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LEKOVI PROTIV BOLA SA POSEBNIM OSVRTOM NA TRAMADOL

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Sažetak
Bol predstavlja značajan medicinski i socijalni problem jer utiče na svakodnevno funkcionisanje, kao i na do psihičko, emocionalno i socijalno blagostanje, uzrokujući značajne zdravstvene i ekonomske posledice. Kontrola bola jedan je od osnovnih ciljeva savremene medicine, a lekovi koji se koriste u tu svrhu nazivaju se analgetici. Ne postoji jedinstveni lek koji odgovara svakoj vrsti bola, zbog čega je individualni pristup svakom pacijentu od ključnog značaja za lečenje. Cilj je dokazati da upotreba tramadola u otklanjanju i ublažavanju bola, uz jasno definisane indikacije, strogo kontrolisan način primene, precizno određenu dozu i ograničeno vreme primene, može predstavljati efikasnu terapijsku opciju za lečenje umerenog i umereno jakog bola kada su lekovi prvog reda nedovoljno efikasni ili kontraindikovani. „Lek istovremeno predstavlja i lek i otrov!" Kada se koristi prema indikacijama i u skladu sa uputstvom za primenu, ispoljava svoje pozitivno dejastvo, dok u slučaju nepoštovanja indikacija, terapiskih doza, vremenskog intervala i dužine trajanja terapije može ispoljiti negativne efekte. Zdravstveni radnici su u obavezi da procene rizik od zavisnosti pre započinjanja terapije.

Ključne reči: tramadol, bol, korist, zavisnost

Uvod

Bol je jedno od najčešćih subjektivnih iskustava kod ljudi i pretstavlja važan zaštitni mehanizam organizma. Kod hroničnih bolesti bol gubi zaštitnu funkciju i postaje izvor patnje i smanjenog kvaliteta života. Bol predstavlja značajan medicinski i socijani problem, posebno kada pređe u hronični oblik (bol koji traje duže od tri meseca), jer utiče na gotovo sve sfere života pojedinca, od svakodnevnog funkcionisanja do psihičkog, emocionalnog i socijalnog blagostanja, uzrokujući značajne ekonomske i zdravstvene posledice (1).

Kontrola bola jedan je od osnovnih ciljeva savremene medicine, a lekovi koji se koriste u tu svrhu nazivaju se analgetici. Ne postoji jedinstveni lek koji odgovara svakoj vrsti bola. Analgetici se dele na nekoliko glavnih kategorija na osnovu mehanizma i jačine delovanja (2). Glavne vrste analgetika su: neopioidni alangetici, opioidni analgetici i adjuvantni lekovi.

Neopioidni analgetici mogu biti:

a) Nesteroidni antiinflamatorni lekovi (NSAIL), koji smanjuju upalu, bol i povišenu temperaturu tako što inhibiraju sintezu prostaglandina. Koriste se za blage do umerene bolove (glavobolja, menstrualni bolovi, bolovi u mišićima i zglobovima). Neželjena dejstva uključuju gastrointestinalne tegobe pri dugotrajnoj primeni. U ovu grupu spadaju ibuprofen (Brufen, Rapidol), diklofenak (Voltaren, Diklofen), naproksen (Nalgezin), acetilsalicilna kiselina (Aspirin), itd;

b) Analgetici i antipiretici koji prvenstveno deluju na centralni nervni sistem, ali nemaju značajno antiinflamatorno dejstvo. Bezbedniji su za gastrointestinalni trakt u odnosu na NSAIL, dok prekomerne doze mogu oštetiti jetru. Najčešće se koriste paracetamol (Panadol, Efferalgan, Paracet) (3).

Opioidni analgetici koriste se za lečenje bola različitog intenziteta, posebno kod hroničnih stanja, postoperativnog bola ili bola izazvanog malignim bolestima. Deluju na opioidne receptore u mozgu i kičmenoj moždini. Opioidi su širi generički naziv za sve prirodne (morfin), sintetske (fentanil) i polusintetske (heroin) supstance koje se vezuju za opinoidne receptore u centralnom nervnom sistemu i organizmu. Ova definicija obuhvata celu klasu jedinjenja, uključujući egzogena poput lekova (legalnih) i heroina

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PAIN MEDICINES WITH SPECIAL REFERENCE TO TRAMADOL

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SUMMARY
Pain represents a significant medical and social problem because it affects daily functioning, as well as psychological, emotional and social well-being, causing significant economic and health problems. Pain control is one of the main goals of modern medicine, and the drugs used for this purpose are called analgesics. There is no one-size-fits-all medicine for every type of pain. That is why an individual approach to each patient is of key importance for the treatment and prevention of the recurrence of the disease. The aim is to demonstrate that the use of tramadol in relieving and reducing pain, with clearly defined indications, strictly controlled administration, precisely determined dosage and limited duration of use, can be an effective therapeutic option for the treatment of moderate and moderately severe pain when first-line medications are insufficiently effective or contraindicated. "The medicine is both medicine and poison at the same time!" When it is used according to the indications and instructions, it exerts its positive effect, and in the second case, when the indications, therapeutic doses, time intervals and length of therapy are not followed, it then exerts its negative effect. Healthcare professionals are required to assess the risk of addiction before starting therapy.

Key words: tramadol, pain, benefit, addiction

Introduction

Pain is one of the most common subjective experiences in humans and represents an important protective mechanism of the body. In many situations, especially in chronic diseases, pain loses its protective function and becomes a source of suffering and reduced quality of life. Pain represents an important medical-social problem, especially when it becomes chronic (pain that lasts longer than three months), because it affects almost all spheres of someone's life, from daily functioning to psychological, emotional and social well-being, causing significant economic and health problems (1).

Pain control is one of the main goals of modern medicine, and the drugs used for this purpose are called analgesics. There is no unique medicine that is effective for every type of pain. Analgesics are divided into several main categories based on the mechanism and strength of action (2). The main types of analgesics are: non-opioid analgesics, opiod analgesics and adjuvant drugs.

Non-opioid analgesics can be: a) non-steroidal anti-inflammatory drugs (NSAIDs) that reduce inflammation, pain and fever by inhibiting the synthesis of prostaglandins. They are used for mild to moderate pain (headache, menstrual pain, muscle and joint pain). Gastrointestinal problems are common adverse effects associated with the chronic use of analgesics. They include ibuprofen (marketed as Brufen and Rapidol), diclofenac (Voltaren and Diclofen), naproxen (Nalgesin), acetylsalicylic acid (Aspirin); b) analgesics and antipyretics that primarily act on the central nervous system, but do not have a significant anti-inflammatory effect. They are safer for the stomach than NSAIDs, and excessive doses can damage the liver. Paracetamol (Panadol, Efferalgan, Paracet) is most often used (3). Opioid analgesics are used to relieve pain of varying intensity, especially in chronic conditions, postoperative pain, or pain caused by malignant diseases. They act on opioid receptors in the brain and spinal cord. Opioids are a broader generic name for all natural (morphine), synthetic (fentanyl) and semi-synthetic (heroin) substances that bind to opioid receptors in the central

(ilegalnih), ali i endogene supstance, tj. peptide koje organizam sam proizvodi - endorfine, enkefaline, dineorfine i endomorfine. Svi opioidni analgetici su opioidi, ali svi opioidi nisu nužno klasifikovani i korišćeni kao analgetici u terapeutske svrhe. U kliničkoj praksi opioidni analgetici dele se na slabe i jake (4). Slabi opioidni analgetici, koji se koriste za lečenje blagih do umerenih bolova (kodein, tramadol) mogu izazvati sledeća neželjena dejstva: mučninu, glavobolju, vrtoglavicu, pospanost, povraćanje, znojenje, umor, slabost, nervozu i smanjen apetit. Jaki opioidni analgetici koriste se za lečenje jakog bola (npr. morfin, fentanil, oksikodon). Imaju veći potencijal za zavisnost i mogu izazvati pospanost, mučninu, opstipaciju i respiratornu depresiju.

