

**NASTAVNO-NAUČNOM VEĆU FARMACEUTSKOG FAKULTETA
UNIVERZITETA U BEOGRADU/
TO THE ACADEMIC COUNCIL OF THE FACULTY OF PHARMACY AT
THE UNIVERSITY OF BELGRADE**

**KOMISIJI ZA POSLEDIPLOMSKE STUDIJE/
TO THE COMMITTEE FOR POSTGRADUATE STUDIES**

Na osnovu člana 94. Statuta i predloga Komisije za poslediplomske studije, Nastavno-naučno veće Farmaceutskog fakulteta Univerziteta u Beogradu, na sednici održanoj 24.11.2011. godine, donelo je odluku o imenovanju Komisije za ocenu ispunjenosti uslova za kandidata diplomiranog farmaceuta Marije Petronijević i naučne zasnovanosti teme doktorske disertacije pod naslovom „Farmakoepidemiološka studija spontano prijavljenih hepatotoksičnih reakcija na lekove i biljne dijetetske suplemente“.

Posle uvida u priloženi materijal i analize predmeta i cilja istraživanja, Komisija u sastavu: doc. dr Katarina Ilic, prof. dr *Herve Le Louet*, prof. dr Nenad Ugrišić, prof. dr Silva Dobrić i prof. dr Slavica Erić, podnosi sledeći

According to the Article 94 of the Statute and the recommendation of the Committee for postgraduate studies, Academic Council of the Faculty of Pharmacy at the University of Belgrade on the sitting held on November 24, 2011 made decision on appointment of the Commission for evaluation of prerequisites' completion for the candidate Ms Marija Petronijevic, a graduate pharmacist, and for the scientifically based topic of her doctoral dissertation entitled "Pharmacoepidemiological study of spontaneously reported hepatotoxic reactions of drugs and herbal dietary supplements".

After an insight into the enclosed material and analysis of the subject and aims of the research, the Commission composed of the following members: Dr Katarina Ilic, assistant professor, Dr Herve Le Louet, lecturer, Dr Nenad Ugresic, professor, Dr Silva Dobric, professor, and Dr Slavica Eric, associate professor, submits following

IZVEŠTAJ/REPORT

A. Biografija kandidata/ Curriculum Vitae

Marija Petronijević rođena je 27. avgusta 1978. godine u Kragujevcu gde je završila osnovnu školu i gimnaziju kao đak generacije. Farmaceutski fakultet u Beogradu upisala je 1997. godine i diplomirala oktobra 2003. sa prosečnom ocenom 9,68. Stručni ispit položila je decembra 2004. godine. U 2008. godini stekla je zvanje specijaliste Farmaceutске zdravstvene zaštite na Farmaceutskom fakultetu u Beogradu.

Tokom studija kao student sa najvišom prosečnom ocenom u svojoj generaciji, dobila je nagradu iz Fonda Kraljevine Norveške (2000. godine), nagradu Vlade Republike Srbije (2002. godine) i stipendiju Fonda Kraljevskog doma Karađorđevića (2002. godine). Nakon

FARMACEUTSKI FAKULTET
BEOGRAD
SEKRETARIJAT

Примиљено: 25. 11. 2012			
Орг. јед.	Број	Предлог	Вредност
01	133/1		

diplomiranja usledile su nagrade od strane Univerziteta u Beogradu i Društva medicinskih biohemičara "Ivan Berkeš".

Svoj profesionalni rad započela je u Institutu za farmaceutsku tehnologiju i kozmetologiju Farmaceutskog fakulteta u Beogradu 2003. godine kao saradnik u praktičnoj nastavi. Od februara 2005. godine do avgusta 2007. godine Marija Petronijević je kao asistent-pripravnik na Institutu za farmakokinetiku Farmaceutskog fakulteta u Beogradu učestvovala u održavanju praktične nastave iz predmeta farmakokinetika. Magistarske studije iz farmakokinetike na Farmaceutskom fakultetu u Beogradu upisala je oktobra 2005. godine. Nakon reforme programa akademskih studija, u oktobru 2006. godine upisala je prvu godinu doktorskih studija iz farmakokinetike.

