Overview

Local anaesthetic toxicity

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Abstract

Local anaesthetic drugs are widely used for the provision of regional anaesthesia and analgesia. When used properly, they are safe and effective and have only few side effects. However, in case of an accidental intravascular injection or an injection of excessive dose, they can be toxic and neurologic and cardiovascular symptoms may occur. Systemic toxicity, although a rare complication, can be life threatening and resistant to treatment. This review offers a brief overview of the current understanding of the circumstances that cause systemic and cardiovascular toxicity in the daily clinical practice and the management of clinical signs and symptoms.

INTRODUCTION

The use of regional anaesthesia, alone or as adjunct to general anaesthesia, is at an all-time high. However, with the development of the equipment, techniques and medication, we are witnessing a significant increase in the use of regional anaesthesia. Although the benefits of regional anaesthesia are well-known and include reduced side effects and enhanced patient's satisfaction, as the number of practitioners and procedures increase, the number of complications and adverse outcome rise as well. Complications of local anaesthesia may range from localized reactions such as edema, urticaria and dermatitis to systemic absorption resulting in severe cardiovascular collapse and neurological toxicity.

Local anaesthetic drugs are used widely for the provision of regional anaesthesia and analgesia, and despite the remarkable efficacy, the risk of systemic toxicity associated with these drugs has been a very important problem since their introduction to clinical practice more than a hundred years ago. While generally safe, they can be toxic if used in excessive doses or administered improperly. An unintentionally high local anaesthetic plasma concentration which may be due to overdosing, rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection may lead to a serious of progressively worsening neurological and cardiac complications. Unexpected local anaesthetic toxicity can also occur where the pharmacokinetics of the drug are altered by co-morbidity such as cardiac, renal or hepatic failure, alterations in plasma protein binding, or interactions with other drugs. Systemic toxicity from local anaesthetics can be life threatening and very often resistant to treatment.

The estimate of clinically important local anaesthetic toxicity is from 7.5 to 20 occurrences per 10,000 peripheral nerve blocks and approximately 4 occurrences per 10,000 epidurals *(1)*. The most important goal of any anaesthesiologist is primarily to avoid toxicity and secondly to

treat toxicity once it has occurred. This review offers a brief overview of the current understanding of the circumstances that cause systemic toxicity in the daily clinical practice and the management of clinical signs and symptoms.

Brief history of local anaesthetics toxicity

The clinical phenomenon of local anaesthetic toxicity has been known for more than a hundred years and had several peaks including introduction of cocaine in 1884, bupivacaine and etidocaine in the 1970s and after the introduction of ropivacaine and levobupivacaine in the 1980s.

Shortly after the introduction of cocaine as a topical anaesthetic into clinical practice, local anaesthetic systemic toxicity has been recognized and reported. Between 1884 and 1891, 200 cases of systemic intoxication and 13 deaths attributed to the cocaine were recorded *(2)*. Wider recognition that LA toxicity could have lethal consequences should have followed reports of 7 deaths in nearly 40,000 patients with the use of topical cocaine or tetracaine anaesthesia to facilitate tracheobronchoscopy or esophagogastroscopy *(3)*. Increasing evidence of toxicity directly attributable to local anaesthetic use led the American Medical Association (AMA) in the early 1920s to establish the Committee for the Study of Toxic Effects of Local Anaesthetics *(4)*. The need for a local anaesthetic with reduced toxicity led to the development of safer local anaesthetics, but despite of their introduction, serious morbidity and mortality continued. For this reason, interest in treatment and prevention of toxicity did not stop until nowadays. In the 1990s, literature describing animal studies and reported cases in humans has shown that lipid emulsions might be effective as an antidote in the reversal of local anaesthetic toxicity. Research is currently ongoing to refine issues related to lipid emulsion therapy for severe toxicity and its prodromes *(5)*. Until 2005 there was no widely agreed approach to the management of LA toxicity. However, The Association of Anaesthetists of Great Britain and Ireland (AAGBI) published in 2007 the first set of standardized guidelines for severe LA toxicity *(6)*. In 2008, the American Society of Critical Care Anaesthesiologists and the American Society of esiologists Committee on Critical Care Medicine *(7)* as well as the Resuscitation Council of the United Kingdom *(8)* also published protocols for the treatment of local anaesthetic systemic toxicity (LAST). In 2010, the American Society of Regional Anaesthesia and Pain Medicine published its practice advisory on LAST *(9)*.

