Management of Local Anesthetic Toxicity

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Local anesthetic systemic toxicity (LAST) is a rare but potentially fatal complication of regional anesthesia. The danger of toxic blood concentrations of local anesthetic (LA) has been recognized and reported since the late 1800s after the purification of cocaine, the first LA.[1] Although the practice of regional anesthesia has evolved since the late 1800s, LAST remains a major concern. This fact was highlighted by an alarming editorial by Albright[2] in 1979, accompanying reports of LAST. This study and similar publications prompted the Food and Drug Administration to address administration of LAs by clinicians. The use of bupivacaine for intravenous regional anesthesia was prohibited and bupivacaine 0.75 was precluded from being used in obstetric epidurals. Over the past 25 years, the overall incidence of LAST has decreased dramatically. The decline in LAST is more significant with epidural anesthesia. In 1981, the incidence of LAST was 100/10,000 epidurals.[3] Brown et al[4] in 1995 retrospectively reviewed the Mayo Clinic experience and found an incidence of LAST of 0.1/1000 epidurals and 2.0/1000 brachial plexus blocks. Auroy et al[5] in 1997 prospectively reported an incidence of LAST of 0.13/1000 epidurals and 0.75/1000 peripheral nerve blocks (PNBs). This trend led to a decreased LAST incidence that was confirmed in 2002 by the same team[6] who reported 7 cases of LAST, 1 associated with an epidural, and 6 with PNBs, in 153,083 regional anesthesia procedures recorded. An incidence of 0.98/

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INTERNATIONAL ANESTHESIOLOGY CLINICS
Volume 48, Number 4, 117–140

1000 PNBs was recently found by Barrington et al.[7] Interestingly, none of the cases reported by these researchers were associated with cardiac arrest. The development of better monitoring, safer techniques, and the use of lower LA concentrations may all have contributed to a reduced incidence of LAST.

However, LAST is still associated with significant morbidity. Records from the American Society of Anesthesiologists Closed Claims Database[8] show that between 1980 and 2000 LAST was associated with one-third of the claims for death and brain damage after regional anesthesia.

In the past decade, a major change occurred in the treatment of cardiovascular (CV) collapse after LAST with the introduction of lipid rescue therapy. The focus of this study is to examine the mechanisms of cardiotoxicity, the new developments in lipid therapy, and the prevention of LAST after the use of long-acting amide LAs. The literature search, using the PubMed Search engine, was based on the following key words: LA toxicity, bupivacaine toxicity, ropivacaine toxicity, L-bupivacaine toxicity, lipid emulsion, lipid rescue, LA cardiotoxicity, LA neurotoxicity, and complications of regional anesthesia. Only animal and human studies published in English and French have been selected.

■ Clinical features of LAST

LAST is a dose-dependent complication characterized by neurological and CV symptoms. The classic description of LAST is a stepwise progression of symptoms with increasing LA blood concentrations. LAs produce central nervous system (CNS) excitation at low plasma concentrations. Subjective symptoms include vertigo, a metallic taste, tinnitus, a sense of foreboding, and perioral numbness. At higher concentration of LA, objective signs occur, which are as follows: agitation, garbled and slurred speech followed by muscle twitching, and eventually generalized tonic-clonic seizures. With even higher blood concentrations, the earlier signs of CNS excitation are replaced with signs of CNS depression, such as coma and respiratory arrest. CV toxicity may occur. Arrhythmias may herald by impending hypotension and CV collapse. However, LAST associated with regional anesthesia does not always present itself in a textbook manner (Figs. 1A, B). CV signs accompagnied CNS toxicity in 44%.[9] Ten patients among the 93 patients recorded in this study, had evidence of cardiac toxicity without any CNS signs of toxicity.

LA agents differ in their CV/CNS ratio. The margin of cardiac safety is less with long-acting LAs than with short-acting LAs.[10] The CV/CNS ratio is lower with bupivacaine when compared with lidocaine. In comparing long-acting LAs, the CV/CNS ratio is 4.2 for bupivacaine and 8.1 for ropivacaine in anesthetized rats.[11]

