPa and a temperature of 40° C for a duration of 2 hours. Mass of the impregnated ibuprofen was determined gravimetrically. Microcrystalline cellulose tablets derived from wheat residues were successfully impregnated with ibuprofen using supercritical carbon dioxide under selected conditions (10 MPa, 40°C, 2h), without showing signs of damage. The yield of ibuprofen impregnation was 2.9% (calculated from the difference between the mass of the solid carrier before and after impregnation). In further experiments, it is necessary to optimize the conditions of impregnation in order to achieve better solubility of ibuprofen in supercritical carbon dioxide, as well as to consider the use of MCC as a powder instead of tablets in order to obtain higher yields of impregnation.

UTICAJ SADRŽAJA LEKA NA DINAMIKU MEĐUPOVRŠINSKOG SLOJA NISKOENERGETSKIH NANOEMULZIJA – STUDIJA SA KURKUMINOM

Ines Nikolić[1], Evgenia Mitsou[2], Dominique Jasmin Lunter[3], Vassiliki Papadimitriou[2], Aristotelis Xenakis[2], Rolf Daniels[3], Snežana Savić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija), [2]Nacionalna helenska istraživačka fondacija, Institut za biologiju, medicinsku biohemiju i biotehnologiju, Atina (Grčka), [3]Institut za farmaceutsku tehnologiju, Eberhard-Karls Univerzitet, Tübingen (Nemačka)

Niskoenergetske nanoemulzije (NE-NE) predstavljaju inovativne i multifunkcionalne nosače, čija su međufazna svojstva važna kako u kontekstu stabilnosti ovih sistema, tako i biofarmaceutskih postignuća. Kurkumin (KU), aktivna supstanca u ovom istraživanju, jeste molekula sa brojnim povoljnim efektima, ali zbog prilično zahtevnih fizičko-hemijskih osobina, njegovi potencijali i dalje ostaju neostvareni. Cilj rada bio je analiza dinamike međufaznog sloja razvijenih NE-NE, kao i procena lokalizacije KU unutar NE-NE i njegovog uticaja na organizaciju međupovršinske membrane, kao nagoveštaja mogućih performansi ovih nosača.

NE-NE su izrađene spontanoemulgujućim metodom, koristeći trigliceride srednje dužine lanca kao masnu fazu (10%), kombinaciju polisorbata 80 i lecitina soje u odnosu 9:1 kao stabilizatora (10%) i visokoprečišćenu vodu. Pripremljene su i formulacije sa 1, 2 i 3 mg/mL KU. Sprovedena je bazična fizičko-hemijska karakterizacija, praćena analizom termalnog ponašanja (diferencijalna skenirajuća kalorimetrija/DSC) i procenom dinamike međupovršinskog sloja (elektron-paramagnetna rezonantna spektroskopija/EPR).

Placebo NE-NE imale su prosečan dijametar kapi 111,3±1,73 nm, koji se povećavao srazmerno sadržaju KU, ostajući uvek ispod 150 nm, uz usku distribuciju veličina kapi u svim slučajevima. DSC merenja su pokazala izražen endotermni pik koji odgovara isparavanju vode iz uzorka, pomerajući se ka nižim temperaturama u formulacijama sa KU (koncentraciono zavisno). To može biti povezano sa interakcijom hidroksilnih grupa KU sa hidrofilnim delom međupovršine, uzrokujući određeno preuređenje u ovom regionu. Slična, ali konkretnija zapažanja zabeležena su primenom EPR, otkrivši 2 različite mikrosredine u međufaznom sloju, zavisno od rasporeda surfaktanata: regioni sačinjeni dominantno od polisorbata 80, i regioni sa prisutnim lecitinom - oba KU-interagujuća. Nakon inkapsulacije, KU je dominantno bio prisutan u lipofilnom delu membrane surfaktanata. Regioni bogati lecitinom su postali fluidniji sa povećanjem koncentracije KU.

Dobijeni rezultati mogu implicirati potencijalnu korist ovih nosača za KU, posebno u topikalnoj primeni, s obzirom na to da je međupovršinska lokalizacija aktivne molekule u ovom slučaju poželjna jer može obezbediti veću raspoloživost na mestu primene.

