Review
Derleme

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Management of local anesthetic toxicity and importance of lipid infusion

Lokal anestezik toksisitesinin yönetimi ve lipid infüzyonunun önemi

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Abstract

Local anesthetics (LA) are one of the groups that block the transmission of sensory, motor and autonomic nerve impulses commonly used in clinical anesthesia. All local anesthetic molecules in clinical use consist of three parts: a lipophilic (aromatic) end, a hydrophilic (amine) end, and a chain that provides the connection between the ends. Physicochemical properties determine the clinical efficacy of local anaesthetics The part that determines the lipid solubility of local anesthetics is the aromatic ring. A higher dose of local anesthetics is required for cardiovascular system (CVS) toxicity. Hypertension, tachycardia and ventricular arrhythmia are the first of the diseases of CVS. Hypotension, arrhythmia, bradycardia and cardiac arrest develop as local anesthetics increase in blood. The symptoms of central nervous system (CNS) toxicity associated with LA are related to the plasma levels of drugs. Initially, there are drowsiness, dizziness, sedation, disorientation, tinnitus, nystagmus, metallic taste, nausea and vomiting. Then, restlessness, irritability, tremors and muscle twitches occur. After this, the tonic-clonic seizure and loss of consciousness develops, finally, apnea, cardiovascular collapse and coma. In the treatment of local anesthetic toxicity, it is recommended to provide airway, avoid the propofol if seizure occurs and treat with benzodiazepine. If cardiac arrest develops, it is recommended to switch to advanced life support, to reduce the given dose of adrenaline, to administer lipid emulsion (20%) and to respond to treatment if cardiopulmonary bypass is not provided.

Keywords: Local anesthetic, Toxicity, Lipid infusion

Öz

Lokal anestezikler (LA), klinik anestezide yaygın olarak kullanılan duyusal, motor ve otonom sinir sinirlerinin iletimini engelleyen ilaçlardır. Klinik kullanımdaki tüm lokal anestezik moleküller üç bölümden oluşur: bir lipofilik (aromatik) uç, bir hidrofilik (amin) uç ve uçlar arasında bağlantı sağlayan bir zincir. Lokal anesteziklerin klinik etkinliğini fizikokimyasal özellikler belirler. Lokal anesteziklerin lipid çözünürlüğünü belirleyen kısım aromatik halkadır. Kardiyovasküler sistem (CVS) toksisitesi için daha yüksek dozda lokal anestezikler gerekir. Hipertansiyon, taşikardi ve ventriküler aritmi, ilk görülen CVS yanetkileridir. Hipotansiyon, aritmi, bradikardi ve kalp durması kanda lokal anesteziklerin artmasıyla gelişir. LA ile ilişkili merkezi sinir sistemi (CNS) toksisitesinin semptomları, ilaçların plazma seviyeleri ile ilişkilidir. İlk başta uyuşukluk, baş dönmesi, sedasyon, oryantasyon bozukluğu, kulak çınlaması, nystagmus, metalik tat, bulantı ve kusma vardır. Sonra, huzursuzluk, sinirlilik, titreme ve kas seğirmesi meydana gelir. Bundan sonra, tonik-klonik nöbet ve bilinç kaybı, sonunda apne, kardiyovasküler kollaps ve koma gelişir. Lokal anestezik toksisitesinin tedavisinde, hava yolunun sağlanması, nöbet meydana gelirse propofoldan kaçınılması ve benzodiazepin ile tedavi edilmesi önerilir. Eğer kardiyak arrest gelişirse, verilen adrenalin dozunu azaltmak, lipit emülsiyonu uygulamak (%20) ve kardiyopulmoner bypass sağlanamadığında tedaviye yanıt vermek için ileri yaşam desteğine geçilmesi önerilir.

Anahtar kelimeler: Lokal anestezik, Toksisite, Lipid emülsiyonu

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Introduction

Local anesthetics (LA) are one of the groups that block the transmission of sensory, motor and autonomic nerve impulses commonly used in clinical anesthesia. When administered in therapeutic doses, these effects are reversible and the nerve function returns completely without any damage to the nerve fiber and cell [1].

The use of LA in neuraxial anesthesia is another important development of James Corning that began in 1885 with a spinal anesthesia experiment on a dog. It was not used clinically until August Bier until 1899. Lumbar epidural anesthesia was described by the Spanish military surgeon Fidel Pages in 1921 and was popularized by the Italian surgeon Dogliotti in the 1930s [2].

