Prikaz slučaja / Case report

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Supstituciona terapija metadonom – dijagnostički izazovi u ordinaciji lekara opšte medicine

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Methadone substitution therapy - diagnostic challenges in the general practice

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Sažetak

Uvod. Zavisnost od opijata je hronično stanje povezano s različitim morbiditetima. Metadonska supstituciona terapija opijatskog zavisnika u kombinaciji sa socijalnim, zdravstvenim i psihološkim uslugama, *zlatni je standard* u lečenju. Svi opioidi ispoljavaju brojna neželjena dejstva. Oštećenje bubrega kod opijatskih zavisnika može nastati zbog sepse, rabdomiolize, pada glomerularne filtracije, hipotenzije, edema pluća, renalne lipidoze ili amiloidoze.

Prikaz slučaja. Pacijent, 40 godina, na metadonskoj supstitucionoj terapiji, oseća slabost, znojenje, bol u mišićima i visoko je febrilan. U laboratorijskim analizama: kaliemija 9.87 *mmol/L*, urea 18.3 *mmol/L*, kreatinin 268 *µmol/L*, klirens uree 0,20 *ml/s* klirens kreatinina 0,81 *ml/s*, eGFR 23 *ml/min*/1,73m^2, kreatin fosfokinaza 1180 *IU/L*, Hgb 79 *g/L*, Er 2.81x10^{12}/*L*, C-reaktivni protein 13.2 *µg/mL*, Le 7.41x10^9/*L*, PCO_2 41 *mmHg*, 22 HCO_3 *mmol/L* i acidoza pH 7.21. Krvni pritisak 130/80 *mmHg* i srčana frekvencija 64/*min*, na EKG produžen PR interval i visoki *T*-talasi. Lečen je infuzijama kristaloidnih rastvora, 8.4% rastvorom bikarbonata, diureticima, kalcijum glukonatom, kratkodelujućim insulinom, antibioticima i antikoagulansima. Dolazi do normalizacije kalijemije, diureze i regresije promena na elektrokardiogramu. Nakon 24 dana bolničkog lečenja, pacijent je otpušten na kučno lečenje.

Zaključak. Pacijenti na metadonskoj supstitucionoj terapiji imaju povećan rizik od multiplog oštećenja funkcije svih organa. Posebno je ugrožena renalna funkcija. Od izuzetne važnosti je da se među lekarima poveća svest o opasnosti nastanka rabdomiolize kod ovih pacijenata. Redovne laboratorijske analize kod pacijenata na supstitucionoj terapiji metadonom, mogu na vreme da otkriju postojanje akutne i hronične bubrežne komplikacije i omoguće blagovremeno sprovođenje terapije.

Ključne reči: oštećenje bubrega, terapija održavanja, primarna zdravstvena zaštita

Abstract

Introduction. Opioid addiction is a chronic condition related to different morbidities. The methadone substitution therapy of the opioid addict, combined with social, health, and psychological services is a gold standard of the treatment. All opioids display numerous side effects. Kidney damage in opioid addicts is due to sepsis, rhabdomyolysis, decreased glomerular filtration, hypotension, pulmonary edema, renal lipidosis, or amyloidosis.

Case report. The male patient, 40, on methadone substitution therapy feels weak, sweats excessively. Lab work: potassium 9.87 mmol/L, BUN 18.3 mmol/L, creatinine 268 µmol/L, urea clearance 0,20 ml/s, creatinine clearance 0,81 ml/s, eGFR 23 *ml/min*/1,73m^2, creatine phosphokinase 1180 IU/L, Hgb 79 g/L, Er 2.81x10^{12}/L, C-reactive protein 13.2 µg/mL, Le 7.41x10^9/L, PCO_2 41 *mmHg*, HCO_3 22 *mmol/L,* and acidosis, pH 7.21. Blood pressure 130/80 mmHg and heart rate 64 bpm, ECG shows prolonged PR interval and high T waves. He was treated with crystalloid iv solutions, 8.4% bicarbonate solutions, diuretics, calcium gluconate, short-acting insulin, antibiotics, and anticoagulants. After therapy, there is an improvement in his potassium levels, diuresis, and ECG. After 24 days of hospital treatment, he was discharged to home care.

Conclusion. Patients on methadone substitution therapy have a higher risk of multiple organ damage. Kidney function is especially at risk. It is of utmost importance to raise awareness among physicians of the danger of rabdomyolysis in these patients. Regular lab checks in patients on methadone substitution therapy can timely detect severe acute and chronic kidney complications and enable timely treatment.