DRUG LOADING INFLUENCE ON THE INTERFACIAL MEMBRANE DYNAMICS OF THE LOW-ENERGY NANOEMULSIONS -A CURCUMIN CASE STUDY

Ines Nikolić[1], Evgenia Mitsou[2], Dominique Jasmin Lunter[3], Vassiliki Papadimitriou[2], Aristotelis Xenakis[2], Rolf Daniels[3], Snežana Savić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy (Serbia), [2]National Hellenic Research Foundation, Institute for Biology, Medicinal Chemistry and Biotechnology, Athens (Greece), [3]Institute of Pharmaceutical Technology, Eberhard-Karls University Tübingen (Germany)

Low-energy nanoemulsions (LE-NEs) represent novel multifunctional carriers. Their interface characteristics are crucial not only in the context of stability, but also for biopharmaceutical behavior. Curcumin (CU), active substance used in this study, is a powerful pleiotropic molecule. Due to its physicochemical issues, its potentials are still beyond the reach. In the scope of this research was assessment of interfacial properties of developed LE-NEs with regard to CU's concentration, as a hint of prospective performances.

LE-NE were prepared via spontaneous emulsification, using medium-chain triglycerides as the oil phase (10%), combination of polysorbate 80 and soybean lecithin in the ratio 9:1 as stabilizers (10%) and ultrapure water. CU-loaded formulations contained 1, 2 and 3 mg/mL of CU. Basic physicochemical characterization was performed, followed by thermal behavior analysis (differential scanning calorimetry/DSC), and interfacial membrane dynamics assessment (electron paramagnetic resonance spectroscopy/EPR).

The placebo LE-NE exhibited mean droplet diameter of 111.3±1.73 nm, which augmented with increase in the CU content, but remained below 150 nm, with narrow distribution in all cases. DSC showed intense endothermic peak corresponding to the water evaporation, shifting towards lower temperatures for CU-loaded formulations (concentration dependent manner). This might be related to the interactions of CU's hydroxyl groups with the hydrophilic part of the interface, causing some rearrangements in this region. Similar, but more specific findings were captured by EPR, revealing 2 different interfacial microenvironments with respect to the surfactant distribution: regions with and without lecithin, both interacting with CU. Upon encapsulation, CU's participation closer to the lipophilic parts of the surfactant layer was disclosed. Lecithin-rich regions became more fluid with increase in CU concentration, but interface still remained rigid.

Obtained results may imply potentially beneficial role of developed LE-NEs for CU delivery, especially for topical application, because, in this case, interfacial localization is a preferred drug locus for higher availability.

BIOKOMPATIBILNE NANOEMULZIJE ZA ISPORUKU ACEKLOFENAKA U/KROZ KOŽU PRIMENOM HEMIJSKIH POJAČIVAČA PENETRACIJE I ČVRSTIH MIKROIGALA

Tanja Ilić[1], Sanela Savić[2], Bojan Batinić[3], Jelena Đoković[1], Bojan Marković[4], Miroslav Savić[5], Snežana Savić[1]

[1]Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]DCP Hemigal, Leskovac, [3]Katedra za fiziologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [4]Katedra za farmaceutsku hemiju, Univerzitet u Beogradu - Farmaceutski fakultet, [5]Katedra za farmakologiju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Tokom poslednje decenije, neželjeni efekti udruženi sa hroničnom oralnom primenom aceklofenaka (ACF), podstakli su brojna istraživanja ka razvoju različitih metoda za poboljšanje isporuke ACF u/kroz kožu kako bi se postiglo efikasno lečenje bolesti koštano-mišićnog sistema. Otuda, cilj ove studije je bio da se ispita sposobnost nanoemulzija stabilizovanih smešom lecitina i saharoznih estara, sa/bez predtretmana kože čvrstim mikroiglama, da poboljšaju isporuku ACF u/kroz kožu.

Tri nanoemulzije ACF koje su se razlikovale u sadržaju lecitina, saharoza palmitata i stearata poređene su sa referentim uzorkom stabilizovanim smešom lecitina i polisorbata 80 u pogledu fizičko-hemijskih karakteristika, dugoročne stabilnosti i *in vitro* oslobađanja/permeacije ACF. Stepen preuzimanja ACF u folikule dlake procenjen je primenom diferencijalnog *stripping*-a na koži uha svinje. Dodatno, određeni su farmakokinetički profili ACF u plazmi (uključujući i sadržaj ACF deponovanog u koži) pacova Wistar soja, nakon transdermalne primene odabranih nanoemulzija, sa/bez predtremana čvrstim mikroiglama, kao fizičkim inhenserima.

