Bolnička farmacija

Hospital Pharmacy

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POTENCIJALNE LEK-BOLEST INTERAKCIJE KOD HOSPITALIZOVANIH PACIJENATA

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U terapiji kardiovaskularnih oboljenja koriste se lekovi koji dokazano utiču na poboljšanje kvaliteta života, morbiditet i mortalitet. Međutim, negativni ishodi terapije mogu nastati kao posledica neodgovarajućeg izbora leka za individualnog pacijenta i pojave lek-bolest interakcija sa postojećim morbiditetima. Cilj istraživanja bila je identifikacija lek-bolest interakcija (kontraindikacija i mera opreza, KI i MO) kod hospitalizovanih pacijenata sa primarno kardiovaskularnim oboljenjima, određivanje prevalence i prediktora zanjihovu pojavu.

Podaci o pacijentima prikupljeni su iz medicinske dokumentacije. Za procenu terapije i identifikaciju prisustva KI i MO korišćeni su podaci iz Sažetka karakteristika o leku (SmPC, ALIMS). Statistička analiza urađena je pomoću SPSS softvera.

U istraživanje je uključeno 100 pacijenata, većinu su činile osobe starije od 65 godina (77%) i muškarci (55%). Prosečan broj lekova po pacijentu iznosio je 9 (interkvartalni opseg 6-11), a najčešći morbiditeti bili su hipertenzija i srčana insuficijencija. MO su bile identifikovane kod 92% pacijenata, a KI kod 27% pacijenata. Kao prediktori za pojavu MO identifikovani su levofloksacin, atorvastatin, broj lekova i broj indikacija. Prediktori za pojavu KI bili su furosemid i verapamil. Poseban oprez potreban je kod pacijenata sa hroničnom bubrežnom insuficijencijom koji primaju ceftriakson, i pacijenata sa dijabetes melitusom tip 1, zbog podataka da statini mogu uticati na kontrolu glikemije. Verapamil ne treba primenjivati kod akutnog infarkta miokarda komplikovanog bradikardijom, značajnom hipotenzijom ili insuficijencijom leve komore, dok je furosemid kontraindikovan kod pacijenata sa hipovolemijom ili dehidratacijom.

Procenjena prevalenca MO i KI ukazuje na potrebu pažljive procene terapije pacijenta i razmatranje terapijskih alternativa, prema prisutnim komorbiditetima. MO zahtevaju dodatno praćenje efikasnosti i bezbednosti terapije, dok kod KI rizik od primene leka prevazilazi korist.

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

POTENTIAL DRUG-DISEASE INTERACTONS IN HOSPITALIZED PATIENTS

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Drugs used in the treatment of cardiovascular diseases improve quality of life, morbidity and mortality rates. However, adverse outcomes may appear as a consequence of inappropriate prescribing for an individual patient or drug interactions with coexisting morbidities. The aim of the study was to identify drug-disease interactions (contraindications and precautions) in hospitalized patients with primarily cardiovascular disease, and to estimate its prevalence and predictors.

Data was obtained from medical charts. Summary of product characteristics (SmPC, available from Medicines and Medical Devices Agency of Serbia) were used for therapy assessment and identification of contraindications and precautions. Descriptive and statistical analysis was performed by SPSS software.

Out of 100 patients included in the study, most of them were elderly (77%) and male (55%). Median number of drugs per patient was 9 (interquartile range 6-11), and the most common morbidities were hypertension and congestive heart failure. Precautions were identified in 92% of patients, and contraindications in 27% of patients treated. Predictors for appearance of precautions were levofloxacin, atorvastatin, number of drugs administered and number of indications. Predictors for appearance of contraindications were furosemide and verapamil. Special caution is warranted for patients with chronic renal failure who were administered ceftriaxone, and patients with type 1 diabetes, because of possible statin effect on blood glucose. Verapamil should not be administered to patients with acute cardiac arrest complicated by bradycardia, significant hypotension or left ventricle failure, while furosemide is contraindicated in hypovolemic and dehydrated patients.

Estimated prevalence of precautions and contraindications points to the necessity of careful therapy assessment and consideration of therapeutic alternatives based on present comorbidities. Precautions require additional efficacy and safety therapeutic monitoring and when contraindications are present, risk assessment of drug use outweighing the benefit.