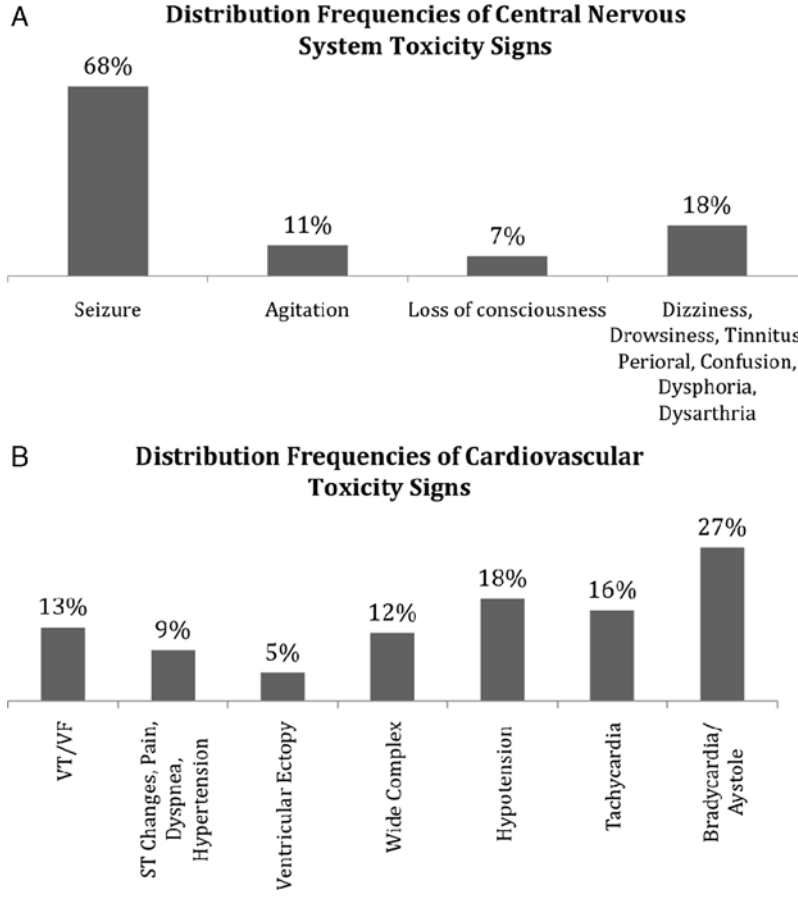

Figure 1. *A, Distribution frequencies of central nervous system toxicity signs. B, Distribution frequencies of cardiovascular toxicity signs. Reprinted with permission from Reg Anesth Pain Med 2010;35:181–187. VF indicates ventricular fibrillation; VT, ventricular tachaycardia.*

■ Mechanisms of Cardiotoxicity After Systemic Absorption of LAs

CV toxicity produces changes in cardiac conduction, impairment of contractility, and myocardial metabolic changes. The exact mechanisms by which LAs induce cardiotoxicity are not fully understood.

Voltage-gated sodium (Na_v) channels contribute to initiation of the action potential in neurons and cardiac cells. Rapid influx of sodium into myocytes produces the initial rapid upstroke of action potential in atrial and ventricular muscle. Ventricular conduction velocity is correlated with the maximum upstroke velocity (V_{max}). Unionized lipophilic LAs will pass through the membrane of neural and cardiac cells and lock the Na_v channel in the inactive state.[12] When binding to Na_v channels, LAs

slow the fast inward sodium current[13] and thus delay the generation and propagation of action potentials. The cell membrane can no longer become depolarized. At low concentrations, bupivacaine induces a dose-dependent depression of the fast action potential V_{max} in the atrium and at infranodal level.[13] Therefore, bupivacaine induces slowing of ventricular conduction.[14] The V_{max} of ventricular and Purkinje cell action potentials are decreased.[12]

There are 7 genetically distinct Na_v channels found in nerves, skeletal muscles, and heart tissue. Neuronal forms of the Na_v channel can also be found in the conduction tissue and contribute to cardiac toxicity. A stereoselectivity of bupivacaine when binding to a Na_v channel has been reported.[11,15] The R(+) bupivacaine isomer blocks channels faster and more strongly than L-bupivacaine.[15] This could explain the greater cardiac toxicity of R(+) enantiomers, as the effect of LAs on Na_v channels is the main determinant of impaired cardiac conduction.

As for myocardial contractility, the action potential V_{max} of the sinoatrial and atrioventricular (A/V) nodes depends mainly on the calcium current through the L-type Ca^{2+} channels. At high plasma levels, bupivacaine slows the action potential V_{max} of the sinoatrial and A/V nodes by a calcium current inhibitory effect. This inhibition of the slow inward current of calcium is moderate but might explain the sinus bradycardia and the slowing of A/V conduction.[16] However, bupivacaine inhibits the fast inward Na_v current at lower concentrations than those at which induces slowing of the inward Ca^{2+} current.[17]

Outward K^+ currents from adenosine triphosphate (ATP)-sensitive K^+ channel accelerate repolarization of the heart. It has been observed[18] that bupivacaine inhibits this K^+ current. This action may result in a prolongation of the action potential duration[19] and an increase in the QT interval corrected for heart rate (HR).[20] A stereoselectivity of LAs on a K^+ channel has been reported.[21] Bupivacaine is more potent than L-bupivacaine and ropivacaine in binding to the cardiac KATP channels.[22] L-bupivacaine is 7-fold less potent in blocking the K^+ channel than the R(+) enantiomer.[21] A greater concentration of bupivacaine is needed to inhibit K^+ channels in comparison with Na_v channels.[23] Boban et al[24] found that the K^+ channel openers improved A/V conduction while worsening cardiac depression by increasing coronary blood flow and oxygen extraction.

Effect of Amino-amide LAs on Cardiac Conduction

Moller and Covino[25] evaluated the cardiac transmembrane electrophysiological effects of LAs in an isolated rabbit Purkinje fiber ventricular muscle preparation. Three drugs were studied: lidocaine, ropivacaine, and bupivacaine. The greatest depression of cardiac excitability and conduction was produced by bupivacaine, followed by

ropivacaine and then lidocaine. The recovery of these parameters tended to be longer with bupivacaine. The researchers also reported a significantly decreased action potential amplitude and a decreased maximal rate of depolarization (V_{max}), bupivacaine >ropivacaine>lidocaine. This suggests the interference of Na_v channel conduction in the cardiac myocyte.[12] Lacombe et al[26] infused rabbit hearts (Langendorff preparation) with bupivacaine and reported that bupivacaine had a depressant effect on conduction at atrial, ventricular, and A/V levels. Moller and Covino[25] and Lacombe et al[26] suggest that the electrophysiological changes induced by bupivacaine provide the basis for ventricular reentrant arrhythmias.

De La Coussaye et al[27] provided evidence of reentrant pathways in relation to LA toxicity. The researchers used high-resolution ventricular epicardial mapping and isolated frozen rabbit hearts to study the effects of varying doses (from 0.2 to 5 μg/mL) of bupivacaine in Langendorff-perfused rabbit hearts. This experimental protocol allowed longitudinal and transversal conduction velocity analysis. Bupivacaine induced ventricular arrhythmias with increasing concentrations both spontaneously and in response to electrical stimulation. Epicardial mapping showed that all ventricular tachycardias were based on reentry of an impulse around an arc of functional conduction block. Ventricular effective refractory period was significantly prolonged by bupivacaine. The researchers concluded that bupivacaine caused ventricular conduction blocks, thereby facilitating the initiation of reentrant ventricular arrhythmias. In addition, they reported that longitudinal and transverse conduction velocities were reduced in both a dose-dependent and a use-dependent (ie, slope of QRS duration-HR relation). The use-dependent slowing of conduction was probably caused by the fast-in-slow-out pattern of sodium channel inhibition.