Adjuvantni lekovi (pomoćni analgetici) predstavljaju lekove koji primarno nisu klasifikovani kao analgetici, ali mogu doprineti kontroli određenih vrsta bola, naročito neuropatskog bola, kao i smanjenju upalnih procesa. U ovu grupu spadaju antidepresivi i antikonvulzivi, kao što su amitriptilin, duloksetin, pregabalin i karbamazepin. Pri primeni antidepresiva i antikonvulziva mogu se javiti neželjena dejstva kao što su suvoća usta, očiju, zatvor, retencija urina, ortostatska hipotenzija, vrtoglavica, sinkopa, srčane aritmije i pospanost. U adjuvantne lekove ubrajaju se i kortikosteroidi, kao što su deksametazon, prednizolon, metilprednizolon i triamcinolon. Ovi lekovi mogu dovesti do retencije tečnosti i nastanka edema, a dugotrajna primena povezana je sa slabljenjem imuniteta, razvojem osteoporoze, Kušingovog sindroma, ostećenjem kože i usporenim zarastanjem rana, povećanjem intraokularnog pritiska i supresijom funkcije nadbubrežne žlezde. (5).

Lokalni preparati primenjuju se direkno na kožu, na mestu bola (mišići, zglobovi) i ne unose se u organizam oralnim putem (6). Najčešće se koriste kreme, gelovi i flasteri koji sadrže NSAIL (npr. diklofenak) ili druge sastojke, kao što su mentol i kapsaicin. Neželjena dejstva ovih lekova mogu da budu iritacija kože, svrab, crvenilo, osip i suva koža. Sistemska neželjena dejstva mogu se ispoljiti izuzetno retko, uglavnom pri dugotrajnoj primeni na velikim površinama.

Prema trostepenoj lestvici bola Svetske zdravstvene organizacije (SZO), analgetici se dele prema jačini bola i efikasnosti na analgetike prvog, dugog i trećeg stepena (7). U lekove prvog stepena, za blagi do umereni bol, ubrajaju se NSAIL i analgetici-antipiretici, sa ili bez adjuvantnih lekova (npr. antidepresivi ili antiepileptici). Ovi lekovi su često dostupni bez lekarskog recepta. U ovu grupu spadaju: paracetamol, ibuprufen, naproksen i diklofenak. U lekove drugog stepena (za umeren do jak bol koji perzistira i pored maksimalnih doza lekova prvog stepena, a koji deluju centralno na nivou mozga i kičmene moždine) ubrajaju se tramadol, kodein i hidrokodon. Ovi lekovi su slabi opioidi sa ili bez adjuvantnih lekova. Lekovi trećeg stepena, koji se koriste za jak bol (akutni ili hronični), naročito kod malignih oboljenja, obuhvataju morfin, fentanil, oksikodon i buprenorfin. Imaju snažno centralno dejstvo, a potencijal za razvoj zavisnosti je veća. To su jaki opoidi, sa ili bez adjuvantne terapije.

Cilj ovog preglednog rada je analiza prednosti i nedostataka korišćenja tramadola u cilju lečenja bola.

Metode

U okviru ovog preglednog rada za pretraživanje baze podataka PUBMED korišćene su ključne reči: tramadol, bol, korist i zavisnost. Pregledom literature, obuhvaćeni su samo radovi objavljeni na engleskom jeziku u periodu od 1996. do 2025. godine.

Tramadol

Tramadol (slika 1) (8) je opioidni analgetik čije je dejstvo usmereno na centralni nervni sistem (CNS). Koristi se za lečenje umerenog i umereno jakog bola, kada lekovi prvog stepena, kao što su paracetamol i NSAIL (npr. ibuprofen), nisu dovoljno efikasni ili su kontraindikovani. Često se primenjuje kod pacijenata sa postoperativnim bolom, bolom nastalim usled trauma (prelomi, uganuća), hroničnim bolom malignog porekla, neuropatskim bolom kod dijabetične neuropatije ili postherpetične neuralgije, kao i kod reumatskog bola kada standardna terapija ne obezbeđuje adekvatno olakšanje. Takođe, koristi se kog bubrežnih ili žučnih kolika, kao i kod pacijenata sa određenim komorbiditetima, poput valvularnih srčanih oboljenja, kod kojih NSAIL mogu biti kontraindikovani zbog povećanog kardiovaskularnog rizika. Tramadol se primenjuje kada intenzitet bola prevazilazi prag efikasnosti paracetamola i NSAIL ili kada postoje ograničenja za njihovu primenu. Tramadol predstavlja lek izbora kao sledeći korak u terapiji bola. U slučajevima kada se odgovarajući analgetski efekat može postići lekovima prvog stepena i kada ne postoje ograničenja za njihovu primenu, neopravdana upotreba tramadola može dovesti do neadekvatnog izbora analgetske terapije i potencijalnog razvoja zavisnosti, naročito usled nepoštovanja preporuka koje se odnose na izbor leka, doziranje i dužinu primene (9).

nervous system and body. This definition includes a whole class of compounds, which are classified into exogenous such as drugs (legal) and heroin (illegal) and endogenous, that is, peptides that are produced inside the body – endorphins, enkephalins, dynorphins and endomorphins. All opioid analgesics are opioids, but not all opioids are used as analgesics for therapeutic purposes. In clinical practice, they are divided into weak and strong opioid analgesics (4). Weak opioid analgesics which are used to treat mild to moderate pain (codeine, tramadol) may have the following side effects: nausea, headache, dizziness, drowsiness, vomiting, sweating, fatigue, weakness, nervousness, and decreased appetite. Strong opioid analgesics are used to treat severe pain (e.g. morphine, fentanyl, oxycodone). They have a high potential for addiction and can cause drowsiness, nausea, constipation and respiratory depression.

Adjuvant drugs (also called co-analgesics) are drugs that are not primarily classified as analgesics, but can help control certain types of pain, especially neuropathic pain, by reducing inflammatory processes. This group includes antidepressants and anticonvulsants, such as amitriptyline, duloxetine, pregabalin, and carbamazepine. When antidepressants and anticonvulsants are used, adverse effects may occur, such as dry mouth, dry eyes, constipation, urinary retention, orthostatic hypotension, dizziness, syncope, cardiac arrhythmias, and drowsiness. Corticosteroids, such as dexamethasone, prednisolone, methylprednisolone and triamcinolone, also belong to adjuvant drugs. These drugs retain fluid and lead to swelling and in the long term weaken immunity and lead to osteoporosis, Cushing syndrome, skin damage – slow healing of wounds, increased eye pressure, adrenal suppression, etc. (5).

Local preparations are applied (6) directly to the skin at the site of pain (muscle, joint) and are not taken into the body orally. Creams, gels, plasters containing NSAIDs (diclofenac cream) or other ingredients (menthol, capsaicin) are most often used. Side effects of these drugs can be skin irritation, itching, redness, rash and dry skin. They can have a systemic effect extremely rarely in case of long-term use on large surfaces.

Based on the three-step analgesic ladder developed by the World Health Organization (WHO), analgesics are classified according to the intensity of pain and the effectiveness of the drug into three steps (7). Step 1 for mild to moderate pain includes NSAIDs and analgesics – antipyretics (with or without added drugs, e.g. antidepressants and antiepileptics). These drugs are often available without a prescription. These include paracetamol, ibuprofen, naproxen and diclofenac. Step 2 drugs for moderate to severe pain that persists despite maximum doses of step 1 drugs, which act centrally on the brain and spinal cord include tramadol, codeine and hydrocodone. These drugs are weak opioids with or without added drugs. Step 3 drugs, which are used for severe pain, acute or chronic pain, often in malignant pain, include: morphine, fentanyl, oxycodone and buprenorphine. They have a strong central effect and the potential for addiction is high. These are strong opioids with or without adjuvant therapy.

The aim of this review article is to analyze the advantages and disadvantages of using tramadol for the treatment of pain.