Keywords: kidney damage, maintenance therapy, primary healthcare

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Uvod

Zavisnost od opijata je hroničan problem recidivantnog karaktera i poslednjih godina ima svoje specifičnosti: obuhvata pretežno mlade ljude, u populaciji od 15 do 64 godine incidencija iznosi 0,4%. U evropskim zemljama taj odnos je čak od 6 do 9/1.000 stanovnika[1]. Upotreba nesterilnih opijata uz korišćenje nesterilnog pribora, može izazvati niz inokulativnih bolesti. Na globalnom nivou, to su najčešće nove infekcije virusom hepatitisa *B* (1%) i nove infekcije virusom *C* (23%)[2]. Prevalencija infekcija uzrokovanih virusom hepatitica *C*, među osobama koje su koristile intravenske opijate, iznosi globalno za hepatitis C 39.2% u regionu Istočne Evrope 48.6%, dok je u Zapadnoj Evropi taj procenat 39.9%[3].

Lečenje zavisnosti od opijata je dugotrajan proces. Osobe koje zloupotrebljavaju opijate ili opioide vrlo brzo postaju zavisne, pri čemu se narušava njihov biološki, sociološki, psihološki i ekonomski milje[4]. U porastu je broj smrtnih slučajeva zbog predoziranja[1]. Mnoge posledice su nemerljive jer se ne mogu kvantifikovati.

Supstituciona terapija opioidima smanjuje učestalost takvog načina primene opijata, čime se smanjuje prenos patogena koji se dalje prenose krvlju među ljudima koji koriste opioide[2]. Supstituciona terapija koristi sličnu ili identičnu supstanciju sa svojstvima i dejstvima sličnim drogi koja se obično koristi. Ova vrsta supstancije se naziva *agonist.* Metadon je primer opijatskog agoniste. U tretmanu zavisnosti primenjuje se i terapija antagonistima, agonističko-antagonistička i simptomatska terapija. Buprenorfin je sintetski parcijalni agonist-antagonist, opioidni antagonist je naltrekson. Simptomatska terapija su klonidin i tramadol[5]. Metadonska supstituciona terapija (MST) i terapija buprenorfinom preporučene su od Svetske zdravstvene organizacije (SZO) kao osnovni model lečenja opijatskih zavisnika, a metadon se uzima kao zlatni standard[5]. U kombinaciji sa socijalnim, zdravstvenim i psihološkim merama je najdelotvornija pomoć[1].

Od 1970. godine metadonska terapija održavanja je dominantan oblik supstitucione terapije za opijatske zavisnike[4]. Procenjuje se da pola miliona pacijenata u svetu koristi ovaj način lečenja. Ublažava apstinencijalne simptome i smanjuje zdravstvene i društvene rizike. Metadon je po svom hemijskom sastavu 6-*dimetilamino*-4,4-*difenil*-3-*heptanon* hlorovodonik. Iako metadon nije isključivo proizvod jednog proizvođača, aktivni sastojak je uvek isti: metadon hidrohlorid. Svi proizvođači dodaju neaktivne supstancije, kao što su aditivi, prezervativi i aroma[1]. Preko 90% supstitucije u Evropi čini metadon, osim u Francuskoj gde preovlađuje buprenorfin[1]. Oko pola miliona ljudi koristi ovaj lek širom sveta[1].

Metadonski program u Srbiji sprovodi se timski na više nivoa zdravstvene zaštite (primarnom, sekundarnom i tercijarnom). Formirana su četiri regionalna centra, koji se nalaze u Beogradu, Novom Sadu, Nišu i Kragujevcu. Uloga ovih regionalnih centara je da implementiraju, sprovode i kontrolišu

Introduction

Opioid addiction is a chronic problem, of recurrent character, and lately, it exhibits some patterns: it occures mainly in younger people, 15-64 years of age, with an incidence of 0,4%. In the European countries, it`s even 6-9/1000 inhabitants[1]. The use of non-sterile opioids and non-sterile syringes may lead to inoculative diseases. Globally, those are usually new hepatitis B (1%), and hepatitis C infections (23%)[2]. The prevalence of hepatitis C infection among iv drug users is globally 39.2%, in Eastern Europe 48.6%, and in Western Europe 39.9%.[3]

The treatment of opioid addiction is a long-term process. Opiates or opioids abusers become addicted very fast and it ruins their biological, social, psychological, and economic setting[4]. The number of death cases due to drug overdose is on the rise[1]. Many consequences are immeasurable because they can`t be quantified.

