Local anaesthetics: Characteristics, uses and toxicities

An understanding of local anaesthetics is essential to successful office-based surgery.

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Surgeons currently perform more and larger procedures in an ambulatory setting. Local anaesthesia is an important aspect of office-based surgery. Local anaesthetics (LAs) vary in their pharmacological properties and are used in various techniques of local anaesthesia administration, i.e. topical, infiltrative, epidural, spinal, and plexus block anaesthesia. A good working knowledge of local anaesthetics is required to enhance patient safety, experience and comfort.

Mechanism of action

LAs are membrane-stabilising drugs that reversibly decrease the rate of depolarisation and repolarisation of excitable membranes. They act by inhibiting sodium influx through sodium channels in neuronal cell membranes so that action potentials cannot arise and signal conduction is inhibited.

Nerves have differing susceptibilities to the effects of LAs, depending on diameter and myelination. Small-diameter unmyelinated fibres, such as type C pain fibres, are the most sensitive to LA-blocking effects, whereas heavily myelinated, thicker fibres, such as type A motor fibres, are less sensitive.

Pharmacology

LAs are composed of a lipophilic aromatic ring connected by an ester or amide chain to a hydrophilic or ionisable secondary or tertiary amine. Ester-linked LAs are generally shorter acting and are rapidly inactivated by plasma cholinesterase. Amide-linked LAs are metabolised in the liver by the cytochrome P450 enzyme system. More than 50% of amide-linked LAs are bound to plasma glycoproteins. Fluctuation in these protein levels influences metabolism.

The toxicity of LAs relates to plasma concentration. The more free LA in the body plasma, the more toxic it is.

Commonly used LAs are 1% or 2% lignocaine with our without adrenaline 1:100 000 or 1:200 000, and bupivacaine (Macaine) 0.25% or 0.5% with or without adrenaline. The search for less toxic, long-acting LAs was prompted by fatalities associated with the cardiovascular toxicity of bupivacaine. The 50:50 racaemic mixture of bupivacaine consists of R- and S-isomers. The latter form, levobupivacaine (Chirocane), has less potential for CNS and cardiovascular toxicity. Ropivacaine (Naropin), a pure S-isomer, invokes better sensorimotor dissociation at lower doses. Although ropivacaine may be associated with acute CNS and cardiovascular toxicity, the incidence appears to be rare.

LAs and vasoconstrictors

Adrenaline (via its alpha effects) prolongs LA effects by delaying uptake in the local vascular bed and diminishing potential systemic toxicity by slowing the rate of rise of LA blood levels. Adrenaline has a serum half-life of less than 1 minute, being rapidly metabolised by catechol-O-methyltransferase in blood, lung, liver, and elsewhere.

Prohibition of the use of LA with epinephrine for digital or other acral regions (e.g. ear, tip of nose) is an established surgical tradition. However, digital necrotic and ischaemic complications are extremely rare. Recent reviews have concluded that when used to effect a digital block, adrenaline-containing LAs are quite safe and provide intraoperative haemostasis and longer post-procedure pain relief. As always, good judgement is necessary – an insulin-dependent, diabetic vasculopathic patient with a finger laceration may not be the best candidate for the injection of adrenaline into the finger.

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Toxicities

Neurological toxicity manifests with agitation, restlessness, tremor and convulsions (presumably by depression of central cortical inhibitory pathways, leaving the excitatory pathways uninhibited). Depression of brain functions occurs at higher concentrations, leading to coma, respiratory arrest and death. Such high tissue concentrations may be due to very high plasma levels after intravascular injection of a large dose or direct exposure of the central nervous system (CNS) through the cerebrospinal fluid, e.g.

overdose in spinal anaesthesia or accidental injection into the subarachnoid space in epidural anaesthesia.

The most important part of managing LA toxicity is recognising it.

Cardiac toxicity results from direct depression of myocardial contractility and dysfunction of the autonomic ganglia. Myocardial contractility is greatly impaired owing to the conduction-blocking effects of LAs. Ventricular dysrhythmias from a LA overdose are rare, except in the case of bupivacaine, which can cause ventricular tachycardia and fibrillation. Cardiac side-effects are usually seen with very high serum concentrations and most often follow neurological manifestations.

Treatment

Inadvertent intravascular injection of LA is the fastest way to elevate serum LA levels and precipitate a reaction. The most important part of managing LA toxicity is recognising it. The first sign may be simple agitation. Under such circumstances, injection or infusion should be stopped immediately. Supportive measures, such as supplemental oxygen, positional change, monitoring of blood pressure, and oxygen saturation are all appropriate.