Local anaesthetic systemic toxicity

Local anaesthetic systemic toxicity is a rare but potentially fatal complication of regional anaesthesia. It may occur as a consequence of unwanted intravascular injection, or after the administration of an excessive dose of these drugs. Systemic toxicity of local anaesthetic affects the central nervous system (CNS) and then the cardiovascular system (CVS). The central nervous system is

more sensitive to local anaesthetic toxicity than the cardiovascular system *(10)*. The dose and blood level of local anaesthetic that produces CNS toxicity is lower than the dose that causes circulatory collapse. Therefore CNS manifestations tend to occur earlier. Although local anaesthetic cardiovascular toxicity occurs less frequently than CNS toxicity, it is more serious and more difficult to treat. Toxicity may be potentiated in patients with renal, hepatic or cardiac failure, respiratory acidosis, during pregnancy, at the extremes of age or in hypoxic patients. Several factors such as physiochemical properties, rate and route of administration of the LA also influence the acute systemic toxicity.

The onset of toxicity is the direct result of the rate and route of drug administration. Inadvertent, direct intravenous injection of an excessive dose can cause rapid and intense level of central nervous and cardiovascular system toxicity. Tissue vascularity is another important consideration. Highly vascular injection sites, such as the pleura, the bronchial mucosa and sublingual regions, have a higher correlation to an increased incidence of local anaesthetic toxicity than do less vascular areas. The uptake of local anaesthetic from greatest to least is as follows: Blood/tracheal > Intercostal > Caudal/paracervical > Epidural > Perivascular brachial plexus > Sciatic > Subcutaneous – BICEPSS.

The central toxic response is related specifically to plasma concentrations of local anaesthetic in the CNS and their effect on the complex interplay between excitatory and inhibitory pathways *(11)*. CNS toxicity is biphasic (Table 1). Initial symptoms are due to CNS excitation manifesting as feeling of lightheadedness, shivering, confusion, abnormal taste, dizziness, and tinnitus, visual and auditory disturbances followed by tonic-clonic convulsions. Subsequent manifestations include CNS depression with a cessation of convulsions and onset of unconsciousness, coma, respiratory depression, and respiratory arrest. This biphasic effect occurs because local

TABLE 1

Symptoms of systemic toxicity.

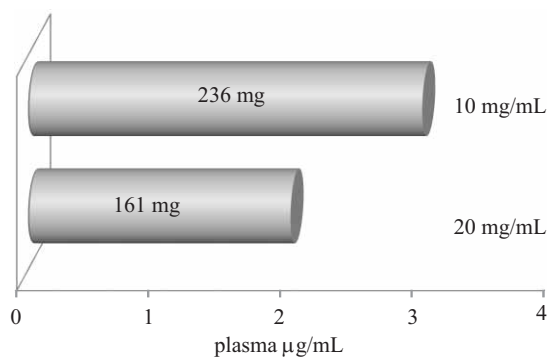| Central nervous system	Cardiovascular system
Excitation	**Early/mild phase**
Feelings of ligheadedness	Hypertension
Shivering	Tachycardia
Confusion	**Severe**
Abnormal taste	Severe hypotension
Tinnitus	Sinus bradycardia
Convulsion	Arrhythmia
Depression	Dysrhytmia
Hypoventilation	Cardiac arrest
Loss of consciousness	
Coma	
Respiratory depression	

Figure 1. *Effect of infusion rate on local anesthetic toxicity (Modified to ref. 16).*

anaesthetics first block sodium channels in the inhibitory neurons allowing the excitatory neurons to act unopposed and creating an excitatory state. Consequently, both inhibitory and excitatory pathways are blocked resulting in the global CNS inhibition. There is a correlation between local anaesthetic potency and the dosage required to produce CNS toxicity *(12)*. The convulsive dose of long acting LAs are up to 4 times more toxic than lidocaine *(13)*. In dogs the relative CNS toxicity of bupivacaine, etidocaine, and lidocaine is 4:2:1. This is similar to their relative local anaesthetic potencies *(14)*. Intravenous infusion studies in human volunteers also show a similar relationship between the intrinsic anaesthetic potency and the dosage that causes CNS symptoms *(15)*.