Using a similar model, Aya et al[28] compared the electrophysiological properties of equimolar concentrations of bupivacaine, L-bupivacaine, and ropivacaine. The ventricular effective refractory period was strongly prolonged by bupivacaine and L-bupivacaine but not by ropivacaine. This effect increased in a concentration-dependent manner. Use-dependent conduction impairment was observed with all 3 agents but with slight differences among them. The use-dependent effect on transverse conduction velocity was the same for all 3 agents. Use-dependent slowing of longitudinal conduction velocity was greater with both bupivacaine and L-bupivacaine than with ropivacaine. The use-dependent effect on longitudinal velocity was similar with racemic bupivacaine and L-bupivacaine.

Mazoit et al[29] studied use dependence of QRS widening in the isolated rabbit heart. They found significant use dependence with an approximate ratio of 1:0.5:0.2 for racemic bupivacaine, L-bupivacaine, and ropivacaine, respectively. Use-dependent QRS widening increased

linearly with racemic bupivacaine dose. According to the researchers, this was probably the same for ropivacaine and L-bupivacaine. The lack of a clear use-dependent effect for ropivacaine in Aya et al's[28] study compared with Mazoit et al's[29] study may be related to the model used. Different conduction parameters were studied in both models. Aya et al[28] studied 2 conduction variables (longitudinal and transverse velocity), whereas Mazoit et al[29] looked at QRS widening. The use-dependent effect of long-acting LAs on cardiac conduction has important clinical implications during resuscitation after LAST.

Cardiac Toxicity Ratios of Amino-amide LAs

In a swine model,[30] using the prolongation of the QRS interval as a measure of electrophysiological toxicity, CV toxicity ratios for racemic bupivacaine, L-bupivacaine, and ropivacaine were 2.1:1.2:1. The same group[31] measured the QRS interval after the injection of LA into the coronary circulation of an anesthetized swine and found a toxicity ratio of 15:6.7:1 for racemic bupivacaine, ropivacaine, and lidocaine, respectively. At similar free plasma concentrations, long-acting LA drugs induced QRS widening in an isolated heart preparation in an approximate ratio of 1:0.4:0.3 for racemic bupivacaine, L-bupivacaine, and ropivacaine, respectively.[29]

It is reported consistently that bupivacaine is the LA most likely to be associated with electrophysiological abnormalities. With regard to this, L-bupivacaine seems to be intermediate between ropivacaine and bupivacaine. In a recent study by Guinet et al,[32] surprisingly L-bupivacaine induced fewer electrophysiological changes compared with ropivacaine at equimolar doses in anesthetized ewes. Although hemodynamic changes were similar, the differences in the experimental model used may explain this unexpected result.

Stereospecificity of Cardiac Electrophysiological Changes

The 3-dimensional structure of long-acting amide agents has important implicatons for toxicity. S(–) and R(+) enantiomers have different affinities and actions on cardiac conduction. Graf et al[33] using a Langendorff guinea pig heart preparation compared stereospecific differences in the cardiotoxicity of bupivacaine and ropivacaine. They showed that these LAs prolonged A/V conduction time in a concentration-dependent manner. Both bupivacaine isomers increased A/V conduction time greater than either of the ropivacaine isomers. Impairment of A/V conduction time was stereospecific for bupivacaine. The R(+) enantiomer produced a greater increase in A/V conduction time than the S(–) enantiomer even at the lowest concentrations. Racemic bupivacaine had an intermediate effect. Ropivacaine only showed this stereospecific

difference at the highest concentrations used. Thus, at clinical concentrations, only bupivacaine showed A/V conduction time stereoselectivity.

There are other stereospecific conduction differences. Mazoit et al[29] showed that racemic bupivacaine prolongs the QRS conduction time greater than L-bupivacaine. In this study, arrhythmias were more frequent in the racemic bupivacaine group.

Effects of LAs on Myocardial Contractility

Cardiotoxicity extends beyond conduction changes and arrhythmias. LAs have a direct effect on contractility. The relative importance and the temporal relationship between these are unclear. Do arrhythmias and cardiac depression occur simultaneously and contribute equally to cardiac toxicity? In experimental studies, death resulting directly from myocardial depression[34,35] and death resulting from ventricular dysarrhythmias[36,37] have been reported. As Butterworth[38] has posed the question "do patients with bupivacaine toxicity die of arrhythmias, contractile failure, or a combination of the two?"

In an anesthetized rat model, it has been shown that the propensity to produce asystole was racemic bupivacaine>L-bupivacaine>ropivacaine.[11] Importantly, cardiac arrest induced by ropivacaine seemed to be more responsive to resuscitation than that induced by racemic bupivacaine or L-bupivacaine. Royse and Royse[39] used pressure volume loops to separate myocardial and vascular depressive effects, and found that L-bupivacaine and bupivacaine reduced both the ejection fraction and the cardiac index greater than ropivacaine. Stereospecificity did not impact on inotropic and chronotropic depression. Bupivacaine and L-bupivacaine produce similar negative inotropic effect,[37] and there is no evidence of stereoselectivity with ropivacaine isomers either.[33] Inhibition of cardiac contractility is proportional to the lipid solubility of the drug.[37]

The mechanisms of impairment of myocardial contractility with long-acting LAs are not fully understood. Higher concentrations of LA (5-fold to 10-fold) are required to produce inotropic depression than arrhythmias. In ferret ventricular muscle, the cardiac depressant effect of bupivacaine is approximately 2-fold greater than that of ropivacaine[40] and this effect may result from inhibition of the sarcoplasmic reticulum function. The inhibitory action of bupivacaine on cardiac contraction has been attributed to the inhibition of Ca^{2+} release,[41] to Ca^{2+} sequestration[42] in the sarcoplasmic reticulum, and to a decrease in myofibrillar activation.[43] De La Coussaye et al[16] reported that bupivacaine produced only moderate inhibition of the slow inward Ca^{2+} current (i_{max}) in isolated frog atrial muscle. Even at high bupivacaine concentrations studied (10^{-4} M), the i_{max} was depressed by only 33%. The researchers[16] suggest that this is not sufficient to explain the impairment of ventricular contractility produced by bupivacaine toxicity.