Chemical structure

All local anesthetic molecules in clinical use consist of three parts: a lipophilic (aromatic) end, a hydrophilic (amine) end, and a chain that provides the connection between the ends. The linkage comprises either an amino ester or an amino amide linkage and local anesthetics are defined as belonging to one of two groups: amino-ester linked local anesthetics or amino-amide bonded local anesthetics. Procaine is a prototype of amino-ester bound local anesthetics, and the prototype of amino-amide linked local anesthetics forms lidocaine [3].

Physicochemical properties

Physicochemical properties determine the clinical efficacy of local anesthetics. The part that determines the lipid solubility of local anesthetics is the aromatic ring. Lipid solubility is the most important feature affecting the potency of local anesthetics. The membranes of the nerve membranes and connective tissues are lipoprotein. Local anesthetics with high fat content are easier to pass than the membrane and require fewer molecules [4].

Binding to protein is associated with the duration of action of the local anesthetic; because the non-free form does not have pharmacological activity. The local anesthetic with a high affinity to the protein remains attached to the nerve membrane for a longer period of time and the duration of action is prolonged [5,6].

Local anesthetics at physiological pH are weak bases until the equilibrium between the lipid soluble base form and water soluble ionized form is established [4]. The effect of local anesthesia occurs when it passes through the lipid-soluble tertiary form at physiological pH (7.4). The ionization constant (pKa) determines the form of the local anesthetic. By definition, pKa represents the pH in which 50% of the local anesthetic is in the oil-soluble tertiary structure with 50% water-soluble quaternary structure. Given the low pKa of the given local anesthetic means higher lipid solubility. This form is a faster passing form of lipid cell membranes, so the onset time of the action is shortened[4].The pKa of all local anesthetics is 8.0-9.0. If the environment is acidotic due to various reasons, the water-soluble quaternary form increases the amount of local anesthetic that enters the nerve tissue, which explains why the effect is diminished especially in the infected tissues [7,8]. Similarly, alkalinity of the pH of the environment causes the lipid-soluble tertiary structure to increase and the amount of local anesthetic that can enter the nerve membrane. It is applied by adding bicarbonate to this local anesthetic in clinical practice [9].

Clinical Use

Local anesthetics are applied in topical anesthesia, infiltration anesthesia, intravenous regional anesthesia, central block, peripheral nerve blocks and sympathetic block in anesthesia practice.

The sensitivity of nerve fibers to local anesthetics is different. It depends on the diameter of the fibers and the degree of myelination. Classically, first the feeling of heat, then the sinking, and then the slight touching sensation disappears. Generally autonomic fibers, small non-myelinized C fibers and small myelinized A kappa are blocked first, while motor and proprioceptive fibers are blocked later [4].

During peripheral nerve block procedures, anesthesia specialists often add lidocaine epinephrine. This application has two advantages. First, it reduces the plasma concentration of local anesthesia and thus minimizes the likelihood of systemic toxicity. Second, it increases the quality of the block and prolongs the duration of the peripheral nerve block [10].

Pharmacokinetics

Local anesthetics are most commonly given to the extravascular tissue close to the target tissue. It determines the plasma concentration of local anesthetics, the rate of absorption from the injection site, the rate of distribution in the tissue and the rate of elimination specific to the local anesthetic. Patient-related factors that determine systemic toxicity include age, cardiovascular, renal and hepatic function, and plasma protein binding [11].

Local anesthetics are very safe when administered in appropriate doses for proper anatomical localization. Local or systemic toxic reactions may occur if high dose local anesthetic application or intravascular or intrathecal injection is performed [6].

In high perfusion tissues, retrieval is faster and more complete. Systemic absorption and peak plasma level (Cmax) increase as the given dose increases. The addition of adrenaline to the local anesthetic reduces systemic absorption and significantly reduces Cmax. The purpose of adrenalin addition to the local anesthetic is to prolong the duration of the local anesthetic and to keep it longer in the tissue [10].

Intravenously administered local anesthetics are initially distributed to organs with large blood supply, such as the brain, kidneys and heart; it follows less canned tissues such as skin, skeletal muscle and fat. Local absorption in these organs will be affected by lipid solubility of local anesthetic, binding to pKa and protein, binding affinity and clearance to tissue. Affects local absorption in patient-specific factors such as cardiac output and metabolic status [12].

The amino-ester bound local anesthetics are hydrolyzed by tissues and blood esterases. Amino-amide-induced local anesthetics are primarily biotransformed with cytochrome P450 enzymes in the liver. Metabolites often retain local anesthetic activity and toxicity potential with a lower force than the parent compound [13].