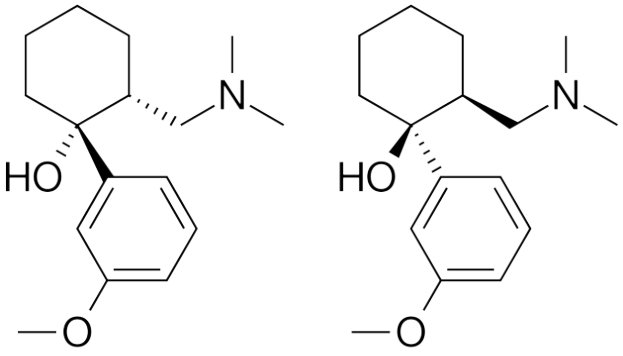
Methods

Within this review article, the key words tramadol, pain, benefit and addiction were used to search the PubMed database. Only studies published in English from 1996 to 2025 were included in the literature search.

Tramadol

Tramadol (Figure 1) (8) is an opioid analgesic whose action is directed at the central nervous system (CNS). It is used to treat and relieve moderate and moderately severe pain, when first-line drugs paracetamol and NSAIDs (ibuprofen) are insufficiently effective or contraindicated. It is often given to patients after operations – postoperative pain, pain caused by trauma (fractures, sprains), chronic pain of cancerous origin, neuropathic pain in diabetic neuropathy or postherpetic neuralgia, rheumatic pain when standard drugs do not provide adequate relief, renal or biliary colic, pain in patients with certain comorbidities (valvular heart disease) where NSAIDs may be contraindicated due to cardiovascular risk. Tramadol is a drug that is given when the intensity of pain is such that it exceeds the threshold of effectiveness of Paracetamol and NSAIDs or when there are limitations for its use. Tramadol is the drug of choice as the next step in pain therapy. In all other cases, when the threshold of effectiveness can be reached with other drugs (from the first line) and when there are no restrictions for the use of first-line drugs, we are talking about the potential initiation of the mechanism of inadequate selection of analgesics and the eventual appearance of possible

Slika 1. Strukturna formula tramadola



(1*R*,2*R*)-tramadol (1*S*,2*S*)-tramadol

Kada govorimo o tramadolu kao sintetičkom opinoidnom analgetiku, reč je o leku koji sadrži dva hiralna centra (na pozicijama C1 i C2 u cikloheksanskom prstenu), zbog čega postoji u obliku četiri različita stereoizomera, odnosno dva para enantiomera: (1R,2R)-tramadol i (1S,2S)-tramadol. Osnovna razlika među njima ogleda se u tome da što (1R,2R) - tramadol ima veći afinitet za vezivanje za μ-opioidne receptore u odnosu na (1S,2S)-tramadol. Još jedna od ključnih karakteristika je da (1R,2R)-tramadol dominantno utiče na preuzimanje serotonina, dok (1S,2S)-tramadol snažnije inhibira preuzimanje noradrenalina. Na ovim mehanizmima se zasniva dualni mehanizam delovanja tramadola. Tramadol se u prometu nalazi isključivo kao racemska smeša, koja sadrži 50% (1R,2R)-tramadola i 50% (1S,2S)- tramadola (10).

Mehanizam delovanja tramadola

Tramadol ima dualni mehanizam delovanja: opioidni i monoaminergički. Opoidni mehanizam delovanja: tramadol i njegovi aktivni metabolit O-dezmetiltramadol (M1) deluju kao agonisti na μ-opinoidnim receptorima u centralnom nervnom sistemu. Vezivanjem za ove receptore menja se percepcija bola u mozgu i kičmenoj moždini, čime se smanjuje intenzitet signala bola koji stiže do mozga. Ovo je tipičan mehanizam delovanja opioidnih analgetika, poput morfina, iako tramadol ima manji afinitet prema μ-receptorima u poređenju sa morfinom. Monoaminergički mehanizam delovanja: tramadol takođe utiče na monoaminergički sistem inhibicijom ponovnog preuzimanja noradrenalina i serotonina u sinaptičkoj pukotini. Povećanje koncentracije ovih neurotransmitera u kičmenoj moždini pojačava aktivnost silaznih inhibitornih puteva bola. Ovi putevi fiziološki modifikuju i smanjuju prenos signala bola od perifernog nervnog sistema ka mozgu.

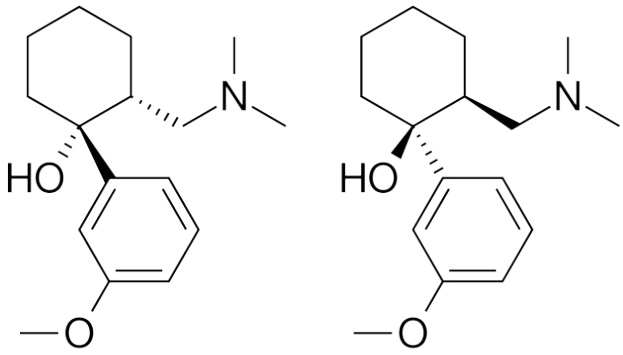
Dualni mehanizam delovanja tramadola kombinuje dva različita puta modulacije bola. Kombinacija ovih mehanizama omogućava značajan analgetski efekat. Monoaminergička komponenta mehanizma delovanja doprinosi smanjenju rizika od respiratorne depresije u poređenju sa klasičnim, potentnijim opioidnim analgeticima, mada taj rizik i dalje postoji (10).

Osnovna razlika u mehanizmu delovanja između jakih i slabih opinoidnih analgetika nije u suštinski različitom principu, već u afinitetu vezivanja i jačini dejstva na opinoidnim receptorima, kao i u njihovoj efikasnosti i maksimalnom terapijskom efektu. Jaki opioidi imaju visok analgetski potencijal i ne pokazuju „plafon efekat" (eng. *celling effect*), što znači da se povećanjem doze može postići veći strepen analgezije, sve do pojave toksičnosti. Za razliku od njih, slabi opioidi imaju manji afinitet za opioidne receptore ili deluju kao parcijalni agonisti i/ili agonisti-antagonisti. Njihova glavna karakteristika je postojanje „plafon efekta", pa se nakon određene doze daljim povećanjem ne povećava analgetički efekat, već samo rizik od neželjenih reakcija. Neželjeni efekti su generalno izraženiji i ozbiljni kod jakih opinoida, što proizilazi iz njihove snažne aktivnosti na receprorima. Dodatna karakteristika pojedinih slabih opioida jeste i monoaminergički mehanizam delovanja, koji uključuje inhibiciju ponovnog preuzimanja serotonina i noradrenalina, čime se posredno doprinosi analgetskom efektu. Ukratko, njihova razlika je prvenstveno kvantitativna (jačina, efikasnost i afinitet vezivanja za receptore), a ne kvalitativna, jer osnovni mehanizam delovanja – vezivanje za opinoidne receptore – ostaje isti (11).

Indikacije za upotrebu tramadola su umeren do jak bol, kada su neopioidni analgetici nedovoljno efikasni, kao i hronična stanja različite etiologije, uključujući bol kod osteoartritisa, fibromialgija ili neuropatski bol, kada je potrebno kontinuirano ublažavanje bola. Takođe se primenjuje u postoperativnom periodu nakon hirurških intervencija. Primena tramadola zahteva lekarski nadzor zbog potencijalnog rizika od razvoja zavisnosti i mogućih neželjenih efekata, uključujući mučninu, pospanost i respiratornu depresiju. Lek je kontraindikovan u slučajevima preosetljivosti na tramadol, akutnog trovanaja alkoholom ili hipnoticima, kao i kod pacijenata sa nekontrolisanom epilepsijom (12).

addiction with non-compliance with the procedure for selecting the drug, and later the dose and duration of its administration (9).

Figure 1. The chemical structure of tramadol



(1*R*,2*R*)-tramadol (1*S*,2*S*)-tramadol

Tramadol as a synthetic opioid analgesic contains two chiral centers (at positions C1 and C2 in the cyclohexane ring), which means that it exists in the form of four different stereoisomers, that is, two pairs of enantiomers: (1R,2R)-tramadol and (1S,2S)-tramadol. The main difference between them is that (1R,2R)-tramadol has a higher affinity for binding to Mu-opioid receptors than (1S,2S)-tramadol. Another key feature is that (1R,2R)-tramadol affects the uptake of serotonin , while (1S,2S)-tramadol inhibits the uptake of noradrenaline more strongly. Its dual mechanism of action is actually based on that. Tramadol is sold in pharmacies exclusively as a racemic mixture (50% 1R,2R-tramadol and 50% 1S,2S-tramadol) (10).

