

Primljen/ Received on:04.09.2019
Revidiran / Revised on: 19.09.2019
Prihvaćen/ Accepted on:30.09.2019

INFORMATIVNI RAD
INFORMATIVE ARTICLE
doi:10.5937/asn1980990T

SISTEMSKE NEŽELJENE REAKCIJE NA LOKALNE ANESTETIKE

SYSTEMIC ADVERSE REACTIONS TO LOCAL ANESTHETICS

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Sažetak

Uvod: Lokalni anestetici su najčešće korišćeni lekovi u svakodnevnoj stomatološkoj i medicinskoj, a sve češće i u kozmetičkoj praksi. Danas postoji veliki broj lokalnih anestetika koji su prema strukturi podeljeni na dve grupe: estarske i amidne lokalne anestetike. Iako je njihova primena u svakodnevnom radu uglavnom bezbedna, nije isključena mogućnost pojave negativnih reakcija koje mogu biti psihogene, toksične, imunološke i specifične neželjene reakcije.

Cilj: ovog rada je da ukaže na mehanizam nastanka i simptomatologiju mogućih negativnih reakcija na lokalne anestetike.

Zaključak: Ukoliko dođe do pojave sistemske neželjene reakcije na lokalni anestetik, najveći problem, u kliničkoj praksi, predstavlja prepoznavanje prirode negativne reakcije i pružanje adekvatne terapije u vezi sa nastalom reakcijom. Brzina i sigurnost u prepoznavanju neželjene reakcije na lokalni anestetik, nekada mogu biti od životnog značaja za bolesnika.

Cljučne reči: lokalni anestetici, toksičnost, alergija

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Abstract

Introduction: Local anesthetics are the most commonly used drugs in everyday dental and medical and increasingly in cosmetic practice. Today there are a number of local anesthetics that are divided into two groups based on their structure: ester and amide local anesthetics. Although their use in everyday work is generally safe, there is a possibility of adverse reactions that may be psychogenic, toxic, immunologic and specific adverse reactions.

The aim of this work is to highlight the mechanism of occurrence and symptoms of possible adverse reactions to local anesthetics.

Conclusion: If you experience systemic adverse reactions to the local anesthetic, the biggest problem in clinical practice, is a recognition of the nature of adverse reactions and providing appropriate therapy in conjunction with the resulting reaction. Speed and security to identify adverse reactions to local anesthetic can be of vital importance for the patient.

Key words: local anesthetics, toxicity, allergy

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Uvod

Lokalni anestetici su supstance koje, na mestu primene, privremeno i reverzibilno sprečavaju sprovođenje impulsa kroz nervno vlakno. Predstavljaju najčešće korišćeni lek u svakodnevnoj stomatološkoj i medicinskoj praksi, a danas se sve češće koriste i u kozmetičke svrhe. Prema načinu primene lokalna anestezija može biti površinska i infiltraciona. Procenjuje se da oko šest miliona ljudi svakodnevno primi neki lokalni anestetik¹.

Početak zvanične primene lokalnih anestetika vezuje se za 1884. godinu, kada je rastvor kokaina upotrebljen kao lokalni anestetik za izvođenje oftalmološke hirurške intervencije, a ubrzo iza toga započeta je upotreba istog lokalnog anestetika i u stomatologiji^{2,3}. Danas postoji veliki broj lokalnih anestetika, koji su prema strukturi, odnosno vrsti veze kojom je lipofilni aromatični prsten spojen sa alifatičnim lancem i supstituisanom hidrofilnom amino grupom na drugom kraju molekula, podeljeni na dve grupe: estarske i amidne lokalne anestetike. Estarski lokalni anestetici metabolišu se preko krvne plazme, pomoću pseudoholinesteraze do paraaminobenzojeve kiseline, dok se amidni lokalni anestetici metabolišu u jetri do neaktivnih supstanci.

Primena lokalnih anestetika u svakodnevnoj praksi uglavnom je bezbedna i do negativnih reakcija retko dolazi, naročito kada se oni aplikuju pravilno i u propisanim dozama. Međutim, pojava negativnih reakcija ipak je moguća. U neželjene reakcije na lokalne anestetike spadaju sistemske toksične reakcije, lokalne reakcije, specifične neželjene reakcije na određene lokalne anestetike, alergija i zavisnost⁴.

Autonomne- psihogene reakcije

Ovaj tip reakcija predstavlja najčešće negativne reakcije na lokalne anestetike, koje nisu vezane za dejstvo samog anestetika. Kod određenog broja bolesnika intolerantnih na strah, bol ili neprijatne mirise u ordinaciji, može doći do ekscitacije vegetativnog nervnog sistema, simpatikusa i parasimpatikusa sa vazovagalnom manifestacijom. Nadražaj je zapravo osećaj straha koji kao nervni impuls iz kore velikog mozga, preko limbičkog sistema (*corpus amygdaloideum* i *area reticularis superficialis ventrolateralis*) silazi na simpatičke ganglije, odnosno jezgara vagusa, izazivajući njihovu aktivaciju.

Introduction

Local anesthetics are substances that temporarily and reversibly inhibit conduction through the nerve fiber. They represent the most commonly used drug in everyday dental and medical practice, and are now increasingly used for cosmetic purposes. According to the method of applying local anesthesia can be superficial and infiltration. An estimated six million people daily receives some local anesthetic¹.

