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REVIEW ARTICLE/BRIEF REVIEW

Local anesthetic systemic toxicity
La toxicité systémique des anesthésiques locaux

Derek Dillane, MB · Brendan T. Finucane, MB

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Abstract

Purpose *The practice of regional anesthesia has been revitalized of late with the popularization of ultrasound-guided techniques. Advocates must be vigilant for the effects of unintentionally high blood levels of local anesthetic. Systemic local anesthetic toxicity, though rare, is a potentially devastating occurrence. This narrative review summarizes the effects of local anesthetic toxicity. We highlight how these toxic effects have motivated the search for a safe and long-acting local anesthetic. We outline current prevention and treatment options and appraise an emerging therapy in light of unfolding evidence.*

Sources *A search of the English language literature was conducted using the PubMed database from the National Library of Medicine. Bibliographies of retrieved articles were used to retrieve additional articles.*

Principal findings *The advent of multiple safety steps has led to a dramatic reduction in the incidence of local anesthetic toxicity over the past 30 years. Rising plasma levels of local anesthetic lead to a progressive spectrum of neurological and cardiac effects. Seizure activity may herald the onset of myocardial depression and ventricular arrhythmias that are often refractory to treatment. In addition to specific measures, such as lipid emulsion therapy, general supportive measures are warranted, for example, Advanced Life Support Guidelines.*

Conclusion *Vigilance during the performance of regional anesthesia and immediate intervention at the earliest sign of toxicity improve the chances of successful treatment.*

Résumé

Objectif *La pratique de l'anesthésie régionale a récemment vécu un second souffle grâce à la popularité croissante des techniques échoguidées. Les défenseurs de ces techniques doivent prêter attention aux effets de taux sanguins involontairement élevés de l'anesthésique local. La toxicité systémique des anesthésiques locaux, bien que rare, est un phénomène potentiellement dévastateur. Ce compte-rendu narratif résume les effets de la toxicité des anesthésiques locaux. Nous soulignons la manière dont ces effets toxiques ont motivé des recherches pour mettre au point un anesthésique local à la fois sécuritaire et à action prolongée. Nous décrivons brièvement les options de prévention et de traitement actuelles et évaluons une nouvelle thérapie en regard des données probantes émergentes.*

Source *Une recherche dans la littérature de langue anglaise a été menée dans la base de données PubMed de la National Library of Medicine américaine. Les bibliographies des articles trouvés ont été utilisées pour extraire d'autres articles pertinents.*

Constatations principales *La mise en place de plusieurs étapes de sécurité a permis une réduction impressionnante de l'incidence de toxicité des anesthésiques locaux au cours des trente dernières années. L'augmentation des taux plasmatiques des anesthésiques locaux provoque une gamme progressive d'effets neurologiques et cardiaques. Une convulsion peut annoncer le début d'une dépression myocardique et d'arythmies ventriculaires, lesquelles sont souvent réfractaires à tout traitement. Outre des mesures*

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D. Dillane, MB (✉) · B. T. Finucane, MB
Department of Anesthesiology and Pain Medicine,
University of Alberta, Room CSB 8-120, 113 Street and 83 Avenue, Edmonton, AB T6G-2G3, Canada
e-mail: dillane@ualberta.ca

spécifiques telles que le traitement par émulsion lipidique, des mesures générales de soutien sont de mise, comme par exemple celles préconisées dans les Directives des soins spécialisés en réanimation cardio-respiratoire.

Conclusion *Le fait d'être vigilant pendant la réalisation d'une anesthésie régionale et l'intervention immédiate dès les premiers signes de toxicité améliorent les chances d'un traitement réussi.*

Introduction

Over the past century, the practice of anesthesia has benefited greatly from advances in regional techniques employing both short- and longer-acting local anesthetics. Despite the remarkable efficacy of local anesthetics, the risk of systemic toxicity associated with these drugs has been a recurring problem since their introduction to clinical medicine. An unintentionally high local anesthetic plasma concentration may lead to a progressive spectrum of neurological and cardiac complications with potentially devastating effects. The estimate of clinically important local anesthetic toxicity is from 7.5 to 20 occurrences per 10,000 peripheral nerve blocks and approximately four occurrences per 10,000 epidurals.[1] There has been a dramatic reduction in the incidence of systemic toxicity to local anesthetics in the past 30 years. Nowhere is there more evidence than in epidural anesthesia, which, until 1982, had a reported incidence of systemic toxicity as high as 100 occurrences per 10,000 epidurals.[1]

The purpose of this brief review is to highlight how the toxic effects of local anesthetics have motivated the search for a safe and long-acting local anesthetic. The need for more specific dosing regimens will be examined in light of new pharmacokinetic knowledge. A new therapy for serious local anesthetic toxicity will be evaluated in light of emerging evidence. Finally, this article emphasizes the importance of preventing unintended intravascular injection of these drugs.

Historical perspective of local anesthetics

Advances in the understanding of local anesthetic systemic toxicity parallel the pharmacological development of these drugs and warrant a brief recount of their evolution into clinical practice. In 1860, cocaine was isolated from the coca leaf by the German chemist, Albert Niemann. In 1884, it was used clinically for the first time by the Viennese ophthalmologist, Carl Koller, when he performed the first surgical procedure using local anesthesia on a patient with glaucoma.[2] Portentously, however, 200 cases of systemic toxicity and 13 deaths were assigned to the drug during the period from 1884 to 1891, tempering its initial widespread use as a local anesthetic.[3] The search began for a safer alternative to cocaine. In 1904, another German chemist, Alfred Einhorn, synthesized the compound, novocaine, later to be renamed procaine in the United States during World War I.[4,5] Initially found to be safe, it became the local anesthetic of choice until it was found that it provoked allergic reactions in many patients and clinicians.[6]

In 1943, the first amino-amide local anesthetic was developed by Löfgren and Lundquist, and this xylidine derivative, which they called lidocaine, was first marketed in 1948.[7] Lidocaine has been in clinical use for more than 60 years. It is the most widely used local anesthetic worldwide and remains one of the safest and most efficacious local anesthetic agents ever manufactured. One of its main drawbacks, however, is its short duration of action. In 1957, bupivacaine was synthesized by Bo af Ekenstam and introduced into clinical practice ten years later.[8] Bupivacaine, an amino-amide local anesthetic belonging to the family of the n-alkyl-substituted pipecholyl xylidines, was found to be long-acting. For the first time, a dose dependent separation between sensory and motor anesthesia was produced, and initial reports about its safety were found to be very encouraging.[9] It would take ten years of clinical use before serious cardiac toxicity was reported.