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STUDIJA PRAKTIČNE STABILNOSTI CITOTOKSIČNIH LEKOVA - ULOGA FARMACEUTA

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Citotoksični lekovi pored industrijske proizvodnje zahtevaju i rekonstituciju/razblaživanje u uslovima bolničke apoteke. Proizvođači kao stabilnost citotoksičnog leka navode period od 24h nakon otvaranja, sagledan samo sa aspekta mikrobiološke stabilnosti, ne uzimajući u obzir hemijsku stabilnost lekova. Kada se priprema lekova vrši pod aseptičnim uslovima, rok upotrebe pripremljenog leka se može produžiti. Cilj studije bio je da se u uslovima bolničke apoteke ispita praktična stabilnost rastvora 5-fluorouracila (5-FU), koncentracije 1,5 mg/ml.

Fizičko ispitivanje - ispitivanje bistrine i potenciometrijsko određivanje pH vrednosti; hemijsko ispitivanje - određivanje sadržaja rastvora 5-FU, metodom tečne hromatografije pod visokim pritiskom (HPLC); mikrobiološko ispitivanje - zasejavanje rastvora 5-FU na hranljive podloge.

Ispitivanjem fizičkih karakteristika pripremljenog rastvora 5-FU nije uočena nestabilnost. Rastvor je ostao bistar. Potenciometrijskim određivanjem pH vrednosti ispitivani rastvor 5-FU imao je pH= 9,01-9,07 što odgovara intervalu pH vrednosti u kom je rastvor najstabilniji. Određivanje sadržaja 5-FU vršeno je HPLC metodom, u vremenskim intervalima (1.-5., 7., 10. i 28. dan). Procentualna zavisnost koncentracije 5-FU od vremena, iznosi 96,60% - 99,93%, što ukazuje da je stepen degradacije aktivne supstance mali, te se rastvor može smatrati hemijski stabilnim u roku od 28 dana. Ispitivanje mikrobiološke stabilnosti vršeno je zasejavanjem na podloge 28. dana ispitivanja. Nakon inkubacije na temperaturi od 37°C i vremenu od 24 do 48h, podloge su ostale sterilne. Ovim je potvrđena mikrobiološka stabilnost preparata.

Na osnovu dobijenih rezultata može se zaključiti da je pripremljeni rastvor 5-FU ostao stabilan 28 dana.

PRACTICAL STABILITY STUDY OF CYTOTOXIC DRUGS - THE ROLE OF PHARMACIST

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In addition to industrial production cytotoxic drugs require reconstitution/dilution under the pharmacy conditions. As the stability of the cytotoxic drug, manufacturers specify a period of 24 hours after opening, seen only from the aspect of microbiological stability, not considering the chemical stability of medicines. When the preparation of medicinal products is carried out under aseptic conditions, the shelf-life of the preparation may be extended. The aim of the study was to evaluate the practical stability of 5-fluorouracil (5-FU) solution, concentration of 1.5 mg/ml under the hospital pharmacy conditions.

Clearance testing and potentiometric determination of pH were used as physical stability tests. For chemical testing, 5-FU content was determined by high-performance liquid chromatography (HPLC) method. Microbiological testing was incubation of 5-FU solution into the substrates.

No physical instability of 5-FU solution was detected. The solution remained clear. By potentiometric pH determination, the test 5-FU solution had pH = 9.01 – 9.07 which corresponds to the pH value interval in which the drug is the most stable. 5-FU content was determined at appropriate time intervals (1st-5th, 7th, 10th and 28th day). The content of 5-FU in solution over time was 96.60% - 99.93%, indicating that the degradation of the active substance is small, and the solution can be considered chemically stable. The microbiological stability test was performed by seeding on the substrates on the 28th day of the test. After incubation at a temperature of 37°C for 24 to 48 hours, the substrates remained sterile. This confirmed the microbiological stability of the preparation.

Based on the results obtained, it can be concluded that the prepared 5-FU solution remained stable for 28 days.

PREGLED TERAPIJE KOD PACIJENATA SA OSLABLJENOM BUBREŽNOM FUNKCIJOM

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Serumski kreatinin i njegov renalni klirens se najčešće koriste kao skrining test za procenu bubrežne funkcije. Različite prediktivne jednačine su razvijene sa ciljem poboljšanja karakteristika kreatinina kao markera bubrežne funkcije. Značaj što preciznije procene bubrežne funkcije ogleda se u individualizaciji terapije pacijenata. Cilj rada bila je procena bubrežne funkcije različitim metodama uz pregled propisane terapije.