Official application of local anesthetic binds to 1884, when the solution cocaine was used as a local anesthetic to perform ophthalmic surgery, and soon after that the same local anesthetic was used in stomatology^{2,3}. Today, there are a large number of local anesthetics which are divided into two groups: ester and amide local anesthetics, based on the structure or the type of connection by which the lipophilic aromatic ring is fused with an aliphatic chain and the hydrophilic substituted amino group at the other end of the molecule. Ester local anesthetics are metabolized by the blood plasma by using pseudo cholinesterase to para amino benzoic acid, whereas amide local anesthetics are metabolized in the liver to inactive substances.

Application of local anesthetics in everyday practice is generally safe and negative reactions occur rarely, especially when they are applied properly and within the prescribed doses. However, the occurrence of adverse reactions is still possible. Adverse reactions to local anesthetics include systemic toxic reactions, local reactions, specific adverse reactions to certain local anesthetics, allergy and addiction⁴.

Autonomous - psychogenic reactions

This type of reaction is the most frequent adverse reaction to local anesthetics, the effect is not related to the anesthetics. A number of patients who are intolerant to fear, pain or unpleasant odors in the office, there may be excitation of vegetative nervous system, sympathetic and parasympathetic nervous system with vasovagal event. Irritation is actually a sense of fear that as a nerve impulse from the cortex of the brain, via the limbic system (*corpus amygdaloideum* and *area reticularis superficialis ventrolateralis*) is moving in sympathetic ganglia or nuclei of the vagus, causing their activation. The stimulation of the vagal centers is reflected in the clinical

Stimulacija vagusnih centara ogleda se u kliničkoj slici: osoba je bleđa, znojna i obično bradikardična, ali ako je jače nadražen simpatikus javlja se tahikardija. Pad krvnog pritiska nastaje zbog vagusne vazodilatacije splanhničkog dela krvotoka. Zbog hipoksije kore velikog mozga, dolazi do kratkotrajnog gubitka svesti. Gubitku svesti mogu prethoditi zamagljenje vida, osećaj mučnine i dispneja. Psihogeni reakcija praćena je, uznemiranošću, znojenjem, vrtoglavicom, dok vazovagalna reakcija u stvari predstavlja progresiju psihološke napetosti, praćenu padom krvnog pritiska, bradikardijom i bledilom, odsustvom reagovanja na spoljne nadražaje sa reverzibilnim gubitkom svesti⁵.

Toksične reakcije na lokalne anestetike

Toksične reakcije na lokalni anestetik mogu biti posledica reakcije na sam lokalni anestetik ili na vazokonstriktor, koji se uobičajeno nalazi u lokalnim anestetičkim rastvorima.

Lokalni anestetici se deponuju u blizinu ciljanih nervnih struktura, ali se značajne količine ubrizganog anestetika uklanjaju sa mesta ubrizgavanja putem sistemske cirkulacije i dospevaju do udaljenih organa. Manje od 3% ubrizganog anestetika prodire u ciljani nerv, dok više od 90% dospeva u sistemska cirkulaciju u roku od 30 minuta⁶. Distribucija lokalnog anestetika u organe zavisi od njihove prokrvljenosti, tako da su gusto vaskularizovani organi, kao što su mozak, srce, pluća, jetra i bubrezi, najviše izloženi delovanju nemetabolisanog lokalnog anestetika. Dotok venske krvi bogate anestetikom u pluća, donekle ublažava uticaj anestetika na ostale organe, ali je sposobnost pluća da brzo ekstrahuju lokalni anestetik ograničena. Najveći deo apsorbovanog anestetika metaboliše se pri prolasku kroz jetru i zavisi od količnika hepatičkog izlučivanja i protoka krvi kroz jetru. Sa druge strane količnik hepatičkog izlučivanja zavisi od odnosa slobodnog anestetika i anestetika vezanog za proteine plazme. Lokalni anestetici vezuju se za plazma proteine, smanjuju slobodnu frakciju LA, što ima klinički značaj, jer su jedini slobodni ili nevezani deo LA. Aktivne koncentracije α_1 -acid glikoproteina (AAG), za koji se vezuje LA, povećavaju se kod onkoloških bolesnika, infarkta miokarda, traume, hirurških intervencija, uremije, što utiče na količinu anestetika koji će se metabolisati u jetri, kao i na njegovu toksičnost⁷. Sistemska oboljenja sa smanjenom funkcijom jetre i ekskretornom funkcijom bubrega, povećavaju mogućnost

presentation: person is pale, sweaty and usually bradycardic, but if sympathetic is highly irritated tachycardia occurs. The fall in blood pressure is due to vasodilation vagal splanchnic work bloodstream. Because of hypoxia cortex, there is a brief loss of consciousness. Loss of consciousness may be preceded by blurred vision, nausea and dyspnea. Psychogenic reaction is followed by disturbance, sweating, dizziness, while vasovagal reaction is in fact a progression of psychological tension accompanied by a drop in blood pressure, bradycardia and pallor, lack of response to external stimuli with reversible loss of consciousness⁵.vagus causing their activation. it is pale, sweaty and usually bradycardic, but if severe

Toxic reactions to local anesthetics

Toxic reactions to a local anesthetics can be caused by a reaction to the local anesthetic itself or vasoconstrictor which is commonly found in local anesthetic solutions.

