MEDICAL PRACTICE

Safe use of local anaesthetics: prevention and management of systemic toxicity

CME

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Local anaesthetic administration is a common clinical practice not only in the operating theatres, but also in other clinical settings. Relevant monitoring and resuscitation facilities in certain clinical settings outside the operation rooms may not be optimal. Despite the low incidence of severe complications associated with administration of local anaesthetics, their safe use is very important since systemic toxicity can be fatal. This article reviews the pharmacology of local anaesthetics, clinical features of systemic toxicity resulting from their local use, and necessary preventive measures and management. The role of lipid emulsion therapy is also discussed.

Introduction

Local anaesthetics are widely used throughout medical practice. They are used to induce anaesthesia and analgesia for surgical procedures and for pain management. Nowadays many minor surgical procedures are performed under local anaesthesia in clinical settings outside the operating theatres, in which case monitoring and resuscitation facilities may be suboptimal compared to operating rooms. Complications of local anaesthesia may range from localised reactions such as oedema, urticaria and dermatitis to systemic absorption resulting in severe cardiovascular collapse and neurological toxicity. Although the incidence of systemic toxicity to local anaesthetics has significantly decreased in the past 30 years, from 0.2 to 0.01%,[1] untoward events with undesirable consequences do occur. Increased concern about patient safety also changes a clinician's perspective on the importance of understanding the pharmacology of drug interactions and complications that can arise from using local anaesthetics. Although the safety of local anaesthetic usage in recent years has improved owing to the introduction of newer agents (eg ropivacaine and levobupivacaine), other factors must also be considered. The latter include: vigilance by clinicians, proper training, safe clinical environments with adequate monitoring and resuscitation equipment, and up-to-date skills in the management of severe systemic toxicity.

This article reviews the pharmacology of local anaesthetics, as well as the clinical features of local anaesthetic systemic toxicity (LAST), and the measures to prevent and manage such events.

Pharmacology

Local anaesthetics block sensory and motor function by impeding the permeability of neuronal cell membranes to sodium. This action prevents the rapid influx of sodium during the depolarisation phase of the action potential and its onward transmission. Local anaesthetics may also exert their pharmacological actions through other ions such as potassium and calcium.[2-4]

All local anaesthetics are weak bases and in solution the dissociated ionised form exists in equilibrium with their non-ionised form. The non-ionised form diffuses readily across the neuronal membranes into the axoplasm, where it ionises and blocks sodium channels within the cell.

Structurally, all local anaesthetics are similar and consist of three parts: a lipiophilic (aromatic) end, a hydrophilic (amine) end, and a link between the two ends. This intermediate link can be either an aminoester or an aminoamide bond, which classifies the local anaesthetics into two different groups: amides and esters. Commonly used ester group local anaesthetics in Hong Kong include cocaine and amethocaine, while those in the amide group include lignocaine, prilocaine, bupivacaine, ropivacaine and levobupivacaine. Figure 1 shows the chemical structures of bupivacaine, ropivacaine, and levobupivacaine.

Key words
Analgesics/pharmacology; Anesthetics, local; Fat emulsions, intravenous; Resuscitation

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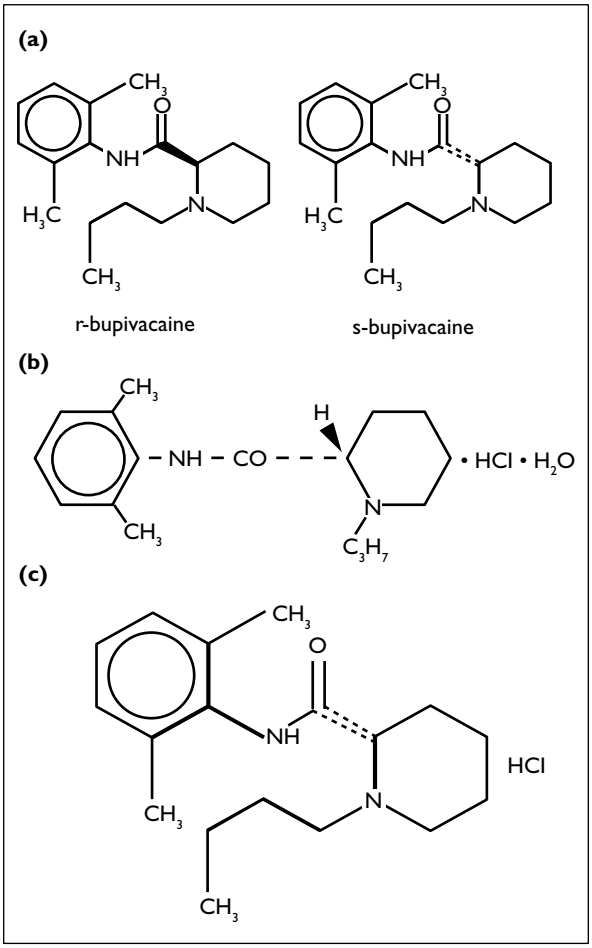