In 1979, George Albright highlighted five anecdotal reports of cardiac arrest following regional anesthesia with bupivacaine.[10] These cases of almost simultaneous convulsion and cardiac arrest required prolonged and largely unsuccessful resuscitation following a presumed intravascular injection, illustrating the narrow margin that exists for bupivacaine-induced cerebral and cardiac toxicity (Figure 1). In October 1983, in an address to the United

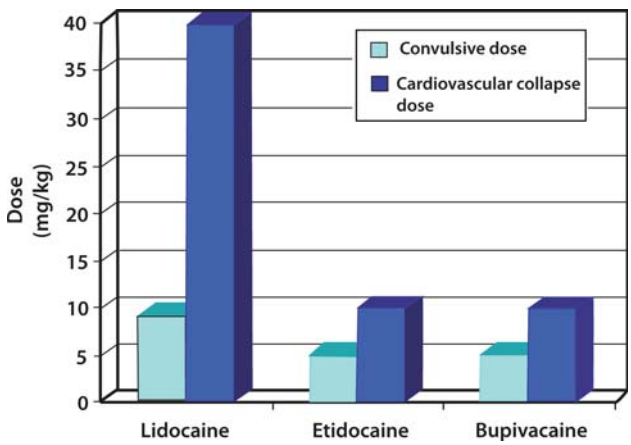

Fig. 1 Relationship among doses of lidocaine, etidocaine, and bupivacaine that cause toxic responses in the CNS and doses that produce cardiovascular collapse. *Covino BG*. Pharmacology of local anesthetic agents. *In*: Rogers MC, Tinker JH, Covino BG, *et al.*(Eds). Principles and Practice of Anesthesiology. St Louis: Mosby Year Book: 1993: 1235-57. Reproduced with permission from publisher. CNS = central nervous system

States Food and Drug Administration's Anesthetic and Life Support Advisory Committee, Albright presented a series of 49 reports of cardiac arrest or ventricular tachycardia requiring cardioversion that occurred over the previous ten years.[11] Most of these cases involved obstetric epidural anesthesia using 0.75% bupivacaine. This information led to the Food and Drug Administration (USA) - sanctioned withdrawal of 0.75% bupivacaine for obstetric use in addition to the introduction of long overdue safety recommendations, including the use of an epinephrine test dose, fractionated dosing, and improved patient monitoring.[12] Similar safety measures were adopted in Canada by the Drugs Directorate of the Health Protection Branch of the Department of National Health and Welfare in Ottawa. The controversial nature of this injunction, which was greeted with initial suspicion rather than complete endorsement, was highlighted in an editorial published in the *Journal* in 1984 entitled, *Trial by media: The bupivacaine story.*[13]

Concurrently in the United Kingdom, a campaign was being conducted by The Council of the Association of Anaesthetists of Great Britain and Ireland to prevent the use of bupivacaine during Bier's intravenous regional anesthesia (IVRA).[14] Up to this juncture, the agent of choice for IVRA, which was considered relatively safe,[15] was now implicated in the deaths of five patients during the period 1979 to 1982. An editorial that appeared in the British Medical Journal in 1982 signified the comparability of these cases: all five were healthy patients being treated for minor conditions in emergency departments, and all five patients had received bupivacaine during IVRA. Two of the patients were eleven-year-old boys.[16] The deaths occurred although the recommended drug dosage was adhered to and early cuff deflation did not occur. The use of bupivacaine for IVRA has since been abandoned, but this has not prevented deaths due to its unintended intravenous administration. In the decade leading up to 2004, bupivacaine was directly responsible for the deaths of three patients in the United Kingdom as a result of accidental intravenous administration. The most recent death involved a 30-year-old parturient whose inquest was held in February 2008.[A]

In the 1980s, the development of new long-acting amides took advantage of the fact that most of these molecules have a chiral centre determined by the presence of a carbon atom bound to four different molecules (Figure 2). These three-dimensional stereoisomers have an identical chemical composition, but they differ in their spatial orientation.[17] There are significant safety implications associated with these new amide local anesthetics, as it has been established that the levorotatory isomer (S−) has less

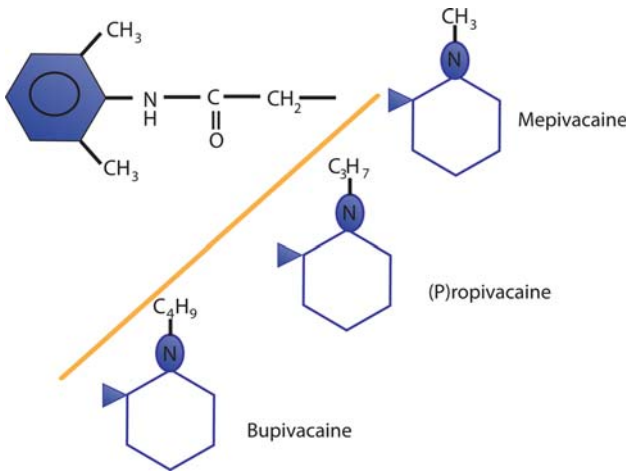

Fig. 2 Structure of the n-alkyl-substituted pipecolyl xylidines, mepivacaine, ropivacaine, and bupivacaine