Local anesthetics are deposited near the target neural structures, but significant amounts of injected anesthetic are removed from the injection site through the circulatory system and reach the distant organs. Less than 3% of the injected anesthetic penetrates the target nerve, while more than 90% reaches the systemic circulation within 30 minutes⁶. Distribution of local anesthetic to the organs depends on their blood supply, so that densely vascularized organs such as brain, heart, lungs, liver and kidneys, are the most exposed to the influence of unmetabolized local anesthetic. The flow of venous blood rich in anesthetic, to the lungs, somewhat mitigates the impact of anesthetic to other organs, but ability of the lungs to extract a local anesthetic quickly is limited. Most of the absorbed anesthetic is metabolized through passage in the liver and depends on the ratio of hepatic extraction and blood flow through the liver. On the other hand hepatic extraction ratio depends on the ratio of free and anesthetic bound to plasma proteins. Local anesthetics bind to plasma proteins, reduce the free fraction of the LA, which has clinical significance because it is the only free or unbound part of LA. The active concentrations of α_1 -acid glycoprotein (AAG) to which LA is bound, are elevated in patients with cancer, myocardial infarction, trauma, surgical intervention, uremia, which affects the quantity of anesthetic to be metabolized in the liver and its toxicity its toxicity⁷.

nastanka sistemskih toksičnih reakcija. Kod osoba sa hepatskom disfunkcijom, koncentracija anestetika dvostruko se povećava u odnosu na zdrave osobe. Lidokain, koji se umereno vezuje za proteine, ima visok količnik hepatske ekstrakcije 70%–75%, dok dugodelujući LA–bupivakain i ropivakain, koji se u visokom procentu vezuju za proteine imaju <50% hepatske ekstrakcije. (Tabela 1. Farmakološki parametri lokalnog anestetika)¹⁰. Kod starijih bolesnika funkcija jetre je značajno smanjena i u 65 godini života ona iznosi svega oko 60% vrednosti u odnosu na funkciju jetre u mladosti¹¹. U toku trudnoće dolazi do niza fizioloških promena koje mogu povećati rizik za ispoljavanje toksičnog efekta lokalnog anestetika. Vezivanje LA za proteine plazme značajno je smanjeno¹², pojačana cirkulacija dovodi do brže apsorpcije anestetika, a progesteron¹³ može povećati osetljivost aksona na blokadu¹³.

Toksični potencijal lokalnog anestetika direktno zavisi od njegove liposolubilnosti. Sa porastom liposolubilnosti lokalnog anestetika sužava se bezbedna granica između poželjnog kliničkog dejstva i neželjenih reakcija. Stepens depresije perifernog nervnog sistema i centralnog nervnog sistema (CNS) u direktnoj su vezi sa koncentracijom lokalnog anestetika u krvi. Lidokain se u manjim serumskim koncentracijama koristi u kliničkoj praksi za supresiju srčanih aritmija, ali u većim koncentracijama indukuje napade. Pri manjim dozama svi lokalni anestetici deluju antikonvulzivno i sedativno¹⁴.

Visoka koncentracija lokalnog anestetika u serumu, izaziva kratkotrajnu stimulaciju, pa depresiju centralnog nervnog sistema. Stimulacija se manifestuje razdražljivošću, nervozom i preteranom govornjivošću bolesnika. Zavisno od nadraženosti nervnih centara javljaju se tremor, glavobolja, mučnina, produbljeno disanje, kao i najteža komplikacija tonično klonični grčevi. U fazi depresije bolesnik može osećati vrtoglavicu, bol u prekordijumu, dezorijentisan je i gubi sposobnost govora, a zatim i svest. Puls je bradikardičan, mada se može javiti i kompenzatorna tahikardija, dok na kraju pada do nemerljivih vrednosti, što vodi akutnom zastoju srca. Disanje je u početku usporeno i plitko, može i potpuno prestati. Različiti lokalni anestetici pokazuju različiti stepen kardiotoksičnosti. Kratkodelujući lokalni anestetici, kojima pripada lidokain, retko dovode do negativnih reakcija i njihova kardiotoksičnost je manja od kardiotoksičnosti dugodeljućih lokalnih anestetika¹⁵.

Systemic diseases with reduced liver function and excretory function of kidneys, increase the possibility of systemic toxic reactions. In patients with hepatic dysfunction, the concentration of the anesthetic is increased twice in comparison to a healthy person⁸. Lidocaine, which is moderately bound to proteins, has a high hepatic extraction ratio of 70-75%, while a long acting LA- bupivacaine and ropivacaine, which are bound to proteins in high percentage, have <50% of hepatic extraction⁹. (Table 1. The pharmacological parameters of the local anesthetic)¹⁰. In elderly patients liver function is significantly reduced and in the 65-th year of life it is only about 60% of the value in relation to the function of the liver in youth¹¹. During pregnancy, there are a number of physiological changes which can increase the risk for manifestation of the toxic effect of the local anesthetic. LA binding to plasma proteins is significantly decreased¹² increased blood circulation leads to faster absorption of the anesthetic, and progesterone can increase the sensitivity of the axon to the blockade¹³.

The toxic potential of local anesthetic directly depends on its liposolubility. With increasing liposolubility of the local anesthetic the safe border between the desirable clinical effects and adverse reactions is narrowed. The degree of depression of the peripheral nervous system and the central nervous system (CNS) is directly related to the concentration of the local anesthetic in the blood. Lidocaine in smaller serum concentrations is used in clinical practice to suppress cardiac arrhythmias, but in higher concentrations induce attacks. At low doses, all local anesthetics act anticonvulsant and sedative¹⁴.