Opioid substitution therapy decreases the incidence the aforemantioned use of opiates, and therefore decreases the blood transmission of the pathogenes among opioid abusers[2]. Substitution therapy uses a similar or identical substance, with characteristics and actions similar to the usually used drug. This sort of substance is called the *agonist.* Methadone is an example of an opiate agonist. In the addiction treatment antagonist, agonist-antagonist, and symptomatic therapies are used. Buprenorphine is a synthetic partial agonist-antagonist, and naltrexone is an opioid antagonist. Clonidine and tramadol are symptomatic therapies[5]. Methadone substitution therapy (MST) and buprenorphine therapy are recommended by the World Health Organization (WHO) as a basic opioid abusers treatment model, and methadone is considered a golden standard[5]. Combined with social, health, and psychological measures are considered the most useful help[1].

Since 1970, methadone maintenance therapy is a dominant form of substitution therapy in opioid addicts[4]. It is estimated half a million patients worldwide use this particular treatment. It alleviates abstinence symptoms and decreases health and social risks. Methadone is 6-dimethylamino-4,4-diphenyl-3-heptanone hydrogen chloride. Although methadone isn`t a single drug producer product, an active ingredient is always the same - methadone hydrogen chloride. All producers add inactive substances, such as additives, preservatives, and aromas[1]. Methadone makes 90% of substitution therapy in Europe, except France, where buprenorphine prevails. About half a million people use this drug all around the world[1].

The methadone program in Serbia is executed by teams, on several healthcare levels (primary, secondary, tertiary). There are four regional centers in Belgrade, Novi Sad, Nis, and Kragujevac. Their role is to implement, conduct, and control the implementation of methadone substitution therapy in their region[4]. The Serbian national guidelines say that after

sprovođenje supstitucione terapije metadonom u svom regionu[4]. U Nacionalnim smernicama Srbije se navodi da se posle donošenja odluke o uključivanju pacijenta na supstitucioni program otvara medicinska dokumentacija - Pompidu upitnik i medicinski karton, u koji se unose podaci o lečenju i toku tretmana. Nakon toga, zavisnik potpisuje ugovor o načinu i pravilima sprovođenja supstitucione terapije koji se redovno evaluiraju[5].

Metadon je relativno bezbedan lek ako se primenjuje u preporučenim dozama. Neželjeni efekti se javljaju kod manje od 20% korisnika, najčešće blagi i doznozavisni. Manifestuju se u neurovegetativnoj sferi i psihičkom funkcionisanju (pospanost, smetnje koncentracije, teškoće usnivanja, impotencija, malaksalost, preznojavanje, suvoća usta, opstipacija, otežano mokrenje, amenoreja, glavobolja, grčevi ekstremiteta, mučnina, gubitak apetita, bolovi u stomaku, ospa i svrab, smetnje u vidu, epileptični napadi)[5]. Jedan od potencijalnih štetnih efekata metadona je nefrotoksičnost[6]. Novija istraživanja ukazuju da je najčešća komplikacija, kao i uzrok smrti usled toksičnosti metadona upravo akutna bubrežna insuficijencija[7,8,9,10]. Tokom poslednje četiri decenije, svedoci smo porasta prijave upravo smrtnih slučajeva kao posledica primene metadona[10].

deciding to include a patient in the substitution program, the medical entry is made – Pompidou questionnaire and medical chart, where all the data about the treatment are entered. The drug addict then signs the contract containing ways and rules of substitution therapy treatment, and it is regularly evaluated[5].

Methadone is a relatively safe drug if used in recommended doses. Side effects occur in less than 20% of users and are usually mild and dose-related. They mainly cause neurovegetative and psychological problems (drowsiness, poor concentration, difficulty falling asleep, impotence, fatigue, sweating, dry mouth, constipation, difficulty urinating, amenorrhea, headache, muscle cramps, nausea, loss of appetite, stomachache, rash, and itching, blurred vision, seizures)[5]. The potential side effect of methadone use is nephrotoxicity[5]. The novel research shows the most frequent complication, and the cause of death due to methadone toxicity is actually acute kidney failure[7,8,9,10]. We witness the raise of death cases due to methadone use in the last four decades[10].