Od avgusta 2007. godine Marija Petronijević zaposlena je u Agenciji za lekove i medicinska sredstva Srbije (ALIMS) na poslovima procena u oblasti farmakovigilance. Usled zahteva novog radnog mesta, Marija Petronijević je oktobra 2007. godine promenila oblast istraživanja i nastavila posle diplomске studije kao student druge godine doktorskih studija iz farmakologije (uža oblast – farmakoepidemiologija).

U periodu koji je usledio, Marija Petronijević je bila uključena u brojne edukativne programe iz oblasti farmakovigilance, među kojima su najznačajniji realizovani u okviru projekta ALIMS-a sa francuskom regulatornom agencijom (*Twinning Project between French Health Product Safety Agency (AFSSAPS) and Medicines and Medical Devices Agency of Serbia (ALIMS)*).

Marija Petronijević je član Međunarodnog društva za farmakovigilancu (*International Society of Pharmacovigilance - ISoP*) od 2008. godine. Organizovala je ISoP edukativne seminare održane 27-28. maja 2010. godine na Farmaceutskom fakultetu u Beogradu. Predstavljala je našu zemlju na dva svetska skupa nacionalnih centara farmakovigilance u organizaciji Svetske zdravstvene organizacije – 2009. godine u Rabatu (Maroko) i 2010. godine u Akri (Gana).

Marija Petronijevic was born in Kragujevac, Serbia, on August 27, 1978, where she graduated from the primary and high school as the best student in the class. She enrolled the Faculty of Pharmacy in Belgrade in 1997, and graduated in October 2003 with the average mark 9.68/10. She passed board exam for pharmacists in December 2004. In 2008 she specialized in pharmaceutical care at the Faculty of Pharmacy in Belgrade.

As the student with the highest average mark in the class, she was awarded during the studies from the Kingdom of Norway (2000), government of the Republic of Serbia (2002), and the Royal House of Karadjordjevic (2002). After graduating, she was awarded from the University of Belgrade and the Society of Medical Biochemists 'Ivan Berkes'.

She started her professional career in 2003 as a teaching assistant in the students' practical training at the Institute of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy in Belgrade. From February 2005 to August 2007, Marija Petronijevic worked as a teaching assistant for practical aspects of the course in pharmacokinetics at the Institute of pharmacokinetics, Faculty of Pharmacy in Belgrade. In October 2005, she enrolled in master

postgraduate studies in pharmacokinetics at the Faculty of Pharmacy in Belgrade. After academic studies program was reformed, in October 2006 she started PhD in the same field.

Since August 2007 Marija Petronijevic has been working in the Medicines and Medical Devices Agency of Serbia (ALIMS) as an assessor of pharmacovigilance data. Due to requirements of the new working position, Marija Petronijevic changed the field of her research in October 2007, and continued her PhD as a student of second year of doctoral studies in pharmacology (narrow area - pharmacoepidemiology).

In the period that followed, Marija Petronijevic has been involved in number of educational programs in the field of pharmacovigilance, the most important being conducted within the twinning project between the French Health Product Safety Agency (AFSSAPS) and the Medicines and Medical Devices Agency of Serbia (ALIMS).

Marija Petronijevic is a member of the International Society of Pharmacovigilance (ISoP) since 2008. She led the local organizing committee for the ISOP training courses held in May 27-28, 2010 at the Faculty of Pharmacy, Belgrade. She was a representative in two world meetings of the national pharmacovigilance centers organized by the World Health Organization - in 2009 at Rabat (Morocco), and in 2010 at Accra (Ghana).

B. Objavljeni radovi i saopštenja/References

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C. Obrazloženje teme doktorske disertacije/ *Background of doctoral dissertation*

1. Naučna oblast/*Scientific area*

Farmakologija, farmakoepidemiologija, farmakovigilanca /*Pharmacology, pharmacoepidemiology, pharmacovigilance.*

2. Predmet naučnog istraživanja/ *Subject of the scientific research*

Predmet ove doktorske disertacije je ispitivanje učestalosti prijavljivanja hepatotoksičnosti lekova i biljnih dijetetskih suplemenata i uticaja pola, uzrasta, upotrebe alkohola, pratećih oboljenja, istovremene primene dva ili više lekova i/ili dijetetskih suplemenata i regionalnih karakteristika na ovu neželjenu reakciju.