The high concentration of local anesthetic in serum induces a short-term stimulation and central nervous system depression. The stimulation is manifested by irritability, nervousness and excessive speech of the patient. Depending on the excitability of nerve centers, tremor, headache, nausea, deepened breathing and one of the most severe complications - tonic clonical spasms occur. At the stage of depression, the patient may feel dizziness, precordial pain, disorientation and loss of the ability to speak and then consciousness. Pulse is bradycardic, compensatory tachycardia can occur, eventually dropping to undetectable levels and leading to cardiac arrest. Breathing is initially slow and shallow, and can completely stop. Various local anesthetics exhibit varying degrees of cardiotoxicity.

Tabela1. Farmakološki parametri lokalnog anestetika
Table 1. Pharmacological parameters of local anesthetic

Lokalni anestetik Local anesthetic	Klirens (L/min) Clearance (L / min)	Polu-život (min) Half life (min)	Količnik hepatičke ekstrakcije Hepatic Extraction Ratio
Lidokain	0.95	96	0.72
Etidokain	1.11	162	0.74
Mepivakain	0.78	114	0.51
Bupivakain	0.58	162	0.40
Ropivakain	0.73	111	0.40
Levobupivakain	0.47	108	0.67

Od kliničkog je značaja da su doze koje izazivaju toksičnost CNS-a vrlo blizu dozama koje izazivaju ireverzibilni kardiovaskularni kolaps¹⁶. Simptomi toksičnosti CNS-a ne moraju se razvijati postepeno, već može odmah doći do kome i respiratornog zastoja, što se najčešće javlja nakon intraarterijske aplikacije anestetika, ali ovo je retka pojava u praksi. Lokalni anestetici ne dovode do trajnog oštećenja CNS-a, pa se funkcija ovog sistema vraća sa padom koncentracije lokalnog anestetika u krvi. Do trajnog oštećenja može doći samo usled dugotrajne hipoksije nastale usled gubitka svesti, respiratornog zastoja i konvulzija. Kod pojedinih tehnika lokalne anestezije u usnoj duplji, kao što su intraligamentarna i intraosealna tehnika, brzina prodora anestetika u cirkulaciju jednaka je kao i kod intravazalnog ubrizgavanja¹¹. Kako bi prevenirali pojavu toksičnih reakcija na lokalni anestetik, treba imati u vidu maksimalne preporučene doze lokalnog anestetika (Tabela 2)¹⁰.

Short acting local anesthetics, including lidocaine, rarely lead to adverse reactions and their cardiac toxicity is lower than in long-acting local anesthetics¹⁵. Of clinical importance is that the doses inducing CNS toxicity are very close to doses that cause irreversible cardiovascular collapse¹⁶. Toxicity symptoms of the CNS do not have to develop gradually, but may immediately cause coma, and respiratory arrest, which often occurs after the intra-arterial application of anesthetic, but is rare in practice. Local anesthetics do not cause permanent damage to the CNS, so the function of this system returns with a decrease in the concentration of local anesthetic in the blood. Permanent damage may occur only due to long-term hypoxia caused by loss of consciousness, respiratory paralysis and convulsions. In some techniques of local anesthesia in the oral cavity, such as intra-ligament and intraosseous technique, the speed of penetration of the anesthetic in the circulation is the same as in intravascular injection¹¹. In order to prevent the occurrence of toxic reactions in the local anesthetic, it is necessary to bear in mind the maximum recommended dose of a local anesthetic (Table 2)¹⁰.

Tabela 2. Maksimalne preporučene doze lokalnih anestetika¹⁰
Table 2. Maximum recommended doses of topical anesthetics¹⁰

Lokalni anestetik Local anesthetic	Maksimalna doza sa vazokonstriktorom Maximum dose with a vasoconstrictor	Maksimalan broj ampula od 1.8ml sa vazokonstriktorom Maximum number of 1.8ml ampoules with vasoconstrictor maximum dose without vasoconstrictor	Maksimalna doza bez vazokonstriktora Maximum dose without vasoconstrictor
Lidokain	7 mg/kg (do 500mg)	13	4.5 mg/kg (do 300mg)
Artikain	7 mg/kg (do 500mg)	7	/
Mepivakain	6.6 mg/kg (do 400mg)	11	4 mg/kg (do 300mg)
Bupivakain	2 mg/kg (do 200mg)	10	1.5 mg/kg (do 150mg)
Prilokain	8 mg/kg (do 500mg)	8	7 mg/kg (do 400mg)
Etidokain	5.5 mg/kg (do 400mg)	/	4 mg/kg (do 300mg)
Ropivakain	/	/	2.5 mg/kg (do 150mg)