The mechanism of action of tramadol

Tramadol has a dual mechanism of action: opioid and monoaminergic. The opioid mechanism of action means that tramadol and its active metabolite O-desmethyltramadol (M1) act as agonists of μ-opioid receptors in the central nervous system. Binding to these receptors changes the perception of pain in the brain and spinal cord, reducing the intensity of pain signals that reach the brain. This is a typical mechanism of action of all opioid analgesics such as morphine, but tramadol has a lower affinity for receptors than morphine. The monoaminergic mechanism of action means that tramadol also affects the monoaminergic system by inhibiting the reuptake of two key neurotransmitters, noradrenaline and serotonin and enhances the release of serotonin in the synaptic cleft. The increase in the concentration of these neurotransmitters in the spinal cord enhances the descending pain inhibitory pathway. These pathways naturally modify and reduce the transmission of pain signals from the peripheral nervous system to the brain.

The dual mechanism of action of tramadol combines two different pain relief pathways. The combination of these two mechanisms provides a powerful analgesic effect. The monoaminergic part of the mechanism also contributes to a reduction in the risk of respiratory depression compared to classical – strong, more potent opioids, although this risk still exists (10).

The main difference between strong and weak opioid analgesics related to their mechanism of action is not in the essentially different principle, but in the binding affinity and strength of antagonistic effect on opioid receptors, as well as in their efficiency and maximal therapeutic effect. Strong opioids have a very high analgesic potential and do not have a “ceiling” effect, which means that by increasing the dose, a higher level of analgesia can be achieved (until the level of toxicity is reached). In contrast, weak opioids have a lower affinity for opioid receptors or act as partial agonists or mixed agonists-antagonists. The main difference is that weak opioids have a “ceiling”, so increasing the dose does not increase the analgesic effect, but only the risk of adverse reactions. Side effects are generally more pronounced and severe with strong opioids and result from their strong receptor activity. The advantage of weak opioids is in their mechanism of action, which is not opioid, but related to inhibiting the reuptake of serotonin and noradrenaline, which indirectly contributes to its analgesic effect. In short, their difference is primarily quantitative (strength, efficiency and affinity of binding to receptors) rather than qualitative (the basic mechanism is the same – binding to opioid receptors) (11).

Indications for the use of tramadol are moderate to severe pain, when non-opioid analgesics are insufficiently effective, and in chronic conditions of various origins, including osteoarthritis pain, fibromyalgia or neuropathic pain, when continuous pain relief is required. It is also used in post-operative recovery after surgical interventions. The use of tramadol requires medical supervision due to the potential risk of addiction and side effects including nausea, drowsiness and breathing problems. It must not be used in cases of hypersensitivity to tramadol, acute poisoning with certain substances (alcohol, sleeping pills) or if the patient has uncontrolled epilepsy (12).

Resorpcija i metabolizam tramadola

Tramadol se dobro resorbuje nakon oralne primene (90%). Analgetski efekat nastupa nakon 20-30 minuta i traje 3-6 sati. Biološka raspoloživost nakon oralne primene iznosi u proseku 65% (70-75% oralno, 77% rektalno, 100% intramuskularno) (13). Metabolizam tramadola se odvija u jetri putem demetilacije i glukuronidacije, uz učešće enzima CYP2D6 i CYP3A4 enzima. Ovi enzimi imaju ključnu ulogu u metabolizmu brojnih lekova i utiču na brzinu biotransformacije, što može dovesti do varijacija u terapijskom odgovoru, ali i do povećanog rizika od toksičnosti. Enzimska aktivnost određuje brzinu metabolizma pojedinih lekova, što može rezultovati sporijom ili bržom biotransformacijom, a samim tim i smanjenom efikasnošću terapije ili povećanim rizikom od toksičnosti i ispoljavanja neželjenih efekata. Odgovarajuće analgetsko dejstvo se ne može postići ukoliko pacijent ima smanjenu funkciju ili potpuni nedostatak ovog enzima. Procene ukazuju da oko 7% populacije pripadnika bele rase ima nedostatak ovog enzima. Međutim, ukoliko pacijent ima izrazito ubrzan metabolizam, postoji rizik od nastanka neželjenih dejstava usled toksičnosti opioida čak i prilikom primene najčešće propisivanih doza (14,15). Učestalost izrazito brzih metabolizera povezana je sa prisustvom razlicitih alelnih varijanti citohroma P450(CYP) 2D6. Aleli se mogu klasifikovati prema nivou aktivnosti enzima CYP2D6 koji kodiraju, na funkcionalne, nefunkcionalne i alele sa smanjenom funkcijom. Poznato je i da učestalost alela CYP2D6 varira među rasnim i etničkim grupama. Generalno, kod evropske bele populacije i njihovih potomaka funkcionalna grupa alela je dominantna sa učešćem od 71%, dok nefunkcionalni aleli pretstavljaju 26% varijabilnosti, pri čemu najčešće dominir alel CYP2D6*4. Kod azijske populacije i njihovih potomaka, funkcionalni aleli predstavljaju samo 50% učestalosti alela CYP2D6. Azijati i stanovnici pacifičkih ostva imaju visoku učestalost alela sa smanjenom funkcijom CYP2D6*10 (medijana oko 41%), što doprinosi pomeranju populacije u desno u odnosu na metaboličke stope i ukazuje na sporiji metabolizam lekova. Informacije o američkim starosedeocima iz Severne, Centralne i Južne Amerike ukazuju na relativno nisku stopu učestalosti CPY2D6*10, što se može objasniti efektom „osnivača". Kod populacije afričkog porekla učestalost funkcionalnih alela iznosi oko 50%. I kod Afrikanaca i kod Afroamerikanaca široko su zastupljeni aleli sa smanjenom funkcijom, koji čine oko 35% ukupne varijabilnosti alela, pri čemu uglavnom dominira CYP2D6*17. Međutim, Afroamerikanci imaju više nego dvostruko veću medijanu učestalosti nefunkcionalnih alela u poređenju sa autohtonim afričkim populacijama (14,5% naspram 6,3%), što je primarno posledica istorijskog genetičkog mešanja sa populacijama evropskog porekla. Nefunkcionalni aleli i aleli sa smanjenom funkcijom zajedno čine oko 50% ukupne učestalosti alela u populacijama afričkog porekla, pri čemu je genetički diverzitet znatno veći u poređenju sa azijskim populacijama.

Budući da aleli koji kodiraju odsutnu ili smanjenu funkciju enzima jasno utiču na metaboličku aktivnost i odgovor na lekove čiji se metabolizam odvija posredstvom CYP2D6, neophodna su dalja istraživanja u populacijama u kojima ovi aleli igraju glavnu ulogu. Takva istraživanja omogućila bi formulisanje optimalnih preporuka za doziranje zasnivano na principima farmakogenetike. Iz svega navedenog prizilazi da individualne razlike u metabolizmu lekova imaju značajan uticaj na izbor doze i dužini primene terapije, čime se opravdava individualni pristup u primeni leka (16).

Tramadol ima linearnu farmakokinetiku unutar terapijskog raspona doza. Veza između koncentracija leka u serumu i analgetskog dejstva zavisna je od doze, ali u izolovanim slučajevima može značajno varirati (17). Terapijski efekat se najčešće postiže pri koncentracijama u serumu od 100 do 300 ng/mL. Linearna farmakokinetika terapijskom rasponu podrazumeva da se koncentracija leka u krvi menja proporcijalno promeni primenjene doze. Tako, povećanje doze dovodi do proporcionalnog povećanja koncentracije leka u plazmi, pod uslovom da se koncentracije i dalje nalaze unutar terapijskog opsega. Ovakva linearna farmakokinetika ukazuje na to da metabolički i eliminacioni putevi leka nisu zasićeni, odnosno da enzimi i transportni proteini koji učestvuju u ovim procesima imaju dovoljan kapacitet za obradu leka čak i pri višim koncentracijama unutar terapijskog opsega. Ovaj princip omogućava lekarima da relativno lako predvide kako će prilagođavanje doze uticati na nivo leka kod pacijenta. Većina klinički korišćenih lekova prati linearnu farmakokinetiku. (18).