Sprovedeno je retrospektivno istraživanje na odseku za nefrologiju internog odeljenja Opšte bolnice u Vranju. Prikupljeni su demografski, klinički, terapijski i laboratorijski podaci, uvidom u medicinsku dokumentaciju. Primenjene su tri jednačine (MDRD, CKD-EPI, MCQ). Sve prikupljene informacije su statistički obrađene u PASW 18.0 (SPSS Inc., Chicago, IL, USA).

U studiju je uključeno 104 pacijenta prosečne starosti 64,55±1,16. Srednja vrednost serumskog kreatinina bila je 332±24,54 μmol/L. Najviše pacijenata je imalo treći stadijum hronične bolesti bubrega. Postoji visok stepen korelacije između serumskog kreatinina i korišćenih jednačina (rs= -0,978, -0,976, -0,957; p<0,001). Visok stepen asocijacije postoji između MDRDi CKD-EPI formule uklasifikaciji pacijenata sa GFR manjomod 60 mL/min (X2 = 85,79, p<0,001). Najčešće primenjeni lekovi bili su diuretici Henleove petlje (81,7%), blokatori kalcijumovih kanala (67,3%), blokatori beta adrenergičkih receptora(62,5%), antiagregacioni lekovi (56,7%) i inhibitori angiotenzin konvertujućeg enzima (45,2%). Od 26 pacijenata, 15 je imalo prekoračenu dozu ramiprila (57,7%). Kod 15 od 27 pacijenata primenjen je lerkanidipin, iako primena nije bila preporučena.

Glomerularna filtracija procenjena MDRD jednačinom je u najvećoj korelaciji sa serumskim kreatininom i kliničkom procenom stadijuma bubrežne slabosti. Lerkanidipin i ramipril su lekovi kod kojih je najčešće dolazilo do prekoračenja doziranja. Kako je ovo često zanemareno u praksi, klinički farmaceut može doprineti značajnom smanjenju terapijskih problema u vezi sa lekom i poboljšanju kliničkih ishoda.

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MEDICATION REVIEW IN PATIENTS WITH DECREASED RENAL FUNCTION

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Serum creatinine and it's renal clearance are the most common parameters used as a screening test for renal function evaluation. Different predictive equations are developed to improve characteristics of creatinine function indicator. Importance of accurate evaluation of the renal function is reflected in individualization of drug therapy. The aim of this study was an assessment of renal function by using different methods and conducting medication review.

A retrospective study was conducted by Nephrology Division at Vranje General Hospital. Demographic, clinical and laboratory data were collected by inspecting medical records. Three equations were used (MDRD, CKD-EPI, MCQ). Statistical analysis was performed with PASW 18.0 (SPSS Inc., Chicago, IL, USA).

One hundred and four patients were included in the study, mean age 64.55±1.16. The mean SCr value was 332 ± 24.54 μmol/L. Most of the patients had third stage chronic kidney disease. The strong correlation exists between serum creatinine and used equations (rs= -0.978, -0.976, -0.957; $p<0.001$). There is a strong association between MDRD and CKD-EPI equations in the classification of patients with GFR lower than 60 mL/min ($X2 = 85.79$, $p<0.001$). Most frequently used drugs were Loop diuretics (81.7%), Calcium channel blockers (67.3%), β-blockers(62.5%), antiplatelet drugs (56.7%) and angiotensin-converting-enzyme inhibitors (45.2%). 15 out of 26 patients had a ramipril overdose (57.7%). For 15 out of 27 patients the use of lercanidipine was not recommended.

Glomerular filtration evaluated by MDRD equation showed the highest correlation with serum creatinine and clinical evaluation of the stage of renal failure. Lercanidipine and ramipril are identified as the most commonly overdosed drugs. As this is frequently neglected in practice, the clinical pharmacist can contribute to the significant decrease in drug-related problems and improvement of clinical outcomes.

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POVEZANOST LEK-LEK INTERAKCIJA SA HIPER/HIPOKALIJEMIJOM KOD HOSPITALIZOVANIH PACIJENATA SA KARDIOVASKULARNIM BOLESTIMA

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Lek-lek interakcije (LLI) su značajan uzrok neželjenih ishoda, zbog promena u efikasnosti i bezbednosti terapije. Cilj studije bila je procena prevalence hiper/hipokalijemije (vrednosti van opsega 3,8-5,5 mmol/L), kao i povezanosti LLI sa njihovom pojavom.