Toksične reakcije na vazokonstriktor

Većina lokalnih anestetika sadrži vazokonstriktor adrenergičkog tipa koji smanjuje resorpciju lokalnog anestetika, smanjuje toksičnost i produžava njegovo dejstvo. Neželjeni toksični efekti vazokonstriktora javljaju se češće nego toksični efekti samih lokalnih anestetika. Treba napomenuti da povišene vrednosti endogenih kateholamina koji se luče direktno u krvotok u slučaju stresa, koji je prisutan u većini stomatoloških, a pogotovo oralnohirurških intervencija, uz unošenje dodatnih količina vazokonstriktora, mogu dovesti do toksičnih koncentracija u krvi. Toksične reakcije na vazokonstriktor ne predstavljaju klasične toksične reakcije već neželjene efekte povećane ekscitabilnosti kardiovaskularnog sistema⁸. Adrenalin je najčešće korišćeni vazokonstriktor u lokalnim anestetičkim rastvorima i deluje kao agonist alfa, beta-1 i beta-2 receptora. Submukozno tkivo sadrži manje krvne sudove u kojima se nalaze samo alfa receptori. Veće sistemske arterije koje utiču na krvni pritisak sadrže daleko više beta-2 receptora, i sa apsorpcijom adrenalina i manje doze izazivaju dilataciju ovih krvnih sudova¹⁷. Najveći uticaj adrenalina najčešće se uočava 5–10 minuta posle injekcije lokalnog anestetičkog rastvora koji sadrži adrenalin, i on naglo opada usled brze razgradnje putem katehol-O-metiltransferaze. Eliminacioni poluživot većine kateholamina (u koje spada i adrenalin) svega je minut do tri minuta, i njihov hemodinamski uticaj kompletno opada 10–15 minuta posle ubrizgavanja¹⁸. Toksično dejstvo vazokonstriktora klinički se manifestuje stimulacijom CNS-a: tahikardijom, porastom krvnog pritiska, palpitacijama, fibrilacijom, glavoboljom i vrtoglavicom. skraćenim dahom, strahom i prisustvom panike, znojenjem, bledilomibolom u sredogruđu^{5,8}.

Specifične neželjene reakcije na određene lokalne anestetike

Kod malog broja bolesnika može doći do razvoja methemoglobinemije, vrlo retkog, ali potencijalno fatalnog oboljenja¹⁹⁻²¹. Methemoglobinemija je retka neženljena reakcija na pojedine lokalne anestetike u kojoj dolazi do razvoja cijanozi sličnog stanja uz odsustvo kardioloških ili respiratornih nepravilnosti.

Toxic reactions to vasoconstrictor

Most local anesthetics contain adrenergic type of vasoconstrictor that reduces the absorption of local anesthetic, reduces toxicity and extends its effect. Undesired toxic effects of vasoconstrictor occur more frequently than toxic effects of local anesthetics themselves. It should be noted that the elevated levels of endogenous catecholamines which are secreted directly into the bloodstream in the event of stress that is present in most of the dental and oral surgery, especially with the introduction of additional quantities of the vasoconstrictor, may lead to toxic levels in blood. Toxic reaction to the vasoconstrictor is not a typical toxic reaction, but a side effect of increased excitability of cardiovascular system⁸. Adrenalin is the most commonly used vasoconstrictor in local anesthetic solutions and acts as agonists of alpha, beta-1 and beta-2 receptors. Submucosal tissue contains smaller blood vessels containing only alpha receptors. Higher systemic arteries which affect blood pressure include far more beta-2 receptors, and with an absorption of adrenaline lower doses cause dilation of these blood vessels¹⁷. The biggest effect of adrenaline is usually observed 5-10 minutes after the injection of local anesthetic solution containing adrenalin, and it declines rapidly due to rapid degradation by catechol-o-methyltransferase. Elimination half-life of most of catecholamines (which include adrenaline) is only 1-3 minutes, and their hemodynamic effect decreases completely after 10-15 minutes after injection¹⁸. Toxic effect of vasoconstrictors is clinically manifested in stimulation of the CNS: tachycardia, increase in blood pressure, palpitations, fibrillation, headaches and dizziness, shortness of breath, fear and panic, sweating, paleness, pain in chests^{5,8}.

Specific adverse reactions to certain local anesthetics

In small number of patients methemoglobinemia can be developed, very rare, but potentially fatal disease¹⁹⁻²¹. Methaemoglobinemia is a rare side effect to the particular local anesthetics which leads to production of cyanosis similar conditions and absence of cardiac or respiratory irregularities.

Dva lokalna anestetika, prilokain i artikain, koja, kada se ubrizgavaju u velikim dozama mogu dovesti do pojave methemoglobinemije, kao što to može učiniti i benzokain koji se koristi za površinsku anesteziju. Methemoglobinemija je uzrokovana metabolitima ovih anestetika-metabolit prilokaina o-toluidin oksidiše gvožđe u hemoglobinu (iz Fe²⁺ u Fe³⁺) i tako izmenjen hem ne vezuje kiseonik a neizmenjeni hemovi na molekulu hemoglobina ne otpuštaju vezani kiseonik. Ovakav oblik hemoglobina naziva se methemoglobin, a stanje kada je prisutan u koncentraciji većoj od 1% naziva se methemoglobinemija. Bolesnik postaje cijanotičan i simptomi se javljaju kada je methemoglobin prisutan u koncentraciji većoj od 15%²². Stanje životno ugrožava bolesnika kada nivo hemoglobina pređe 50%–60%. Simptomi methemoglobinemije obično se javljaju 3–4 časa posle primene većih doza prilokaina (600mg) ili artikaina. Simptomi variraju u zavisnosti od nivoa methemoglobina, ali se kod većine bolesnika javljaju letargičnost i poremećaj disanja, mukoza i nokti postaju cijanotični, a koža pepeljasta. Dijagnoza methemoglobinemije postavlja se na osnovu prisustva cijanoze koja ne reaguje na primenu čistog kiseonika, a karakteristična je arterijska krv braon boje. Definitivni tretman podrazumeva sporu intravensku primenu jednog procentnog metilenaplavog (interesantno je da veće količine izazivaju methemoglobinemiju). Methemoglobinemija uobičajeno se ne javlja kod zdravih bolesnika ukoliko su primenjene doze lokalnih anestetika u granicama preporučenih doza. Kod bolesnikasa urođenom methemoglobinemijom primena artikaina i prilokaina predstavlja relativnu kontraindikaciju¹⁷ i kod njih se preporučuje upotreba drugih lokalnih anestetika.