Prikaz bolesnika

Pacijent starosti 40 godina, javio se na pregled zbog pospanosti, zamaranja, bolova i slabosti u mišićima, visoke temperature (39^{0}C), bolova u stomaku i grudima, znojenja i nedostatka apetita. Petnaest godina je bio heroinski zavisnik, konzumira veće količine alkohola i četiri godine je korisnik metadonske supstitucione terapije. Sarađivao je sa stručnim timom za spovođenje supstitucione terapije i obavljao redovne laboratorijske analize. Iz anamneze saznajemo da je paralelno sa metadonom prethodnih dana upotrebljavao i alkohol i benzodiazepine. Nije bila utvrđena infekcija virusima hepatitisa *B* i *C* i HIV-a. U laboratorijskim analizama urađenim tri meseca ranije, bilo je znakova oštećenja bubrega sa blagim smanjenjem jačine glomerularne filtracije (eritrociti 3,10x10^{12}/*L*, hemoglobin 102 *g/L*, urea 11.6 *mmol/L* i kreatinin 145 *μmol/L*, aspartat transaminaza 120 *IU/L*, alanin aminotransferaza 113 *IU/L*, kreatin kinaza 740 *IU/L*, laktatdehidrogenaza 530 *IU/L*, proteinurija 1,6 *g/DU*, eGFR 66 *ml/min/1*,73*m*^{2}). U međuvremenu se nije javljao na preglede u ordinaciju primarne zdravstvene zaštite.

Auskultatorni nalaz nad srcem i plućima bio je u fiziološkim granicama, abdomen mek palpatorno bolno neosetljiv, postojao je diskretan otok obe potkolenice. Elektrokardiografski nalaz: normalna osovina, sinusni ritam, srčana frekvencija 64/*min*, bez hipertrofije komora, bez elevacije i depresije ST segmenta, normalan QRS kompleks, visoki T talasi u D1, aVL, V_5, V_6, produžen PR interval u svim od-

Case report

The male patient, 40, presents with drowsiness, overexertion, muscle pain and weakness, high fever (39^{0}C), stomach and chest pain, sweating, and loss of appetite. He was a heroin addict for 15 years, consumes huge amounts of alcohol, and MST user for 4 years. He cooperated with a professional team for implementing substitution therapy and did regular lab checkups. His personal history reveals he used alcohol and benzodiazepines together with methadone, the previous day. He was negative for HIV, HCV, and HBsAg. There were signs of early kidney disease in his lab work, from three months ago, (erythrocytes 3,10x10^{12}/*L*, hemoglobin 102 *g/L*, urea 11.6 mmol/L, creatinine 145 μmol/L, aspartate transaminase 120 *IU/L*, alanine aminotransferase 113 *IU/L*, creatine kinase 740 *IU/L*, lactate dehydrogenase 530 *IU/L*, proteinuria 1,6 *g/DU*, eGFR 66 *ml/min/1*,73*m*^{2}). In the meantime, he didn`t show up for his appointments with his GP.

Auscultation findings of heart and lung were normal, abdomen soft and non-tender, there was slight edema of lower extremities. ECG findings: normal heart axis, sinus rhythm, HR 64 bpm, no signs of ventricular hypertrophy, no elevation or depression of ST segment, normal QRS complex, high T waves in D1, AVL, V5, V6, prolonged PR interval in all leads. Blood pressure 130/80 *mmHg*. Lab work: hemoglobin 79 *g/L*, erythrocytes 2,81x10^{12}/L, ESR 88 *mm/1h*, C-reactive protein 13,2 *μg/mL*, leukocytes 7,41x10^9/L, BUN 18,3 *mmol/L*, creatinine 268 *μmol/L*, urea clearance 0,20 *ml/s*, creatinine clearance 0,81 ml/s, eGFR 23 *ml/min*/1,73*m*^{2}, proteinuria 9,03 g/