S obzirom na to da u rutinskoj kliničkoj praksi ne postoji mogućnost individualnog određivanja aktivnosti ovog enzima pre uvođenja tramadola, neophodan je oprez i pažljivo praćenje kliničkog odgovora kod svakog pacijenta. Posebnu pažnju treba posvetiti titraciji doze i dužini primene leka, kako bi se

Absorption and metabolism of tramadol

Tramadol is well absorbed after oral administration (90%). The effect is manifested after 20-30 minutes and lasts 3-6 hours. Bioavailability after oral administration is on average 65% (70-75% oral, 77% rectal, 100% intramuscular) (13). Metabolism of tramadol takes place in the liver (mediated by demethylation and glucuronidation) through CYP2D6 and CYP3A4 enzymes (it is crucial for the metabolism of 60% of drugs). These enzymes and their presence are responsible for the metabolism, speed of absorption and the possibility of achieving a good effect through their action, but also for the occurrence of toxicity. This enzyme has impact on how quickly the body processes certain drugs, which can lead to slower or faster absorption of the drug, and therefore, potentially less effective therapy or the risk of toxicity or side effects. An adequate analgesic effect cannot be achieved if the patient has a reduced function or a complete lack of this enzyme. Estimates indicate that 7% of the Caucasian population is deficient in this enzyme. However, if a patient has extremely fast metabolism, there is a risk of side effects due to opioid toxicity even when using the most commonly prescribed doses (14,15). The frequency of extremely fast metabolizers is seen based on the presence of different allelic variants of cytochrome P450 (CYP) 2D6. However, they can be classified according to the level of the activity based on which they encode the enzyme CYP2D6 into functional, non-functional and groups with reduced function. It is also known that the frequency of CYP2D6 allele varies between racial/ethnic groups. In general, in European Caucasians and their descendants, the functional group of alleles is dominant with a participation of 71%, and non-functional alleles represent 26% of the variability, mainly CYP2D6*4. In Asians and their close descendants, functional alleles account for only 50% of CYP2D6 allele frequency. Asians and Pacific Islanders have a high frequency (median = 41%) of alleles with reduced function, CYP2D6*10, which contributes to a rightward metabolic shift in relation to metabolic rates, which indicates slower metabolisms. Information on American Indians from the North (Canada), Central and South America points to a relatively low frequency rate of CPY2D6*10, which may be attributed to a “founder” effect. On the other hand, in populations of African origin, the frequency of functional alleles is about 50%. In both Africans and African Americans, alleles with reduced function are widely represented, accounting for about 35% of the total allelic variability, with CYP2D6*17 mostly dominating. However, African Americans have more than twice the median frequency of non-functional alleles compared to native Africans (14.5% vs. 6.3%), which is primarily the consequence of the genetic admixture with populations of European origin. Non-functional alleles and alleles with reduced function together represent about 50% of allele frequency in black populations, exhibiting significantly greater genetic diversity compared to Asian populations.

Since alleles encoding no or reduced function clearly affect the metabolic activity of drugs mediated by CYP2D6, further research is needed in populations where these alleles play a major role in order to ensure that optimal dosing recommendations are based on empirical pharmacogenetics. Therefore, it can be concluded that the individuality in metabolizing the drug is an important factor and has impact on the dosage of the drug, which justifies the individual approach to the dosage and length of drug administration (16).

Tramadol has a linear pharmacokinetics within the therapeutic dose range. The relationship between serum concentrations and analgesic effect is dose-dependent, but in isolated cases it can vary significantly (17). Effectiveness is usually achieved at serum concentrations 100-300 nanograms/ml. Linear pharmacokinetics during the therapeutic range means that the concentration of the drug in the blood changes proportionally to the change in the dose of the drug within doses used to achieve the therapeutic effect. If the drug dose is doubled, the concentration of the drug in the plasma will also double, provided that this new concentration is still within the therapeutic range. The linear pharmacokinetics of this drug means that the metabolic (degradation) and elimination (excretion) pathways of the drug are not saturated. Enzymes and transport proteins that participate in these processes have sufficient capacity to process the drug even at higher concentrations within the therapeutic range. This principle allows doctors to predict relatively easily how dose adjustments will affect drug levels in patients. Most clinically used drugs follow linear pharmacokinetics (18).

Given that in routine practice, there is no possibility of individually determining the activity of this enzyme before the introduction of tramadol, caution and careful monitoring of the clinical response in each patient is necessary. Special attention should

blagovremeno prepoznali znaci neželjenih reakcija i sprečilo njegovo toksično delovanje.

Tramadol se izlučuje iz organizma je preko bubrega, putem urina (oko 95%). Približno 30% primenjene doze izlučuje se nepromenjeno, dok se oko 60% eliminiše u obliku metabolita. Preostali deo izlučuje se u obliku neidentifikovanih metabolita (19).

Poluvreme eliminacije tramadola

Dosadašnja istraživanja pokazuju da poluvreme eliminacije tramadola iznosi od 1,4 do 6,3 sata. Sve ovo je veoma bitno kada se radi o primeni leka kod onih pacijenata koji imaju oštećenu funkiju bubrega i jetre (9), bilo da se radi o oštećenju zbog bolesti ili smanjenoj funkciji povezanoj sa starenjem. U terapiji je potrebno koristiti najmanju efektivnu dozu za postizanje analgezije. Ukupna dnevna doza od 400 mg tramadol-hidrohlorida ne bi trebalo da bude prekoračena. Kod odraslih i adolecsenata starijih od 12 godina, u akutnim stanjima primenjuje se početna doza od 100 mg. Nakon toga daju se doze od 50 mg ili 100 mg u vremenskim intervalima od 4 do 6 sati, dok trajanje terapije treba uskladiti sa kliničkim potrebama i indikacijama. Kod hroničnih stanja preporučuje se početna doza od 50 mg, nakon čega se doza prilagođava intenzitetu bola. Kod starije populacije (iznad 75 godina), kao i kod osoba sa oštećenjem funkcije jetre i bubrega, neophodan je poseban oprez i razmatranje produženja intervala između doza, u skladu sa individualnim potrebama pacijenta i izmenjenim metabolizmom i eliminacijom leka iz organizma. Kratkotrajna primena tramadola (od nekoliko dana do nekoliko nedelja) generalno se smatra bezbednom. Međutim, kod dugotrajne primene neophodno je kontinuirano praćenje od strane lekara, pošto rizik od zavisnosti i drugih neželjenih efekata značajno raste nakon tri meseca neprekidne upotrebe (20).

Kada je upotreba tramadola sigurna, a kada nije?

Tramadol se moze primenjivati nekoliko dana do nekoliko nedelja uz nadzor lekara. Dugotrajna primena leka (npr. duže od tri meseca u kontrolisanim studijima, a u pojedinim slučajevima i do šest meseci kod bola povezanog sa malignim oboljenjima) opravdana je samo ukoliko se proceni da je terapijska korist veće od potencijalnih rizika i uz adekvatno praćenje. Ako se lek koristi duže vreme, prekid terapije mora biti postepen, uz smanjivanje doze prema preporuci lekara, kako bi se izbegla pojava apstinencijalnih simptoma.

Primena tramadola smatra se rizičnom u sledećim situacijama: upotreba leka duže od nekoliko meseci, zbog povećanog rizika od razvoja zavisnosti, prekoračenje maksimalne dnevne doze od 400 mg ili češćim uzimanjem leka, naročito kod starijih pacijenata, nagli prekid terapije, kao i istovremena primena sa određenim lekovima, kao što su pojedini antidepresivi, MAO inhibitori ili drugi opioidi, što može dovesti do ozbiljnih stanja, uključujući serotoninski sindrom (21).