Podaci o pacijentima preuzimani su iz medicinske dokumentacije, u trenutku prijema na odeljenje kardiologije. *LexiInteract*® je korišćen za identifikaciju LLI, dok je statistička analiza izvršena pomoću programa SPSS®.

Istraživanje je obuhvatilo 110 pacijenata, prosečne starosti 71±10 godina. Najčešće dijagnoze bile su hipertenzija (61%), srčana insuficijencija (49%), aritmija (43%) i dijabetes (36%). Oslabljena bubrežna funkcija zabeležena je kod 14% pacijenata, ali nije bila statistički značajno povezana sa pojavom hiper/hipokalijemije. Vrednost serumskog kalijuma bila je van opsega kod 24 pacijenta (22%). U ovoj grupi pacijenata bio je statistički značajno veći broj lekova i C interakcija ($p<0,05$). Pacijenti koji su primenjivali kombinaciju inhibitori angiotenzin-konvertujućeg enzima/tiazidnih diuretika imali su 4,82, i digoksin/spironolakton 4,95 puta veću šansu da imaju hiperkalijemiju ($p<0,05$). Koterapija hipotenzivni lekovi/pentoksifilin i teofilin/amjodaron nosila je 11,88 i 7,13 puta veći rizik za pojavu hipokalijemije, respektivno, u poređenju sa pacijentima koji nisu bili izloženi ovim LLI ($p<0,01$). Rezulati su bili korigovani za starost, pol, broj lekova i komorbiditete, izražene preko *Charlson Comorbidity Index*-a. Sa svakim povećanjem broja lekova, verovatnoća za pojavu hiperkalijemije povećava se za 26%, a za pojavu hipokalijemije 30%.

Prevalenca odstupanja serumskog kalijuma iz referentnog opsega kod pacijenata hospitalizovanih zbog kardiovaskularnih bolesti procenjena je na 22%. LLI koje su bile povezane sa pojavom hiper/hipokalijemije, svrstane su u klasu C, za koje je potreban češći monitoring pacijenta. Svako uvođenje novog leka u terapiju povećava rizik za pojavu hiper/hipokalijemije. Posledice mogu biti veoma značajne kod pacijenata sa prisutnim kardiovaskularnim oboljenjem. Alati za identifikaciju LLI mogu značajno doprineti kvalitetu zdravstvene zaštite, kroz procenu rizika od pojave hiper/hipokalijemije i preporukama za monitoring pacijenta.

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DRUG-DRUG INTERACTIONS ASSOCIATED WITH HYPER- AND HYPOKALEMIA IN HOSPITALISED CARDIOVASCULAR DISEASE PATIENTS

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Drug-drug interactions (DDIs) are one of the causes of adverse therapy outcomes through deteriorated efficacy or safety. The study investigated the prevalence of serum potassium level out of range (3.8-5.5 mmol/L), as well as the association of DDIs with the identified high/low potassium.

Data were obtained from medical records at the admission on the Cardiology ward. LexiInteract® was used as the screening tool for DDIs. Statistical analysis was performed by SPSS®software.

A total of 110 patients entered the analysis, with mean age 71±10 years. Mean diagnoses were hypertension (61%), heart failure (49%), arrhythmia (43%), and diabetes (36%). Decreased renal function was noted for 14% patients, whereas it was not significantly associated with hyper/hypokalemia. Patients with potassium imbalance (N=24, 22%) had significantly higher number of drugs, and higher number of C class DDIs, compared to patients with normal potassium. Patients taking angiotensin-converting enzyme inhibitors/thiazide diuretics were 4.82, and digoxin/spironolactone 4.95 times more likely to have hyperkalemia ($p<0.05$). Patients with blood pressure lowering agents/pentoxifylline and theophylline/amiodarone were 11.88 and 7.13 times more likely to have hypokalemia, respectively ($p<0.01$). In both analyses, odds ratios were adjusted for age, gender, number of drugs and comorbidity, expressed by Charlson Comorbidity Index. With each increase in number of drugs, the odds ratio for hyperkalemia increased for 26%, and 30% for hypokalemia.

The prevalence of serum potassium imbalance in patients hospitalized for cardiovascular disease, was estimated to 22%. DDIs identified to be significantly associated with hyper/hypokalemia were in C class, which require only patients monitoring. Each introduction of new drug in the cardiovascular disease therapy increases the likelihood for potassium levels being out of range. DDI screening tools may be beneficial in assessing the patients risk for hyper/hypokalemia, and may help in awareness for patients monitoring.