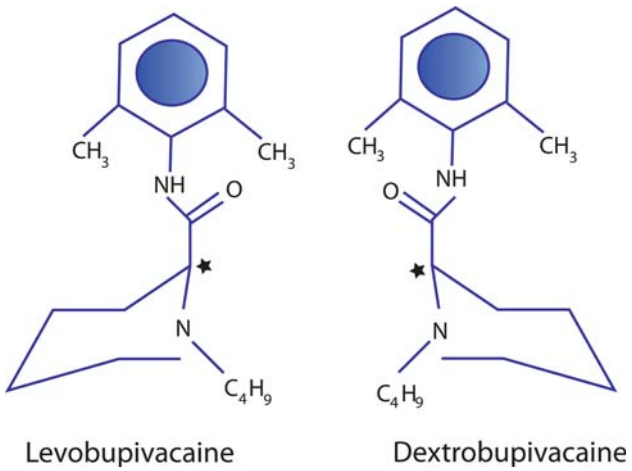

Fig. 3 The molecular structures of levobupivacaine and dextrobupivacaine. The asterisk indicates the asymmetric carbon atom

potential for systemic toxicity compared with the dextrorotatory isomer (R +) (Figure 3).[18] This observation has led to the development of the single stereoisomers, levobupivacaine and ropivacaine, first approved for clinical use in North America in 1996.

Toxicity-related pharmacokinetic considerations of local anesthetics

Local anesthetics differ from most other pharmacological agents because they are deposited in close proximity to the target neural structure. However, they are still subject to absorption, and a large fraction of the injected drug is removed by the systemic circulation and distributed to distant organs. Direct measurement in an animal model demonstrated that < 2-3% of an injected dose entered the target nerve. In addition, more than 90% of an injected

[A] Drug storage at hospital was "chaotic". 2008; Available from URL: http://www.guardian.co.uk/society/2008/feb/05/nhs.health2 (accessed December 2009).

Table 1 Tissue-plasma partition coefficients (λ) for lidocaine in various organs

Organ	Tissue-plasma partition co-efficient (λ)
Spleen	3.5
Lung	3.1
Kidney	2.8
Stomach	2.4
Fat	2.0
Brain	1.2
Heart	1.0
Muscle	0.7
Liver	0.6
Skin	0.6
Bone	0.4 - 0.9

(*de Jong R.H.* Local Anesthetics. Mosby – Year Book 1994: 165. Adapted with permission from author)

dose is taken up by the systemic circulation within 30 min of injection.[19]

Local anesthetic is distributed to organs according to their vascular density. This accounts for the fact that highly vascular organs, such as the brain, heart, lung, liver, and kidneys are exposed to unmetabolized local anesthetic at peak concentration. The local anesthetic is taken up within each organ according to its tissue-plasma partition co-efficient. To highlight the differential organ responses, the tissue-plasma partition coefficients for lidocaine are summarized in Table 1. The lungs play an important buffering role by taking the full impact of drug-laden venous blood. A variety of investigational techniques, including autoradiography, scintillation counts, and tissue assays, confirm the lung's ability to quickly extract local anesthetic.[20] However, this buffering action of the lung is saturable.

Most absorbed local anesthetic is cleared from the liver. Hepatic clearance is a function of the hepatic extraction ratio and hepatic blood flow. The hepatic extraction ratio, in turn, is dependent on the ratio of free to protein-bound drug. Local anesthetics bind tightly to plasma proteins greatly limiting the free fraction of available drug. This is clinically relevant, as it is only the free or unbound fraction that is bioactive. Like most weak bases, local anesthetics bind mainly to alpha-1-acid glycoprotein (AAG). Lidocaine, being moderately protein-bound, has a high hepatic extraction ratio (70-75% per pass). Clearance is therefore flow-limited and is reduced by factors that limit hepatic blood flow, e.g., upper abdominal and laparoscopic surgery, volatile anesthetic administration, hypocapnia, congestive cardiac failure, and intravascular volume depletion. Through its relationship to hepatic blood flow, cardiac output may modify local anesthetic clearance. Heart failure, for example, reduces hepatic blood flow and so reduces lidocaine clearance. Conversely, bupivacaine and ropivacaine, being highly protein-bound, are cleared $< 50\%$ per pass; hence, their clearance depends on free drug concentration (Table 2). Low cardiac output states may not greatly affect the plasma concentration of the highly protein-bound agents, as their clearance is not flow-limited. Intrinsic hepatic disease may alter clearance by altering plasma protein content and degree of protein binding, by decreasing the enzyme activity of the liver, and by reducing hepatic blood flow. The practical implications of these pharmacokinetic principles are not without clinical relevance. Patients with liver disease may have single-shot blocks with normal doses. Doses for continuous infusion and repeat blocks need to be significantly reduced (10-50% relative to the degree of dysfunction) due to the risk of accumulation of the primary compound and its metabolites. Patients with mild or controlled cardiac failure may not need a dose reduction for single-shot blocks. Doses of ropivacaine and bupivacaine for continuous infusion and repeat blocks need to be reduced, as their metabolites will be eliminated slowly.[21]

Table 2 Pharmacokinetic parameters of local anesthetics

Local anesthetic	Clearance ($L \cdot min^{-1}$)	Terminal half-life (min)	Hepatic extraction (ratio)
Lidocaine	0.95	96	0.72
Etidocaine	1.11	162	0.74
Mepivacaine	0.78	114	0.51
Bupivacaine	0.58	162	0.40
Ropivacaine	0.73	111	0.40
Levobupivacaine	0.47	108	0.67

(*de Jong R.H.* Local Anesthetics. Mosby 1994: 67. Reproduced with permission from author. Data for ropivacaine from A. Lee *et al.*[117]