Karakterizacija je pokazala zadovoljavajuć opseg veličina kapi (~180nm), relativno usku raspodelu veličina (<0,15), visoko površinsko naelektrisanje (oko –40mV), i zadovoljavajuću dugoročnu stabilnost (godinu dana na 4±1°C) formulacija kostabilizovanih saharoza palmitatom i polisorbatom 80. *In vitro* ispitivanje oslobađanja/permeacije i diferencijalni *stripping* potvrdili su superiornost nanoemulzija na bazi saharoznih estara u odnosu na nanoemulziju sa polisorbatom 80. Međutim, rezultati dobijeni *in vitro* nisu bili u potpunosti u skladu sa nalazima *in vivo* – nisu uočene značajne razlike između ispitivanih formulacija u farmakokinetici i ukupnoj količini ACF deponovanog u koži 24h nakon primene, pri čemu su, istovremeno, ukazali na odloženu isporuku ACF u sistemsku cirkulaciju. Konačno, predtretman kože mikroiglama rezultovao je 1,4–2,1 puta povećanjem biološke raspoloživosti, kao i 1,2–1,7 puta povećanjem sadržaja aceklofenaka zadržanog u koži pacova.

Dobijeni rezultati ukazuju da je kombinacija mikroigla i nanoemulzije kostabilizovane saharoza palmitatom korisna za postizanje veće koncentracije ACF u koži, dok je kombinaicija mikroigala i nanoemulzije kostabilizovane polisorbatom 80 pogodnija za postizanje veće koncentracije ACF u krvotoku.

BIOCOMPATIBLE NANOEMULSIONS FOR ACECLOFENAC DELIVERY INTO/THROUGH THE SKIN USING CHEMICAL PENETRATION ENHANCERS AND SOLID MICRONEEDLES

Tanja Ilić[1], Sanela Savić[2], Bojan Batinić[3], Jelena Đoković[1], Bojan Marković[4], Miroslav Savić[5], Snežana Savić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, [2]DCP Hemigal, Leskovac, [3]Department of Physiology, University of Belgrade-Faculty of Pharmacy, [4]Department of Pharmaceutical Chemistry University of Belgrade-Faculty of Pharmacy, [5]Department of Pharmacology University of Belgrade-Faculty of Pharmacy (Serbia)

Over the past decade, adverse effects associated with chronic oral administration of aceclofenac (ACF) enforced intensive research efforts towards exploring different penetration enhancement technologies aiming to ensure effective treatment of musculoskeletal disorders via skin. Hence, this study was designed to investigate the potential of lecithin-based nanoemulsions costabilized by sucrose esters, with/without skin pretreatment with solid microneedles, to improve delivery of ACF into/across the skin.

Three ACF-loaded nanoemulsions differing in the ratio of lecithin, sucrose palmite and stearate, were compared, and with the reference stabilized with lecithin/polysorbate 80, regarding physicochemical properties, long-term stability and in vitro drug release/permeation. The extent of ACF follicular uptake was assessed using differential stripping on porcine ear skin. Additionally, the plasma pharmacokinetics of ACF (including quantification of ACF amount retained in the skin) after topical administration of formulated nanoemulsions, with/without skin perforation using solid microneedles, as physical enhancers, was investigated in Wistar rats.

The characterization revealed favorable droplet size (~180nm), narrow size distribution (<0.15), high surface charge (about –40mV) and satisfying long-term stability (one year at 4±1°C) of the formulations costabilized by sucrose palmitate and polysorbate 80. In vitro release/permeation testing and differential stripping proved the superiority of sucrose ester- over polysorbate-based nanoemulsion. However, in vitro findings were not fully indicative of the in vivo performances – no significant differences were observed between investigated formulations in pharmacokinetics and total amount of ACF deposited in the skin 24h after dosing, simultaneously pointing to delayed ACF delivery into the systemic circulation. Finally, skin pretreatment with microneedles led to 1.4–2.1-fold increased bioavailability and 1.2–1.7-fold enhanced level of ACF retained in the skin.