The rate of injection affects the maximum concentration of LA in the serum and time to peak levels. For example, when etidocaine is infused into human volunteers at the rate 10 mg/mL, (mean dose of 236 mg) symptoms of CNS occur when the blood levels reaches 3,0 mg/mL. Increasing the infusion rate to 20 mg/mL CNS symptoms occur when the blood concentration reaches only 2.0 mg/mL (mean dose 161 mg) (Figure 1) Therefore, subjects could tolerate twice the dose of etidocaine at a lower infusion rate of 10 mg/min *(16)*.

The acid-base status of the patient can also influence the central nervous system toxicity. In cats, with increasing arterial PCO_2, the lower doses of LA were required to produce convulsions. Increasing the PCO_2 from 25 to 40 mmHg to 65 to 80 mmHg decreased the dose required to produce convulsions for different local anaesthetics by approximately 50 % *(12)*.

It can also be considered that, in terms of CNS toxicity, a decrease in pH is probably more important than a change in $PaCO_2$. Respiratory acidosis decreases the threshold for occurrence of seizures. Acidosis and hypercarbia may alter the convulsive threshold in several ways. CO_2 increases cerebral blood flow so more local anaesthetic is delivered to the brain and has itself an excitatory effect on subcortical brain structure. Additionally, hypercarbia and/or acidosis also decrease the plasma protein binding of local anaesthetic agents thus making more drugs available in brain. Seizures produce hypoventila-

tion and a combined respiratory and metabolic acidosis, which further exacerbates the CNS toxicity.

The cardiovascular system (CVS) is generally more resistant to local anaesthetic toxicity than the CNS. Cardiovascular toxicity usually occurs at doses and blood concentrations higher than those required to produce CNS toxicity. A study by Lin et al. demonstrated that in dogs there was a three to five fold difference between blood concentrations of LA required to produce cardi-circulatory collapse and those to produce convulsion *(14)*.

Relative potency for CV toxicity also seems to follow the relative anaesthetic potency. More potent agents, such as bupivacaine, etidocaine, and tetracaine have been shown to be more cardiotoxic than less potent agents such as lidocaine, mepivacaine, or prilocaine *(17)*.

CV toxicity is also biphasic (Table 1). The first signs of cardiac toxicity are related to the CNS excitatory phase with activation of the sympathetic nervous system which leads to tachycardia and hypertension and can mask direct myocardial depression. However with increasing plasma concentration of LA, this phase is followed by bradycardia, arrhythmia and profound cardiac depression, resulting in cardiovascular collapse *(18, 19)*.

The mechanism of cardiovascular toxicity is based on direct and indirect effect of LA on the myocardium and on vascular smooth muscle, but is not fully elucidated *(20, 21)*. Direct effects on myocardium include negative inotropy and conduction delay while the indirect effects include effect on the cardiac centre in the middle brain *(22)*.

Calcium ion channel blockade is considered to be one of the main mechanisms of LA induced cardiac depression and negative inotropy. Displacement of calcium from cardiac muscle would result in a decrease in myocardial contractility. Blockade of sodium ion channel which reduces action potential duration and effective refractory period, induces inhibition of cyclic adenosine monophosphate (cAMP) and inhibition of carnitine transporter system may also contribute to cardiac toxicity. LA also increases PR interval and QRS complex duration resulting in prolongation of conduction time. In the isolated rabbit heart it has been shown that racemic bupivacaine, levobupivacaine and ropivacaine induce an increase in QRS duration in the ratio of 1:0.4:0.3 *(23)*.

The direct peripheral vascular effects include a biphasic response of vascular smooth muscles characterized by initial vasoconstriction followed by vasodilatation. Peripheral vasodilatation worsens the hypotension.

Cardiotoxic effects of different local anaesthetics can be compared using the CC/CNS ratio. This is the ratio of the dosage required for cardiovascular collapse and dosage that will produce convulsion. The lower the ratio, the more cardiotoxic the drug is. The cardiovascular to CNS ratio for bupivacaine is 2.0, for lignocaine it is 7.1, for ropivicaine it is 2.2, which indicates that the toxic effects are more pronounced with bupivacaine. Ventricular arrhy-

