RCS ADVANCING SURGICAL STANDARDS

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Local anaesthetics are being used increasingly as analgesia and for anaesthesia, as a supplement to or as an alternative to general anaesthesia. In the current economic climate, general anaesthesia for a number of procedures is now rapidly becoming an unaffordable luxury. New techniques for plexus and nerve blocks coupled with ultrasonography technology have made many operations eminently suitable for a local anaesthetic technique.

The surge in popularity of local anaesthetic use for operating brings with it greater patient comfort and effective pain relief, with faster convalescence. Greater understanding of the agents and their controversies has resulted in a new and stabilised relationship between their use and their toxicity. However, the plethora of available agents, their concentrations and adjuvants may lead to complications, dosing errors and potential toxicity. This article by French and Sharp is a practical guide for all surgeons who may only occasionally use these agents.

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Local anaesthetics

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Question

A 70-year-old man had a spinal anaesthetic for an inguinal hernia repair but at skin closure he is beginning to experience discomfort. The anaesthetist suggests local infiltration for supplementation. What are the local anaesthetic choices? Which should I choose and how much? Are there any problems I may encounter?

In this article we will help answer these questions by explaining the basic principles of how local anaesthetics (LAs) work. We will also deal with some other commonly asked questions regarding their use.

Basic principles

LAs reversibly block neuronal transmission and stabilise electrically excitable membranes. They exist in two states: acidic (ionised) and basic (non-ionised). There are two mechanisms of action:

Blockade of Na^+ channels: Unionised, lipid-soluble drug passes through the phospholipid membrane (charged molecules do not cross the cell membrane). It becomes ionised and binds to the *intracellular* surface of fast Na^+ channels, preventing further depolarisation.

Membrane expansion: Unionised drug dissolves into the phospholipid membrane, expanding and disrupting the Na^+ channel/lipoprotein matrix causing inactivation.

Physiochemical characteristics

Structure

LAs can be divided into two groups according to the linkage (amide or ester) between the two main molecular parts (Table 1).

Activity

Onset of action

> pKa (the pH at which there are equal amounts of ionised and non-ionised molecules) is the main factor

Table 1 Properties of amides and esters

	Esters	Amides
Stability	Less heat stable	Heat stable (can be autoclaved)
Shelf life	Short	Approximately 2 years
Metabolism	Plasma cholinesterase	Slow, hepatic
Allergy	Metabolism produces para-aminobenzoate (higher risk of allergic reactions)	Rare
Examples	Cocaine, procaine, tetracaine	Lidocaine, bupivacaine, prilocaine

Table 2 Clinical characteristics of the commonly used local anaesthetics

Local anaesthetic	Type	Onset of action	Duration of action	Preparations	Uses	Recommended maximum dose
Lidocaine	Amide	Fast (2-4 mins)	Moderate (30-60 mins)	Solution 0.5–2% Gel 2% Ointment 5% Spray 10mg/ml or solution 4%	Infiltration Nerve blocks Topical	3mg/kg 7mg/kg with adrenaline
Prilocaine	Amide	Fast (2–4 mins)	Moderate (30-90 mins)	Solution 0.5–2%	Infiltration Dentistry Intravenous regional anaesthesia Can induce methaemoglobinaemia at high doses	6mg/kg
Lidocaine and prilocaine cream	Amide	Slow (needs at least an hour to work)		EMLA® (eutectic mixture containing lidocaine 2.5% and prilocaine 2.5%) Tubes contain 5g or 30g	Before cannulation Skin graft harvest site	Essentially, cream 25mg/ml prilocaine and 25mg/ml lidocaine 0.8ml/10kg
Bupivacaine	Amide	Moderate (6-10 mins)	Long (120–140 mins)	Solution 0.25% and 0.5% (with/without 1:80,000-200,000 adrenaline) Solution 0.75% 4ml solution 0.5% with 80mg/ml dextrose	Infiltration Nerve block Epidural Subarachnoid block Ophthalmology Can last 180-420 mins with adrenaline	2mg/kg
Levobupivacaine	Amide	Moderate	Long	Enantiopure L-bupivacaine 2.5, 5.0 and 7.5mg/ml solution	Infiltration Nerve blocks Spinal Epidural	2mg/kg
Ropivacaine	Amide	Moderate	Long (120-360 mins)	2, 7.5 and 10mg/ml solution	Infiltration Nerve blocks Epidural For continuous infusion	3mg/kg
Cocaine	Ester			Moffat's solution (2ml cocaine 8%, 2ml sodium bicarbonate 1%, 1ml 1:1,000 adrenaline) Paste 1–4%	ENT All cocaine mixtures are controlled drugs.	
Tetracaine	Ester	Slow	Long	Drops 0.5% and 1% Cream 4% (Ametop®)	Topical (ophthalmic drops and skin cream) High systemic toxicity	

determining onset of action. Lower pKa shortens the onset of action.