Simptomi i znaci zavisnosti od tramadola

Zavisnost od tramadola može se razviti pri dugotrajnoj primeni ili pri upotrebi doza većih od preporučenih. Znaci koji ukazuju na razvoj zavisnosti su: vrtoglavica, mučnina, povraćanje, gubitak apetita, opstipacija, pospanost, suva usta i glavobolja. Kod pojedinih pacijenata mogu se javiti i grčevi ili epileptički napadi (22). Lečenje zavisnosti obično uključuje kombinaciju farmakološke terapije i psihološke podrške, uz postepeno smanjivanje doze pod medicinskim nadzorom, kako bi se izbegli simptomi apstinencijalnog sindroma. Kratkoročni efekti zloupotrebe su euforija, smanjenje osećaja bola, pospanost, smanjena budnost, mučnina, povraćanje i respiratorna depresija. Ovi efekati mogu biti opasni jer smanjen osećaj bola može dovesti do toga da pacijent ne prepozna povrede ili druge zdravstvene probleme, što može imati teške posledice. Smanjena budnost dodatno povećava rizik od nesreća ukoliko osoba zaspi na poslu ili tokom vožnje. Dugoročni efekti zloupotrebe su fizička i psihička zavisnost, tolerancija, kao i fizički i mentalni zdravstveni problem. Ako je osoba koristila tramadol duži vremenski period, razvijaju se dugoročni efekti koji mogu ostaviti trajne posledice. Dugotrajno korišćenje tramadola u neodgovarajuće svrhe može dovesti do fizičke ili psihičke zavisnosti, za čije je lečenje potrebna stručna pomoć. Ako se tramadol uzima u većoj dozi od propisane, može se razviti tolerancija, koja može dovesti do potrebe za sve većom dozom leka. Osim toga, fizički i mentalni problemi su gotovo uvek prisutni, a neki od njih su problemi sa srcem, jetrom, depresija i anksioznost (23). Zloupotreba tramadola predstavlja ozbiljan problem, a osobi koja pokušava da prevaziđe zavisnost treba pružiti kostantan medicinski nadzor kao podršku okoline. Zavisnost od tramadola počinje prekoračenjem doze leka ili smanjivanjem intervala uzimanja leka. Zavisnost se razvija postepeno, a brzina njenog napredovanja zavisi od individualnih karakteristika. Kao i kod svake zavisnosti, postoje

be paid to the titration of the dose and the duration of drug administration, in order to recognize the signs of adverse reactions in a timely manner and prevent its toxic effects.

Excretion from the body is through the kidneys via urine (95%). About 30% of the administered dose is excreted unchanged, while approximately 60% is eliminated as a metabolite. The remaining part is excreted as an unidentified or non-extractable metabolite (19).

The elimination half-time of tramadol

Previous research shows that the elimination half-time of tramadol is from 1.4 to 6.3 hours. This is very important when it comes to the application of this drug in those patients who have problems with the kidneys and liver (9), whether the damage is caused by disease or reduced function is caused by patients' age. It is necessary to use the smallest effective dose in therapy to achieve analgesia. The total daily dose of 400 mg tramadol hydrochloride should not be exceeded. Adults and adolescents from 12 years of age in acute conditions receive an initial dose of 100 mg. After that, doses of 50 mg or 100 mg are applied, in time intervals of 4-6 hours, and the length of therapy should be in accordance with clinical needs according to indications. In chronic conditions, an initial dose of 50 mg is administered, and then the dose is adjusted to the intensity of the pain. In the elderly population (over 75 years) and those with liver and kidney disorders, one should be careful and carefully consider extending the dosing interval, in accordance with patient's needs (with special emphasis on altered metabolism and elimination of the drug from the body). The use of tramadol is generally considered safe for the short-term use (a few days to a few weeks). For the long-term use, safety depends on continuous monitoring by a physician, and the risk of addiction and other side effects increases significantly after three months of continuous use (20).

When is tramadol safe to use?

Tramadol can be used from several days to several weeks, under the supervision of a doctor. Longer use of this drug (e.g. longer than three months in controlled studies, and in some cases up to six months for cancer pain) is allowed only if it is estimated that benefits outweigh the risks with adequate monitoring. If the drug is used for a long time, the cessation must be gradual, with a reduction in the dose according to the doctor's instructions in order to avoid withdrawal symptoms.

The use of tramadol is not safe in the following situations (21): the use of the drug for more than several months because the risk of developing addiction increases, by exceeding the dose (maximum daily dose 400 mg) or by taking the drug more often, especially in elderly patients as well as by abruptly stopping the drug and taking the drug with some other drugs (such as some antidepressants, MAO inhibitors or other opioids), which can lead to serious conditions such as serotonin syndrome.

Symptoms and signs of tramadol addiction

Addiction to tramadol can develop when the drug is used for a long period of time or in higher doses than recommended. Signs of addiction are: dizziness, nausea, vomiting, loss of appetite, constipation, drowsiness, dry mouth and headache. Some patients using tramadol may also experience convulsions or epileptic seizures (22). The treatment of addiction usually involves the combination of therapy and support, as well as gradual drug dose reduction under the medical supervision in order to avoid side effects of withdrawal. Short-term effects of abuse include euphoria, decreased pain sensation, drowsiness, decreased alertness, nausea, vomiting, and breathing problems. Some of the short-term effects can be dangerous, because due to excessive use of the drug, there may be a reduced sensation of pain, which can further endanger the patient's health. The inability to feel pain can lead to some injuries or other health problems, which in some cases can be fatal. Decreased alertness can cause a person to fall asleep at work or while driving. Long-term effects of abuse are physical dependence, psychological dependence, tolerance, physical and mental health problems. If a person has used tramadol for a long period of time, long-term effects are created and they can leave permanent consequences. Long-term use of tramadol for wrong purposes can lead to physical or psychological dependence, whose treatment requires professional help. If tramadol is taken in a higher dose than prescribed, tolerance may develop, which may lead to a strong desire for an ever-increasing dose of the drug. In addition, physical and mental problems are almost always present, and some of them include problems with the heart, liver, depression and anxiety (23). The abuse of tramadol is a serious problem, and a person who tries to solve the problem of addiction should be provided constant medical supervision and surrounding support. Addiction

određeni faktori koji utiču na to: biološki, psihološki, socijalni, tj. terapiska upotreba, samolečenje, euforija, stres i genetska predispozicija. Tramadol je jedan od onih lekova koji, iako propisan u terapijske svrhe, ipak može dovesti do razvoja zavisnost. U tom slučaju pacijent nesvesno i nenamerno razvija zavisnost. Lek vremenom prestaje da deluje u propisanoj dozi, i dolazi do prekomerne upotrebe, bilo povećanjem pojedinače doze, bilo skraćivanjem intervala između uzimanja leka ili povećanjem maksimalne dnevne doze. Genetska predispozicija ima značajnu ulogu u stvaranju zavisnosti, pa tako pacijenti koji u porodičnoj anamnezi imaju prekomernu upotrebu ili zloupotrebu uzimanja lekova poput tramadola ili drugih psihoaktivnih supstanci mogu biti pod većim rizikom od razvoja zavisnosti (npr. zavisnost od droga ili alkohola). Treba naglasiti da zavisnost od tramadola nije uvek namerna niti svesna.

Odvikavanje od tramadola

nakon što pacijent koji redovno uzima tramadol naglo prekine sa korišćenjem leka ili smanji dozu, dolazi do pojave simptoma povlačenja, koji se najčešće ispoljavaju u vidu anksioznosti, depresije, nervoze, povraćanja i bolova u mišićima. Ovi simptomi obično počinju 12-24 sata nakon uzimanja poslednje doze leka i ponekad mogu trajati i nekoliko nedelja (24).

Prema navodima pacijenata, simptomi su najizraženiji izmedju drugog i četvrtog dana, kada su tegobe na vrhuncu. Medicinska i psihološka podrška imaju veoma važnu ulogu u procesu odvikavanja od upotrebe tramadola. Postepeno smanjenje doze leka značajno je i u prevenciji razvoja simptoma apstinencijalne krize. Tokom odvikavanja od tramadola često dolazi do različitih emocionalnih stanja, tako da je psihološka podrška od velikog značaja za uspešno postizanje terapijskog cilja. Preporučuje se i izbegavanje svih situacija koje kod pacijenta mogu izazvati ponovnu želju za uzimanjem leka i dovesti do recediva zavisnosti. Preporučuje se i usvajanje zdravih životnih navika. Tretman zavisnosti od tramadola obično uključuje kombinaciju medicinskih intervencija, terapijske podrške i psihološke terapije. Proces odvikavanja sastoji se od nekoliko međusobno povezanih koraka: postavljanje dijagnoze, detoksikacija, psihološka podrška i terapija, edukacija, kao i održavanje postignutih rezultata nakon tretmana.