thmias including fibrillation are more common with bupivacaine and cardiac resuscitation is more difficult after bupivacaine induced cardiovascular collapse. Bupivacaine is more arrhythmogenic than lidocaine and other LA. Bupivacaine blocks the SA node, prolongs the P-R interval and induces more reentrant type of arrhythmias. All this is due to the fact that bupivacaine is more strongly bound to the receptor site within the sodium channel compared to lidocaine, especially in cardiac muscle *(24)*. Cardiac toxicity of local anesthetic is more pronounced in some conditions. Acidosis and hypoxia markedly potentiate the cardiotoxicity of bupivacaine. Pregnancy also may increase sensitivity to cardiotoxic effect of bupivacaine more than ropivacaine and some other LA *(25)*. Physiological changes that occur during pregnancy increase the risk of LA toxicity. A higher cardiac output enhances blood perfusion to the site of LA injection and leads to more rapid absorption. Progesterone may increase neural sensitivity to neural blockade. Lower doses of local anesthetic are needed per dermatomal segment of epidural or spinal block. The plasma protein binding of bupivacaine is reduced in pregnancy, which also may increase the risk of toxicity.

Management of severe local anaesthetic toxicity

In the patient with suspected local anaesthetic toxicity, the first step is to ensure adequate ventilation and oxygenation, since hypoxemia, hypercarbia and acidosis enhance the toxicity. The second step is controlling the seizure with the administration of small doses of benzodiazepines, followed by thiopental or propofol if seizures persist. Convulsions are often followed by hypoxia and hypercapnia, which additionally significantly increase the risk of cardiac depression. The generally recommended doses to stop the seizure are 2–5 mg of midazolam, 50–100 mg of thiopental and 1mg/kg of propofol all given intravenously. Benzodiazepines are the drug of choice because of their minimal cardio-depressant effects. Clinicians should be aware that propofol and thiopental can cause significant hypotension or cardiac depression that can further compromise the cardiovascular status of the patient. In the case of cardiac arrest standard basic life support (BLS) and advanced cardiac life support (ACLS) should be started.

As already mentioned, The Association of Anaesthetists of Great Britain and Ireland (AAGBI) published the first set of standardized guidelines for severe LA toxicity *(6)*. In the next three years, the American Society of Critical Care Anaesthesiologists, the American Society of Anaesthesiologists Committee on Critical Care Medicine *(7),* the Resuscitation Council of the United Kingdom *(8)* and the American Society of Regional Anaesthesia and Pain Medicine also published protocols for the treatment of local anaesthetic systemic toxicity *(9)*. These guidelines highlighted the importance of oxygenation and early cardiopulmonary resuscitation but also highlighted the use of intravenous lipid emulsion (ILE) as a new potential in the treatment of local anaesthetic toxicity. Wein-

berg *et al. (26)* reported the first use of lipid emulsion therapy in animals. They demonstrated that pretreatment or resuscitation with intravenous lipid emulsion resulted in amelioration of bupivacaine cardiotoxicity in rats. The same authors later confirmed these finding in dogs *(27)*. Rosenblatt *et al. (28)* and Litz *et al. (29)* reported the first clinical application of such therapy. Their patients had undergone an interscalene block with bupivacaine and mepivacaine and an axillary block with ropivacaine, respectively. When the patients were failing to respond to routine cardiopulmonary resuscitation (CPR) measures, lipid emulsion therapy was administrated. The use of this therapy led to the patients' quick reversal of cardiac arrhythmias and successful resuscitation. Use of lipid emulsion as antidote in this clinical situation triggered number of subsequent reports describing the successful resuscitation of toxicity due to LAs. The mechanism of action of lipid emulsions is not fully established, but there are several possible mechanisms by which they could act as an antidote for drug toxicity. The »lipid sink« phenomenon is the most widely accepted mechanism of action of ILE. Intravenous lipid emulsion might acts as a circulating lipid sink, drawing LA out of the plasma and binding it, so that no more free fraction exists to bind to the receptors.

The second possible mechanism is reversal of mitochondrial fatty acid transport inhibition. It is known that those local anaesthetics inhibit carnitine acylcarnitine translocase (CACT), which is essential in transport of fatty acids across the inner mitochondrial membrane. Because fatty acids are involved in 80% to 90% of cardiac adenosine 5'-triphosphate (ATP) synthesis, inhibition of CACT may contribute to cardiac toxicity *(30)*. Lipid emulsion could theoretically increase intracellular fatty acid content and therefore overcome this inhibition. The third possible mechanism is that the intravenous lipid emulsion could have a direct inotropic effect by increasing intramyocyte calcium concentration.