FIG 1. Chemical structures of (a) bupivacaine, (b) ropivacaine, and (c) levobupivacaine

局部麻醉劑的安全使用：全身性毒症的預防與處理

局部麻醉劑不但在手術室內，也會在手術室外作臨床使用。在手術室以外使用局部麻醉劑，有關的監察和復甦設施可能不足而引致併發症的發生。雖然與局部麻醉有關的嚴重併發症很少見，但因全身性毒症可致命，安全使用局部麻醉劑相當重要。本文探討局部麻醉劑的藥理學、因局部麻醉而可能引發的全身性毒症的臨床症狀，以及必要的預防措施與處理方法。此外亦會討論有關脂肪乳劑在全身性毒症治療中的角色。

The ester and amide type local anaesthetics show differences in their pharmacological profiles. The ester type local anaesthetics are hydrolysed by esterases in tissues and blood, while the amide types are metabolised primarily in the liver by cytochrome P450 enzymes. In addition, allergic reactions to local anaesthetics are usually more commonly associated with the ester than amide type agents, and are mainly due to ester derivatives of para-aminobenzoic acid.

Stereoisomerism contributes to differing pharmacological activity of local anaesthetics. Molecules with an asymmetric carbon atom exist in forms that are mirror images (enantiomers and stereoisomers), distinguished by how they rotate polarised light according to the orientation of the structures in three dimensions. The terms R and S are used to designate two different enantiomers. This structural characteristic allows the development of technology that permits separation of racemic mixtures of local anaesthetics into pure enantiomers and the search for local anaesthetics with greater safety margins (in theory at least). Whereas bupivacaine is marketed as a racemic mixture with equimolar amounts of both R and S enantiomers, levobupivacaine consists of pure S (-) - enantiomer and is 13% less potent than bupivacaine. Ropivacaine also consists of pure S (-) - enantiomer. Experimental studies and case studies indicate that levobupivacaine and ropivacaine may be less neurotoxic and cardiotoxic than bupivacaine.[5,6]

Factors affecting the anaesthetic activity of local anaesthetics include the dissociation constant (pKa), protein binding, lipid solubility, pH, and vascularity at the injection site.

The dissociation constant and pH of the medium in which it is present affects the onset of action. Local anaesthetic with a pKa value near physiological pH has a greater proportion of drug in the non-ionised form (diffusing more readily across the nerve sheaths and membrane to its site of action) than an agent with a higher pKa. Therefore, local anaesthetics with pKa values close to physiological pH tend to have a more rapid onset of action. Factors that promote local extracellular acidosis—for example, infection—increase drug ionisation and therefore reduce local anaesthetic diffusion and penetration of the nerve membrane. Addition of sodium bicarbonate to local anaesthetics increases the pH of the solution, which increases the ratio of non-ionised to ionised form, resulting in a more rapid onset of action.

Lipid solubility affects the potency of local anaesthetics. A highly lipid-soluble drug readily penetrates cell membranes. In general, highly lipid-soluble local anaesthetic agents are more potent than those with low lipid solubility.

The degree of protein binding and vascularity at the injection site affects the local anaesthetic's duration of action. Those with high plasma protein binding have longer durations of action. Addition of a vasoconstrictor like epinephrine to lipid-soluble local anaesthetics decreases vascularity at the injection site, which prolongs the duration of action (via reduced absorption into the systemic circulation). Table 1 summarises the pharmacological properties of commonly used local anaesthetics in Hong Kong.[7,8]

TABLE 1. Pharmacological properties of commonly used local anaesthetics in Hong Kong

Local anaesthetic	Structure	pKa (25°C)	Protein binding (%)	Partition coefficient (lipid solubility) pH=7.4	Onset time	Duration of action	Half-life (hours)	Maximum dose (mg/kg)*
Cocaine	Ester	N/A†	N/A	N/A	Long	Long	N/A	1.5-3
Lignocaine	Amide	7.9	60-75	2.9	Short	Medium	1.6	4-5
Prilocaine	Amide	8.9	55	0.9	Short	Medium	1.5	5-7
Bupivacaine	Amide	8.1	90-97	28	Medium	Long	2.7	1-2.5
Ropivacaine	Amide	8.07	94	2.83	Medium	Long	1.8	2.5-3
Levobupivacaine	Amide	8.1	>97	27.5	Medium	Long	1.3	2-2.5

* Dosing depends on the clinical situation; higher doses may be allowed with the co-administration of adrenaline
† N/A denotes not available