The location of injected local anesthetics has the highest peak levels at plasma levels, intercostal and caudal injections,

followed by lumbar epidural, brachial plexus, sciatica and femoral injections [12].

Lungs

Most of the local anesthetics are temporarily removed during the first pass in the lungs. This effect may be due to the low pH of the lung tissue relative to the plasma, resulting in a degree of ion retention [14,15].

As a result; lungs may relieve the toxic sequelae of accidental intravenous injections of local anesthetics. Patients with right to left heart shunts do not have this safety net and have an increased risk of toxicity. The local anesthetic is re-washed in a slower circulation following lung absorption [15,16].

Placenta transfer

Local anesthetics may spread to the placenta; however, ester local anesthetics are rapidly hydrolyzed in the blood, so they do not pass the placenta in significant amounts. Local anesthetics with amide structure vary significantly at placental transfer rates and fetal retention degrees. Increased protein binding in the mother reduces the amount of local anesthetic that can be released and released through the placenta. The fetus has low levels of α1-acid glycoprotein, so it has a low concentration of local anesthetic binding sites. Fetal pH is lower than the maternal pH, which results in ion retention of agents with higher pKa values [17].

Systemic side effects of local anesthetics

Allergic reactions

Allergic events due to local anesthesia are rare. It develops against ester type local anesthetics, which is more para-amino benzoic acid derivative. The reaction against amide group local anesthetics is rare. The cause of allergy in the amide group of drugs is methyl-paraben, which is incorporated in these solutions as a preservative, similar to para-amino benzoic acid [18].

Tissue toxicity

Local anesthetics used in the clinic, rarely cause localized nerve damage. Chlorprocaine may show neurotoxicity after epidural and caudal anesthesia. A 5% solution of lidocaine may lead to cauda-equina syndrome. Local anesthetics are prepared in physiological effective concentrations, but are used by diluting [19].

Methemoglobinemia

The only anesthetic that causes this is high doses of prilocaine. The metabolism of this agent in the liver results in the formation of orthotoluidin, which is responsible for converting hemoglobin into methemoglobin. Methemoglobin shifts the oxyhydrogen dissociation curve to the left, thus preventing the release of oxygen to the tissues. These effects are proportional to the concentration of methemoglobin and are reversible. The return of methemoglobinemia can be accelerated by IV given methylene blue (1 mg / kg) [20].

Cardiovascular side effects

A higher dose of local anesthetics is required for cardiovascular system (CVS) toxicity. In general, local anesthetics suppress myocardial automatism and reduce the duration of the refractory period. Hypertension, tachycardia and ventricular arrhythmia are the first of the diseases of CVS. Hypotension, arrhythmia, bradycardia and cardiac arrest develop

as local anesthetics increase in blood. Ropivacaine and levobupivacaine are less cardiotoxic than bupivacaine[12].

The main mechanism of cardiovascular toxicity is the blockage of myocardial voltage-dependent sodium channels. PR interval provokes dose-dependent prolongation of QRS duration and conduction time, and spontaneously depressing cardiac activity. These electrophysiological effects combine with the direct negative inotropic effect of local anesthetic drugs [21].

Side effects in central nervous system

The symptoms of central nervous system (CNS) toxicity associated with LA are related to the plasma levels of drugs. Initially, there are drowsiness, dizziness, sedation, disorientation, tinnitus, nystagmus, metallic taste, nausea and vomiting. Then, restlessness, irritability, tremors and muscle twitches occur. After this, the tonic-clonic seizure and loss of consciousness develops, finally, apnea, cardiovascular collapse and coma. Rapid systemic administration of LA may cause death without signs of CNS stimulation or with very short-term symptoms [22,23]. In some cases, the risk of local anesthetic toxicity increases (Table 1).

Table 1: Risk factors for local anesthetic toxicity

Risk factors
Elderly or child patient
Hepatic dysfunction or altered hepatic perfusion
Low cardiac output
High cardiac output
Cardiac pathology
Reduction in plasma proteins
Pregnancy
Beta blockers, digoxin, calcium antagonists, cytochrome P450 inhibitors

The appropriate dose of LA should be the desired time and the lowest dose to achieve the degree of analgesia or anesthesia. A specific dose of LA will show inter-individual variation in plasma concentrations depending on the region and rate of administration or patient demography. These observations have been attempted to be standardized per kilogram in adults and with the recommended maximum doses, in particular the maximum weight-based dose varies between countries and texts. Maximum doses should be observed, especially in patients with low body weight [22].