Effects of Amino-amide LAs on Myocardial Metabolism

There is some evidence that long-acting LAs interfere with mitochondrial metabolism. It is postulated that this may contribute to cardiac depression associated with toxicity. Bupivacaine uncouples oxidative phosphorylation and inhibits the respiratory chain leading to a decrease in ATP synthesis by the mitochondria. The high-energy requirements by the myocyte can then no longer be met. LAs inhibit almost every component of the respiratory chain but mainly complex I (reduced nicotinamide adenine dinucleotide ubiquinone reductase). Bupivacaine and ropivacaine have the same inhibitory effect on isolated complex I, but Sztark et al[44] showed that bupivacaine impaired myocyte mitochondrial metabolism significantly greater than ropivacaine. The greater lipophilicity of bupivacaine may result in a higher mitochondrial concentration and explain this finding. The LA concentration needed to impair ATP synthesis is 50 to 100 times greater than that needed to produce cardiac toxicity. However, after accidental intravascular injection, the maximum concentration of LA achieved at the mitochondrial level is unknown. It seems that bupivacaine stereospecificity does not alter mitochondrial metabolic effects.[45] Another effect of bupivacaine on mitochondrial metabolism, which may contribute to toxicity, has been suggested.[46] Bupivacaine inhibits carnitine-acylcarnitine translocase decreasing fatty acid—the main source of energy—transport into the mitochondria of cardiac myocytes.

■ Lipid Therapy for the Treatment of LA Toxicity

Hypoxemia and acidosis potentiate LAST. Early recognition and early airway management remain of primary importance in the treatment of LAST. When seizures occur, benzodiazepines are the drugs of choice. Anesthetic induction agents, such as propofol and thiopental, are less than ideal but acceptable alternatives. The ability of these anesthetic induction agents to produce cardiac depression may worsen their toxic effects. The American Society of Regional Anesthesia (ASRA) guidelines[47] recommended their use only if benzodiazepines are not immediately available. Rapid seizure suppression helps prevent the development of acidosis and hypoxemia, which can otherwise exacerbate cardiac toxicity and decrease the efficacy of lipid therapy.

Successful resuscitation after prolonged cardiac arrest has confirmed that LAST does not produce irreversible myocardial damage per se. Inadequate resuscitation carries the risk of permanent ischemic myocardial injury. Restoring adequate coronary perfusion and oxygenation is therefore a key treatment goal. If resuscitation is prolonged, cardiopulmonary bypass should be considered.[48] Until recently, cardiopulmonary bypass was the only rescue method shown to be effective for resuscitation of bupivacaine-induced cardiac arrest.[49]

Mechanisms of the Action of Lipid Therapy

The first clinical report of successful resuscitation using lipid emulsion after bupivacaine overdose was published in 2006 by Rosenblatt et al.[50] A 58-year-old patient developed signs of CNS toxicity 30 seconds after an interscalene block (20 mL of 0.5% bupivacaine and 20 mL of mepivacaine) rapidly followed by asystolic arrest. After 20 minutes of unsuccessful resuscitation, plans were being made to institute cardiopulmonary bypass. Following the recent animals data suggesting potential benefit of lipid therapy,[51–53] the team decided to administer an intravenous bolus of 100 mL of 20% lipid emulsion. Within seconds sinus rhythm returned. The patient fully recovered without neurological sequelae. This landmark case report of successful and rapid resuscitation was followed by other similar reports.[54–58] Lipid emulsion has since been used to successfully treat both adults and children[58] with bupivacaine, ropivacaine,[54,58] L-bupivacaine,[55] mepivacaine,[56,57] and prilocaine[57] systemic toxicity. Lipid therapy is the most significant recent advancement in the treatment of LAST.

The first evidence that lipid emulsion might be an useful treatment in LAST came from a study on rat reported by Weinberg et al.[51] When animals were pretreated with lipid emulsion, the median dose of bupivacaine required to induce asystole was significantly higher. Lipid infusion increased 48% of lethal dose of bupivacaine in 50% of animals. These results were later confirmed in nonrodent and larger animal models.[53] Bupivacaine-induced asystole dogs treated with lipid emulsion had an increased survival rate after 10 minutes of resuscitation without the use of vasopressors. All dogs in the lipid treatment group survived with rapid recovery of hemodynamic parameters. There was no survival among the control group.

The exact mechanism underlying how lipid rescue works is not fully established despite proof of laboratory and clinical efficacy. Several theories have been proposed (Fig. 2).[59] The "lipid sink theory" is the main theory that has proposed.[51] Long-acting LAs are highly lipophilic. Lipid emulsion provides a lipid phase within plasma into which bupivacaine partitions. The mean lipid/aqueous ratio of bupivacaine in a plasma-intralipid mixture is 12.[51] Zausig et al[60] showed that the effects of lipid emulsions after LA-induced cardiac arrest were greater with bupivacaine than with ropivacaine and mepivacaine. It has been related to the higher lipophilicity of bupivacaine, which could facilitate the "lipid sink" mechanism. Using radiolabeled bupivacaine, the same team[61] showed that lipid emulsion increased the removal of bupivacaine from the cardiac tissue and accelerated recovery from bupivacaine-induced asystole in an isolated rat heart model. Thus, the sequestration of lipophilic LA molecules into a lipidemic plasma results in lesser availability of LA to the cardiac tissue. Lipid may act as a "sink" by binding and extracting LA, reducing free LA in the aqueous plasma phase. The 'lipid sink' is an