Subject of this doctoral dissertation is an investigation of reporting frequency of hepatotoxicity caused by drugs and herbal dietary supplements, and the influence of gender, age, alcohol consumption, comorbidities, concomitant use of two or more drugs and/or dietary supplements, and regional characteristics on this adverse reaction.

3. Naučna zasnovanost teme/*Scientific background of the topic*

Hepatotoksičnost je potencijalno neželjeno dejstvo velikog broja lekova (> 1000), koji se izdaju na lekarski recept ili bez recepta, kao i biljnih dijetetskih suplemenata [1-3]. Oštećenje jetre izazvano lekovima posredovano je raznovrsnim mehanizmima i može se manifestovati različitim hepatobilijarnim oboljenjima [1,2,4]. U razvijenim zemljama oštećenje jetre izazvano lekovima vodeći je uzrok akutne hepatičke insuficijencije [5-7], koja često ima smrtni ishod. Dodatno, hepatotoksičnost lekova je glavni razlog za sprovođenje regulatornih mera iz bezbednosnih razloga, uključujući i povlačenje leka iz prometa (npr. bromfenak, troglitazon, pemolin) [1].

Dijetetski suplementi ne podležu standardnoj regulatornoj proceduri provere efikasnosti, bezbednosti i kvaliteta, koja je obavezna za lekove [8]. Iako su dostupni, generalno se smatraju bezbednim i sve više se koriste. Međutim, na osnovu objavljenih individualnih slučajeva toksičnog oštećenja jetre izazvanih biljnim dijetetskim suplementima [9,10], njihova bezbednost se dovodi u pitanje. Zbog primene u samomedikaciji, nestandardizovanog sastava i potencijala za interakcije sa lekovima, otkrivanje hepatotoksičnog dejstva biljnih dijetetskih suplemenata je dodatno otežano.

Hepatotoksične reakcije su retke ili vrlo retke i nepredvidive, te se u kliničkim ispitivanjima leka uglavnom ne zapažaju, već se otkrivaju tokom postmarketinškog praćenja leka (faza IV) sistemom spontanog prijavljivanja neželjenih reakcija [11]. Iako je prijavljivanje neželjenih reakcija na lekove profesionalna obaveza zdravstvenih radnika, na ovaj način evidentira se samo manji broj neželjenih reakcija (*underreporting*) [12]. Zbog toga, kao i nezadovoljavajućeg kvaliteta prijava, otežana je interpretacija podataka dobijenih spontanom prijavljivanjem. Međutim, na osnovu većeg broja prijava neželjenih reakcija moguća je detekcija i pojačanje bezbednosnih signala [13-16]. Zato je u ovakvoj vrsti istraživanja izuzetno važno da se koriste kvalitetne baze spontano prijavljenih slučajeva neželjenih reakcija.

Za kliničku praksu posebno je važno identifikovati faktore rizika za ispoljavanje hepatotoksičnog dejstva lekova i biljnih dijetetskih suplemenata, kao što su: uzrast i pol

pacijenta, način ishrane, upotreba alkohola, sistemske bolesti, genetski faktori, istovremena primena dva ili više lekova, ili istovremena primena lekova i dijetetskih suplemenata [1]. Većina navedenih faktora varira između zemalja, pa se mogu očekivati regionalne razlike u ispoljavanju hepatotoksičnog dejstva lekova i biljnih dijetetskih suplemenata.

Generalno je zapaženo da je ženski pol osetljiviji na hepatotoksično dejstvo lekova, ali su objavljeni rezultati nekonzistentni [17,18]. Neke studije su ukazale na povezanost ženskog pola sa razvojem težih formi hepatotoksičnosti [19-21].