TABLE 2. Differential diagnoses of local anaesthetic reactions

Aetiology	Main clinical features
Local anaesthetic toxicity	
Intravascular injection	Immediate convulsions ± cardiac arrhythmias
Relative overdose	Onset of irritability within 5-15 minutes, progression to convulsions
Reaction to vasoconstrictors	Tachycardia, hypertension, headache, apprehension
Vasovagal reaction	Rapid onset of bradycardia, hypotension, pallor, faintness
Anaphylaxis	Hypotension, bronchospasm, urticaria, oedema

Local anaesthetic systemic toxicity

Local anaesthetic systemic toxicity has been recognised and reported after the introduction of cocaine in the 1880s. Local anaesthetics with better safety profiles have been released over the years. Despite this, LAST continues to occur and is a major source of morbidity and mortality in regional anaesthetic practice. Epidemiological studies report statistics that vary widely depending on how toxicity is defined, the clinical scenario in which it occurs, and how the data are collected. The incidence of seizure associated with brachial plexus blockade, particularly the interscalene and supraclavicular approaches, reported by Brown et al[9] in 1995 was up to 79 in 10 000 patients. A large surveillance study of French anaesthesiologists determined the overall frequency of seizures to be 0 to 25 in 10 000, depending on the type of block performed.[10]

Local anaesthetic systemic toxicity can be caused by accidental rapid intravascular injection, exceeding the maximum recommended dose, or rapid absorption after injection into a highly vascular site, for example, the brachial plexus and intercostal regions. Local anaesthetics also differ with regard to their toxicity. The ascending order of cardiotoxicity is ropivacaine, levobupivacaine, bupivacaine.[5,6]

Clinical features

Toxic effects primarily involve the central nervous system (CNS) and cardiovascular system (CVS).

The severity of CNS toxicity correlates with plasma local anaesthetic concentrations. It exhibits initial excitement followed at higher doses by depression. The earliest signs of toxicity include circumoral and tongue numbness, which may proceed to tinnitus, light-headedness, metallic taste, and nystagmus. Further elevations in plasma concentration cause excitation like confusion, tremors, and agitation. Further increases in plasma concentration lead to seizures, coma, or respiratory arrest.

Cardiovascular system toxicity also demonstrates this biphasic effect of excitation and depression. Early toxic features include hypertension, tachycardia and ventricular arrhythmias, followed by late toxic features like bradycardia, heart block, hypotension, decreased contractility and asystole. Acidosis and hypoxia markedly potentiate the cardiotoxic effect and pregnant patients are more susceptible.

Classically, CNS toxicity usually precedes CVS toxicity. The presentation, however, can be extremely variable with respect to the time of onset, initial manifestations, and their duration. When high plasma concentrations develop rapidly, prodromal CNS symptoms may not occur or only cardiac toxicity ensues.

Diagnosis

The diagnosis of LAST is mainly clinical. However, some of the clinical features may also be the result of other complications. Therefore, clinicians should maintain a suitably balanced yet vigilant attitude to the possibility of LAST. Table 2 lists the differential diagnoses of local anaesthetic reactions.[11] Blood samples can be drawn for laboratory measurement

of local anaesthetic levels if possible. This, however, should not result in any delay of definitive treatment.

Prevention

There is no single clinical measure that can prevent LAST. Essential precautions before administering local anaesthetic injections include: the presence of access to a secure intravenous line, adequate resuscitation equipment, and medications. The lowest effective dose of local anaesthetic should be used and dosing recommendations should be followed. When administering large volumes of local anaesthetic, the injection should be given in divided doses, and vital signs should be continuously monitored. The needle or catheter should be aspirated before each injection to exclude inadvertent intravenous administration. Use of an intravascular marker, eg adrenaline, is recommended when a high dose of local anaesthetic is to be given. Use of ultrasound-guided regional anaesthesia may reduce the incidence of intravascular injection, but there are no randomised controlled studies to confirm or refute this assertion.[12]

Management

In 2007, the Association of Anaesthetists of Great Britain and Ireland published guidelines for the management of severe local anaesthetic toxicity.[13] In 2008, the American Society of Critical Care Anesthesiologists and the American Society of Anesthesiologists Committee on Critical Care Medicine,[14] as well as the Resuscitation Council of the United Kingdom[15] also published protocols for the treatment of LAST. In 2010, the American Society of Regional Anesthesia and Pain Medicine published its practice advisory on LAST.[16] These guidelines not only emphasise the importance of airway management and early cardiopulmonary resuscitation, but also incorporate the use of lipid emulsion therapy in the management of LAST.

If signs and symptoms of LAST ensue, the injection should be stopped immediately and help called for. The airway should be maintained and secured, by endotracheal intubation if necessary. The patient should be given 100% oxygen and adequate lung ventilation ensured, so as to prevent hypoxia and acidosis, both of which are believed to potentiate LAST.