Obtained results suggest that combination of microneedles and sucrose palmitate-costabilized nanoemulsion could be useful to attain higher skin concentration, while combination of microneedles with polysorbate 80-costabilized one could be preferable for enhancing ACF delivery into the bloodstream.

ISPITIVANJE VARIJABILNOSTI U KONCENTRACIJAMA METOTREKSATA IZMEĐU CIKLUSA TERAPIJE

Biljana Škorić[1], Marija Jovanović[1], Branislava Miljković[1], Miloš Kuzmanović[2,3], Dragan Mićić[3], Katarina Vučićević[1]

[1]Katedra za farmakokinetiku i kliničku farmaciju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Univerzitet u Beogradu - Medicinski fakultet, [3]Institut za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić", Beograd (Srbija)

Primena intenzivnih terapijskih protokola u lečenju akutne limfomblastne leukemije (ALL) i non-Hodgkin limfoma (NHL), uz istovremenu primenu više različitih citotoksičnih agenasa, dovodi do visokog procenta izlečenja pedijatrijskih pacijenata. Metotreksat se primenjuje u visokim dozama i zbog značajne inter- i intra-individualne varijabilnosti u farmakokinetici indikovano je terapijsko praćenje leka (*Therapeutic drug monitoring*, *TDM*). Cilj ovog rada je bio da se ispita individualna varijabilnost u koncentracijama metotreksata između različitih ciklusa terapije.

U studiju su uključeni pedijatrijski pacijenati sa dijagnozom ALL ili NHL lečeni na Institutu za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić". Podaci o pacijentima su prikupljeni retrospektivno iz medicinskih istorija. Etički odbor Instituta je odobrio sprovođenje studije. Statistička analiza podataka kod pacijenata koji su primenjivali dozu od 5 g/m^2 metotreksata je izvršena primenom programa *R*®.

Kod 38 pacijenata je izmereno ukupno 122 koncentracije metotreksata 24 h nakon početka terapije (76,7±37,7 μmol/L), pri čemu je broj ciklusa bio od 1 do 4. Medijana koeficijenta varijacije izmernih koncentracija metotreksata, uzimajući u obzir individualnu varijabilnost između ciklusa kod svakog pacijenta, je bila 32.3%, dok je raspon bio od 6,69 do 106%. Kod 36 pacijenata je bilo dostupno 113 koncentracija nakon 48 h (0,47±1,26 μmol/L), a broj ciklusa je bio od 1 do 4. Koeficijent varijacije je iznosio od 7,07 do 152%, dok je medijana bila 44%. 72 h nakon početka terapije je izmereno 17 koncentracija metotreksata (0,263±0,442 μmol/L) kod 8 pacijenata, pri čemu je broj ciklusa bio od 1 do 4. Medijana koeficijenta varijacije je iznosila 26,2%, dok je raspon bio u opsegu od 10,9 do 129%.

Rezultati analize pokazuju značajnu varijabilnost u koncentracijama metotreksata uzimajući u obzir individualnu varijabilnost između ciklusa kod svakog pacijenta, ukazujući na značaj *TDM*-a i ispitivanje faktora koji doprinose varijabilnosti.

Istraživanje je realizovano u okviru projekta broj 175023 finansiranog od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije.

INVESTIGATION OF VARIABILITY IN METHOTREXATE CONCENTRATIONS BETWEEN THERAPY CYCLES

Biljana Škorić[1], Marija Jovanović[1], Branislava Miljković[1], Miloš Kuzmanović[2,3], Dragan Mićić[3], Katarina Vučićević[1]

[1]Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade - Faculty of Pharmacy, [2]University of Belgrade - School of Medicine, [3]Institute for Mother and Child Healthcare „Dr Vukan Čupić", Belgrade (Serbia)

The application of intensive therapeutic protocols for the treatment of acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL), with the simultaneous administration of several different cytotoxic agents, leads to good treatment outcomes in paediatric patients. Methotrexate is administered in high doses and due to significant inter- and intra-individual variability in the pharmacokinetics therapeutic drug monitoring (TDM) is indicated. The aim of the study was to evaluate individual variability in methotrexate concentration between different therapy cycles.