In patients with renal dysfunction, reduced clearance and faster absorption of local anesthetic lead to an elevation in plasma concentration.[21] Clearance of both bupivacaine[22] and ropivacaine[23] has been shown to be reduced in uremic patients. The clearance of one of the main metabolites of ropivacaine, 2,6-pipecoloxylidide (PPX), is also decreased in uremic patients. In rat studies, its cardiotoxicity is reported as being half that of bupivacaine. The hyperdynamic circulation associated with uremia may be responsible for the rapid rise in plasma concentration of both ropivacaine and bupivacaine.[21] The surgically stimulated increase in the plasma protein, α_1-acid glycoprotein (AAG), acts as a counterbalance to these factors, which may prevent the accumulation of toxic levels of free or unbound local anesthetic. Adding further to its protective effect, AAG concentration is increased in uremic patients.[24] Consequently, there is a need for a 10-20% dose reduction relative to the degree of renal dysfunction in single-shot blocks and continuous infusion.[21]

Drug toxicity in elderly patients

Drug toxicity is less predictable in elderly patients due to a combination of opposing factors. A reduction in muscle mass and total body water, together with an increase in body fat, may result in a larger volume of distribution of lipophilic local anesthetics with a prolonged clearance time. Reduced blood flow and deteriorating organ function further prolong clearance times.[21] Although increasing age has little effect on AAG concentration, many elderly patients have diseases that may lead to elevated plasma concentrations of this buffer. Cancer, trauma, myocardial infarction, uremia, and inflammatory disease all lead to elevated AAG concentration. The concentration of free drug in the plasma and distribution to various tissues will change accordingly.

Toxicity related to pediatric regional anesthesia

Regional anesthesia is rarely used as the sole anesthetic technique in infants and children. The focus in this population has been on improving postoperative analgesia with a concomitant reduction in parenteral opioid use.[25] Pediatric regional anesthesia techniques are usually performed after induction of anesthesia. This distinction from adult practice entails a number of important safety considerations.

Neonates and infants present significant pharmacokinetic peculiarities that may lead to an increased risk of toxicity. Immature hepatic metabolism and marked differences in plasma protein binding serve to increase plasma concentrations of unbound amide local anesthetic. α_1-acid glycoprotein concentration is very low at birth (less than 30% of the adult concentration) and progressively increases to adult levels during the first year of life.[26] Subsequently, the unbound fraction of local anesthetic is greater during infancy, which increases susceptibility to toxicity.

Clearance of local anesthetics is low at birth and does not effectively reach adult levels until six to nine months.[27,28] The terminal half-life of amide local anesthetics is three to eight times longer in neonates than in adults.[29] Amide local anesthetics are metabolized in the liver by oxidative pathways involving the cytochrome P450 enzyme superfamily. Lidocaine and bupivacaine are mainly metabolized by CYP3A4, an enzyme system that is not fully mature at birth. However, most of its biotransformation activities are achieved by CYP3A7, an enzyme that is present only in the fetus and during the first months of life.[30] Ropivacaine is metabolized by CYP1A2, which is not fully functional before three years of age.[30] Consequently, it is reasonable to assume that bupivacaine clearance should be at or near normal adult levels from birth and that ropivacaine clearance should be markedly deficient. However, this is not the case. Clearance of bupivacaine is markedly deficient at birth and increases slightly in the first year of life. Conversely, ropivacaine clearance is not very low at birth but does not fully reach adult values before five years of age.[31] This enzyme immaturity is clinically relevant to a limited extent but does not preclude the use of these local anesthetics in neonates and infants.

Local anesthetics have the same toxic effects in infants and children as those seen in adults. In the adult patient, neurologic toxicity occurs at lower concentrations, followed by cardiac toxicity at higher concentrations. This is not always true for bupivacaine because of its lower threshold for cardiac toxicity. Regardless of choice of local anesthetic, cardiac toxicity may precede neurotoxicity in pediatric patients. Early signs of cerebral toxicity are subjective (dizziness, drowsiness, and tinnitus). These will not be conveyed by the young or anesthetized child. Moreover, general anesthesia itself raises the cerebral toxicity threshold, and neuromuscular blockade will preclude the onset of generalized tonic-clonic seizures.[32] Consequently, the first manifestation of an accidental intravascular injection or rapid absorption may be cardiovascular collapse.[33]

The reported incidence of cerebral toxicity is low. Two large surveys (each more than 20,000 regional anesthesia procedures in the pediatric population) indicate that the incidence of seizures is < 0.01-0.05%.[34,35] There have been several case reports of children experiencing seizures after a regional anesthesia procedure. Most of these cases involved continuous lumbar or caudal epidural anesthesia with bupivacaine.[36,37] Bupivacaine is associated with seizures at a plasma concentration as low as 4.5-5.5 $\mu g \cdot mL^{-1}$. Rather alarmingly on occasion, these toxic plasma concentrations were reached even after adhering to the recommended therapeutic range.[36,38] The overall incidence of cardiac toxicity in this population is also remarkably low. Several large series of regional anesthesia procedures in infants and children report no cases of cardiovascular toxicity.[36,37,39,40] A prospective study of more than 24,000 regional anesthesia procedures report four patients who developed a cardiac arrhythmia, and none of these progressed to cardiac arrest or collapse.[35]

When performing a regional technique in a patient under general anesthesia, care must be taken to avoid inadvertent intravascular injection by using a slow incremental approach. The use of an epinephrine marker can be useful in this situation. Even a small intravenous dose of 1-2 $\mu g \cdot kg^{-1}$ of epinephrine in a 1:200,000 solution with 0.25% bupivacaine will produce T wave elevation on the ECG, particularly in the lateral leads. The V5 lead appears to be most sensitive to these changes, which do not occur when either drug is injected alone.[32]

Toxicity related to pregnancy

A number of physiological changes occur during pregnancy that enhance the risk of toxicity of local anesthetics.[41] The plasma protein binding of bupivacaine is significantly reduced, which increases the risk of toxicity.[42] A higher cardiac output increases blood perfusion to the site of local anesthetic injection and leads to more rapid absorption.[43] In addition to these changes, progesterone may increase the sensitivity of nerve axons to neural blockade.[44] Therefore, it is indicated to reduce the dose of local anesthetic in blocks where large doses are normally required, e.g., brachial plexus block.