Management of cardiovascular toxicity includes use of conventional therapy to treat hypotension, bradycardias or tachyarrhythmias. If cardiac arrest supervenes, standard basic life support (BLS) and advanced cardiac life support (ACLS) should be started. Arrhythmias should be managed using the same ACLS protocol. Lidocaine should not be used as an anti-arrhythmic. Arrhythmias may turn out to be very refractory to treatment. Vasopressin is not recommended. Cardiopulmonary resuscitation should be continued for at least 60 minutes because the response can be delayed. Management of CNS toxicity is mainly supportive. If a seizure persists, it should be rapidly controlled with a benzodiazepine. Small doses of propofol or thiopentone are alternatives, but may give rise to cardiac depression, which may worsen the hypotension.

Lipid emulsion therapy should be considered at the first sign of LAST after airway management. If lipid emulsion and vasopressor therapies fail, use of cardiopulmonary bypass should be considered if available. The patient should be transferred safely to a clinical area with appropriate equipment and suitable staff, until sustained recovery is achieved.

Lipid emulsion therapy

In 1998 Weinberg et al[17] first reported that lipid emulsion infused during resuscitation increased the median lethal dose (LD_{50}) of bupivacaine in rats by 50%. Few years later, in 2006 Rosenblatt et al[18] and Litz et al[19] reported successful clinical use of lipid emulsion to reverse local anaesthetic-induced cardiac arrest. Subsequent clinical reports have provided growing support for this form of management for LAST caused by different local anaesthetic agents, namely bupivacaine, levobupivacaine, and ropivacaine.[19-21]

The exact mechanism of action of lipid emulsion therapy is not known. It may serve as a "lipid sink", providing a large lipid phase in the plasma, enabling capture of the local anaesthetic molecules and making them unavailable to tissues. Alternatively they may work to counter the impaired fatty acid delivery caused by local anaesthetics in the mitochrondria, and enable energy production.[22,23]

The commonly used lipid emulsion preparation is Intralipid 20%, whilst the utility of other lipid preparations is not known. Propofol is not a suitable substitute for Intralipid. The recommended Intralipid regimen entails an initial intravenous bolus injection of a 20% emulsion at 1.5 mL/kg over 1 minute, followed by an infusion of 15 mL/kg/h. Cardiopulmonary resuscitation should be continued.

If cardiovascular stability is not restored after 5 minutes or if haemodynamics deteriorate, a maximum of two repeated boluses (1.5 mL/kg) may be given at 5-minute intervals. The intravenous infusion rate should also be doubled to 30 mL/kg/h. A maximum of three boluses can be given, and a cumulative dose of 12 mL/kg should not be exceeded.

Contra-indications to lipid emulsion therapy include lipid metabolism disorders and egg allergy, and caution is required for patients with anaemia, severe liver disease, coagulopathy, and pulmonary

FIG 2. Intralipid 20% (Fresenius Kabi AB, Uppsala, Sweden)

disease.

Potential complications include allergic reaction, fluid overload, impaired liver function, hypercoagulability and pancreatitis. To date however, no such severe complications have been associated with lipid emulsion therapy. It has therefore been recommended that 1000 mL of 20% lipid emulsion should be available in clinical areas where treatment of LAST might become necessary.[13,15,24,25] In our hospital, Intralipid 20% (Fig 2) is available in the operating theatres and the obstetric labour room.

Conclusion

The safe use of local anaesthetics depends on adequate monitoring, clinicians being aware of their pharmacology, good clinical skills, and vigilance. Preventive measures should be in place to minimise the risk of systemic toxicity. Numerous guidelines and protocols for the management of LAST have been published in recent years. Clinicians should acquire the relevant skills and knowledge to manage LAST. Relevant clinical settings should also be equipped with relevant monitoring and resuscitation facilities for BLS or ACLS, as appropriate. Increasing evidence supports the use of intravenous lipid emulsion therapy in the management of LAST. Although the optimal timing and dosing of such treatment requires further study, it is recommended that suitable quantities of 20% lipid emulsion should be available in clinical settings where high dose of local anaesthetics will be administered to patients.

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Answers to CME Programme

Hong Kong Medical Journal October 2010 issue

Hong Kong Med J 2010;16:347–53

I. Primary percutaneous coronary intervention for ST elevation myocardial infarction: performance with focus on timeliness of treatment

A	1. True	2. False	3. False	4. False	5. True
B	1. True	2. False	3. False	4. False	5. True

Hong Kong Med J 2010;16:362–6

II. Ten-year review of epidemiology, clinical features, and treatment outcome of achalasia in a regional hospital in Hong Kong

A	1. False	2. False	3. True	4. True	5. True
B	1. False	2. True	3. False	4. False	5. True