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USAGLAŠENOST TERAPIJE KOD STARIJIH HOSPITALIZOVANIH KARDIOLOŠKIH PACIJENATA SA START/STOPP KRITERIJUMIMA

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Populacija starijih od 65 godina je pod povećanim rizikom od neodgovarajuće upotrebe lekova, zbog promena u fiziologiji, farmakokinetici i farmakodinamici leka, kao i prisustvu polimorbiditeta i polifarmacije. Primena validiranih instrumenata *Screening Tool of Older Person's Prescriptions* (STOPP) i *Screening Tool to Alert doctors to Right Treatment* (START) predstavlja značajnu alatku za procenu prevalence i predikciju terapijskih problema u ovoj populaciji pacijenata. Cilj istraživanja bila je procena prevalence i identifikacija prediktora START/STOPP kriterijuma kod starijih hospitalizovanih pacijenata sa kardiovaskularnim bolestima.

Demografski, klinički i podaci o terapiji prikupljeni su iz medicinske dokumentacije pacijenata hospitalizovanih na odeljenju kardiologije KBC „Bežanijska Kosa". Deskriptivna i statistička analiza urađena je pomoću SPSS® softvera.

Populacija je obuhvatila 77 pacijenata, većinom muškaraca (53%). Prosečan broj lekova po pacijentu iznosio je 9. Prevalenca START kriterijuma bila je 80,5% (62 pacijenata) i približno ista prevalenca STOPP kriterijuma od 79,2% (61 pacijent). Ukupno je identifikovano 117 START i 141 STOPP kriterijuma; prosečan broj po pacijentu (opseg) iznosio je 1,52 (0-4), odnosno 1,83 (0-7). Najčešći START kriterijumi bili su upotreba inhibitora angiotenzin-konvertujućeg enzima (ACEI) kod hipertenzije i srčane insuficijencije i primena statina i aspirina u sekundarnoj prevenciji infarkta miokarda. Najčešći STOPP kriterijumi bili su primena digoksina iznad 0,125 mg/dan, primena omeprazola duže od 8 nedelja i kombinacija dva ACEI u terapiji. Logistička regresiona analiza identifikovala je broj lekova u toku hospitalizacije, broj indikacija, prisustvo dijagnoze hipertenzije i izosorbid-mononitrata kao prediktore pojave START, dok je ukupan broj lekova pokazao statistički značajnu povezanost i sa pojavom STOPP kriterijuma.

Utvrđena je visoka prevalenca START/STOPP kriterijuma u ispitivanoj populaciji pacijenata i identifikovani su prediktori njihove pojave. Primenom START/STOPP kriterijuma klinički farmaceut može značajno doprineti proceni usaglašenosti terapije i predlaganju intervencija što dalje može doprineti minimalizaciji neželjenih događaja povezanih sa neodgovarajućom upotrebom lekova.

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THE ASSESSMENT OF THERAPY IN ELDERLY HOSPITALIZED CARDIOVASCULAR PATIENTS USING START/STOPP CRITERIA

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Elderly patients are under increased risk of inappropriate medication use, due to physiological, pharmacokinetic and pharmacodynamic changes, as well as the polimorbidity and polypharmacy. Use of validated instruments of Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) presents a valuable tool for assesing drug-related problems in this population. The study aimed to assess the prevalence and predictors of START/STOPP criteria in elderly hospitalized patients with cardiovascular disease.

Data was collected from medical documentation of patients hospitalised on cardiology ward of UMHC Bežanijska Kosa. Descriptive and statistical analysis was performed by SPSS® software.

The population included 77 patients, predominantly men (53%). Average number of drugs per patient was 9. The prevalence of START criteria was around 80.5% (62 patients), and STOPP criteria 79.2% (61 patient). In total, there were 117 START and 141 STOPP criteria identified; average number (range) of 1.52 (0-4) and 1.83 (0-7) respectively. The most common START criteria included use of angiotensin-converting enzyme inhibitors (ACEI) for hypertension and heart failure and statins and aspirin for secondary prevention of myocardial infarction. Among STOPP criteria, the most common ones were use of digoxin in dose higher than 0.125 mg/day, omeprazole longer than 8 weeks and combination of two ACEI in therapy. Logistic regression analysis determined number of drugs during hospitalization, number of indications, hypertension diagnosis and use of isosorbide mononitrate as predictors of START, whereas the predictor of STOPP criteria was total number of drugs.