Osim toga, smatra se da je rizik za nastanak hepatotoksičnih reakcija veći kod starijih pacijenata zbog izmenjene farmakokinetike, komorbiditeta i polifarmacije [1]. Starost pacijenta je jedan od kriterijuma CIOMS/RUCAM metode za procenu kauzaliteta (uzročno-posledične veze) između leka i hepatotoksične reakcije. Prema ovoj metodi, osobe starije od 55 godina smatraju se rizičnom grupom [22]. Međutim, ovakav generalizovan pristup je dosta kritikovan zbog zapažanja da zavisno od primenjenog leka i mlade i starije osobe mogu biti izložene povećanom riziku za nastanak hepatotoksičnog dejstva lekova [17,18].

Postmarketinška istraživanja baza spontano prijavljenih neželjenih reakcija omogućavaju otkrivanje hepatotoksičnog potencijala pojedinih lekova i iniciranje odgovarajućih regulatornih mera, što je naročito važno za nove lekove. Osim sporadičnih slučajeva ili serija slučajeva, u literaturi nedostaju rezultati ispitivanja hepatotoksičnosti biljnih dijetetskih suplemenata na osnovu većih baza evidentiranih slučajeva. Rezultati o uticaju pola na ispoljavanje hepatotoksičnosti su nekonzistentni, dok je uticaj starosti pacijenta na ispoljavanje hepatotoksičnosti pojedinih lekova ili grupa lekova nedovoljno ispitan, ili su ova istraživanja bila zasnovana na manjim bazama podataka. Baza Svetske zdravstvene organizacije (SZO) raspolaže velikim brojem pojedinačnih slučajeva neželjenih reakcija i do sada nije korišćena za istraživanja učestalosti prijavljivanja lekovima izazvane hepatičke insuficijencije i hepatotoksičnosti biljaka. Takođe, nisu ispitivane regionalne specifičnosti slučajeva hepatotoksičnosti izazvane lekovima i biljnim dijetetskim suplementima prijavljenih u Republici Srbiji.

Hepatotoxicity is a potential side effect of many drugs (> 1,000), either prescription only or over the counter, as well as herbal dietary supplements [1-3]. Drug induced liver injury is mediated by various mechanisms and may manifest as a wide range of hepatobiliary diseases [1,2,4]. In developed countries, drug induced liver injury is the leading cause of acute hepatic failure [5-7] commonly with fatal outcome. In addition, drug induced hepatotoxicity is a major reason for conducting regulatory measures for safety reasons, including drug withdrawal from the market (e.g. bromfenac, troglitazone, pemoline) [1].

Dietary supplements are not subject to standard regulatory procedure for testing the efficacy, safety and quality, which is compulsory for medicinal products [8]. They are easily available, generally considered safe and increasingly used. However, based on published case reports of liver injuries induced by herbal dietary supplements, concerns for their hepatotoxic potential have been raised [9,10]. Due to their use for self-medication, no standardized composition, and potential for drug interactions, detection of herbal hepatotoxicity is particularly difficult.

Because they are rare or very rare and unpredictable, hepatotoxic reactions remain largely unidentified in clinical trials and are detected during post-marketing monitoring of drugs (phase IV) through the system of spontaneous reporting of adverse reactions [11]. Although reporting of adverse drug reactions is a duty of health care professionals, only a minor part of adverse reactions is documented in this way ('underreporting') [12]. This fact and inadequate quality of reports significantly limit the interpretation of the results obtained from spontaneous reports. However, analysis of large databases of spontaneously reported

adverse reactions enables detection and strengthening of safety signals [13-16]. For that reason, use of high quality databases is very important for this type of research.

It is of particular importance for clinical practice to identify risk factors, such as age, gender, diet, alcohol consumption, underlying diseases, genetic factors, concomitant use of two or more drugs, or concomitant use of drugs and dietary supplements [1]. Most of these factors vary between countries, thus regional differences in hepatotoxic effects of drugs and herbal dietary supplements are expected.

Female gender is generally perceived as a more susceptible to hepatotoxic reactions, but published results regarding female gender as a risk factor for hepatotoxicity are conflicting [17,18]. Some studies suggested strong relationship between severe forms of drug induced hepatotoxicity and female gender [19-21].