U specifične neželjene reakcije može se ubrojati i pojava trizmusa kod pojedinih bolesnika nakon primene etidokaina²³.

Alergijske reakcije na lokalne anestetike

Alergijske reakcije na lokalne anestetike vrlo su retke.

Estarski lokalni anestetici imaju veći alergijski potencijal od amidnih, zbog svog metabolita-paraaminobenzoave kiseline, koja ima određeni antigeni potencijal. Danas se uglavnom primenjuju u vidu gelova i krema za površinsku anesteziju ili kao

dodaci medikamentima za topikalnu primenu.

Two local anesthetics prilocaine and articaine, which when injected in high doses can cause methemoglobinemia, and benzocaine which is used for topical anesthesia. Methemoglobinemia is caused by the metabolites of these anesthetics - prilocaine metabolite o-toluidine oxidizes iron in hemoglobin (Fe²⁺ + from Fe³⁺ + in) and thus changed hem does not bind oxygen and unmodified hems on hemoglobin molecule do not release the bound oxygen. This form of hemoglobin is called methemoglobin, and condition when it is present in a concentration greater than 1% is referred to as methemoglobinemia. The patient becomes cyanotic and symptoms occur when methemoglobin at a ratio greater than 15% lifetime²². This condition endangers the patient when hemoglobin levels exceed 50-60%. Methaemoglobinemia symptoms usually appear 3-4 hours after having higher doses of prilocaine (600mg) or articaine. Symptoms vary depending on the level of methemoglobin, but in most patients lethargy and impaired breathing, mucosa occurs, nails become cyanotic, and skin ashens. Methaemoglobinemia diagnosis is made based on the presence of cyanosis, which does not respond to the use of pure oxygen, and arterial brown blood is characteristic. A definitive treatment involves a slow intravenous administration of 1% methylene-blue (it is interesting that larger amounts cause methemoglobinemia). Methaemoglobinemia does not normally occur in healthy subjects if administered doses of local anesthetics are within the recommended dose. In patients with congenital methemoglobinemia application of articaine and prilocaine represents the relative contraindication¹⁷ and they are advised to use other local anesthetics.

Specific adverse reactions also include the occurrence of trismus for some patients after the administration of etidocaine²³.

Allergic reactions to local anesthetics

Allergic reactions to local anesthetics are very rare.

Ester local anesthetics have a larger allergic potential than amide local anesthetics, due to its metabolites-para-amino-benzoic acid that has a specific antigenic potential. It is generally applied in the form of gels and creams for topical anesthesia, or as an adjunct medicament for topical administration.

Kreme protiv hemoroida ili neke kreme za sunčanje sadrže benzokain. Smatra se da oko 5% bolesnika koji primenjuju ove preparate razvija neku od reakcija preosetljivosti na njih²⁴. Kod topikalne primene estarskih lokalnih anestetika načešće se razvija IV tip reakcije preosetljivosti tj. kontaktni dermatit koji se manifestuje eritemom, svrabom, makulo-papuloznom ospom ili pojavom vezikula²⁵. Ovaj tip odložene alergijske reakcije dešava se posredstvom T limfocita u periodu od 12h–72h od izloženosti alergenu, mada se prvi simptomi mogu pojaviti već 2 sata nakon od izloženosti. Kod primene amidnih lokalnih anestetika ovaj tip reakcije javlja se znatno ređe. Ako se radi o infiltracionoj anesteziji javijaju se eritem i edem mekog tkiva na mestu uboda.

Anafilaktička reakcija, tj. prvi tip alergijske reakcije razvija se posredstvom IgE, koji dovodi do degranulacije mastocita i bazofila sa oslobađanjem histamina i ostalih vazoaktivnih supstanci. Anafilaktička reakcija najopasnija je komplikacija primene lokalnih anestetika i javlja se u manje od 1% slučajeva¹⁵. Zbog relativno retke pojave, lekar može podsvesno zanemariti ovu mogućnost i usredsrediti se na lečenje druge nuspojave, što u nekim slučajevima može ugroziti život bolesnika. Postoje slučajevi sa smrtnim ishodom kao posledicom anafilakse posle primene lokalne anestezije²⁶. Simptomatologija podseća na sinkopu, ali bez gubitka svesti – vrtoglavica, bledilo, vlažna koža i suve sluzokože, glavobolja, mučnina, povraćanje, opšta slabost, dispneja, slab puls. Pojava edema mekih tkiva, periorbitalno, usana i jezika može biti praćena edemom laringsa i unutrašnjih organa koji vodi fatalnom ishodu.

Alergija se najčešće javlja kao reakcija na neku od komponenti lokalnog anestetickog rastvora: stabilizirajuće sredstvonaatrijum-bisulfit ili metilparaben, antiseptik ili fungicide i lateks iz instrumenata za anesteziju. Metilparaben je metilestar parahidrobenezove kiseline. Estarski lokalni anestetici metabolišu se u plazmi, pomoću pseudoholinestaze do paraaminobenzoeve kiseline, pa bolesnici koji su alergični na estarske lokalne anesteičke rastvore mogu imati ukrštenu reakciju na amidne lokalne anestetike koji sadrže metilparaben. Osim toga, paraaminobenzoeva kiselina je čest sastojak kozmetičkih preparata. Na natrijum metabisulfit, kao stabilizirajuće sredstvo, naročito su osetljive osobe sa astmom.