vodima. Krvni pritisak 130/80 *mmHg*. Laboratorijske analize su pokazale sledeće vrednosti: hemoglobin 79 *g/L*, eritrociti 2,81x10^{12}/*L*, sedimentacija eritrocita 88 *mm/1h*, C-reaktivni protein 13,2 *μg/mL*, leukociti 7,41x10^{9}/*L*, urea 18,3 *mmol/L*, kreatinin 268 *μmol/L*, klirens uree 020 *ml/s*, kreatinina 0,81 *ml/s*, eGFR 23 *ml/min*/1,73m^2, proteinurija 9,03 *g/DU*, albumini 27 *g/L*, diureza 2140 ml/D, kalijum 9,87 *mmol/L*, natrijum 137 *mmol/L*, hloridi 90 *mmol/L*, proteini 59 *g/L*, kalcijum 1,84 mmol/L, kreatin kinaza 1180 IU/L, laktatdehidrogenaza 885 IU/L, troponin < 0.01 *μg/L*, aspartat transaminaza 180 *IU/L*, alanin aminotransferaza 159 *IU/L*. U arterijskim gasnim analizama su ustanovljene vrednosti PCO_2 41 *mmHg* i 22 HCO_3 *mmol/L*, metabolička acidoza (*pH* 7.21), sa anjonskom prazninom od 25 *mol/L*. U laboratorijskom nalazu urina je bilo sveže krvi i leukocita. Laboratorijski nalaz je ukazivao na ozbiljan elektrolitni poremećaj i pogoršanje bubrežne slabosti i pacijent je hospitalizovan.

Na nefrološkom odeljenju je nastavljena dijagnostika. Virusološkim analizama otkrivena je nova infekcija virusom hepatitisa *C*. Radiološki nalaz nad srcem i plućima bio je uredan. Ehosonografski pregled abdomena vizualizovao je normoehogen parenhim viđenog dela jetre, bez fokalnih promena, bez ultrazvučnih znakova cirotične konfiguracije, bubrezi normalnog položaja, oblika, veličine i debljine, sa heterogenim parenhimom, promera oko 95 *mm*, sa mikroodjecima, bez hidronefroze, bez slobodne tečnosti u abdomenu (Slika 1). Gornja ezofagogastroduodenoskopija ukazala na infekciju *Helicobacter pylori*.

DU, albumins 27 *g/L*, diuresis 2140 *ml/D*, potassium 9,87 *mmol/L*, sodium 137 *mmol/L*, chloride 90 *mmol/L*, proteins 59 *g/L*, calcium 1,84 *mmol/L*, creatine kinase 1180 IU/L, lactate dehydrogenase (LDH) 885 IU/L, troponin < 0.01 *μg/L*, aspartate transaminase 180 IU/L, alanine aminotransferase 159 IU/L. Arterial blood gases showed PCO_2 41 *mmHg* and HCO_3 22 *mmol/L*, metabolic acidosis (*pH* 7.21), with anion gap of 25 *mol/L*. There were fresh blood and leucocytes in the urine sample. Lab work indicated serious electrolyte disorder and deterioration of kidney disease, so the patient was hospitalized.

The diagnostics were continued at the nephrology ward. The viral tests revealed a new hepatitis C infection. Chest X-ray was normal. Abdominal ultrasound revealed heterogeneous liver structure, no focal changes or signs of hepatic cirrhosis, kidneys were of normal shape and size, in place, had heterogeneous parenchyma, 95 *mm* in diameter, with micro echoes, no signs of hydronephrosis, no fluid in the abdomen (Figure 1). Upper esophagogastroduodenoscopy pointed to *Helicobacter pylori* infection,

Slika 1. Ehosonografija abdomena sa normoehogenom strukturom viđenog dela jetre i bubregom sa heterogenim parenhimom, sa mikroodjecima i bez hidronefroze.
Figure 1. *Abdominal echo sonography with normoechogenic structure of the seen part of the liver and the kidney with heterogeneous parenchyma, with micro echoes and without hydronephrosis.*

Na osnovu anamneze, kliničkog pregleda i sprovedene dijagnostike, zaključeno je da je akutna bubrežna insuficijencija povezana sa rabdomiolizom uzrokovanom metadonom. Sprovedena je intenzivna konvencionalna terapija infuzijama kristaloida, 8.4% rastvorom natrijum bikarbonata, furosemidom (10 x 2 *ml*), diureticima, kalcijum glukonatom, insulinom, kiseonikom, ciprofloksacinom u ampuliranoj formi (5x100*mg*/10*ml*), antibioticima i antikoagulansima. Acidobazni status je korigovan i normalizovan je elektrolitni disbalans.

Budući da je diureza bila zadovoljavajuća i vrednosti kalijuma, azotemije i kreatinina su opadale, nije dijaliziran (kalijum 5,7; 5,6 *mmol/L*, urea 12,2; 10,1 *mmol/L*, kreatinin 206; 223 *μmol/L*). Vrednosti CK i LDH su pokazale opadajući trend (CK 912 *IU/L*; 432 *IU/L* i LDH 612 *IU/L*; 435 *IU/L*). Febrilnost je prestala četvrtog dana. Anemija je korigovana oralnim preparatima gvožđa. Na otpustu, nakon 24 dana, pacijentu su ordinirani diuretska terapija, kalcijum, gvožđe, polivitaminska terapija. Nastavljena je MST i predloženo praćenje renalne funkcije (eGFR 65 *ml/min*/1,73 m^2 na otpustu). Nakon evaluacije ove epizode akutnog pogoršanja renalne slabosti, pacijent se neredovno javlja na preporučene kontrolne preglede.