A high prevalence of START/STOPP criteria and predictors of their appearance were identified. By using START/STOPP criteria in practice, a clinical pharmacist can significantly contribute to the assessment of therapy and suggesting the interventions which can minimize adverse events related to inappropriate drug use.

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SPROVOĐENJE FARMACEUTSKE ZDRAVSTVENE ZAŠTITE U CILJU UNAPREĐENJA ADHERENCE PACIJENATA SA HRONIČNOM OPSTRUKTIVNOM BOLEŠĆU PLUĆA I ASTMOM

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Postizanje kontrole astme i HOBP su glavni ciljevi terapije ovih bolesti jer je kod većine pacijenata suboptimalna usled neadekvatne inhalacione tehnike i niskog stepena adherence. Cilj ovog istraživanja je ispitati doprinos pružanja koncepta farmaceutske zdravstvene zaštite (FZZ) edukaciji pacijenata sa astmom i HOBP, s osvrtom na pravilnu primenu inhalacione terapije, kao i identifikacija prediktora nižeg stepena adherence i većeg broja grešaka pri primeni različitih tipova uređaja za inhalaciju.

Ispitivanje je sprovedeno na Institutu za pulmologiju Kliničkog centra Srbije u periodu april-maj 2016. godine. Učestvovali su pacijenti sa postavljenom dijagnozom astme ili HOBP, koji samostalno koriste uređaj za inhalacju. Prikupljeni su podaci o pacijentima, tipovima uređaja, prethodnim edukacijama i načinu primene inhalacionih preparata. Pružena im je FZZ, koja je obuhvatala usmene i pisane informacije o prirodi bolesti, farmakoterapiji, nefarmakološkim merama, pravilnoj tehnici inhalacije sa praktičnom demonstracijom.

U istraživanju je učestvovalo 96 pacijenata. Prosečan broj grešaka pri korišćenju MDI je 2,51; Turbuhalera 3,75;Diskusa 3,17; Handihalera 2,93. Prediktori koji statistički značajno koreliraju sa brojem grešaka pri korišćenju inhalacionih preparata su npr. napad dispneje, praktična demonstracija, prekidanje uzimanja leka, edukacija od strane lekara i farmaceuta, itd. Nakon što je FZZ pružena, pacijenti su se izjasnili da bolje vladaju tehnikom inhalacije, koja je statistički značajno unapređena ($r<0,001$), i naglasili su značaj edukacije i pisanog materijala.

Pacijenti sa astmom i HOBP ne vladaju potrebnim znanjem o bolesti i inhalacionoj terapiji. Često greše u tehnici inhalacije. Karakteriše ih nizak stepen adherence. Farmaceuti pružanjem FZZ mogu značajno doprineti poboljšanju na ovim poljima i povećati efikasnost i bezbednost terapije pacijenata obolelih od astme i HOBP.

IMPLEMENTATION OF PHARMACEUTICAL CARE IN ORDER TO IMPROVE ADHERENCE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ASTHMA

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The main objectives of asthma and COPD treatment is achieving the control that is suboptimal in most patients, due to inadequate inhalation techniques and low level adherence. The aim of this study is to evaluate a contribution to pharmaceutical care (PC) by educating patients with asthma and COPD about proper application of inhalation therapy, identification of predictors of lower degree of adherence and a number of errors in the application of different types of inhaler device.

The study was conducted at the Institute of Pulmonology, Clinical Center of Serbia in the period from April to May 2016. The participants were patients with a diagnosis of asthma or COPD, who independently use the inhalation device. Data was collected on patients, the types of devices they use, previous training and manner of applying inhaled preparations. They received PC, which included oral and written information about the nature of disease, pharmacotherapy, non-pharmacological measures, proper inhalation technique which is further covered by a practical demonstration.

Predictors that significantly correlated with the number of errors in the use of inhaled products are attack of dyspnea, practical demonstrations, interrupting the use of medication, education by physicians and pharmacists, etc. After PC had been provided, patients declared that they achieved a better inhalation technique, which was significantly improved ($p<0.001$), and they stressed the importance of training and written materials

Patients with asthma and COPD often make mistakes in inhalation technique because they lack knowledge about the disease and inhalation therapy. Pharmacists can significantly increase the efficiency and safety of their treatment by providing PC.