The study included paediatric patients diagnosed with ALL or NHL treated with 5 g/m^2 of methotrexate at the Institute for mother and child healthcare „Dr Vukan Čupić". Data were retrospectively collected from medical charts. The Ethics Committee of the Institute approved the study protocol. Statistical analysis was performed with program R®.

In 38 patients, a total of 122 methotrexate concentrations were measured 24h after initiation of therapy (76.7±37.7 μmol/L), while the number of cycles was 1-4. Median value of coefficient of variation (CV) in methotrexate concentrations, taking into account the individual variability between cycles in each patient, was 32.3%, while the range was 6.69-106%. In 36 patients, 113 concentrations were available after 48h (0.47±1.26 μmol/L) and the number of cycles 1-4. Values of CV were from 7.07 to 152%, while the median was 44.0%. 72h after initiation of therapy, 17 concentrations of methotrexate (0.263±0.442 μmol/L) were measured in 8 patients, with the number of cycles from 1 to 4. The median value of CV was 26.2%, while the range was from 10.9 to 129%.

The results of the analysis present significant variability in methotrexate concentrations taking into account the individual variability between cycles in each patient, indicating the importance of TDM and assessment of the sources of variability.

This work was conducted as a part of the project No. 175023 funded by the Ministry of Education, Science and Technological Development, Republic of Serbia.

OPTIMIZACIJA PROTOKOLA ZA SAKUPLJANJE UZORAKA KRVI ZA ISPITIVANJE FARMAKOKINETIKE ZONISAMIDA KOD PEDIJATRIJSKIH PACIJENATA

Maša Roganović[1], Branislava Miljković[1], Marija Jovanović[1], Anđelija Malenović[2], Nebojša Jović[3], Katarina Vučićević[1]

[1]Katedra za farmakokinetiku i kliničku farmaciju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za analitiku lekova, Univerzitet u Beogradu - Farmaceutski fakultet, [3]Klinika za neurologiju i psihijatriju za decu i omladinu Kliničkog centra Srbije, Univerzitet u Beogradu - Medicinski fakultet (Srbija)

Pri terapijskom praćenju antiepileptika (*Therapeutic Drug Monitoring*, TDM) najčešće se uzima jedan uzorak biološkog materijala koji odgovara minimalnoj koncentraciji leka u krvi. Prilikom planiranja kliničke studije, sa ciljem procene farmakokinetičkih parametara za odgovarajući/e proces/e, neophodno je proceniti optimalan broj uzoraka biološkog materijala i vremena uzorkovanja u odnosu na primenjenu dozu leka. Dodatno, sa aspekta razvoja i validacije bioanalitičke metode za određivanje koncentracije leka, od značaja je poznavanje očekivanog raspona koncentracija nakon uobičajenih režima doziranja. Cilj ovog rada jeste predviđanje raspona koncentracija zonisamida u plazmi i optimizacija protokola uzimanja uzoraka krvi kod pacijenata na kombinovanoj terapiji zonisamidom kako bi se obezbedila adekvatna procena parametara u okviru populacione farmakokinetičke analize.

Za optimizaciju protokola uzimanja biološkog materijala, korišćen je softver PFIM (v.4. 0). Ulazni podaci obuhvataju literaturno dostupne vrednosti populacionih farmakokinetičkih parametara (ka, Vd, CL) zonisamida i njihove interindividualne varijabilnosti i rezidualne greške, očekivan broj pacijenata u planiranoj studiji i uobičajene režime doziranja zonisamida (100-400 mg/12 h). Na osnovu navedenih podataka, simulirani su koncentracija-vreme (C-t) profili zonisamida, a dodatno uz inicijalno predložen broj uzoraka i vremena uzorkovanja izvršena je optimizacija eksperimentalnog dizajna preko Fedorov-Wynn algoritma.

Očekivan raspon koncentracija zonisamida uplazmi je 2-65 μg/mL. Predložena vremena za sakupljanje uzoraka krvi su 0,5, 1, 1,5, 2, 4, 6, 8, 11,5, 12 h nakon primenjene doze. Optimizacija je izvršena za tri, odnosno četiri uzorka po pacijentu. Ukoliko je maksimalan broj uzoraka po pacijentu (u grupi od 30 pacijenata) četiri, optimalno vreme uzorkovanja je u sledećim vremenskim tačkama: 1,5, 4, 8, 12 h. Za tri uzorka po pacijentu, optimalno uzorkovanje je 2, 6 i 12 h nakon primenjene doze.