Although, initial recommendations suggested that lipid rescue be applied only after standard resuscitation measures have failed, most recent recommendations suggest that intralipid therapy should be considered at the first signs of local anaesthetic induced cardiotoxicity.

The recommendation is to administer an initial intravenous bolus injection of 20% Intralipid at 1.5 mL/kg over one minute followed by infusion of 0.25 mL/kg/min. Cardiopulmonary resuscitation should be continued. If cardiovascular stability is not restored after 5 minutes the bolus should be repeated twice at 5 minute intervals with doubled infusion rate to 0.5 mL/kg/min. It is recommended that the infusion rate is continued until an adequate stable circulation has been restored. A maximum of three boluses can be given, and a cumulative dose of 10 mL/kg should not be exceeded (Table 2). If all of this fails, cardiopulmonary bypass, if available, may be instituted until the local anaesthetic has been metabolized.

Recommended methods to minimize risk of intravascular injection and management of severe local anesthetic toxicity.

Standard monitoring
Slow, incremental injection
Aspiration after positioning the needle
Use indicator of intravascular injection (epinephrine)
Use ultrasound-guided regional anesthesia (?)
Protocol, equipment and pharmacologic agents necessary for the treatment of local anesthetic toxicity available at all time
Airway management (100% oxygen)
Seizure suppression (benzodiazepine, thiopental, propofol)
Basic and Advanced Cardic Life Support (BLS/ACLS)
Administer 20% lipid emulsion
Bolus of 20% Intralipid 1.5 mL/kg over 1 min
Infusion of Intralipid at a rate 0.25 mL/kg/min
Chest compression (lipid must circulate)
Repeated bolus of 20% Intralipid every 3 to 5 min up to 3 mL/kg total dose until circulation restored
Intralipid infusion continued until hemodynamic stabillity and infusion rate increased up to 0.5 mL/kg/h if the blood pressure decline
A maximum total dose of 10 mL/kg is recommended

In the setting of anaesthetic toxicity, it is also important to mention that the aforementioned 2010 ASRA guidelines recommend the use of low dose epinephrine, and avoiding vasopressin completely in the setting of LAST. Although epinephrine is a first line drug for treating cardiac arrest, it has been shown to induce arrhythmias and seizures at lower doses of bupivacaine. There is laboratory evidence that epinephrine can impair resuscitation from LAST and reduce the efficacy of lipid rescue. Hiller *et al.* (31) demonstrated that adding epinephrine to the lipid emulsion at doses above 10 μg/kg led to considerable decline in all hemodynamic and metabolic parameters. Weinberg *et al.* (32) and Di Gregorio *et al.* (33) also showed that lipid emulsion therapy provides superior hemodynamic and metabolic recovery from bupivacaine-induced cardiac arrest than epinephrine and vasopressin.

Prevention

Regional anaesthesia should always be prepared in environment equipped to mange anaesthesia and cardiac arrest (oxygen, monitoring of NIBP, SpO$_2$ and ETCO$_2$, suction). Although new medication, equipment and techniques may improve outcome when unintended high blood levels of local anaesthetics occur, the primary focus of daily practice should remain the prevention of such events. As most systemic toxic reactions to local anaesthetics occur as a result of unintended intravascular in-

jection, it is important to take certain measures to prevent the risk of such occurrences. There is no single clinical measure that can prevent LAST. The first steps are to limit effective doses, aspiration after positioning the needle and adding epinephrine to the LA as an indicator of intravascular injection. The injection of relatively large volume of LA should be done in increments, thus reducing the toxic doses if it is inadvertently injected intravascularly (Table 2). In addition, complication such as intravascular or intraneural injection can be avoided by using ultrasound-guided regional anaesthesia. Compared with alternative techniques ultrasound guidance is associated with an increased success rate, reduced onset time, moderately prolonged duration, reduced need for local anaesthetics and lower costs, and may also be considered to reduce the risk for complications, although there are no randomized controlled studies to confirm or deny this assertion *(34)*.

Although the toxicity of local anaesthetic is indisputable and can be life-threatening, it should be emphasized that this drugs are very safe. The safe and effective use of local anaesthetics depends primarily on good clinical skills, proper dosage, correct technique, adequate precautions and readiness for emergencies. Numerous guidelines and protocols for the management of local anaesthetic systemic toxicity have been published in recent years. All clinicians should be familiar, prior to use of local anaesthetics, with these protocols and lipid emulsion must be available in all areas where regional anaesthesia is practiced.

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