Detoksikacija podrazumeva potpuno isključivanje leka ili smanjenje telesne zavisnosti od leka. Paralelno sa detoksikacijom sprovodi se psihoterapija, koja ima ključnu ulogu u postizanju dugoročnog uspeha lečenja. Kako bi se pomoglo pacijentu koji se bori sa zavisnošću, potrebna su inidividualna savetovanja, kao i porodična i grupna terapija. Na taj način se pacijent lakše suočava sa problemom zavisnosti. Za lekare je veoma važna činjenica da „lek istovremeno predstavlja i lek i otrov!" Kada se koristi prema indikacijama i u sklasu sa uputstvima, ispoljava svoje pozitivno dejstvo, dok u slučaju nepoštovanja indikacija, terapiskih doza, vremenskih intervala i dužine trajanja terapije može ispoljiti negativne efekte. Veoma je važno edukovati pacijenta tokom lečenja, odnosno odvikavanja od tramadola, kako bi naučio da izbegne ponovnu upotrebu i zloupotrebu leka (25).

Pravna regulativa za propisivanje tramadola

Lek tramadol se od 1994. godine propisuje u skladu sa zakonskim propisima koji regulišu izdavanje lekova koji sadrže opijate, ali bez statusa strogo kontrolisane opojne droge, kakav imaju morfin ili heroin (9). U Srbiji se propisuje od sredine 1990-ih godina. Tramadol je prvi put sintetizovan 1962. godine, dok je na svetsko tržište uveden 1977. godine u Nemačkoj. Ubrzo nakon toga počeo je da se registruje i primenjuje širom sveta, uključujući i tadašnju Jugoslaviju. Iako precizan datum prve registracije u Srbiji nije lako utvrditi, dostupni podaci Agencije za lekove i medicinska sredstva Srbije (ALIMS) pokazuju da su dozvole za lekove koji sadrže tramadol, uključujući i brend „Trodon" proizvođača Hemofarm, obnavljane i izdavane tokom 2000-ih i 2010-ih, što ukazuje na to da je lek bio prisutan na tržištu i znatno ranije. Od 1994. godine, kao što je prethodno navedeno, lek je bio dostupan i propisivan, ali pod drugačijim, manje strogim režimom kontrole nego danas.

Tramadol je sintetički opioidni analgetik i koristi se za lečenje umerenog do jakog bola. Iako je opioid, u mnogim zemljama, uključujući Srbiju (tadašnju SR Jugoslaviju), nije bio klasifikovan u istu, najstrožu, kategoriju kontrolisanih supstanci kao klasični opijati (Lista I ili II opojnih droga), što je značilo da je njegovo propisivanje bilo jednostavnije, ali i dalje podložno određenim kontrolama. Propisivao se na lekarski recept, pri čemu je lekar procenjivao intenzitet bola i individualni odgovor pacijenta na lek, uz preporuku primene najniže efektivne doze. Već tada, kao i danas, postojala su upozorenja o riziku od zloupotrebe, razvoja zavisnosti i simptoma obustave, zbog čega je bilo neophodno procenjivati potrebu za nastavkom terapije u redovnim intervalima. Zbog potencijala za zloupotrebu, često je pominjan u kontekstu lakog

to tramadol begins with exceeding the dose of the drug or reducing the interval of taking the drug. Addiction develops gradually, and the speed at which the addiction will progress is individual and depends on the person. As with any addiction, there are certain factors that influence it: biological, psychological, social, that is, therapeutic use, self-medication, euphoria, stress and genetic predisposition. Tramadol is one of those drugs that, although prescribed for therapeutic purposes, can still be addictive. In that case, the patient begins to develop addiction completely unconsciously and unintentionally. The drug stops working in the prescribed amount, so excessive consumption begins, by increasing the individual dose or shortening the time between doses, thus increasing the maximum dose. Genetic predisposition plays a great role in creating addiction, so patients who have a family history of excessive use or abuse of drugs like tramadol or other substances may be at a higher risk (drug or alcohol addicts). It should also be said that addiction to tramadol is not always intentional or conscious.

Weaning off tramadol

After a patient who regularly takes tramadol abruptly stops using the drug or reduces the dose of the drug, withdrawal symptoms appear, and they are most often manifested in the form of anxiety, depression, nervousness, vomiting and muscle pain. These symptoms usually begin 12-24 hours after taking the last dose of the drug and sometimes last up to several weeks (24).

According to the testimony of patients, these symptoms are mostly felt between the second and fourth day, when these discomforts are at their peak. Medical and psychological support plays a very important role in weaning off tramadol. A gradual reduction in the dose of the drug is very important in preventing the development of addiction symptoms. When weaning off tramadol, different emotional states often occur, so psychological support is very important for achieving the goal. It is recommended to avoid all situations in which the patient may return to the desire to repeat situations that can cause addiction again. The recommendations also include introducing healthy habits. The treatment of tramadol addiction usually involves a combination of medical interventions, therapeutic support, and psychological therapy. The withdrawal process consists of several steps, which are connected: diagnosis, detoxification, psychological support and therapy, education and maintenance after treatment.

Detoxification means a complete discontinuation of drugs, or reducing the body's dependence on the drug. In parallel with detoxification, psychotherapy is carried out, which plays a key role in the long-term success. In order to help a patient who struggles with addiction, individual counseling is needed, as well as family and group therapy. In this way, it is easier for the patient to face the problem he has. It is very important for doctors not to forget that: "Medications act as both medicine and poison at the same time!" When they are used according to the indications and instructions, they exhibit their positive effect, and in the other case, when indications, therapeutic doses, time intervals and duration of the therapy are not respected, then they exhibit their negative effect. It is very important to educate the patient during treatment (withdrawal from tramadol) so that the patient learns how to avoid repeated use – abuse (25).

Legal regulations for prescribing tramadol

The drug tramadol has been prescribed since 1994 in accordance with the legislation that regulates the prescription of drugs that contain opiates, but without a status of a strictly controlled narcotic drug such as morphine or heroin (9). It has been prescribed in Serbia since 1990s. Tramadol was synthesized first in 1962, and was introduced to the world market in Germany in 1977. Soon after, it began to be registered and administered all over the world, including the former Yugoslavia. Although the precise date of the first registration in Serbia is not easy to determine, available data of the Agency for Medicines and Medical Devices of Serbia show that licenses for drugs containing tramadol, including the brand "Trodon" produced by Hemofarm were renewed and issued during the 2000s, which implies that the drug was present on the market long before this time. Since 1994, as previously stated, the drug has been available and prescribed, but under a different, less strict regime of control than today.

Tramadol is a synthetic opioid analgesic and is used to treat moderate to severe pain. Although it is an opiod, in many countries including Serbia (then the former Yugoslavia), it was not classified in the same, strictest category of controlled substances as classic opiates (List I or II narcotic drugs), which meant that its prescription was simpler, but still subject to certain controls. It was prescribed by a doctor's prescription, whereby the doctor assessed the intensity

dobijanja i preprodaje, uprkos tome što je snažan lek. Detaljni propisi o izdavanju i propisivanju lekova koji sadrže tramadol definisani su pravilnicima o načinu propisivanja i izdavanja lekova. Ukratko, od 1994. godine Trodon se propisuje kao snažan analgetik na lekarski recept, uz svest o rizicima zavisnosti i zloupotrebe, ali bez najstrožijih ograničenja koja važe za druge opijate. Zbog svog dejstva koje može izazvati euforiju, postoji potencijal za zloupotrebu. Svetska antidoping agencija zabranila je upotrebu tramadola u svim sportskim takmičenjima od 1. januara 2024. godine. Tramadol se izdaje isključivo na lekarski recept i ne sme se koristiti bez medicinskog nadzora, niti se sme naglo prekidati njegova upotreba nakon dužeg perioda korišćenja. Propisivanje leka Trodona (tramadol) u Srbiji (i šire) doživelo je značajne izmene i dopune u regulativi tokom poslednjih godina, prvenstveno zbog sve veće svesti o potencijalu za zloupotrebu i zavisnost, uprkos tome što je i dalje esencijalni lek za lečenje umerenog do jakog bola.