The utilization of multiple safety steps has perhaps benefited maternal morbidity and mortality more than any other group, as detailed by Hawkins *et al.* who reported a "significant decline in maternal mortality related to regional anesthesia techniques following 1984".[45] A similar trend can be seen in the American Society of Anesthesiologists Closed Claims study project.[35] There were no claims related to intravascular injection of local anesthetic after 1990. This reflects the changes in clinical practice in the mid-1980s with the withdrawal of 0.75% bupivacaine, the widespread use of test doses, and fractionated dosing.[46] The past two decades have seen further advances in obstetric epidural anesthesia. Opioids in the form of fentanyl 2 $\mu g \cdot mL^{-1}$ or sufentanil 0.75 $\mu g \cdot mL^{-1}$ are commonly added to the local anesthetic solution to reduce the high concentrations of local anesthetic associated with systemic toxicity. This has permitted a reduction in the concentration of bupivacaine from 0.5% to 0.065% while maintaining satisfactory analgesia.[47] The use of patient-controlled epidural analgesia is associated with a decrease in the total dose of local anesthetic used when compared with continuous infusion.[48,49] Combined spinal-epidural (CSE) anesthesia has become increasingly popular in the past decade. In one of the largest studies of this practice to date, Albright reported a safety profile for CSE that was comparable with epidural anesthesia alone.[50]

Use of intravenous lidocaine infusions

Intravenous lidocaine has well-established analgesic and anti-inflammatory properties.[51-53] Its use as a systemic analgesic was described as early as 1954 in a study involving over 2,000 patients. Three cases of convulsion were reported, and the authors emphasized the need for vigilance against toxicity.[54] Over the past 25 years, a number of randomized controlled trials (RCT) indicate that continuous intravenous lidocaine administration may have a beneficial effect on outcomes after colorectal surgery.[52,55] A recent meta-analysis of eight RCTs in patients undergoing colorectal surgery demonstrated a reduced duration of postoperative ileus, pain, nausea and vomiting, and shortened hospital stay with perioperative intravenous lidocaine administration.[51] In seven of the eight RCTs, a lidocaine bolus 1.5-2 $mg \cdot kg^{-1}$ was given before surgical incision. Intraoperative infusion rates were in the range of either 2-3 $mg \cdot min^{-1}$ or 1.5-3 $mg \cdot kg^{-1} \cdot hr^{-1}$. In this meta-analysis, no local anesthetic toxicity was observed apart from a single episode of transient arrhythmia.[56] However, the safety of continuous intravenous lidocaine has not been established in large clinical trials.

Local anesthetic in the surgical wound

In recent years, there has been renewed interest in the direct application of local anesthetic to wounds through continuous infusion or high volume infiltration.[57] Liu *et al.* conducted a systematic review of 44 randomized controlled trials involving over 2,141 patients in the 40 years prior to 2006.[58] In these studies, wound catheters were placed in subcutaneous, suprafascial, subfascial, intra-articular, peripleural, and periosteal locations. No cases of local anesthetic systemic toxicity were reported in any of these studies.

Tumescent anesthesia for liposuction is a widely used technique that is based on the subcutaneous infiltration of a large volume of dilute lidocaine (0.1% or less) with epinephrine. The pharmacokinetic profile of this dilute mixture differs from that used for epidural and peripheral nerve blockade.[59] The low concentration of the local anesthetic together with epinephrine-induced vasoconstriction allows for a maximum dose of lidocaine far in excess of that which is conventionally accepted. A safe dose is reported as 35 $mg \cdot kg^{-1}$. However, practice varies widely, and doses as high as 50 $mg \cdot kg^{-1}$ are not uncommon.[59] A very slow absorption rises to a plateau plasma concentration of 2 $\mu g \cdot mL^{-1}$ and remains at this level for up to twelve hours.[60] Drug competition at cytochrome P450 1A2 or 3A4 further slows metabolism.[61] Tumescent anesthesia does not have an exemplary safety record. There continues to be reports of serious complications, including death.[62,63]

Central nervous system toxicity of local anesthetics

As the systemic concentration of local anesthetic increases, central neurotoxicity is seen in a stereotypical and sequenced manner. The amygdala appears to be the principal neurophysiologic focus for seizures, while the hippocampus has been posited as a secondary focus.[64] The amygdala is situated in the pole of the temporal lobe just below the cortex on the medial side. It appears to be a critical element in the brain circuitry that processes fear and aggression. It is a complex of nuclei that receives

afferents from a large variety of sources, including the neocortex in all lobes of the brain as well as the hippocampus. Ultimately, information from all sensory systems feeds into the amygdala.[65]

The central toxic response is related specifically to plasma concentrations of local anesthetic in the central nervous system (CNS) and their effect on the complex interplay between excitatory and inhibitory pathways that facilitate neurotransmission. Initially, there is a generalized excitatory phase as manifest by seizure activity. This initial phase appears to be the result of blocking inhibitory pathways in the amygdala, which allows excitatory neurons to function unopposed. The gaba-amino butyric acid (GABA)-gated chloride channel may well be an initial target of local anesthetics.[65] Interestingly, distinct ligand binding sites exist on the $GABA_A$ receptor for benzodiazepines and barbiturates whose actions result in an enhanced inhibitory Cl^- current and a reversal or termination of seizure activity (Figure 4). Historically, Tatum, Atkinson, and Collins established this fact as early as 1925 by demonstrating that the prophylactic administration of barbiturates to a dog increased its tolerance fourfold in response to a toxic dose of local anesthetic.[66] These investigators also identified that seizures related to local anesthetic toxicity are completely controlled by barbiturate injection, and the likelihood of recovery is inversely proportional to the duration of the seizure.