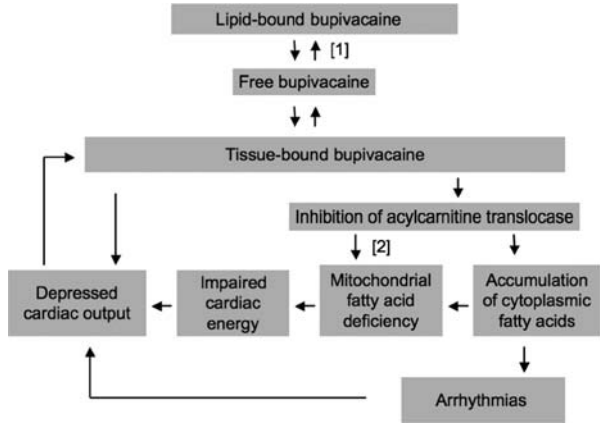

Figure 2. *Sites of maintenance and potentiation of bupivacaine cardiotoxicity. Lipid intervention might exert a positive effect secondary to 2 postulated mechanisms: [1] lipid sink, with bupivacaine partitioned into lipid, reducing the effective unbound fraction available for binding to cardiac tissue; [2] Lipid-providing substrate, which may overcome the loss of cardiac energy because of the inhibition of acylcarnitine translocase by bupivacaine. Printed with permission from Reg Anesth Pain Med. 2010;35:162–166.*

indirect effect. The rapidity of lipid reversal in animal and clinical models seems inconsistent with a process that requires the movement of a toxic concentration of hydrophobic LAs out of the tissue.

An alternative direct mechanism of action has been proposed. A direct metabolic effect of lipid emulsion has been shown in rats.[62] Lipid infusion in L-bupivacaine induced cardiac depression, had a positive inotropic effect. Lipid infusion significantly improved cardiac contractility (+ dp/dt) and restored ventricular systolic pressure. A similar improvement in myocardial contractility after lipid infusion had already been shown by Weinberg et al,[61] who used rate pressure product [= heart rate × (left ventricular systolic pressure – left ventricular diastolic pressure)] as a measure of contractility.

Weinberg et al[53] evaluated pH and pO_2 of myocardial tissue in dogs after bupivacaine-induced cardiac toxicity and found that lipid emulsion improved myocardial metabolic function. A mitochondrial effect of lipid emulsion has been suggested. Fatty acids are the primary source of ATP production by the mitochondria. Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria.[46] One hypothesis is that lipid emulsion improves mitochondrial fatty acid uptake by providing a high plasma triglyceride concentration or more specifically by acting on the flux of acylcarnitine.[61] However, Sther et al[62] reported no change in ATP production by the mitochondria after lipid therapy. Whether there is a direct effect of lipid emulsion on mitochondrial function is not yet clear.

Although Sther et al[62] failed to show an effect of lipid emulsion on electrophysiological parameters, Candela et al[63] recently showed that lipid

emulsions reversed electrophysiological changes induced by intravenous infusion of bupivacaine. However, the study was not powered to detect a difference between the 2 lipid emulsions (long-chain triglycerides and the mixture of long-chain and medium-chain triglycerides).

Lipid Therapy and the Use of Vasopressors in LAST

The available animal data might lead to an assumption that vasopressors are not first-line therapy in the treatment of bupivacaine-induced cardiac toxicity. Vasopressors are, however, recommended by all LAST guidelines. The benefit of vasopressors in combination with lipid therapy in the treatment of LA-induced cardiac toxicity is controversial. The main issue is whether vasopressors in combination with lipid therapy provide benefit over lipid therapy alone.

After bupivacaine-induced asystole, Weinberg et al[64] compared the effect of lipid with epinephrine and saline infusion. The hemodynamic (rate pressure product) and metabolic indices (pH, arterial oxygen tension, and central venous oxygen saturation) were significantly better after lipid therapy than those of the epinephrine group which were similar to the saline control group. Compared with the lipid group, the epinephrine group had higher lactate, more ventricular arrhythmias, pulmonary edema, hypoxemia, and mixed metabolic and respiratory acidosis. In a similar experimental model, the same team recently showed better cardiac function and tissue perfusion after lipid treatment compared with vasopressin (0.4 U/kg bolus) alone or combined with epinephrine (30 mcg/kg bolus).[65] Mayr et al[66] reported that the combination of vasopressin and epinephrine significantly improved both coronary perfusion pressure during resuscitation and survival compared with lipid therapy, in a porcine model of asphyxial cardiac arrest after intravenous injection of a toxic dose of bupivacaine. In a swine model of bupivacaine cardiac toxicity, Hicks et al[67] showed that lipid therapy did not improve the return of spontaneous circulation when added to a resuscitation protocol with epinephrine (100 mcg/kg) and vasopressin (1.5 U/kg).