- pKa is affected by tissue inflammation and may slow the onset of action.
- Lipid solubility: the greater the lipid solubility, the greater the penetration of nerve membranes resulting in an increased rate of onset.

Duration of action

- Protein binding reflects the ability of the drug to bind to membrane proteins. The greater the protein binding, the longer the duration of action.
- Additives such as adrenaline and felypressin bring about vasoconstriction to the area, increasing the duration of action.

Clinical characteristics

Different agents have different clinical characteristics (Table 2). Knowledge of these allows us to choose the right agent for any specific use.

FAQs

Below are some commonly asked questions regarding LAs and their use.

Table 3 Examples of concentration, percentage of hydrochloride salt content and dose equivalent for various local anaesthetics

Percentage	Concentration for additives	Dose equivalent	Examples
1%	–	10mg/ml	Lidocaine 1%
0.5%	–	5mg/ml	Bupivacaine 0.5% Levobupivacaine 5mg/ml
0.2%	–	2mg/ml	Ropivacaine 2mg/ml
0.1%	1:1,000 (1g in 1,000ml)	1mg/ml	Concentrated adrenaline for cardiac arrest
0.0005%	1:200,000 (1g in 200,000ml)	0.005mg/ml	Diluted adrenaline contained in local anaesthetic mixtures

What is the difference between Marcain®, bupivacaine and Chirocaine®?

- *Marcain*® (AstraZeneca) is the trade name for racemic bupivacaine, a preparation containing mixed L- and R-bupivacaine isoforms.
- *Bupivacaine* is the generic drug name.
- *Chirocaine*® (Abbott) is the trade name for the enantiopure preparation of levobupivacaine, the L-isomer of bupivacaine. It is marketed as having a better safety profile than racemic bupivacaine. For licensing reasons, the maximum safe dose is stated as being the same as the racemic preparation.[1] However, some clinicians are using higher doses for infiltration techniques (eg 2.5mg/kg).

Why are some LAs quoted in % (and what does this mean?) and others in mg/ml?

Current legislation requires newly licensed LAs to be described in terms of quantity of free base present. Older drugs are still described in terms of quantity of total hydrochloride salt present, represented as a percentage. Referring to solutions by their free base amount is a much clearer representation of the drug content of the solution. It also reduces the risk of calculation mistakes. For this reason, it is preferable to describe LA solutions in this way. *Drug concentrations that are expressed as a percentage can also be thought of in terms of grams per 100ml.* On a practical note, 1% solution contains 10mg/ml LA salt whereas 0.5% contains 5mg/ml. Table 3 gives further examples. A 0.5% bupivacaine (racemic mixture) contains fewer LA molecules than the same volume of levobupivacaine 5mg/ml. Clinically, there is little difference between the two.

What happens if I mix different LA preparations, eg lidocaine and levobupivacaine? How does this affect calculation of the maximum dose?

Mixing of LAs is not recommended by the pharmaceutical industry but is a standard technique for some clinicians. Most preparations are miscible as the pH of the solutions is similar.

The theory behind the mixing of LA solutions is that one gets the benefits of both drugs (eg rapid onset of lidocaine and the prolonged duration of levobupivacaine). Conversely, it could be argued that the resulting solution is a diluted mixture of both drugs, containing half the concentration of each (if mixed to equal volumes). This may be true but there is surprisingly little evidence supporting or refuting either of these arguments. We believe the answer comes down to clinical preference.

What must be remembered is that each LA in the mixture acts on *all* excitable membranes so an excess may result in toxic effects (see below). If mixing LAs, we recommend that the safest practice is not to exceed 100% of the *combined* maximum dose. For example, 10ml of lidocaine 1% contains 100mg of drug, ie 50% of the maximum dose for a 50kg patient. Furthermore, 10ml of 2.5mg/ml levobupivacaine would represent 25% of the maximum in the same patient. Using a 20ml mixture of the two would mean that the solution contains 75% of the maximum and should therefore be safe. However, 40ml of the same mixture would be 150% of the recommended maximum and may result in toxicity. If either of the solutions chosen contains adrenaline, then this increases the maximum dose for lidocaine, meaning a larger volume can be used.

Does pregnancy affect LA use?

The decreased plasma protein concentration in pregnancy results in a greater degree of free unbound (active) LA. This is offset by the increased volume of distribution in pregnancy so there is little difference in clinical practice from the non-pregnant patient.

Drugs with high lipid solubility and low molecular weight diffuse readily across the placenta while large polar molecules diffuse poorly. Due to its higher pKa and hence greater ionisation at physiological pH, bupivacaine crosses the placenta less readily than lidocaine. The concern is in the acidotic fetus, where ion trapping can occur. The lower pH of the fetus results in increased ionisation of the LA in the fetus. The ionised fraction has reduced ability to diffuse back from fetal to maternal circulation.