Early clinical signs that herald CNS toxicity include light-headedness, dizziness, blurred vision, and tinnitus. With increasing plasma concentrations, muscle twitching and tremors involving facial musculature and distal parts of the extremities are often observed. As blood and brain levels of local anesthetic concentration increase, generalized tonic-clonic reactions occur.[67]

When plasma concentrations of local anesthetic in the CNS increase further, both inhibitory and excitatory pathways (being more resistant to the effects of local anesthetic toxicity) are inhibited, which leads to CNS depression, reduced levels of consciousness, and eventually coma.

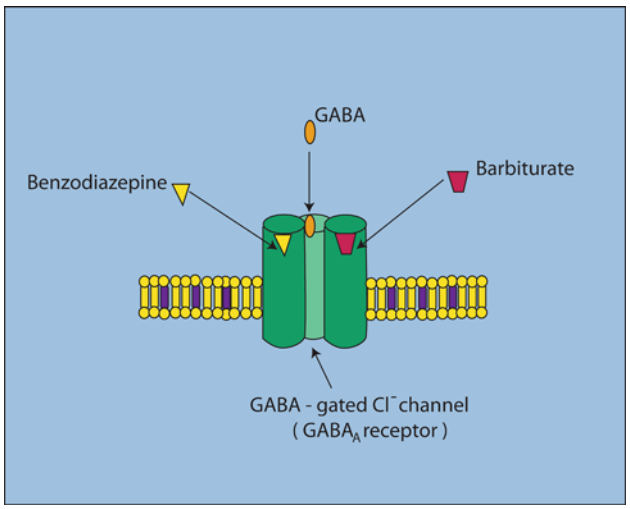

Fig. 4 The binding of benzodiazepines and barbiturates to the $GABA_A$ receptor. Distinct ligand binding sites exist on the $GABA_A$ receptor for benzodiazepines and barbiturates whose actions result in an enhanced inhibitory Cl^- current and a reversal or termination of local anesthetic-induced seizure activity

Cardiac toxicity of local anesthetics

Most commonly attributed to excessively high or rapidly increasing plasma concentrations, cardiotoxicity also follows a biphasic pathway. At lower concentrations, sympathetic nervous system activation during the CNS excitatory phase can lead to hypertension and tachycardia. This may conceal the direct myocardial depressant effects occurring at higher concentrations epitomized by ventricular arrhythmias, myocardial conduction delays, and profound contractile dysfunction ultimately leading to cardiovascular collapse.[68]

For obvious ethical reasons, most available information on cardiac toxicity is from animal studies and case reports. The principal mechanism of cardiac toxicity relates to the blockade of myocardial voltage-dependent sodium channels, which leads to an increase in the PR interval and QRS duration provoking a dose-dependent prolongation of conduction time and eventual depression of spontaneous pacemaker activity. Persistent sodium channel blockade predisposes to re-entrant arrhythmias. These electrophysiological effects are compounded by a direct negative inotropic effect of local anesthetic drugs. Blockade of potassium and calcium channels may also contribute to cardiotoxicity, signifying up to three sites of action.[69] When comparing lidocaine with bupivacaine in guinea pig ventricular muscle, Clarkson and Hondeghem developed the concept that lidocaine blocks sodium channels in a "fast-in fast-out" fashion, whereas bupivacaine blocks these channels in either a "slow-in slow-out" manner in low concentrations or a "fast-in slow-out" manner at higher concentrations.[70] On the other hand, ropivacaine has been shown to block sodium channels in a "fast-in medium-out" fashion.[71] In fact, the dissociation constant (between ligand and receptor) for bupivacaine is almost ten times longer than that of lidocaine, resulting in a prolonged and near irreversible cardiac depressant effect.[70] Moreover, the dissociation constants for the R(+) and S(-) bupivacaine enantiomers demonstrate that the dextrorotatory isomer is seven times more potent in blocking the potassium channel than the levorotatory isomer.[72] There is a positive correlation between local anesthetic lipid solubility and inhibition of cardiac contractility, further evidence for the clinically relevant finding that ropivacaine is less

toxic than levobupivacaine, which, in turn, is less toxic than racemic bupivacaine.

Toxicity of ropivacaine and levobupivacaine

Animal studies have demonstrated that both levobupivacaine and ropivacaine have less potential for both cardiotoxicity[73,74] and cerebral toxicity.[75] It is difficult to compare and extrapolate the results of animal studies to the clinical environment, but a few clinical studies do exist. In human volunteer studies, both ropivacaine and levobupivacaine require doses that are 10-25% larger than doses of racemic bupivacaine before signs of cerebral toxicity occur.[76, 77] Several case reports on unintentional intravascular injection of either levobupivacaine or ropivacaine describe complete recovery, and all cases were preceded by cerebral toxicity.[78-82]

If ropivacaine and levobupivacaine are indeed the safest of currently available local anesthetics, it would be important to compare and contrast their toxicity profiles. Animal models of local anesthetic toxicity[83,84] suggest that the systemic toxicity of levobupivacaine is intermediate, i.e., between that of bupivacaine and ropivacaine. The superior safety profile of ropivacaine may be related to its reduced potency or, as suggested by Groban *et al.*,[84] ropivacaine-induced myocardial depression may be suppressed because of intrinsic vasoconstrictor properties.