Hemorrhoidal creams or some sunscreens contain benzocaine. It is believed that about 5% of patients who use these preparations develop a reaction of hypersensitivity to it²⁴. Topical application of ester local anesthetics most commonly develop type IV of hypersensitivity reactions, i.e. contact dermatitis, which is manifested by erythema, itching, macula or the appearance of vesicles²⁵. This type of delayed allergic reactions occurs through T cells over a period of 12h-72h of exposure to the allergen, although the first symptoms may appear after only 2 hours of exposure. When using amide local anesthetic this type of reaction occurs less often. In the case of infiltration anesthesia, erythema and edema of the soft tissue at the injection site occur.

Anaphylactic reaction, the first type of allergic reaction is developed through IgE, which leads to degranulation of mast cells and basophils with a release of histamine and other vasoactive substances. The most dangerous complication of local anesthetics and occurs in less than 1% cases¹⁵. Because of the relatively rare phenomenon, the doctor may unconsciously ignore this feature and focus on the treatment of other side effects, which in some cases can endanger the patient's life. There are cases with fatal outcome as a result of anaphylaxis after administration of local anesthesia²⁶. Symptomatology reminiscent of syncope but without loss of consciousness. Dizziness, paleness, clammy skin and dry mucous membranes, headache, nausea, vomiting, weakness, dyspnea, weak pulse. Periorbital edema of soft tissue, on lips and tongue can be accompanied by edema of the larynx and the viscera leading to a fatal outcome.

Allergies often occur as a reaction on one of the components of a local anesthetic solution: stabilizing appliance -Na-bisulfite, methyl paraben or, antiseptic or fungicide. Methyl paraben is methyl para-dihydrobenzo acid. Ester local anesthetics are metabolized by plasma, by means of pseudo holinestrase to para- amino- benzoic acid, and patients who are allergic to an ester local anesthetic solutions can have the cross-reaction to an amide local anesthetics containing methyl paraben. In addition, para-amino-benzoic acid is a common ingredient of cosmetic products.

To a sodium meta-bisulfite, as the stabilizing agent, are particularly vulnerable persons with asthma.

Povećan senzibilitet na metabisulfit svakako je i posledica njegove upotrebe u agronomiji, gde se koristi kao antioksidans naprskan na sveže voće i povrće, kako bi se očuvala njihova svežina i izgled. Bolesnici koji navode alergiju na takvu hranu mogu imati ukrštenu reakciju sa lokalnim anestetikima koji sadrže i vazokonstriktor¹⁷. Senzibilitet na bisulfite može biti prisutan kod atopičnih i astmatičnih bolesnika kod kojih se može razviti teži oblik reakcije (bronhospazam)^{27,28}.

Dostupni podaci ukazuju da se skoro na svaki amidni lokalni anestetik u praksi pojavljuje alergijska reakcija, sa određenom rastućom stopom²⁹⁻³⁶. U slučaju sumnje na alergiju na lokalne anestetičke rastvore, preporučuje se primena čistog lokalnog anestetika, bez prisustva stabilizatora koji je mogući antigen, ili upotreba drugog anestetika. Estarski lokalni anestetici imaju ukrštenu reakciju pa stoga alergija na jedan podrazumeva moguću alergiju na drugi anestetik ove grupe. Postoje različiti stavovi po pitanju zamene amidnog lokalnog anestetika koji je izazvao alergijsku reakciju. Nema sigurnih podataka u literaturi da li postoji ukrštena reakcija između anestetika amidne grupe. Ipak postoji verovatnoća da je mogući antigen metaksilen, koji je deo aromatičnog prstena skoro svih amidnih lokalnih anestetika³⁷. Osobama senzibilnimna lidokain, kao pogodna zamena preporučivan je mepivakain, ali se pokazalo da i on daje ukrštenu reakciju sa lidokainom, verovatno zbog prisustva metaksilena u aromatičnom radikal³⁸⁻⁴². Artikain se čini kao sigurnija zamena kod osoba senzibilnih na lidokain, verovatno zato što u svom aromatičnom prstenu umesto metaksilena sadrži tiofen^{37,45}.

Difenhidramin je antihistaminik koji deluje kao antiholinergik, antitusik, antiemetik i sedativ, a poseduje i svojstva lokalnog anestetika⁴⁵. Kod bolesnika sa dokazanom alergijom na lokalne anestetike, može se primeniti rastvor difenhidramin-hlorida sa sličnim dejstvom kao jednog procentni lidokain^{46,47}. Međutim njegovu primenu ograničavaju bolna aplikacija, blag otok na mestu uboda i moguća prolazna ošamućenost koja prati parenteralnu primenu. Neka istraživanja ukazuju na to anestetički efekat difenilhidramina ipak nije zadovoljavajući⁴⁸.

Osim imunoloških reakcija preosetljivosti, žmortalni tip reakcije na amidne lokalne anestetike može biti pseudoanafilaksa-anafilaktoidna reakcija ili neimunološki tip anafilakse^{49,50}.

Increased sensitivity to meta-bisulfite is certainly the result of its use in agriculture, where it is used as an antioxidant sprayed on fresh fruits and vegetables, in order to preserve their freshness and appearance. Patients who confirm to have that food allergy may have a cross-reaction with local anesthetic agents containing vasoconstrictor¹⁷. Sensibility to the bisulfite can be present in atopic patients and asthmatic patients and may cause a more severe form of the reaction (bronchospasm)^{27,28}.