Based on his medical history, clinical examination, and diagnostics, we concluded his acute kidney failure was caused by rhabdomyolysis due to methadone. He was started on intensive conventional therapy with crystalloid solutions, 8,4% NaHCO3 solutions, furosemide (10x2 ml), diuretics, calcium gluconate, insulin, oxygen, ciprofloxacin (5x100*mg*/10*ml* amp), antibiotics, and anticoagulants. Acido-base status was corrected as well as electrolyte disbalance.

Since his diuresis was satisfactory and potassium levels, azotemia, and creatinine levels were declining he wasn`t dialyzed (potassium 5,7; 5,6 *mmol/L*, urea 12,2; 10,1 *mmol/L*, creatinine 206; 223 *μmol/L*). CK and LDH levels were also declining (CK 912 IU/L; 432 IU/L and LDH 612 IU/L; 435 IU/L). He stopped being febrile on day four. Anemia was corrected with oral iron supplements. Twenty-four days after hospital discharge the patient was prescribed diuretics, calcium, iron, multivitamin therapy and continuation of MST, and follow- up of renal function due to his prior CKD (eGFR 65 *ml/min*/1,73 m^2 on discharge). After the evaluation of the acute episode of kidney failure, the patient irregularly visits for follow-ups.

Diskusija

Medicini, tačnije, psihijatriji pripada onaj deo zavisnosti koji ima karakteristike bolesti zavisnosti zbog telesnih i psihičkih oštećenja i zbog posledica hroničnih intoksikacija. Zavisnost ili žudnja za drogama potiskuje i menja osećanja, moral, odgovornost, vrednosne sisteme i podstiče one osobine koje služe zadovoljenju žudnje[5]. Zavisnost od opijata je hronično stanje povezano s različitim morbiditetom i mortalitetom[8,11]. Terapija zavisnosti metadonom počinje niskim dozama koje se povećavaju. Danas se doze niže od 60 *mg* smatraju neefikasnim. Doze kojima se kod većine pacijenata postižu najbolji rezultati kreću se od 60 do 120 *mg/dan*[1]. Ima primenu u terapiji kancerskog bola, mada nije preporučen u prvoj liniji medikamenata. Ranije se široko koristio u terapiji hroničnih i neuropatskih bolova zbog kompetitivnog antagonizma *n-metil-d-aspartat* (*NMDA*) receptora, što se prema najnovijim vodičima više ne preporučuje[12,13]. Metadon ima potencijal za zloupotrebu i može uzrokovati smrtne ishode bilo direktno ili indirektno[10].

Bioraspoloživost metadona nakon oralne primene je 70%-90%, najvišu koncentraciju u plazmi dostiže za 2–4 časa, analgetski efekat počinje 15 minuta nakon supkutane administracije. Poluvreme eliminacije je 15*h*–55*h*. Metaboliše se u jetri preko citohrom P450 a 40% leka se eliminiše putem bubrega[14]. Metadon je relativno bezbedan lek i, pod uslovom da se primenjuje u dozama i na način preporučen od strane lekara, neželjeni efekti javljaju se kod manje od 20% korisnika[5]. Neželjeni efekti metadona najčešće su blagi i za-

Discussion

The disease part of the addiction belongs to medicine, or more precisely psychiatry due to bodily and psychic damage and consequences of chronic intoxication. Addiction or craving the drugs repress and change feelings, morale, responsibility, value systems, and encourage characteristics serving to satisfy craving[5]. Opioid addiction is a chronic condition related to different morbidities and mortality[8,11]. Methadone therapy starts with low doses of the drug and they are gradually increased. Nowadays, doses lower than 60mg are considered inefficient. The doses that showed the best efficacy in these patients range from 60-120 mg/day[1]. It`s also used in the treatment of cancer pain, although not as the first line treatment. Before, it was widely used in the treatment of chronic and neuropathic pain due to the competitive antagonism of n-methyl-d-aspartate (NMDA) receptors but the new guidelines don`t recommend it[12,13]. Methadone has a great potential for abuse and may cause death outcomes either directly or indirectly[10].