Prevention of local anesthetic toxicity

When the potential severity and refractory nature of local anesthetic toxicity is being considered, it is perhaps best to employ a cautious and preventive approach. As most systemic toxic reactions to local anesthetics occur as a result of unintended intravascular injection, it is important to take steps that minimize the risk of this occurrence. The importance of patient monitoring is often overlooked but impossible to overemphasize. While oxygen therapy remains a prerequisite, all patients undergoing a regional anesthesia technique should have electrocardiography, blood pressure monitoring, and pulse oximetry. This is especially important when regional anesthesia is practiced in so-called "block rooms" outside the immediate operating room environment.

Despite the relative safety of the long-acting single enantiomer local anesthetics, many practitioners have an allegiance to bupivacaine. In a recent survey of 135 academic anesthesiology departments by Corcoran *et al.*, 55% *vs* 43% of respondents reported a preference for bupivacaine over ropivacaine for the long-acting local anesthetic of choice for peripheral nerve blockade.[85] Factors other than safety, such as perceived quality and duration of nerve blockade, may influence choice of local anesthetic. Much controversy surrounds the true equipotency ratio between the three long-acting agents. Results from a number of animal studies and clinical observation would suggest a rank order of potency of ropivacaine < levobupivacaine < bupivacaine.[17]

What constitutes a safe dose of local anesthetic? Recommendations for maximal doses based on patient weight are widely available.[86,87] These recommendations have been extrapolated largely from animal research, clinical case reports, and measured blood concentrations during routine clinical use. It is wise to adhere to these recommendations when using potent local anesthetic drugs such as bupivacaine and ropivacaine. Maximal recommended doses have their limitations. Differential absorption from injection site leads to a large variation in peak plasma concentrations. The highest plasma concentration of local anesthetic is observed after intercostal block followed by epidural and brachial plexus block.[41] These recommendations have been developed for the normal non-intravascular injection of local anesthetic and, therefore, do not apply during unintended intravascular injection.

The introduction and widespread use of ultrasound-guided regional anesthesia may be as important for local anesthetic systemic toxicity as the pharmacological advances of previous decades. For the first time in the century-old practice of regional anesthesia, it is now possible to visualize the target neural structure in addition to potential vascular hazards. This may allow for the more accurate deposition of smaller volumes of local anesthetic.[88-91] In addition, slow injection allows for direct visualization of the spread of local anesthetic solution, which ensures increased confidence in exact localization.

Particular care is required when using nerve stimulation-guided regional techniques without the aid of ultrasound. There is a tendency to inject local anesthetic solution more rapidly under these circumstances to achieve maximal local anesthetic deposition at the correct location**.** Incremental administration of local anesthetic with ongoing patient assessment for signs of toxicity is very important. Additionally, the value of frequent aspiration for blood cannot be overstated. The dose of local anesthetic should be determined according to the patient's lean body mass and modified according to American Society of Anesthesiologists physical status. Careful use of sedation helps to ensure patient cooperation and comfort. Adding a cardiovascular marker to the local anesthetic solution (epinephrine 1:200, 000 or 1:400, 000) provides an additional safety measure. In addition to alerting the practitioner to the possibility of an intravascular injection, epinephrine decreases peak plasma concentration (C-max) of local anesthetic; it delays the time to peak plasma concentration (T-max) and decreases the bioavailability of the rapid absorption phase, all of which serve to reduce local anesthetic toxicity.[92]

Treatment of local anesthetic toxicity

Immediate intervention at the earliest sign of local anesthetic toxicity is of paramount importance and improves the chances of successful treatment.[93] Management involves general supportive measures involving Advanced Life Support Guidelines (ACLS) and specific measures directed at local anesthetic toxicity (Figure 5).[94] Since hypercapnia, hypoxia, and acidosis enhance the toxic effects of bupivacaine,[95] there must be no delay in airway management, administration of 100% oxygen, or seizure control. Convulsions may be treated with small doses of thiopentone, propofol, or a benzodiazepine. A neuromuscular blocking agent should be administered without hesitation to enable optimal airway control**.** Propofol may benefit treatment in early local anesthetic toxicity through a number of independent mechanisms,[96,97] including seizure suppression and antioxidant properties that may improve recovery from tissue hypoxia. However, propofol is a cardiodepressant, and its use is not advisable when there are signs of cardiac instability.

Recent literature describing experimental animal studies and clinical case reports suggest that lipid emulsion is effective in the reversal of local anesthetic toxicity. Intralipid® 20% is a United States Food and Drug Administration (FDA)-approved hyperalimentation source comprised of soybean oil, glycerol, and egg phospholipids. The mechanism of action of lipid emulsion in the reversal of local anesthetic toxicity has not been fully elucidated. It may act as a circulating lipid sink extracting lipophilic local anesthetic from plasma or tissues.[98] An alternative proposed mechanism is the reversal of local anesthetic inhibition of myocardial fatty acid oxidation, thereby restoring myocardial adenosine triphosphate (ATP) supply.[99] Weinberg *et al.* conducted the original research involving the successful resuscitation of rats in which cardiovascular collapse was induced with intravenous bupivacaine.[100] These findings were successfully repeated in a canine model of bupivacaine toxicity.[98] It would take a further eight years after publication of the original animal studies before the first clinical case report of the successful use of lipid emulsion appeared in the literature.[101] This involved a prolonged cardiac arrest following placement of an interscalene block with bupivacaine and mepivacaine. There have been a number of subsequent reports describing the successful resuscitation of toxicity due to bupivacaine, either as the sole agent[102] or when used in combination with ropivacaine[103]and mepivacaine.[104] It has also been used successfully in the treatment of toxicity due to ropivacaine,[105] levobupivacaine,[106] and mepivacaine,[107] when each was used as the sole agent and in the treatment of toxicity due to a combination of lidocaine and ropivacaine.[108] Interestingly, only one of the multitude of case reports to date describes the use of an ultrasound-guided technique,[109] and there is no indication in this report that extravascular spread of local anesthetic was observed.