In addition, advanced age is also considered to be a risk factor for developing hepatotoxicity due to altered pharmacokinetics, comorbidity and polypharmacy [1]. Patient age is one of the criteria of the CIOMS/RUCAM method for the causality assessment of drug-liver reaction relationship. According to this method, age ≥ 55 is scored as a risk factor [22]. However, this generalized approach is much criticized for the observations that depending on type of administered drug, both very young and elderly patients might be at a higher risk for the onset of drug induced hepatotoxicity [17,18].

Postmarketing researches of the databases of spontaneously reported adverse reactions allow detection of hepatotoxic potential of individual drugs and initiation of appropriate regulatory measures, which is particularly important for new drugs. Except isolated cases or case series, the literature is missing results of herbal hepatotoxicity from the studies using large databases of case reports. Results referring to gender influence on hepatotoxicity are inconsistent, while impact of patient age on hepatotoxicity induced by certain drugs or drug classes is not well understood or it is investigated only from the small data sources. The World Health Organization (WHO) database contains a large number of individual case safety reports, and so far has not been studied for the reporting frequency of drug induced hepatic failure and herbal hepatotoxicity. In addition, no investigation of regional specificities of hepatotoxic cases caused by drugs and herbal dietary supplements recorded in Serbia has been performed.

4. Ciljevi istraživanja/Aims of the research

- Utvrditi koji lekovi/grupe lekova su najčešće bili povezani sa ispoljavanjem teških hepatotoksičnih reakcija u bazi spontanijh prijava SZO i identifikovati neočekivane slučajeve.
 - Utvrditi za koje biljne vrste postoji najveći broj spontanijh prijava hepatobilijarnijh reakcija u bazi SZO i identifikovati neočekivane slučajeve.
 - Ispitati uticaj pola, uzrasta, pratećijh oboljenja pacijenta, upotrebe alkohola, istovremene primene dva ili više lekova, ili istovremene primene lekova i biljniijh dijetetskiijh suplemenata na nastanak teških hepatotoksičnih reakcija na lekove.
 - Ispitati uticaj pola, uzrasta, pratećijh oboljenja pacijenta, upotrebe alkohola, istovremene primene dva ili više biljniijh dijetetskiijh suplemenata, i/ili istovremene primene biljniijh dijetetskiijh suplemenata i lekova na nastanak hepatobilijarnijh poremećaja izazvaniijh biljniim dijetetskiim suplementima.
 - Utvrditi regionalne specifičnosti registrovanog hepatotoksičnog dejstva lekova i biljniijh dijetetskiijh suplemenata u Republici Srbiji.
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- *To determine which drugs/drug classes were the most commonly associated with manifestation of severe hepatotoxic reactions according to the WHO database of spontaneous case reports, and to identify unexpected case.*
- *To determine which herbal species were the most commonly reported for hepatobiliary reactions to the WHO database and to identify unexpected cases.*
- *To investigate influence of patient gender, age, comorbidities, alcohol consumption, concomitant use of two or more drugs, or concomitant use of drugs and herbal dietary supplements, on the onset of severe form of drug induced hepatotoxic reactions.*
- *To investigate influence of patient gender, age, comorbidities, alcohol consumption, concomitant use of two or more herbal dietary supplements, and/or concomitant use of herbal dietary supplements and drugs, on the onset of hepatobiliary reactions induced by herbal dietary supplements.*
- *To determine regional specificities of hepatotoxicity of drugs and herbal dietary supplements recorded in Serbia.*

5. Metodologija naučnog istraživanja/Research methodology

5.1. Istraživanje baza spontano prijavljenih individualnih slučajeva hepatotoksičnosti lekova (*Individual Case Safety Reports – ICSRs*)

U predloženom istraživanju koristiće se dve baze ICSRs, baza SZO i nacionalna baza Republike Srbije. Lekovi će biti klasifikovani prema Anatomsko-terapijskom klasifikacionom (ATC) sistemu [23], dok će se za biljne lekove i/ili biljne dijetetske suplemente koristiti herbalni ATC (HATC) sistem [24]. Neočekivanost slučajeva procenjivaće se u odnosu na referentni Sažetak karakteristika leka (SPC) i objavljenu literaturu.