Available data indicate that almost every amide local anesthetic in practice causes allergic reaction, with a specific growing pace²⁹⁻³⁶. In the case of suspected allergy to the local anesthetic solutions use of pure local anesthetic is recommended, without the presence of a stabilizer which is a potential antigen, or use of a different anesthetic. Ester local anesthetics have a cross-reaction and allergy involves a possible allergy to other anesthetic in this group. There are different views on the issue of replacing the amide local anesthetic that caused an allergic reaction. There are no reliable data in the literature whether there is a cross-reaction between the anesthetics of the amide groups. Yet there is a possibility that a possible antigen is metaxilen, which is part of the aromatic ring of almost all amide local anesthetic³⁷. Persons sensitized to lidocaine as a suitable replacement is widely recommended mepivacaine, but it resulted that it provides cross-reaction with lidocaine, probably due to the presence of the aromatic radical metaxilena³⁸⁻⁴². Articaine seems like a safer substitute for persons sensitized to lidocaine, probably because it contains thiophene instead metaxilena in its aromatic ring^{37,44}.

Diphenhydramine is an antihistamine which acts as an anticholinergic, antitussive, antiemetic and sedative, and it also has the properties of a local anesthetic⁴⁵. In patients with known allergy to local anesthetics a solution of diphenhydramine chloride can be applied, with similar effect as 1% lidocaine^{46,47}. However its application is limited because of severe application, mild swelling at the injection site and possible transient dizziness that accompanies parenteral use. Some studies suggest that the anesthetic effect of diphenhydramine is not satisfactory⁴⁸.

In addition to immunological hypersensitivity reactions, type of reactions to amide local anesthetics may be pseudoanaphylaxis - anaphylactoid reactions or non-immunological type anaphylaxis^{49,50}.

Ovaj tip reakcije preostljivosti dešava se bez posredstva IgE i razvija se već pri prvom kontaktu sa antigenom. Simptomi liče na pravu anafilaksu. Naročitu preosetljivost i sklonost anafilaktoidnoj reakciji, koja se dešava bez posredstava IgE, imaju bolesnici koji boluju od sistemske mastocitoze⁵¹. Kod ovog oboljenja nepoznate etiologije, postoje mastocitni infiltrati u koži, koštanoj srži i unutrašnjim organima. Zbog otpuštanja histamina iz obilja mastocita razvijaju se simptomi anafilakse.

U kliničkoj praksi, veliki problem može da predstavlja prepoznavanje prirode negativne reakcije na aplikovani anestetik. Često se dešava da samibolesnici svoju psihogenu reakciju, koja je praćena prolaznim nadražajnim simptomima, proglašavaju alergijskom. Kod bilo koje sumnje na alergijsku reakciju na lokalni anestetik, lekar mora uputiti bolesnika na alergološka ispitivanja, zbog sličnosti simptoma koji prate psihološke i toksične reakcije sa alergijskim. Ukoliko se dokaže alergijska reakcija na aplikovani anestetik, akupunktura i hipnoza mogu tada biti od koristi, kao alternativne ili dopunske metode lokalne anestezije, kako bi izbegli uvođenje bolesnika u opštu anesteziju.

Zaključak

Negativne reakcije na lokalne anestetike uglavnom su privremenog karaktera i reverzibilne prirode. U najvećem broju slučajeva javljaju se do 2 sata nakon aplikovanja anestetika⁵², pa autori smatraju da je u ovom vremenskom periodu neophodno paratiti bolesnika. U kliničkoj praksi, naročito je važno utvrditi prirodu negativne reakcije, kako bi se pružila odgovarajuća pomoć u vezi sa nastalom reakcijom, i preporučila odgovarajuća alternativa datom lokalnom anestetiku. U tom smislu, naročito je važno razlikovati psihogenu reakciju na anestetik od toksične i alergijske reakcije, što u praksi predstavlja najveći problem.

This type of sensitivity reaction occurs without using IgE and develops already at the first contact with the antigen. Symptoms of anaphylaxis resemble the real one. Particular sensitivity and tendency to anaphylaxis reaction that occurs without using IgE, have patients suffering from systemic mastocytosis⁵¹. In this disease of unknown etiology, there are mast cell infiltrated in the skin, bone marrow and internal organs. Due to the release of histamine from mast cells abundance, symptoms of anaphylaxis are developed.

In clinical practice, the big problem may represent a recognition of the nature of the negative reaction to an anesthetic. It often happens that patients themselves declare their psychogenic reaction, which is accompanied by transient irritable symptoms, as allergic. In any suspicion of an allergic reaction to a local anesthetic, the doctor should refer the patient to the allergy testing, because of the similarity of symptoms associated with psychological and toxic reactions with allergic. If the allergic reaction to the applied anesthetic is confirmed, acupuncture, and hypnosis may then be used as an alternative or additional method for local anesthetic.

Conclusion

Negative reactions to local anesthetics are generally temporary and reversible. In the majority of cases, they occur up to 2 hours after application of anesthetic⁵², so authors believe that at this time it is necessary to watch on the patient. In clinical practice, it is particularly important to determine the nature of the adverse reactions, in order to provide aid in connection with the resulting reaction, and recommend an alternative to the given local anesthetic. In this regard it is particularly important to distinguish psychogenic reaction to the anesthetic from toxic and allergic reactions, which in practice is the biggest problem.

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