Safety steps in the prevention of toxicity

Several security steps have been advocated to identify or reduce the risk of toxicity. For safe implementation of LA, the following has been proposed: limiting the cumulative dose, ultrasound or direct visualization for catheter insertion, test dosage, incremental injections, negative catheter aspiration, and adherence to guidelines [24].

Limiting the cumulative effects of anesthetics

Simultaneous administration of multiple local anesthetics contributes to a single systemic toxic threshold. Although specific serum concentration levels are associated with toxicity, weight based (mg / kg) dosing guides cannot reliably estimate these levels and cause potential toxicity at lower doses than expected [11].

For topical LA and subcutaneous solutions, doses higher than the substantially recommended levels are administered. Based on pharmacokinetic data, it appears that these routes of administration are associated with a lower risk of systemic toxicity, yet toxicity may occur. American Association of Regional Anesthesia and Pain Medicine (ASRA) recommend the use of the lowest concentration and dose required for neuraxial and non-neuro-axial analgesia [25].

In postoperative period, analgesic concentrations (<0.25% bupivacaine or ropivacaine) are used for continuous infusion. The anesthesia team is limited to the recommended doses after the anesthesia is applied simultaneously by the anesthesia team. Liposomal bupivacaine should not be administered with other local anesthetics due to the risk of toxicity [11].

Incremental injections and catheter aspiration

Lack of objective data, it is recommended that small doses (3-5 mL) of local anesthetic doses be administered to allow the anesthetist or surgeon to easily monitor for unwanted intravascular injection. Data on the reliability of this technique are lacking because it is not practical to expect a complete circulation time (30-45 seconds) between each 3 mL injection. Although recommended, the catheter aspiration of blood is not reliable for identifying intravascular catheters [26,27].

Intravascular Test Dose Application

Several studies have identified evidence-based techniques for catheter testing dosing, but test dosing with an intravascular marker is recommended when doses of potentially toxic LA are planned to be administered [28]. Potential test dose agents include epinephrine, local anesthesia, air, opioid and isoproterenol. Test solutions containing epinephrine are widely used during electrocardiography and when monitoring heart rate and blood pressure [29].

Regional anesthesia in ultrasound guidance

Ultrasound has been shown to reduce the risk of local anesthetic systemic toxicity (LAST) alone by 60% to 65% compared to peripheral nerve stimulation [30]. A lower dose of LA is used for ultrasound injection. At the same time, the incidence of vascular puncture decreases and visual indications indicating intravascular injection allow the termination of injection prior to administration of LA dose. However, despite the use of ultrasound, LAST events continue to occur and ultrasound guidance does not affect the risk of LAST caused by systemic absorption of LA [31].

Treatment of local anesthetic toxicity

Airway control and respiratory support are the basis of treatment. Benzodiazepines or a small amount of propofol administered IV are preferred to terminate seizures. The use of benzodiazepine in premedication may be used to increase the seizure threshold, but respiratory depression may cause acidosis with its excess sedation, which increases the concentration of free drug in the serum [19].

In 2010, ASRA published a guide on LAST management and revised in 2012 and 2017. Measures to be taken in accordance with this guideline include: applying the lowest effective dose, for example applying a test dose with adrenaline (5 mcg/mL) and taking the drug by aspiration before each injection. In the treatment of local anesthetic toxicity, it is recommended to provide airway, avoid the propofol if seizure occurs and treat with benzodiazepine. Local anesthetic, calcium channel blocker, beta-blocker, and vasopressin use should be avoided. If cardiac arrest develops, it is recommended to switch to advanced life support, to reduce the given dose of adrenaline (<1 mcg/kg), to administer lipid emulsion (20%) and to respond to treatment if cardiopulmonary bypass is not provided [25].

Lipid emulsion

20% lipid infusion is the first intravenous lipid emulsion safely used in parenteral nutrition since 1962 [32].Lipid emulsion consists mainly of soybean oil, glycerol, egg phospholipid, omega-3 and omega-6 essential fatty acids [33].

Weinberg et al. [32] he observed that intravenous lipid infusions not only increased the dose of bupivacaine needed to produce asystoles in rats, but also improved survival after bupivacaine intravenous bolus doses were taken in rats. They then applied this observation to dogs as a model of a species closer to humans and discovered that lipid infusions during boutsivacaine-induced cardiac arrest increased survival during resuscitation [34].

Rosenblatt et al. [35] successfully performed intravenous lipid emulsion (ILE) clinical practice in 2006, and many studies have supported the use of ILE for bupivacaine, levobupivacaine and ropivacaine cardiotoxicity [36-38].