I Baza podataka Svetske zdravstvene organizacije

Ia U cilju identifikacije lekova koji su izazvali hepatičku insuficijenciju, baza SZO biće pretražena za period od 10 godina. Pretraživanjem će biti izdvojeni slučajevi neželjenih reakcija kodiranih kao „*hepatic failure*“ na nivou *preferred terms* WHO-ART rečnika (*World Health Organization Adverse Reaction Terminology*) [25]. U identifikovanim slučajevima hepatičke insuficijencije analiziraće se dostupne informacije o prijavljenom suspektom leku, polu, uzrastu, pratećim oboljenjima pacijenta, upotrebi alkohola, istovremeno primenjivanim lekovima i/ili biljnim dijetetskim suplemenatima, i zemlji porekla.

Ib U cilju identifikacije biljnih vrsta koje su najčešće delovale hepatotoksično, zbog relativno malog broja ovakvih prijava, baza SZO će biti pretražena na sve hepatotoksične reakcije, za celokupan period od njenog osnivanja. Kao kriterijumi pretraživanja prijavljenih slučajeva hepatotoksičnosti biljnih dijetetskih suplemenata koristiće se: prijavljene suspektne biljne vrste i reakcije kodirane u okviru **hepatobilijarnih poremećaja** („*Hepatobiliary disorders*“) kao klase organskih sistema (*System Organ Class – SOC*) prema Medicinskom rečniku za regulatorne poslove (MedDRA) [26]. U identifikovanim slučajevima analiziraće se dostupne informacije o prijavljenoj suspektnoj biljnoj vrsti, tipovima hepatobilijarnih reakcija, polu, uzrastu, pratećim oboljenjima pacijenta, upotrebi alkohola, istovremeno primenjivanim lekovima i/ili biljnim dijetetskim suplemenatima, i zemlji porekla.

II Baza Nacionalnog centra za farmakovigilancu Agencije za lekove i medicinska sredstva Srbije

U cilju utvrđivanja regionalnih specifičnosti hepatotoksičnog dejstva lekova i biljnih dijetetskih suplemenata u Republici Srbiji, izvršiće se pretraživanje baze Nacionalnog centra za farmakovigilancu (NCF) Agencije za lekove i medicinska sredstva Srbije (ALIMS) za period od njenog osnivanja. Kriterijum pretraživanja će biti prijavljene neželjene reakcije kodirane u okviru **hepatobilijarnih poremećaja** („*Hepatobiliary disorders*“), kao klase organskih sistema (*System Organ Class* – SOC), prema Medicinskom rečniku za regulatorne poslove (MedDRA) [26]. U identifikovanim slučajevima hepatotoksičnosti izazvane lekovima i biljnim dijetetskim suplementima analiziraće se dostupne informacije o prijavljenom suspektom leku, odnosno biljnom dijetetskom suplementu, vrstama hepatobilijarnih reakcija, polu, uzrastu, pratećim oboljenjima pacijenta, upotrebi alkohola, istovremeno primenjivanim lekovima i/ili biljnim dijetetskim suplemenatima, i izveštaču (lekar ili farmaceut).

5.2. Statistička analiza

Statistička analiza vršiće se primenom SPSS 16 softvera (SPSS Software, Chicago, Ill). Osim deskriptivne statistike, koristiće se neparametarski testovi - *Binomial test* i *Chi-square test*.

5.1. Investigation of databases of spontaneous individual case safety reports (ICSRs) on drug induced hepatotoxicity

Two ICSR databases will be used for the proposed research – the WHO database and the national database of the Republic of Serbia. Drugs will be classified according to the Anatomical Therapeutic Classification (ATC) system [23], and Herbal ATC (HATC) system will be used for the herbal medicines and/or herbal dietary supplements [24]. Unexpectedness of the cases will be evaluated in relation to the reference summary of product characteristics (SPC) and published literature.