ANALIZA FARMAKOKINETSKIH PARAMETARA 25-HIDROKSI VITAMINA D KOD STUDENATA BIOMEDICINSKIH NAUKA: POPULACIONI PRISTUP

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Vitamin D je u fokusu istrazivanja tokom poslednjih nekoliko decenija usled velikog broja pozitivnih efekata koje ostvaruje u humanom organizmu. Rezultati epidemioloških studija širom sveta ukazuje na epidemijske razmere hipovitaminoze D i na značaj adekvatne suplementacije. Cilj našeg istraživanja bio je da identifikujemo varijable koje mogu da utiču na vrednost klirensa 25-hidroksi vitamina D u zdravoj populaciji i da definišemo populacioni farmakokinetski model klirensa.

Studijski uzorak obuhvatao je 86 studenata Fakulteta medicinskih nauka, Univerziteta u Kragujevcu u Srbiji. Istraživanje je sprovedeno tokom prolećnog perioda i svaki ispitanik je vodio dnevnik ishrane i upisivao koliko vremena je provodio na suncu dnevno tokom perioda od mesec dana. Plazmatska koncentracija 25-hidroksivitamin D kod ispitanika određivana je pomoću metode visoko efikasne tečnehromatografije sa UV detektorom. Nelinearno modelovanje kombinovanh efekata (NONMEM) je korišćeno za populacionu analizu podataka (subrutina ADVAN 1, ver 5,level 1.1).

Od dvanaest ispitivanih faktora (demografski, biohemijski, nutritivne i životne navike) u finalnom populacionom farmakokinetičkom modelu dve kovarijante su pokazale značajan uticaj na vrednost klirensa i to su bile prosečna vrednost vitamina D unetog putem hrane (DD) i vrednost fosfata u serumu (PHO). Smanjenje inter- i intra-individualne varijabilnosti od baznog do finalnog modela je iznosila 10,27 i 7,19 %, respektivno. Jednačina finalnog modela je glasila CL(L/h) = 0,0711+ 0,738 * DD + 0,618 * PHO. Ovo je prva analiza farmakokinetskog modela 25-hidroksi vitamin D kod zdravih odraslih osoba u Evropskom regionu. Studije koje su ispitivale prosečan unos vitamina D putem hrane u Evropi beležile su slične vrednosti koje su ispod evropskih preporuka. Rezultati jasno ukazuju na dve varijable koje treba uzeti u razmatranje prilikom određivanja suplementacione doze vitamina D u zdravoj populaciji.

ANALYSES OF PHARMACOKINETICS PARAMETERS OF 25-HYDROXY VITAMIN D IN BIOMEDICAL STUDENTS: POPULATION APPROACH

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Vitamin D has been in a focus of research for over several decades due to large numbers of positive effects in the human organism. Results from epidemiological studies, all over the world, indicate epidemic form of hypovitaminosis D and importance of vitamin D supplementation in adequate dose. Our research had aim to identify the most important covariates that could influence on clearance value of 25-hydroxy vitamin D in healthy population and to build up population pharmacokinetics models for clearance.

Study sample included 86 students from Faculty of Medical Sciences, University of Kragujevac, Serbia. Research was performed during spring and every participant was taken food diary and sun exposure report during one month. The plasma concentrations of 25-hydroxyvitamin D were measured by using isocratic high performance liquid chromatography system with UV detection. Non-linear mixed-effect modeling (NONMEM) software (subroutine ADVAN 1,ver. 5, level 1.1) was used for population analysis.

From twelve examined covariates (demographic, biochemical, nutrition and life habits) at final form of population pharmacokinetic model two covariates showed significant influence on clearance and that were mean intake of vitamin D from foods (DD) and value of phosphate in serum (PHO). Decrease of inter- and intra-individual variability was noted from the base model to the final model. The equation of final population model was CL (L/h) = 0.0711+ 0.738 * DD + 0.618 * PHO. This was the first analysis of pharmacokinetics model of 25-hydroxy vitamin D in healthy adults in European region. Several studies that measured intake of vitamin D from food in Europe noted similar value which was under European recommendation. Results clearly pointed out two factors which should be considered at vitamin D supplement dose determination in healthy population.