ILE has been included in safety guidelines for management of cardiotoxicity in LA in the United States since 2007 in the United States and since 2008 in the United States(39, 40).In 2010, the American Regional Association of Regional Anesthesia and Pain Medicine (ASRA) published the application guide on LAST, emphasizing the importance of airway management and early cardiopulmonary resuscitation with the addition of ILE therapy [40]. In 2010, a special case of the American Heart Association (AHA) ACLS rules recommended the use of lipid emulsion for LAST-induced cardiac arrest [41].

The efficacy of ILE in treating cardiotoxicity not well defined, but in vitro studies are thought to form a lipid pool. This expanded intravascular lipid pool to absorb the circulating lipophilic toxin, thereby reducing the free toxin that is not able to bind to the myocardium [42]. Weinberg et al. [43] studied isolated rat heart on the mechanism of action of lipid emulsions. As a result of this study, it was found that lipid therapy accelerated the recovery in case of bupivacaine-induced cardiac arrest. It has also been found that this treatment helps to reduce the bupivacaine content in cardiac tissue and clear the tissue from the bupivacaine. This study demonstrates the efficacy of lipid therapy and supports the theory of fat precipitation. In addition, lipid therapy has been reported to have a positive inotropic and chronotropic effect on the heart under bupivacaine. Another theory is explained by the increase in lipid emulsion, increased fatty acid flow to cardiac cells and reduction of reduced fatty acid transport caused by bupivacaine [44].

The 2017 checklist simplifies the dosing of lipid emulsions to contain 100 mL of bolus fixed by 200 to 250 mL of infusion for 15 to 20 minutes for all patients weighing more than 70 ml.

Weight-based dosing is reserved for patients with less than 70 kg, but even these recommendations emphasize that the exact volume and flow rate are not critical. In response to the further indications of percepted lipid emulsion dosing proposals, the checklist suggests that a 30-minute resuscitation process may comprise lipid emulsion volumes approaching 1 L. As a result, the recommended content for a lipid LAST Rescue Kit is 1 total L lipid emulsion %20 (Table 2) [25].

Table 2: Lipid Emulsion Therapy

Lipid Emulsion %20	
>70kg	<70kg
100ml 20% lipid emulsion bolus (2-3 min)	1.5 ml/kg %20 lipid infusion (2-3 min)
Lipid emulsion infusion 200-250 ml (15-20 min)	Lipid emulsion infusion 0,25ml/kg/min (ideal body weight)
Patient unstable	
Re-bolus once or twice at the same dose and double infusion rate: be aware of dose limiting (12ml/kg)	
Total volume of lipid emulsion can approach 1 L in a prolonged resuscitation (<30 min)	

The American Society of Regional Anesthesia and Pain Medicine Checklist for Managing Local Anesthetic Systemic Toxicity: 2017 Version

AAGBI involves the introduction of a large initial intravenous bolus injection containing a 20% lipid emulsion at 1.5 mL/kg for 1 minute after administration of a LAST cardiac arrest; followed by an infusion of 15 mL/kg/h. Cardiopulmonary resuscitation should be continued. Two additional flakes (1.5mL/kg) can be given at 5-minute intervals in the absence of spontaneous circulation or deterioration after 5 minutes. The intravenous infusion rate should be doubled to 30 mL/kg/h. A maximum of three boluses can be given and a total dose of 12 mL/kg should not be exceeded. The ASRA guidelines differ only in terms of suggesting an additional bolus, and after the hemodynamic stability has been reached, the infusion at a maximum dose of 10 mL/kg should be continued for 10 minutes [39,40].

In response to candida, IN infusions modulate cytokine production by mononuclear white cells, which increase the risk of infection. With infusions, thrombophlebitis may develop during peripheral IV administration. They may cause impaired reticuloendothelial system function and altered inflammatory responses during prolonged treatment. They may cause allergic reactions, including anaphylaxis, especially if they contain soybean oil. If the fat particles are larger than 5 microns, they may result in pulmonary, splenic, placental and cerebral fat embolism. When administered at rates greater than 100 mg/kg/h, they can cause pulmonary hypertension; can cause warfarin resistance by facilitating binding of warfarin to albumin [45].

Conclusion

In clinical practice, local anesthetics are used quite frequently and the early diagnosis and treatment of toxicity is very important. LAST is a life threatening adverse event. The use of the lipid emulsion at the right time and at an effective dose will be life-saving. Therefore, each area where LA is used in potentially toxic doses should be equipped with a basic resuscitation device and a 20% lipid emulsion.

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