I Database of the World Health Organization

Ia *In order to identify cases of hepatic failure, the WHO database will be retrieved for the ten-year period. Search criteria will be reported adverse reaction coded as "hepatic failure" at the level of preferred terms using the World Health Organization Adverse Reaction Terminology (WHO-ART) [25]. In the cases identified, available information on reported suspected drug, patient gender, age, comorbidities, alcohol consumption, concomitant drugs and/or herbal dietary supplements, and reporting country, will be analyzed.*

Ib *In order to identify herbal species the most commonly reported for hepatotoxicity, the WHO database will be retrieved for all hepatotoxic reactions reported during the entire period since its establishment because of relatively small number of these reports. Search criteria will be reported suspected herbal species and all the coding terms for reactions within the System Organ Class (SOC) "Hepatobiliary disorders" according to the Medical Dictionary for Regulatory Affairs (MedDRA) [26]. In the cases identified, available information on reported herbal species, type of hepatobiliary reactions, patient gender, age,*

comorbidities, alcohol consumption, concomitant drugs and/or herbal dietary supplements, and reporting country, will be analyzed.

II Database of the National Centre of Pharmacovigilance within the Medicines and Medical Devices Agency of Serbia

In order to identify regional specificities of hepatotoxicity induced by drugs and herbal dietary supplements in Serbia, the database of the National Centre of Pharmacovigilance (NCP) within the Medicines and Medical Devices Agency of Serbia (ALIMS) will be retrieved for the entire period since its establishment. Search criteria will be all the coding terms for reported reactions within the System Organ Class (SOC) "Hepatobiliary disorders" according to the Medical Dictionary for Regulatory Affairs (MedDRA) [26]. In the cases identified, available information on reported drug or herbal dietary supplement, type of hepatobiliary reactions, patient gender, age, comorbidities, alcohol consumption, concomitant drugs and/or herbal dietary supplements, and reporter (physician or pharmacist), will be analyzed.

5.2. Statistical analysis

Statistical analysis will be performed by using the SPSS 16 software package for Windows (SPSS Software, Chicago, Ill). Beside descriptive statistics, nonparametric tests – the Binomial test and the Chi-square test will be applied.

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7. Očekivani rezultati/Expected results

Ovim istraživanjem će se utvrditi koji lekovi, odnosno grupe lekova, najčešće ispoljavaju hepatotoksično dejstvo i identifikovati neočekivani slučajevi. Takođe, biće identifikovane biljne vrste koje mogu delovati hepatotoksično, o čemu za sada postoje oskudni podaci. Dobijeni rezultati će biti značajni za sagledavanje uticaja pojedinih faktora rizika na ispoljavanje hepatotoksičnog dejstva lekova i biljnih dijetetskih suplemenata, kao što su pol, uzrast, prateća oboljenja pacijenta, upotreba alkohola, polifarmacija. Dodatno, istraživanje sprovedeno u okviru ove doktorske teze ukazaće na sličnosti i razlike između slučajeva hepatotoksičnih reakcija izazvanih lekovima i biljnim dijetetskim suplementima u Srbiji u odnosu na druge zemlje sa razvijenijim sistemima farmakovigilance.

In this research, drugs and drug classes the most commonly associated with hepatotoxicity will be determined and unexpected cases identified. Furthermore, herbal species associated with hepatotoxic potential will be identified, for which there is only scant data. Obtained results will be important for understanding the impact of certain risk factors

on the manifestation of hepatotoxic effects of drugs and herbal dietary supplements, such as gender, age, comorbidities, alcohol consumption, polypharmacy. In addition, this PhD thesis will point out the similarities and differences between the cases of hepatotoxicity caused by drugs and herbal dietary supplements in Serbia compared to other countries with developed systems of pharmacovigilance.

D. Zaključak/Conclusion

Na osnovu podataka koje je kandidat Marija Petronijević navela u prijavi doktorske disertacije i pregleda dostupne literature, Komisija smatra da je predložena tema doktorske disertacije naučno zasnovana i dobro obrazložena. Metodologija u potpunosti odgovara ciljevima ispitivanja.