Simulacija C-t profila daje adekvatnu podršku u razvoju i validaciji bioanalitičke metode, dok optimizovani protokoli uzimanja uzoraka omogućavaju precizniju i tačniju procenu populacionih vrednosti farmakokinetičkih parametara, njihovih interindividualnih varijabilnosti kao i rezidualne greške.

Istraživanje je realizovano u okviru projekta broj 175023 finansiranog od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije.

OPTIMIZATION OF THE BLOOD SAMPLING PROTOCOL FOR THE ZONISAMIDE PHARMACOKINETIC STUDY IN PEDIATRIC PATIENTS

Maša Roganović[1], Branislava Miljković[1], Marija Jovanović[1], Anđelija Malenović[2], Nebojša Jović[3], Katarina Vučićević[1]

[1]Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade - Faculty of Pharmacy, [2]Department of Drug Analysis, University of Belgrade - Faculty of Pharmacy, [3]Clinic of Neurology and Psychiatry for Children and Youth, University of Belgrade - School of Medicine (Serbia)

During the therapeutic drug monitoring (TDM) of antiepileptics, blood samples are taken just before the next oral dose. To adequately estimate specific pharmacokinetic parameter/s, it is necessary to estimate the optimal number of blood samples and sampling times. For the development and validation of a bioanalytical method for measuring drug levels, expected concentration ranges following the typical dosing regimens are required. The aim of this study is to predict the range of plasma concentrations, and to optimise blood sampling protocol in patients receiving zonisamide.

PFIM (v.4.0) was used to optimise the study protocol. The input data include available values of the population pharmacokinetic parameters (ka, Vd, CL) of zonisamide, the interindividual variabilities and residual errors, the expected number of patients in the planned study and the usual dosing regimens of zonisamide (100-400 mg/12 h). Based on the given data, concentration-time (C-t) zonisamide profiles were simulated. Additionally, optimization of the experimental design was carried out through the Fedorov-Wynn algorithm and using the initially proposed number of samples and the sampling times.

The expected range of zonisamide plasma concentrations is 2-65 μg/mL. The suggested times for blood samples collection were: 0.5, 1, 1.5, 2, 4, 6, 8, 11.5, 12 h after the dose. Optimization was done for three and four samples per patient. If the maximum number of samples per patient (in a group of 30 patients) is four, the optimum sampling times are at: 1.5, 4, 8, 12 h. For three samples per patient, optimal sampling was at 2, 6, 12 h.

C-t profile simulation provides adequate support for the development and validation of the bioanalytical method, while optimised sampling protocols allow accurate estimation of the population pharmacokinetic parameters, their interindividual variability, and residual errors.

This work was conducted as a part of the project No.175023 funded by the Ministry of Education, Science and Technological Development, Republic of Serbia.

ISPITIVANJE UTICAJA FUNKCIONALNOG VOLUMENA ŠTITASTE ŽLIJEZDE NA VJEROVATNOĆU ISHODA TERAPIJE 131I KOD PACIJENATA SA BENIGNIM OBOLJENJIMA ŠTITASTE ŽLIJEZDE

Valentina Topić Vučenović[1], Dijana Jelić[1], Zvezdana Rajkovača[2], Branislava Miljković[3], Katarina Vučićević[3]

[1]Odsjek za farmaciju, Univerzitet u Banjoj Luci - Medicinski fakultet, [2]Univerzitet u Banjoj Luci - Medicinski fakultet (Bosna i Hercegovina), [3]Katedra za farmakokinetiku i kliničku farmaciju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Cilj ove studije je bio ispitivanje i kvantifikovanje uticaja funkcionalnog volumena štitaste žlijezde na vjerovatnoću ishoda terapije 131I kod pacijenata sa benignim oboljenjima štitaste žlijezde razvojem binarnog logističkog regresionog modela.