The perceived increased sensitivity and shorter onset of action often demonstrated with neuraxial blockade in women in late pregnancy is probably more related to physiological factors such as decreased volume of epidural and subarachnoid space.

How does adrenaline affect LAs?

Adrenaline acts as a vasoconstrictor and therefore reduces the rate of removal from the site of action. The contraindication of adrenaline in extremities supplied by terminal arteries is much debated and beyond the scope of this article. Denkler searched 120 years of medical literature from around the world and found no digital gangrene where

Table 4 Clinical manifestations of local anaesthetic toxicity	
Central nervous system	**Cardiovascular system**
Circumoral tingling	
Tinnitus	
Slurred speech	
Muscle twitching	
Loss of consciousness	
Convulsion	Myocardial depression
Coma	
Respiratory arrest	Cardiac arrhythmias
	Ventricular arrest

addition of adrenaline alone could be indicated; all 21 cases had additional factors implicated.[2]

How does the addition of glucose affect LAs?

Glucose is added to bupivacaine and prilocaine preparations used for spinal (subarachnoid) anaesthesia. Glucose increases the baricity of the LA solution to greater than that of cerebrospinal fluid (CSF) and allows the LA to sink under gravity to the most dependent part of the CSF. This prevents uncontrolled spread throughout the CSF, which could cause catastrophic effects in the brain.

What are the signs of LA toxicity and how do I treat it?

LA toxicity results from either accidental intravascular injection ('the right dose in the wrong place') with rapid onset of symptoms or from excessive dose ('the wrong dose in the right place') with slower onset. LA not only exerts a membrane stabilising effect on peripheral neurones but will also act on excitable membranes in the central nervous system (CNS) and cardiovascular system (CVS) (Table 4). The inhibitory neurones in the CNS are suppressed before the central ones. Symptoms of excitation (circumoral tingling, tinnitus and muscle twitching) are therefore followed by symptoms of depression (loss of consciousness and coma). CVS changes occur at a higher plasma level than those in the CNS. (Myocardial depression occurs at a similar plasma concentration to muscle twitching.) This means that subtle sensory changes usually present long before catastrophic cardiovascular events.

Treatment of toxicity

Most importantly, recognise the symptoms. Only then can you respond to the events unfolding and treat the patient appropriately. Both basic and advanced life support treatment may be appropriate (Table 5). The Association of Anaesthetists of Great Britain and Ireland recommends that any hospital carrying out procedures where potentially toxic doses of LA are used should have resuscitation packs of Intralipid® 20% available in those clinical areas.

In answer to the questions at the start of the article, we would suggest two choices for wound infiltration:

1. 20ml lidocaine 1% with adrenaline (rapid onset, long enough duration)
2. 20ml mixture of lidocaine 1% and 2.5mg/ml levobupivacaine (slower but still rapid onset, longer duration)

Table 5 Treatment of local anaesthetic toxicity	
Recognition of symptoms	> CNS and CVS manifestations (see Table 4)
Immediate management	> Stop injecting LA. > Call for help. > Maintain/secure airway. > Administer O_2 100%. (Hyperventilation may help by increasing plasma pH). > Confirm/establish intravenous access. > Control seizures using benzodiazepine in small increments. (If an anaesthetist is present he/she may chose to use propofol or thiopentone). > Assess CVS status throughout.
Treatment **(all cases)**	> Give intravenous lipid emulsion (Intralipid® 20% – see below). > Recovery may take >1 hour. > Use current advanced life support guidelines to treat arrhythmias or myocardial depression.
If cardiac arrest occurs	> Use current advanced life support cardiopulmonary resuscitation protocols.
Lipid rescue (Intralipid® 20%)[2]	> Give intravenous bolus injection of Intralipid® 20% at 1.5ml/kg over 1 minute. > Start an intravenous infusion of Intralipid® 20% at 0.25ml/kg/min. > Repeat bolus injection twice at 5-minute intervals if adequate circulation has not been restored. > Continue infusion until a stable and adequate circulation has been restored.
Follow-up	> Arrange transfer to clinical area with appropriate equipment and staff. > Monitor daily amylase or lipases for 2 days and assess clinically for pancreatitis. > Report cases to the National Patient Safety Agency.

SUMMARY

- Although there are two types of LA, amides are now more commonly used.
- Understanding the pharmacology and physicochemical properties of LAs enables prediction of speed of onset, duration of action and determination of the correct LA for a particular clinical requirement.
- Drug concentration is expressed as a percentage such that 1% = 1g/100ml = 1,000mg/100ml = 10mg/ml.
- Lipid rescue therapy has been shown to be a very effective treatment for LA toxicity.[3,4]

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