Najvažnija promena odnosi se na klasifikaciju tramadola. U mnogim zemljama, uključujući i Srbiju, tramadol je premešten ili je podvrgnut strožoj kontroli, iako nije uvek svrstan u najstrožu listu opojnih droga kao morfin. Propisivanje je regulisano Zakonom o psihoaktivnim kontrolisanim supstancama i pratećim pravilnicima. Izdavanje se vrši na poseban lekarski recept, uz strožija pravila o načinu propisivanja i izdavanja. Izmenama pravilnika o načinu propisivanja i izdavanja lekova uvedene su mere koje imaju za cilj smanjenje zloupotrebe. U nekim zdravstvenim sistemima je uvedena obaveza propisivanja na „zaštićen" ili poseban (narkotički) recept, dok u Srbiji podrazumeva recepte sa posebnim režimom izdavanja, za razliku od standardnih recepata. To uključuje korišćenje posebnog obrasca recepta, duplog recepta i evidentiranje u knjizi narkotika.

Propisi često ograničavaju količinu leka koja se može izdati na jedan recept, kao i mogućnost ponovnog izdavanja (oznaka „non repetatur" ili slična ograničenja). Zdravstveni radnici su obavezni da procene rizik od zavisnosti pre započinjanja terapije i da redovno prate pacijente, uspostavljajući strategiju za bezbedan prekid terapije. Prelazak na elektronske zdravstvene informacione sisteme omogućava bolje praćenje propisivanja opioda i sprečavanje višestrukog dobijanja recepata od različitih lekara

Agencija za lekove i medicinska sredstva Srbije (ALIMS) uskladila je sažetke karakteristika leka (SmPC) i uputstva za pacijente sa međunarodnim preporukama, uz dodatak strožih upozorenja. Posebno je naglašen rizik od fizičke i psihičke zavisnosti, te je lekarima naloženo da pacijentima objasn bezbednog prekida terapije. Uvedena su stroga ograničenja ili kontraindikacije za primenu tramadola kod dece mlađe od 12 godina, kao i kod adolescenata (12-18 godina) sa određenim respiratornim problemima (npr. opstruktivna sleep apnea). Pojačana su upozorenja o interakcijama sa drugim lekovima, posebno onima koji deluju na centralni nervni sistem ili povećavaju rizik od serotoninskog sindroma. Od 1. januara 2024. godine, Svetska antidoping agencija (WADA) zvanično je dodala tramadol na Listu zabranjenih supstanci u sportu, što nameće dodatna pravila za sportiste i lekare koji ih leče. Svakom profesionalnom sportisti koji bude koristio tramadol počev od navedenog datuma preti doživotna zabrana bavljenja sportom. Ove izmene odražavaju globalni trend ka opreznijem i kontrolisanijem propisivanju opioidnih analgetika.

Zaključak

Tramadol predstavlja efikasan analgetik sa dualnim mehanizmom delovanja, namenjen lečenju umerenog do jakog bola kada neopioidni analgetici nisu dovoljni. Njegova bezbednost i terapiski efekat direktno zavise od individualnog metaboličkog profila pacijenta, prvenstveno od aktivnosti enzima CYP2D6, čiji genetski polimorfizam može dovesti do izostanka dejstva ili pojave toksičnosti. Iako je nezaobilazan u kliničkoj praksi, dugotrajna ili neadekvatna upotreba tramadola nosi visok rizik od razvoja tolerancije, fizičke i psihičke zavisnosti, kao i pojave simptoma apstinencijalne krize. Zbog sve učestalije zloupotrebe, savremena zakonska regulativa i preporuke ALIMS-a zahtevaju stroži nadzor, korišćenje posebnih recepata i pažljivo planiranje prekida terapije. Uloga lekara je presudna u edukaciji pacijenta i individualnom pristupu doziranja, kako bi se iskoristio pun analgetski efekat leka uz minimalizaciju rizika po zdravlje pojedinca i društva.

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of pain and the patient's individual response to the drug, recommending the use of the lowest effective dose. Even then, as today, there were warnings related to the risk of abuse, the development of addiction and withdrawal symptoms, which is why it was necessary to assess the need for continued therapy at regular intervals. Because of its potential for abuse, it is often mentioned in the context of easy acquisition and resale, despite being a powerful drug. Detailed rules on prescribing and dispensing drugs that contain tramadol are defined in the Regulations on prescribing and dispensing medicines. In short, since 1994, tramadol has been prescribed as a powerful analgesic, with awareness of risks of addiction and abuse, but without the strictest restrictions that apply to other opiates. Because of its effect that can cause euphoria, there is a potential for abuse. The World Anti-Doping Agency has prohibited the use tramadol in all sports competitions from January 1st, 2024. Tramadol is only available with a prescription and must not be used without medical supervision, and it should never be stopped abruptly after a long period of use. The prescription of the drug Trodon (tramadol) in Serbia (and beyond) has undergone significant changes and amendments in the regulations in recent years, primarily due to the increasing awareness of the potential for abuse and addiction, despite the fact that it is an essential drug for moderate to severe pain.

The most important change relates to the classification of tramadol. In many countries, including Serbia, tramadol has been moved from the list or subject to stricter control, although it is not always on the strictest list of narcotic drugs such as morphine. Prescription is regulated by the Act on Psychoactive Substances and accompanying regulations. The dispensing of controlled medicines is subject to a special doctor's prescription, with stricter rules on prescribing and dispensing medications. Amendments to the Regulations relating to prescribing and dispensing medications introduced measures aimed at reducing abuse. In some healthcare systems, the obligation to prescribe medications on a "protected" or special (narcotic) prescription has been introduced (which in Serbia means that prescriptions have a special dispensing regime, in contrast to standard prescriptions). This means that a special prescription form is used, including a double prescription and entry in the narcotics book.

Regulations often limit the amount of medicine that can be dispensed per prescription, as well as the possibility of repeated dispensing (label "non repetatur" or similar restrictions). Healthcare professionals are required to assess the risk of addiction before starting therapy and to regularly monitor patients, establishing a strategy for safe discontinuation of therapy. The transition to electronic health information systems enables better monitoring of prescribed opioids and prevention of multiple prescriptions from different doctors.

The Agency for Medicines and Medical Devices of Serbia (Serbian: ALIMS) aligned the summaries of product characteristics (SmPC) and instructions for patients with international recommendations, adding stronger warnings. The risk of physical and psychological dependence was especially emphasized, and doctors were instructed to explain to patients how to safely stop therapy. Strict restrictions or contraindications have been introduced for the use of tramadol in children under 12 years of age, as well as in adolescents (12-18 years) with certain respiratory problems (e.g. obstructive sleep apnea). Warnings about interactions with other drugs, especially those affecting the central nervous system or serotonin syndrome, have been increased. Since January 1st, 2024, the World Anti-Doping Agency (WADA) has officially added tramadol to the List of Prohibited Substances in Sports, which imposes additional rules on athletes and doctors who treat them. Any professional athlete who uses tramadol starting from the specified date is threatened with a lifetime ban from playing sports. These changes reflect a global trend towards more cautious and controlled prescribing of opioid analgesics.

Conclusion

Tramadol is an effective analgesic with a dual mechanism of action intended to suppress moderate to severe pain when non-opioid drugs are insufficient. Its safety and therapeutic effect directly depend on the individual metabolic profile of the patient, primarily the activity of the CYP2D6 enzyme, the variability of which can lead to the absence of effect or the appearance of toxicity. Although it is unavoidable in clinical practice, long-term or inadequate use of tramadol carries a risk of developing tolerance, physical and psychological dependence, with serious symptoms of abstinence crisis. Due to the increasingly frequent misuse, modern legislation and ALIMS recommendations require stricter supervision, use of special prescriptions and careful planning of discontinuation of therapy. The role of the

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doctor is crucial in patient education and individual approach to dosage, in order to use the full analgesic potential of the drug while minimizing health risks for individuals and society, as well.

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