Treatment of CNS complications and toxicity is still controversial because no single remedy exists. CNS manifestations, such as seizures, have been treated successfully with benzodiazepines (e.g. diazepam 0.1 - 0.2 mg/kg IV, IM or per rectum), thiopental 2 mg/kg, or propofol (Diprivan) 1 mg/kg IV. Propofol can cause significant bradycardia, further compromising cardiovascular status. Avoid phenytoin (Epanutin) because it shares pharmacological properties with lignocaine and may potentiate toxicity.

Propofol is usually contraindicated when there is any evidence of cardiovascular toxicity.

Lipid rescue with lipid emulsion (e.g. 20% Intralipid) has been shown to reverse both neurological and cardiac toxic effects quickly and effectively. The mechanism of action is not clear – the lipid may act as LA sink, rapidly decreasing the serum levels of the offending LA.

Weinberg's recommended dosing regimen in cardiac collapse secondary to LA toxicity unresponsive to standard therapy is: 1 ml/kg IV bolus over 1 minute, repeated twice at 3 - 5-minute intervals; then (or sooner if stable) convert to infusion at 0.25 ml/kg/min, continuing until haemodynamic stability has been restored. Increasing the dose beyond 8 ml/kg is unlikely to be useful. In practice, to resuscitate an adult weighing 70 kg, use a 500 ml bag of fat emulsion (e.g. Intralipid 20%). Give 70 ml stat IV, repeat up to twice and administer adrenaline if necessary or appropriate. Then, attach the fat emulsion bag to an administration set and infuse the rest over 15 minutes. Note that propofol is not a component of lipid rescue. It is formulated in a 10% lipid emulsion and therefore an overdose of propofol would be necessary to provide an adequate dose of lipid emulsion. Propofol is usually contraindicated when there is any evidence of cardiovascular toxicity.

Allergies to LAs are quite rare. True IgE allergic reactions can occur. Ester-linked LAs are most often linked to true anaphylaxis, usually due to a sensitivity to their metabolite, para-aminobenzoic acid (PABA), and do not result in cross-allergy to amides. Therefore, amides can be used as alternatives in these patients. Sulphites used to stabilise vasoconstrictors and methylparaben, a bacteriostatic agent similar to an ester linkage found in some LAs, can cause non-IgE-mediated allergic reactions.

There have been reports of prilocaine causing methaemoglobinaemia. Hydrolysis of prilocaine initially leads to the formation of o-toluidine products that can bind to haemoglobin and cause methaemoglobinaemia.

Most reactions not related to LA toxicity can be classified into psychosomatic responses and idiosyncratic reactions. Hyperventilation, tachycardia, or vagal episodes may well be due to anxiety.

Other local adverse effects of anaesthetic agents include neurovascular manifestations, such as haematoma, oedema, pain, blanching, infection, prolonged anaesthesia, facial paralysis and paraesthesias. These are caused by localised nerve damage. The risk of temporary or permanent nerve damage varies between different locations and types of nerve blocks. Permanent nerve damage after a peripheral nerve block is rare. Symptoms are very likely to resolve within a few weeks to months.

Dosing and administrative technique

Deciphering anaesthetic concentration and dilution

Concentration. Drug concentration is expressed as a percentage, i.e. grams per 100 ml (e.g. 1%=1 g/100 ml (1 000 mg/100 ml) or 10 mg/ml). (Bupivacaine 0.25%=2.5 mg/ml; lignocaine 1%=10 mg/ml.)

Dilution. When adrenaline is combined in an anaesthetic solution the result is expressed as a dilution (e.g. 1:100 000):

- 1:1 000 means 1 mg/1 ml (0.1%)
- 1:10 000 means 1 mg/10 ml (0.01%)
- 1:2 000 means 1 mg/2 ml (0.05%)
- 1:20 000 means 1 mg/20 ml (0.005%)
- 0.1 ml of 1:1 000 adrenaline added to 10 ml of anaesthetic solution = 1:100 000 dilution or 0.01 mg/ml
- 50 ml of lignocaine 1% with adrenaline 1:100 000 contains lignocaine 500 mg and adrenaline 0.5 mg.

Dosing guidelines

Dosing guidelines for LAs encompass generous margins of safety. Co-morbidities, anatomical location, surface area to be treated, concentration of the LA, addition of adrenaline, and rapidity of the infusion are all factors to consider in safe dosing guidelines (Table I). Reduced dosages are indicated in debilitated or acutely ill patients, very young children, geriatric patients and patients with liver disease or atherosclerosis.