Methadone bioavailability, after oral intake, is 70-90% and maximum plasma concentration is reached in 2–4 hours. The analgesic effect starts within 15 minutes of subcutaneous administration. Half-life elimination time is 15–55 hours. It is metabolized in the liver through cytochrome P450 and 40% of the drug is eliminated through kidneys[14]. Methadone is a relatively safe drug if used in proper doses and in line with the instructions given by the physician. Side effects occur in less than 20% of users[5]. Methadone side effects are usually

vise od doze. Najčešće nuspojave metadona manifestuju se u neuro-vegetativnoj sferi i na planu psihičkog funkcionisanja. najozbiljniji neželjeni efekat tretmana predstavlja mogućnost pojave epileptičnih napada, što se kod pacijenata na metadonskoj terapiji javlja izuzetno retko[5].

Smatra se da je 20% akutne renalne insuficijencije uzrokovano upotrebom različitih lekova[14]. Opioidi utiču na renalnu funkciju različitim mehanizmima. Nefrotoksičnost može nastati direktnim ili indirektnim uticajem leka[14,15]. Oštećenje bubrega može biti uzrokovano infekcijama zbog korišćenja kontaminiranih igala[10], što kod našeg prikazanog pacijenta nije potvrđeno. Kod pacijenata koji simultano koriste i heroin i metadon, a kojih je puno, rabdomioliza ne samo da predstavlja realnu opasnost, već se može dogoditi da se javlja i paralelno sa cerebrovaskularnim insultom[10]. Kao farmakološke supstancije koje najčešće uzrokuju rabdomiolizu, često se navode kokain, amfetamin, statini i heroin[10]. Osim statina, može se reći da se dominantno radi o psihoaktivnim supstancijama[10]. Opioidi ili psihostimulansi kao što su heroin i kokain, često su povezani sa rabdomiolizom[10]. koju uzrokuje oslobađanje toksičnih intracelularnih sastojaka u cirkulaciju zbog oštećenja skeletnih mišića. Rabdomioliza nastaje usled imobilisanosti, toksičnog efekta narkotika, alergijske reakcije, tremora i spazma mišića i hipoksemije[9]. Korisnici heroina imaju veliku verovatnoću i za razvoj amiloidoze, nefrotskog sindroma i progresiju u završnu fazu bubrežne bolesti. Oni takođe imaju veće šanse za razvoj rabdomiolize u poređenju sa osobama koje nisu koristile heroin a koje su inficirane virusom hepatitisa *C*, kao i virusom humane imunodeficijencije[8]. Snižen krvni pritisak uzrokovan dejstvom opijata na μ receptore može dovesti do opadanja antidiuretskog hormona i povećane simpatičke aktivnosti, što smanjuje renalnu perfuziju[9]. Metadon može uzrokovati edem pluća, bubrezi su osetljivi na hipoksiju i reaguju infiltracijom inflamatornih ćelija[9]. Opijati i metadon mogu uzrokovati renalnu lipidozu glomerula i tubula[9]. Sekundarna renalna amiloidoza sa nefritičkim sindromom, proteinurijom i renalnom insuficijencijom, takođe je opisana[9]. Metadon može da uzrokuje oštećenje mišića zloupotrebom tableta u intravenskoj injekciji, jer one sadrže mikrokristale celuloze i uzrokuju gangrenu[16].

Mogući uzroci koji su doveli do zatajivanja bubrega kod prikazanog pacijenta su rabdomioliza (visoke vrednosti kreatin kinaze, troponin u referentnim vrednostima), infekcija ili neki drugi potencijalni uzrok koji nam je ostao nepoznat jer nije redovno kontrolisan.

Izbegavanje nefrotoksičnih lekova, redovne kontrole albuminurije, merenje koncentracije kreatinina u serumu i procena JGF, predstavljaju mere kojima se prati progresija hronične bolesti bubrega[17]. Bubrežna insuficijencija snažno utiče na farmakokinetiku mnogih lekova, uključujući opioide. Kad je JGF<60 *ml/min*/1,73 m^2, potrebno je smanjiti dozu opioida[17]. Metadon se izlučuje se fecesom i čini se sasvim

mild and dose-dependent. The most common side effects manifest in the neurovegetetative sphere and psychological functioning. The most severe side effect is the possibility of seizures, which is very rare in methadone therapy users[5].