These apparent contradictions between laboratory studies may be because of differences in the experimental and animal model chosen (ie, interspecies differences). Mayr et al[66] began resuscitation treatment only after hypoxemia had occurred, whereas Weinberg et al[64] induced asystole and started resuscitation immediately. The resuscitation protocols, open-chest cardiopulmonary resuscitation versus closed-chest cardiopulmonary resuscitation experimental endpoints, and bupivacaine doses used to induce asystole were also different.[64,66] Another suggested explanation for the poor outcome with use of vasopressors is that the doses of epinephrine and vasopressin used for resuscitation were too high in some studies.[68] Vasopressors are known to increase lactate,[69] to worsen acidosis, and to induce pulmonary edema[70] and ventricular arrhythmias.[71] In a

dose-response study, Hiller et al[72] reported a 10-mcg/kg threshold dose above which epinephrine impaired lipid resuscitation in a rat model of bupivacaine overdose. To date, there is no evidence of a detrimental effect of epinephrine when coadministered with lipid therapy. However, caution against excessive doses must be kept in mind. Vasopressors remain the first-line treatment drugs for advanced cardiac life support to improve coronary perfusion according to the American Heart Association Guidelines for cardiac arrest.[73]

Choice of Lipid Emulsion

Intralipid 20% is a soy-based lipid emulsion and contains predominantly long-chain fatty acids. Intralipid 20% was the first lipid emulsion to be used in both experimental and clinical settings for the treatment of LA-induced cardiac toxicity. Ludot et al[58] reported successful resuscitation after ropivacaine and lidocaine cardiac toxicity using a different lipid emulsion; Medialipid 20%, which contains 10 g of soya and 50/50 medium-chain and long-chain fatty acids. Mazoit et al[74] have recently shown in a laboratory-based study that both Intralipid and Medialipid bind bupivacaine, L-bupivacaine, and ropivacaine. However, the binding capacity of Intralipid was 2 to 3 times greater than that of Medialipid. In addition, racemic bupivacaine and L-bupivacaine bound more avidly (2.0 to 2.6 times) than ropivacaine to both Intralipid and Medialipid. This is probably a function of their greater lipophilicity and also would explain why racemic bupivacaine and L-bupivacaine cleared more rapidly than ropivacaine. This suggests that Intralipid may be preferable to Medialipid in bupivacaine poisoning. At present, the use of Intralipid seems preferable to Medialipid in the treatment of LAST until additional data become available.

It is important to realize that propofol cannot be used as a source of lipid in the treatment of LAST. In its standard formulation (1% propofol in 10% lipid emulsion), the propofol volume needed to provide sufficient lipid is too high and it would worsen CV collapse after LAST.

Treatment of CNS Toxicity and Lipid Therapy

A benefit to the early use of lipid emulsion in the treatment of CNS toxicity before the development of significant cardiotoxicity has been reported.[55,56,75] In all cases, lipid was infused with the intent of preventing progression to CV collapse. Spence[75] reported a case of inadvertent intravenous bupivacaine injection leading to CNS toxicity during an epidural anesthetic in a pregnant woman. This was quickly and successfully managed with intravenous administration of 20% Intralipid. Within 30 seconds seizures stopped and the patient regained full consciousness. The exact mechanisms of action of lipid emulsion in CNS toxicity remains unknown.

Safety of Lipid Therapy

Complications of lipid emulsion therapy include thrombophlebitis during intravenous administration, pulmonary, splenic, placental and cerebral fat emboli, pulmonary hypertension, and pancreatitis.[76] Altered inflammatory responses may occur with long-term therapy. During short-term administration, lipid emulsion has the potential to cause transient reductions of PaO_2/FiO_2 in neonates and adults[77] and also allergic reactions including anaphylaxis.[78]

Hiller et al[79] recently studied the safety profile of high dose lipid emulsion in rats. The lethal dose, 50% (dose required to kill 50% of the animals) was significantly higher than the mean dose used in clinical reports to reverse LAST. Microscopic abnormalities such as hemorrhagic vascular congestion and extensive necrosis in the lung and liver occurred only with the highest doses of lipid emulsion (60 and 80 mL/kg).

Availability and Timing of Lipid Rescue After LAST

To date, intravenous lipid emulsion used to treat LAST has a good track record of experimental and clinical use without any major complications. Lipid emulsion has become a crucial "antidote" to treating LAST.[80] It should be readily available in all locations in which peripheral and neuraxial blocks are carried out. Prevention of LAST remains the key element of improved patient safety.[81]

However, once signs of LA toxicity occur, there is increasing evidence that the early use of lipid infusion limits the severity of LAST.[82–84] In a case report[57] in which an infusion of lipid was commenced without an initial bolus, although resuscitation was successful, delayed recovery was noted. The researchers speculated that a loading dose might have been able to shorten the resuscitation. To date, there are no published clinical reports of treatment failure when lipid emulsion has been used to treat LAST. However, more data are needed.

Marwick et al[85] reported the first case of recurrence of CV instability, that is, ventricular dysrhythmias, 40 minutes after completion of lipid rescue after bupivacaine-induced cardiac arrest. The researchers used 500 mL of Intralipid after which no more was available. Amiodarone and inotropic support at that point resulted in successful recovery. However, this possibility of recurrence has led to the recommendations that a bolus of lipid emulsion should be followed by an infusion,[86,87] and that at least 1000 mL of 20% lipid emulsion should be immediately available.[86]

Finally, in the treatment of LAST, it is recommended to consider an early cardiopulmonary bypass.[87] It is the last rescue option when other treatments have failed.

■ Recommendations for the treatment of LAST (Table 1)

Evidence combined with expert opinion has resulted in the publication of new treatment guidelines. Clear recommendations on lipid therapy have now been given by both the ASRA[47] and the Association of Anesthetists of Great Britain and Ireland.[86] Lipid