For the treatment of local anesthetic toxicity, Intralipid 20% should be administered as a bolus of 1.5 mL·kg^{-1} *iv*

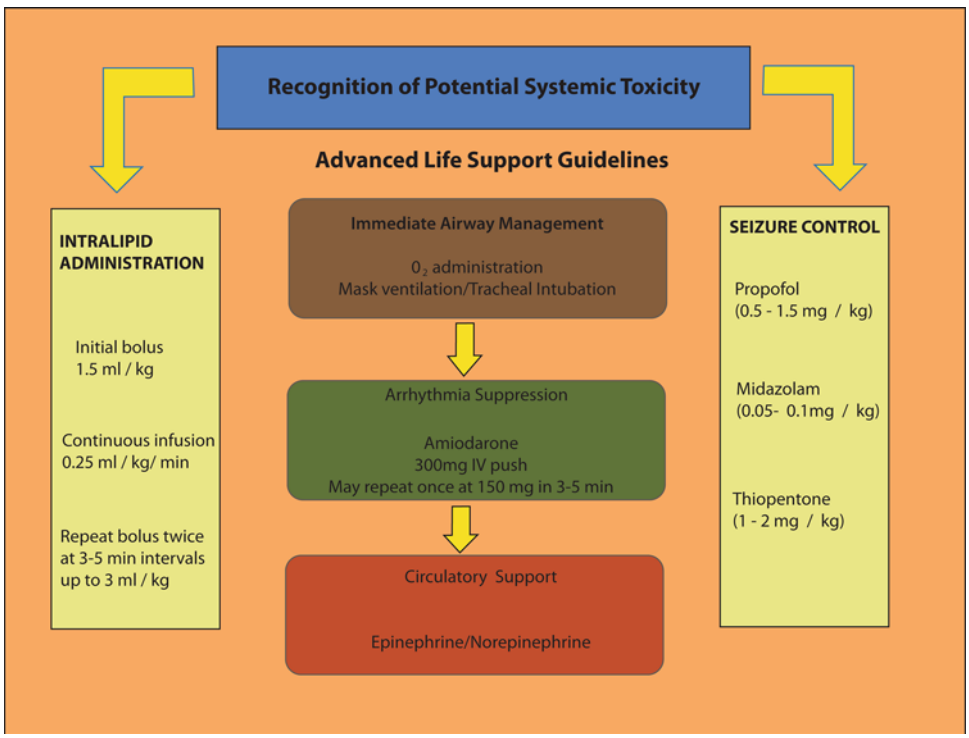

Fig. 5 Algorithm for the management of local anesthetic systemic toxicity

over one minute followed immediately by an infusion at a rate of 0.25 $mL \cdot kg^{-1} \cdot min^{-1}$.[110] It is important that chest compressions continue to allow the lipid to circulate. The bolus may be repeated every three to five minutes up to a total of 3 $mL \cdot kg^{-1}$. The infusion may be continued until hemodynamic stability is restored. The infusion rate may be increased to 0.5 $mL \cdot kg^{-1} \cdot min^{-1}$ if the blood pressure declines.

Despite the paucity of information regarding the use of lipid emulsion for this indication, in light of the current evidence, it would appear prudent to ensure immediate availability in areas where regional anesthesia is performed. It is appropriate to administer lipid emulsion to patients in cardiac arrest due to local anesthetic toxicity when they are being resuscitated following current ACLS guidelines. In an attempt to preempt cardiac toxicity, it may be equally justifiable to administer lipid emulsion to patients displaying overt neurologic toxicity.

In the past, animal studies have demonstrated the value of vasopressor agents in improving outcome, particularly epinephrine and norepinephrine.[111] However, epinephrine may worsen local anesthetic-induced arrhythmias.[111,112] Recent animal studies have demonstrated a superior hemodynamic and metabolic recovery from bupivacaine-induced cardiac arrest when lipid infusion is compared to epinephrine [113,114] and vasopressin.[115]

Even though ACLS guidelines now support the use of vasopressin (40 U in a single intravenous dose) in addition to epinephrine during cardiopulmonary resuscitation, the authors do not recommend its use in local anesthetic-induced toxicity. The efficacy and safety of vasopressin in cardiac arrest is controversial, while laboratory data and human trials fail to provide conclusive evidence.[115] Amiodarone, a primary drug in the ACLS arrhythmia treatment algorithm, should be considered the treatment of choice for serious ventricular arrhythmias induced by potent local anesthetic agents, and it appears to be widely accepted as the first line therapy.[85] It has a complex spectrum of electrophysiological effects, including the inhibition of outward potassium channels that prolong repolarization and an anti-adrenergic effect that is independent of and additive to that of β-blockers. Calcium channel blockers are contraindicated due to the additive myocardial depressant effect when used in combination with bupivacaine.[94] Phenytoin increases anesthetic toxicity[116] and use of bretylium is no longer supported.

Conclusions

The development of regional anesthesia over the past century has followed some of the most innovative discoveries in the history of medicine. There has been a considerable groundswell of enthusiasm amongst anesthesiologists in recent years to use regional techniques in order to moderate sympathoadrenal stimulation during surgery and to improve postoperative analgesia. The use of portable ultrasonography to guide placement of needles and catheters has become increasingly popular and has generated renewed interest in regional anesthesia. Despite considerable progress, fundamental elements of the practice of regional anesthesia require further scientific justification. Doses of local anesthetics should be site specific and should be modified according to patient age, physiology, and disease-related influences. The greater safety profile of the single enantiomer agents, particularly ropivacaine, is evident. Signs of local anesthetic toxicity must be recognized at the earliest possible stage in order to provide appropriate and effective treatment and to minimize complications. Slow incremental injection of local anesthetic, frequent aspiration, and addition of epinephrine as a cardiovascular marker are recommended to prevent intravascular injection. Lipid emulsion therapy has gained acceptance as an effective treatment for local anesthetic toxicity, and it should be available in all areas where regional anesthesia is practiced.

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