It is considered that 20% of cases of acute renal failure are caused by drug use[14]. Opioids affect renal function with different mechanisms. Nephrotoxicity is caused by direct and indirect drug influence[14,15]. Kidney damage is caused by infections due to using contaminated needles[10] which wasn`t the case in our patient. In patients using heroin and methadone simultaneously, and there are a lot, rhabdomyolysis is not only the real danger but could be concomitant with stroke[10]. The most common pharmacological causes of rhabdomyolysis are cocaine, amphetamines, statins, and heroin[10]. Beside statins, all others are predominantly psychoactive substances[10]. Opioids or psychostimulants, such as heroin and cocaine, are often connected with rhabdomyolysis[10]. They may also lead to atraumatic rhabdomyolysis caused by the release of toxic intracellular ingredients into circulation due to skeletal muscle damage. Rhabdomyolysis appears due to immobilization, the toxic effect of the narcotics, allergic reaction, tremor, muscle spasm, and hypoxemia [9]. Heroin addicts are more likely to develope amyloidosis, nephrotic syndrome, and progress to the final stages of kidney disease. They also have a greater chance to develop rhabdomyolysis, compared to persons who didn`t use heroin but are HIV or hepatitis C infected[8]. Low blood pressure is caused by opioids` effect on μ receptors that leads to a decline in antidiuretic hormone and increased sympathetic activity, leading further to decreased renal perfusion[9]. Methadone may cause pulmonary edema, and kidneys are sensitive to hypoxia and react by infiltration of inflammatory cells[9]. Opioids and methadone may cause renal lipidosis of glomeruli and tubulae[9]. Secondary renal amyloidosis, with nephritic syndrome, proteinuria, and renal failure, was also described[9]. Methadone may cause muscle damage by using tablets in intravenous injections because they contain microcrystals of cellulose and cause gangrene[16].

The possible causes leading to kidney failure in this particular patient were rhabdomyolysis (high creatine kinase, normal troponin level), infection or some other potential cause that remained unknown because the patient didn`t have regular check-ups.

Avoiding nephrotoxic drugs, regular check-ups, checking creatinine levels, and assessment of GFR are the measures that may be of use in following the progression of the kidney disease[17]. Kidney failure strongly affects the pharmacokinetics of many drugs, including opioids. When GFR <60 *ml/min*/1,73 m^2, it is necessary to lower opioid dose[17]. Methadone is excreted with feces which makes it quite safe in patients with CKD, considering their plasma concentrations are similar to controls[18]. However, added damage caused by opiate abuse relapses should be considered, as well as concomitant use of alcohol and anxyolitics. The final goal doesn`t

bezbednim za upotrebu u bolesnika sa hroničnom bubrežnom bolešću, budući da su koncentracije u plazmi kod ovih pacijenata slične onima kod kontrolnih ispitanika[18]. Međutim, treba imati u vidu dodatnu štetnost po zdravlje koju izazivaju relapsi u zloupotrebi opijata kao i kontomitantna upotreba alkohola i anksiolitika. Krajnji cilj lečenja ne mora biti pacijent bez droga, već što duži boravak na lečenju, bolje zdravlje i društveno funkcionisanje, smanjenje upotrebe ilegalnih droga, smanjenje smrtnosti povezanih sa zloupotrebom droga, kontrola rizika od transmisivnih bolesti, prevencija kriminala i smanjenje troškova prouzrokovano problemima zavisnosti u društvu[19].

Zaključak

Pacijenti na metadonskoj supstitucionoj terapiji imaju povećan rizik od multiplog oštećenja funkcije svih organa zbog upotrebe opioida. Posebno je ugrožena renalna funkcija. Od izuzetne važnosti je da se među lekarima poveća svest o opasnosti nastanka rabdomiolize kod pacijenata na terapiji metadonom. U ordinaciji izabranog/porodičnog lekara potrebno je obezbediti poverenje pacijenata na ovoj terapiji i kontinuirani monitoring njihovih parametara renalne funkcije.

have to be a drug-free patient but the longer treatment period, better health and social functioning, decrease of the use of illegal drugs, lower mortality from drug abuse, risk control of transmissive diseases, crime prevention, and decrease of costs caused by addiction problems in the society[19].

Conclusion

Patients on methadone substitution therapy have an increased risk of multiple organ damage due to prior use of opioids. Renal function is especially jeopardized. It is of utmost importance to raise awareness among physicians of the danger of rabdomyolysis in these patients. It is necessary to provide the trust of patients in this sort of therapy and continuous monitoring of their kidney function parameters in a GP office.

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