Table 1. *Recommendations for Treatment of LAST*

- If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia and acidosis, which are known to potentiate LAST (I;B)
- If seizures occur, they should be rapidly halted with benzodiazepines. If benzodiazepines are not readily available, small doses of propofol or thiopental are acceptable. Future data may support the early use of lipid emulsion for treating seizures (I;B)
- Although propofol can stop seizures, large doses further depress cardiac function; propofol should be avoided when there are signs of CV compromise (III;B). If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxemia (I;C)
- If cardiac arrest occurs, we recommend standard advanced cardiac life support with the following modifications:
  - If epinephrine is used, small initial doses (10-100 μg boluses in the adult) are preferred (IIa;C)
  - Vasopressin is not recommended (III;B)
  - Avoid calcium channel blockers and β-adrenergic receptor blockers (III;C)
  - If ventricular arrhythmias develop, amiodarone is preferred (IIa;B); treatment with local anesthetics (lidocaine or procainamide) is not recommended (III;C)
- Lipid emulsion therapy (IIa;B):
  - Consider administering at the first signs of LAST, after airway management
    - Dosing:
    - 1.5 mL/kg 20% lipid emulsion bolus
    - 0.25 mL/kg per minute of infusion, continued for at least 10 min after circulatory stability is attained
    - If circulatory stability is not attained, consider rebolus and increasing infusion to 0.5 mL/kg/min
    - Approximately 10 mL/kg lipid emulsion for 30 min is recommended as the upper limit for initial dosing
- Propofol is not a substitute for lipid emulsion (III;C)
- Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of CPB (IIa;B). Because there can be considerable lag in beginning CPB, it is reasonable to notify the closest facility capable of providing it when CV compromise is first identified during an episode of LAST

The class of recommendations and level of evidence for each intervention are given in parenthesis.
CPB indicates cardiopulmonary bypass; CV, cardiovascular; LAST, local anesthetic systemic toxicity.
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emulsion dose should be based on an estimate of lean body weight. The maximum recommended dose of lipid emulsion is 10 mL/kg within the first 30 minutes.

■ Recommendations for Preventing Systemic Toxicity From LAs (Table 2)[88]

Complications of regional anesthesia resulting in toxic blood levels of LA are accidental intravascular injection, systemic absorption, and LA overdose. Guidelines have been published by the ASRA[81] for preventing them.

Table 2. *Recommendations for Preventing LAST*

- There is no single measure that can prevent LAST in clinical practice.
- Use the lowest effective dose of local anesthetic (dose = product of volume × concentration) (I;C).
- Use incremental injection of local anesthetics-administer 3-mL to 5-mL aliquots, pausing 15-30 s between each injection. When using a fixed needle approach, eg, landmark, paresthesia-seeking, or electrical stimulation, time between injections should encompass circulation time (approximately 30-45 s); however, this ideal may be balanced against the risk of needle movement between injections. Circulation time may be increased with lower-extremity blocks. The use of larger dosing increments would dictate the need for longer intervals to reduce the cumulative dose from stacked injections before an event of LAST. Incremental injection may be less important with ultrasound guidance, given that frequent needle movement is often used with the technique (I;C).
- Aspirate the needle or catheter before each injection, recognizing that there is approximately 2% false-negative rate for this diagnostic intervention (I;C)
- When injecting potentially toxic doses of local anesthetic, use of an intravascular marker is recommended. Although epinephrine is an imperfect marker and its use is open to physician judgment, its benefits likely outweigh its risks in the majority of patients (IIa;B):
  - Intravascular injection of epinephrine 10-15 μg/mL in adults produces a ≥10-beat HR increase or a ≥15-mm Hg SBP increase in the absence of β-blockade, active labor, advanced age, or general/neuraxial anesthesia.
  - Intravascular injection of epinephrine 0.5 μg/kg in children produce subjective symptoms of mild systemic toxicity (auditory changes, excitation, metallic taste, etc.) in unpremedicated patients.
  - Fentanyl 100 μg produces sedation if injected intravasculary in laboring patients.
- Ultrasound guidance may reduce the frequency of intravascular injection, but actual reduction of LAST remains unproven in humans. Individual reports describe LAST despite the use of ultrasound-guided regional anesthesia. The overall effectiveness of ultrasound guidance in reducing the frequency of LAST remains to be determined (Iia;C).

The class of recommendations and level of evidence for each intervention are given in parenthesis
LAST indicates local anesthetic systemic toxicity; SBP, systolic blood pressure.
Adapted with permission from *Reg Anesth Pain Med.* 2010;35:177–180.

Accidental Intravascular Injection

Unintentional direct intravascular injection is characterized by a short-time interval between LA injection and first signs of toxicity. When intra-arterial injection occurs, the patient will quickly manifest signs of toxicity. Intra-arterial injection occurs more often when giving regional anesthesia in the neck (interscalene and cervical plexus blocks). If LA is accidentally injected into an artery supplying the brain, immediate seizure may be the first sign of toxicity. In this case, seizures may be precipitated by very small doses of LA. Seizures usually terminate quickly as the drug is rapidly removed by the cerebral blood flow. Intravenous injection is more common and results in a more gradual rise in blood levels.

Intermittent gentle aspiration and incremental injection (generally 3 to 5 mL) have long been recommended to prevent LAST. One of the presumed benefits of both intermittent aspiration and incremental injection is to slow the injection of LA. However, these measures alone may fail to identify intravascular injection and have not been validated.[89]

The aim of a test dose is to immediately recognize an unintended intravascular injection and to avoid its consequences. The use of epinephrine in a test dose has been commonly used but again its efficacy has not been confirmed. There are safety concerns specifically in pregnant women in whom there is a potential risk of impairing uteroplacental perfusion.[90] When an epinephrine test dose[91] of 10 to 15 μg is used, a HR increase of 10 beats/min or greater and/or an increase in the systolic blood pressure of 15 mm Hg or higher have both an 80% sensitivity and positive predictive value in nonpregnant adults. In children 0.5 μg/kg of epinephrine is used as a test dose. Intravascular injection should be suspected if there is a 15 mm Hg or higher increase in the systolic blood pressure. There are some limitations to the reliability of an epinephrine test dose. HR response is attenuated in the elderly individuals, in patients treated with β-blockers, in patients under sedation, or anesthetized (general or neuraxial anesthesia) patients.[92,93] The interpretation of HR response may be confusing in pregnant women with simultaneous uterine contraction. Administration of an epinephrine test dose is not often used when performing PNB. The French Society of Anesthesiology[94] suggests its use only when performing deep PNB such as psoas compartment block.