Clinicians modify the formulations after manufacture by mixing, diluting and adding fresh adrenaline or bicarbonate to achieve their own particular cocktail.

pH plays an important role in LA function. Anything that alters the pH of the local tissue will affect the LA's ability to penetrate the cell membrane. With local infection

Table I. Local anaesthetic agents commonly used for infiltrative injection

Agent	Duration of action	Maximum dosage guidelines (total cumulative infiltrative injection dose per procedure)
Lignocaine without adrenaline	Medium (30 - 60 min)	4.5 mg/kg; not to exceed 300 mg
Lignocaine with adrenaline	Long (120 - 360 min)	7 mg/kg; not to exceed 500 mg
Bupivacaine without adrenaline (Macaine)	Long (120 - 240 min)	2.5 mg/kg; not to exceed 175 mg total dose
Bupivacaine with adrenaline	Long (180 - 420 min)	Not to exceed 225 mg total dose
Levobupivacaine (Chirocane)	Long (180 - 420 min)	150 mg (400 mg/24 h)
Ropivacaine (Naropin)	Long (120 - 360 min)	5 mg/kg; not to exceed 300 mg for minor nerve block

the environment is acidic, and the LA is charged and cannot pass through the cell membrane to exert its effect.

LAs are found on the surgeon's shelf as slightly acidic hydrochloride water-soluble salts. Injection of the drug results in a painful burning sensation. If 1 ml of an 8.4% solution of Na-bicarbonate is added to 9 - 10 ml of lignocaine the pH increases to 7.4. If a lignocaine-adrenaline solution is used, 2.0 - 2.5 ml of an 8.4% solution of Na-bicarbonate should be added. The burning effect disappears, patient comfort is improved, and the nerve block is speedier and lasts longer.

Plastic surgeons have developed so-called tumescent solutions, i.e. highly dilute solutions of LA, adrenaline and buffer to minimise blood loss, enhance removal of fatty tissue and improve patient comfort. Although formulations of tumescent solution vary, a typical mixture to be injected into the subcutaneous space would contain lignocaine 0.1%, sodium bicarbonate 12 mmol/l and adrenaline 1:1 000 000, usually warmed to body temperature. Using tumescent solution, lignocaine doses as high as 50 mg/kg have been administered without toxicity (although 35 mg/kg or lower is considered a safer dose).

Topical LAs

Topical LAs are used alone or in conjunction with an injectable LA. The absorption of topical LA is related to the concentration used, the amount of surface area covered, and the type of surface to which it has been applied. Systemic toxicity has been reported with the use of these compounds.

Lignocaine applied to a mucosal surface can lead to plasma levels approaching those reached with parenteral administration. Lignocaine 1% spray (Xylocaine) delivers 10 mg per pump dose. Care must be taken when using these compounds.

EMLA cream (2.5% lignocaine, 2.5% prilocaine) delivers maximal benefit after 30 - 60 minutes with an occlusive dressing. Systemic absorption, even of large amounts of EMLA on large surface areas, has been shown to be far below toxic levels. EMLA works very well in anaesthetising the skin before minor vascular access procedures and in superficial laser skin treatments.

Summary

LAs are compounds unparalleled in their ability to alleviate pain. Surgeons with a good understanding of the actions and toxicities of these medications, as well as the skill to deliver them, will find that the minor procedure room is an enjoyable, a comfortable and a safe place for their patients.

The risk of toxicity from LA use can be minimised by the following simple rules:

- Use the lowest concentration of LA required – diluting is allowed.
- Avoid direct injection into the intravascular space.
- Use adrenaline to slow absorption of LAs into the bloodstream to prolong anaesthetic effect and minimise blood loss.
- Modify the dose of LA/adrenaline for patients with risk factors for toxicity.
- Use enough LA to adequately anaesthetise the area of interest.

Further reading

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In a nutshell

- A good working knowledge of local anaesthetics will enhance the patient's safety, experience and comfort.
- LAs are membrane-stabilising drugs that block nerve impulses.
- A low pH, e.g. in the case of infection, impairs LA efficacy.
- Adrenaline prolongs LA effects by delaying uptake from the injection site.
- The toxicity of LAs relates to plasma concentration.
- An overdose causes CNS and cardiovascular complications.
- L-bupivacaine and ropivacaine lessen CNS and cardiovascular toxicity.
- Lipid rescue has been shown to reverse both neurological and cardiac toxic effects.
- Allergies to LAs are quite rare.
- Dosing guidelines with a generous margin of safety are recommended.
- Reduce dosages in debilitated, acutely ill patients, in very young or old patients, and in patients with liver disease or atherosclerosis.
- Clinicians often modify the formulations post manufacture by mixing, diluting and adding fresh adrenaline or bicarbonate to achieve their own particular cocktail.