UTICAJ ANTIPSIHOTIKA U PRVOJ EPIZODI SHIZOFRENIJE NA PROLAKTIN I BIOHEMIJSKE LABORATORIJSKE PARAMETRE

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Shizofrenija je težak i ozbiljan mentalni poremećaj hroničnog karaktera. Antipsihotici su lekovi izbora u tretmanu shizofrenije i veoma su efikasni u tretmanu akutne epizode. Hiperprolaktinemija je endokrinološka neželjena reakcija povezana sa primenom antipsihotika. Cilj ovog rada je da se ispita uticaj antipsihotika (u zavisnosti od primenjenog leka) na nivo prolaktina i vrednosti biohemijskih parametara u krvi, kao jedan od najznačajnijih neželjenih dejstava.

Istraživanje je sprovedeno u Klinici za psihijatrijske bolesti „Dr Laza Lazarević", u kojoj su učestvovali pacijenati kod kojih su dijagnostikovani shizofreni poremećaji (dijagnoze F20.0- F20.9) i koji su prvi put lečeni nekim antipsihotikom. Za prikupljanje podataka korišćene su istorije bolesti i vrednosti laboratorijskih analiza krvi (nivo prolaktina, krvna slika, glukoza, urea, kreatinin, proteini, holesterol, trigliceridi, CRP, mokraćna kiselina, transaminaze, γGT, bilirubin, sedimentacija).

U istraživanju je učestvovalo ukupno 52 pacijenta, od toga 26 osoba muškog pola, prosečne starosti 21,75 ± 2,86 godina. Antipsihotike prve generacije primalo je 19,2% pacijenata, dok je antipsihotike druge genaracije primalo 80,8% ispitanika. Pacijenti su bili podeljeni u grupe u zavisnosti koji su lek koristili (haloperidol, risperidon, olanzapin, aripiprazol). U sve četiri grupe ispitanika zapaženo je povećanje vrednosti prolaktina, ali između grupa nije zabeležena statistički značajna razlika. Kod pacijenata koji su primali olanzapin došlo je do statistički značajnog povećanja vrednosti glukoze i ukupnog holesterola u krvi. Zapaženo je i povećanje u vrednostima AST-a, ALT-a i γGT-a, kod bolesnika lečenih olanzapinom i risperidonom, a kod onih lečenih aripiprazolom samo u vrednostima γGT-a.

Kontinuirano praćenje laboratorijskih parametara, uključujući i vrednosti prolaktina, kod pacijenta koji se leče antipsihoticima, su neophodni od samog početka terapije zbog pojave mogućih neželjenih dejstava ovih lekova a u cilju korigovanja doze terapije ili zamene drugim lekom.

THE EFFECT OF ANTIPSYCHOTIC DRUGS IN THE FIRST EPISODE OF SCHIZOPHRENIA ON PROLACTIN AND BIOCHEMICAL LABORATORY PARAMETERS

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Schizophrenia is a difficult and serious mental disorder of chronic character. Antipsychotics are medication choices in the treatment of schizophrenia and are very useful in the treatment of acute episodes. Hyperprolactinaemia is an endocrinologically undesirable reaction associated with the use of antipsychotics. The aim of this paper is to investigate the effect of antipsychotics (depending on the drug) on the level of prolactins and the value of biochemical analyses of the blood, as one of the most significant adverse effects.

The research was conducted at the „Dr Laza Lazarevic" Clinic for PsychiatricDisorders, who were diagnosed with schizophrenia (F20.0-F20.9 diagnosis) and treated for first time by some antipsychotics. Disease histories and laboratory analysis values in the blood (prolactin level, blood cells, glucose, urea, creatinine, proteins, cholesterol, triglycerides, CRP, uric acid, transaminases, γGT, bilirubin, sedimentation) have been used to collect data.

A total of 52 patients were enrolled in the study, of which 26 were male, average age 21.75 ± 2.86 years. In the study, 19.2% of patients received first generation antipsychotics, while 80.8% of patients received the second generation antipsychotics. Patients were divided into groups dependently on drugs they used (haloperidol, risperidone, olanzapine, aripiprazole). In the value of prolactin, a statistically significant difference was not observed among the groups, but in all four groups of patients, an increase in prolactin levels was observed. In patients receiving olanzapine there was a statistically significant increase in blood glucose and total cholesterol levels. An increase in the levels of AST, ALT and γGT was found in olanzapine and risperidone treated groups, and in aripiprazole treted group it was observed in the values of γGT only.

Continuous monitoring of laboratory parameters and prolactin values in an antipsychotic patient is necessary from the very beginning due to possible adverse effects of these drugs in order to correct their dose or to replace them with another drug.