The recent development of ultrasound guidance for regional anesthesia offers several potential clinical benefits. It facilitates visualization of the needle, the target nerve, the surrounding structures, and the spread of LA in real time. In theory, ultrasound imaging should lead to a decrease in block-related complications such as accidental intravascular injection. Another advantage of ultrasound guidance is to allow precise placement of LA reducing the volume needed to achieve the block and

thus the potential risk of systemic toxicity.[95,96] However, when videos of ultrasound guidance blocks performed by trainees were analyzed, the most common errors were failure to recognize the spread of LA, failure to recognize the needle, and failure to identify the needle tip.[97] Thus, it is not surprising that reports of accidental intravascular injection despite the use of ultrasound guidance have been published.[98–100] With the slightest transducer pressure, veins may be collapsed and therefore intravascular injection might go unnoticed. Veins may also be displaced by the injected LA solution and lend a false sense of security as they may mimic the spread of LA. Brull et al[101] suggests the following steps to minimize the risk of intravenous injection during ultrasound-guided blocks: (i) systematic scanning distal and proximal to the target area and (ii) using color Doppler to identify any vessels that may cross the planned trajectory of the needle. Intravascular injection must be strongly suspected when hypoechoic fluid is not seen around the target nerve simultaneously with the injection.

Tissue Absorption of LA Agents

The absorption of LA into the systemic circulation is influenced by the site of injection, the presence of added vasoconstrictors, and the characteristics of the agent. If large doses are injected into well-perfused sites, there may be considerable uptake of LA into the circulation. This results in the gradual onset of symptoms from 20 to 30 minutes after injection. The blood level of LA may remain elevated for a much longer period of time than after the intravenous injection. Systemic absorption occurs in the following order: cervical plexus>intercostal>brachial plexus>femoral>ilioinguinal>sciatic blocks.[94] Addition of a vasoconstrictor such as epinephrine may reduce systemic absorption. Epinephrine (5 μg/mL; 1:200.000) provides a decrease in blood level of lidocaine, mepivacaine, bupivacaine, and the mixture of lidocaine/bupivacaine but not ropivacaine.[94] The intrinsic vasoactivity of the LA does not influence its own absorption.[102]

The pKa and protein binding of bupivacaine, L-bupivacaine, and ropivacaine are similar. The pKa of the LA agent is important to determine the fraction of unionized drug. Only unionized LAs are available for systemic absorption and to cross the phospholipid membrane. LAs are bases, thus, at normal pH an agent with a lower pKa will have a higher fraction of unionized molecules. The toxicity of LA is also dependent on the free unbound drug. LAs with high protein binding have a smaller fraction of free drugs available to produce toxic effects. When LAST occurs, the protein bound portion acts as a reservoir of LA susceptible to prolong systemic effects. A massive intravenous bolus will overwhelm this buffer system.[103] Lipid solubility also improves uptake from the injection site.

LA Overdose

The recommendations regarding the maximum dose (the product of volume and concentration) of LA, which can be administered, are given by the manufacturers, and their scientific basis has been questioned.[104] LA overdose can occur with doses lower than the maximum dose recommended. "Stating a single blanket maximum recommended dose of LA to avoid systemic toxicity is neither scientifically valid nor clinically relevant. It is time to abandon the practice."[105] When using a drug, it seems more appropriate to tailor the dose based on patient characteristics and specific site of injection rather than the dose based on milligram/kilogram. It is recognized that some patients have a greater risk of LAST. However, the following recommendations are based on poor evidence. The dose of LA should be reduced by 10% to 20% in patients over the age of 70 years, or less than 4 months, in those with renal dysfunction or advanced heart failure.[104] In patients with liver failure, a normal bolus dose can usually be given safely but continuous infusions should be reduced by 10% to 50%.[104] During pregnancy, the dose of LA should be reduced in PNBs.[104] Progesterone increases the risk of cardiotoxicity.[106] It has been showed that LAs may be safely used in patients with asymptomatic A/V conduction defect.[107] A/V conduction mainly depends on calcium channels, which are impaired by LAs at higher concentrations only.

■ Conclusions

Prevention of LAST remains a milestone during the performance of PNBs.[81] Identification of patients at risk, especially when large volumes of LA are required, should lead to a considered choice of LA drug. Cardiac toxicity is associated particularly with dextro R(–) enantiomers rather than with S(+) enantiomers (ie, L-bupivacaine and ropivacaine). L-bupivacaine and ropivacaine have a greater safety margin and were developed as alternatives to bupivacaine after recognition of its high toxicity. These should be prioritized when high risk of systemic toxicity is impending.[71,81] However, the anesthetic potency of these long-acting LA decreases from racemic bupivacaine>L-bupivacaine>ropivacaine. Lipid solubility is the primary determinant of intrinsic LA potency. This has mainly been shown for neuraxial blocks.[108] The lesser potency of ropivacaine in PNB compared with L-bupivacaine has not been clearly shown.[109] Although experimental, clinical, and pharmacological studies provide evidence that L-bupivacaine and ropivacaine have similar profiles and lead to lower systemic toxicity than bupivacaine, ropivacaine seems to have the greatest margin of safety.[110]

Lipid therapy after LAST is clearly recommended by international guidelines. Standard advanced cardiac life support, however, remains

the first-line of treatment. Although the exact mechanism of lipid therapy in this setting is still debated, there is enough evidence to suggest its early use. Vasopressors (particularly high-dose epinephrine) potentiate "use-dependent" slowing of cardiac conduction, resulting in a synergy with cardiotoxicity. Educational programs and advanced scenario training may facilitate prevention, early detection, and management of LAST in light of the recently published guide lines.[111] Finally, there is need for more experimental and clinical data to refine the therapeutic regimens of lipid therapy in the treatment of LAST to ensure the best outcome for the patient.

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