Podaci za analizu su retrospektivno prikupljeni iz medicinskih kartona pacijenata. Dimenzije štitaste žlijezde su određene ultrazvučnom metodom. Za pacijente sa Grejvsovom bolešću (GB) i multinodularnom gušom (MNG) funkcionalni volumen je određen kao ukupni volumen štitaste žlijezde, dok je kod pacijenata sa toksičnim adenomom (TA) volumen autonomnog („vrućeg") čvora uzet kao funkcionalni volumen. Za aproksimaciju volumena režnjeva, istmusa i čvorova štitaste žlijezde upotrijebljena je formula za volumen elipsoida (V= π/6 x dužina (cm) x širina (cm) x dubina (cm)). Klinički ishod je procijenjen godinu dana nakon terapije 131I, a kao uspješan ishod je razmatran eu ili hipotireoidizam. Analiza je sprovedena pomoću softvera NONMEM® (v7.3), PsN® (v4.6.0) i R Studio (v1.0.153).

Podaci za analizu su obuhvatili 95 kliničkih ishoda određenih godinu dana nakon primjene 131I kod 95 odraslih pacijenata (57 (60%) sa GB, 21 (22,1%) sa MNG i 17 (17,9%) sa TA). Prema dobijenom modelu, odnos šansi za uspješan ishod terapije se smanjuje za 19,3% (CI: 17,2 – 21,4%) za svakih 5 mL povećanja funkcionalnog volumena preko vrijednosti medijane (31,06 mL za GB, 46,13 mL za MNG i 10,13 mL za TA) pri medijani apsorbovane doze zračenja (199,43 Gy). Vjerovatnoća uspješnog ishoda pri vrijednostima medijane prediktorskih varijabli iznosi 0,695.

Analiza je pokazala da je funkcionalni volumen štitaste žlijezde statistički značajan prediktor vjerovatnoće ishoda terapije 131I i da ga je potrebno uzeti u obzir pri određivanju doze radioaktivnosti za uspješan ishod terapije kod pacijenata sa benignim oboljenjima štitaste žlijezde.

INVESTIGATION OF THE INFLUENCE OF FUNCTIONAL THYROID VOLUME ON THE PROBABILITY OF 131I THERAPY OUTCOME IN PATIENTS WITH BENIGN THYROID DISEASE

Valentina Topić Vučenović[1], Dijana Jelić[1], Zvezdana Rajkovača[2], Branislava Miljković[3], Katarina Vučićević[3]

[1]Department of Pharmacy, University of Banja Luka - Faculty of Medicine,
[2]University of Banja Luka - Faculty of Medicine (Bosnia and Herzegovina),
[3]Department of Pharmacokinetics and Clinical Pharmacy, University of Belgrade - Faculty of Pharmacy (Serbia)

The objective of the study was to investigate and quantify the influence of functional thyroidal volume on the probability of the outcome of 131I therapy in patients with benign thyroid disease by a development of a binary logistic regression model.

Data for analysis were retrospectively collected from patients' medical records. The dimensions of the thyroid gland were determined by ultra-sonography. For the patients with Graves' disease (GD) and multi-nodular goitre (MNG) functional volume was total thyroid volume, whereas in patients with toxic adenoma (TA) autonomous („hot") nodule was considered as functional volume. The ellipsoid volume formula (V= π/6 x length (cm) x width (cm) x depth (cm) was used for approximation of the volume of thyroid lobes, isthmus and nodules. The clinical outcome was evaluated 1 year after 131I therapy and a successful outcome was eu- or hypothyroidism. The analysis was performed using NONMEM® (v7.3), PsN® (v4.6.0) and R Studio (v1.0.153) software.

Data for analysis included 95 clinical outcomes obtained 1 year after 131I therapy from 95 adult patients (57 (60%) with GD, 21 (22.1%) with MNG and 17(17.9%) with TA). According to the model, the odds ratio of having successful outcome decreased by 19.3% (CI: 17.2 – 21.4%) for each 5 mL increase of the functional volume over the median value (31.06 mL, 46.13mL and 10.13 mL for GD, MNG and TA, respectively) at median value of absorbed radiation dose (199.43 Gy). Baseline probability of successful outcome at median values of the predictor variables was 0.695.

The analysis showed that the functional thyroidal volume is statistically significant predictor of the probability of 131I therapy outcome in hyperthyroid patients and should be considered when determining dose of radioactivity necessary for a successful outcome in patients with benign thyroid disease.