Predloženo ispitivanje će pružiti dodatne informacije o hepatotoksičnom potencijalu lekova koje nisu bile dostupne nakon sprovedenih kliničkih studija. Takođe, dodatne informacije o bezbednosnom profilu lekova koji u farmakoterapijskoj praksi Srbije najčešće dovode do medikamentoznih oštećenja jetre doprineće sagledavanju regionalnih specifičnosti, o čemu do sada nije bilo podataka. Rezultati dobijeni pretraživanjem globalne baze SZO dodatno će ukazati na geografske specifičnosti hepatotoksičnog dejstva lekova i biljnih dijetetskih suplemenata. S obzirom da će u ovom istraživanju biti korišćena jedna od najvećih baza spontano prijavljenih neželjenih reakcija, baza SZO, prikupljeni podaci će omogućiti dalje rasvetljavanje uticaja pola, uzrasta, komorbiditeta, polifarmacije i drugih faktora rizika na nastanak hepatičke insuficijencije izazvane primenom pojedinačnih lekova/grupa lekova. Kako do sada, osim procene pojedinačnih slučajeva ili serije slučajeva, nije bilo sistematskih istraživanja hepatotoksičnosti biljnih lekova i biljnih dijetetskih suplemenata zasnovanih na većim bazama spontanih prijava, rezultati ovog istraživanja doprineće boljem sagledavanju rizika od njihove primene. Pošto je reč o proizvodima koji se najčešće koriste u sklopu samomedikacije, informacije o njihovom bezbednosnom profilu su od posebnog značaja za javno zdravlje. Značaj ovog istraživanja ogleda se i u tome što će njegovi rezultati omogućiti postavljanje hipoteza za buduće kontrolisane studije.

Prema mišljenju članova Komisije, tema doktorske disertacije je aktuelna i opravdana. Komisija predlaže Nastavno-naučnom veću da Mariji Petronijević odobri izradu ove doktorske disertacije pod izmenjenim naslovom „**Farmakoepidemiološka studija spontano prijavljenih hepatotoksičnih reakcija na lekove i biljne dijetetske suplemente**“, jer se njime definiše dizajn studije i vrsta korišćenih podataka.

According to data presented by candidate Marija Petronijevic in her doctoral dissertation application, and literature review, Commission finds that proposed topic of doctoral dissertation is scientifically based. The topic of dissertation proposed is adequately justified with references to the literature, and planned methodology is in line with defined aims of research.

The proposed research will provide additional information about the hepatotoxic potential of drugs that was not obtained from conducted clinical trials. Furthermore, additional information on the safety profile of drugs the most commonly associated with liver injuries in the Serbian pharmacotherapeutic practice will contribute to understanding of regional specificities, for which so far there are no data. The results obtained from the global WHO database will additionally indicate the geographical features of hepatotoxicity of drugs

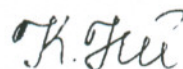
and herbal dietary supplements. Since one of the largest database of spontaneously reported adverse reactions (the WHO database) will be used, the data collected in this study will enable further elucidation of the impact of gender, age, comorbidities, polypharmacy and other risk factors on the onset of hepatic failure induced by particular drugs/drug classes. With exception of isolated cases or series of cases, there were no systematic studies of hepatotoxicity of herbal medicines/dietary supplements using large databases of spontaneous reports; thus, the results of this research will contribute to better understanding of the risks associated with their use. Since these products are commonly used for self-medication, information on their safety is of special interest for the public health. The significance of this research is also reflected in the hypothesis generation on the basis of obtained results for the future controlled studies.

In the opinion of the Commission members, topic of doctoral dissertation is actual and justified. The Commission recommends to the Academic Council to approve Marija Petronijevic performing this doctoral dissertation under the amended title **"Pharmacoepidemiological study of spontaneously reported hepatotoxic reactions of drugs and herbal dietary supplements"**, as it defines study design and source of analyzed data.

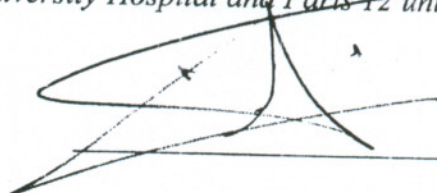
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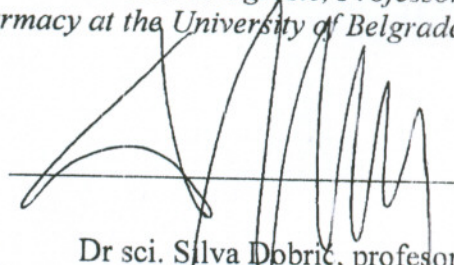
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