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FCA REFRESHER COURSE

Local anaesthetics

K Mogotsi

Department of Anaesthesia, School of Clinical Medicine, Faculty of Health Sciences, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, South Africa
Corresponding author, email: *mogotsikl@gmail.com*

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Introduction

Local anaesthetics (LAs) are drugs that reversibly inhibit the transmission of a nerve impulse where they are applied and they can be used as a sole anaesthetic or as analgesia, either intraoperatively or postoperatively.[1] The routes of administration include but are not limited to, topical, subcutaneous, peripheral nerve blocks, and neuraxial.[2]

To accurately and confidently use any LA, one must understand the pharmacology of these drugs as a group and as individuals, as well as the importance of anatomy and physiology.[1] Individual drugs are not discussed in this refresher.

Structure and classification of a LA

The structure of a LA is made up of three parts, a lipid-soluble aromatic group, which is hydrophobic, a hydrophilic amine group, and an intermediary link between the two groups (Figure 1).[2] This intermediary link determines what class the LA drug belongs to; the two types described are esters and amides.[1] Table I describes the characteristics of both groups in comparison to each other.[1]

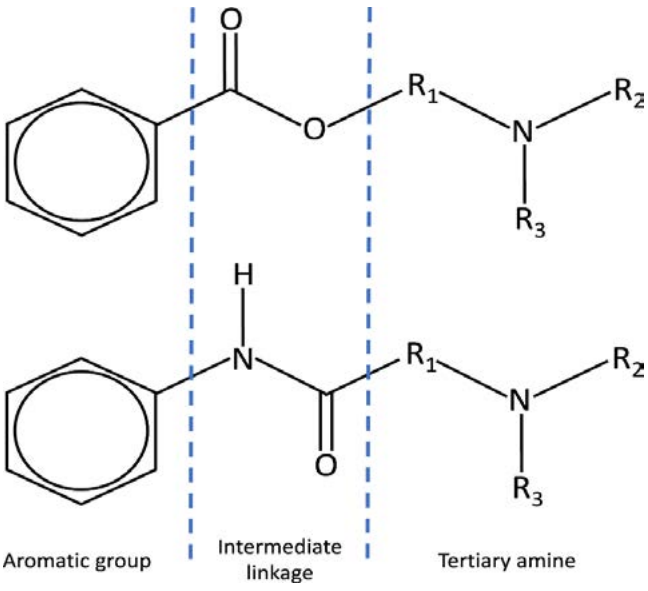

Figure 1: Structure of ester and amide LAs; each contains an aromatic group, an intermediate linkage (ester/amide), and a tertiary amine[2]

Table I: Comparisons of differences between ester and amide LAs[1]

Esters	Amides
Unstable in solution	Stable in solution
Shorter storage period	Longer storage period
Metabolised by plasma cholinesterase	Hepatic metabolism via microsomal hepatic systems
Rapid metabolism	Slow metabolism
More allergic reactions were seen due to the production of PABA	Rare allergic reactions
E.g. cocaine, procaine, benzocaine, tetracaine	E.g. lidocaine, bupivacaine, ropivacaine, prilocaine

The aromatic group is crucial for the anaesthetic activity because it is involved in the attachment of the drug to the sodium-channel site.[3]

Mechanism of action

The main theory described is the blockage of voltage-gated sodium-channels (VGSC) intracellularly by the LA. Other theories, which are beyond the scope of this update, propose ion-channel involvement (potassium and calcium) and receptor involvement (transient receptor potential vanilloid subtype 1 channel).[3] These theories are believed to be the reason for the other actions of LAs, such as their anti-inflammatory action and analgesic action along with their side effects.[4]

Neural transmission

The nerve fibre has a resting membrane potential between -50 mV and -90 mV, which is maintained by the sodium-potassium (Na/K) ATPase pump found as an integrated membrane in the lipid bilayer of the cell. This sodium-channel has a gate mechanism that can be found in three states, resting (meaning the channel is closed), activated (the channel is open), and inactivated (the channel is closed).[3]

Stimulation of the nerve causes an increase in permeability to sodium and changes the configuration of the sodium-channel from closed to open, this causes the nerve to be depolarised and the membrane potential increases to +20 mV due to an influx of sodium into the cell. The sodium inflow ceases when the electrochemical and concentration gradients of sodium are equal, at this point the sodium-channel is inactive and the

potassium efflux starts, which repolarises the nerve to its resting state.[3,5] The Na/K pump will then restore the concentration gradients and the resting membrane potential.[5]

Effect of LAs

LA drugs are weak bases, therefore a large proportion is in an ionised state. Only the un-ionised form of the LA can cross through the lipid membrane and enter the cell. The LA then dissociates again in the cell and reaches a new equilibrium of ionised and un-ionised forms according to the intracellular pH and the pKa of the LA (pKa will be discussed later).[2] The ionised form inside the cell then binds to the open VGSC. This binding increases with the frequency of nerve depolarisation so high-activity nerves are easily blocked in a phenomenon called use-dependant block.[2]

Physicochemical properties of LAs

The physiochemical properties of the drug, as determined by the aromatic structure and the length of the hydrocarbon chain, affect the function of the LA.[1] Any changes to the basic structure of these drugs, whether by lengthening the intermediate group or changing the number of carbon atoms, will entail a change in the drug's activity regarding things such as the onset of action, duration of action, potency, etc.[3] Table II summarises the physiochemical properties of LAs.

The anatomy of the nerve also contributes to the physiochemical properties of a LA; the more easily blocked the nerve, the faster the onset of action:[3]

- Nerves that fire more frequently or are used often tend to be more amenable to sodium blockage, therefore they are more easily blocked.
- Nerve fibres with a small diameter are blocked more easily.
- Myelinated fibres are more easily blocked compared to unmyelinated ones.

Pharmacokinetics

Absorption

The regional blood flow determines how much of the LA will be taken up into the systematic circulation.[3] The more vascular the area into which the LA is injected, the more rapid the uptake. The order from the highest absorption from a single dose is intrapleural > intercostal > lumbar epidural > brachial plexus > subcutaneous.[2] The vasoactivity of a LA may sometimes prevent this; it has been shown that at low doses LAs are vasodilatory, thus increasing their absorption.[2] Other factors to consider are the site of injection, the rate of injection, drug tissue binding, and the dose of the drug given as repeated dosing or a high single dose contributes to toxicity.[3,8]

Distribution

Distribution is influenced by protein binding.[1] Ester LAs are more protein-bound than the amide LAs, therefore they have a longer duration of action.[2] Distribution is also influenced by organ perfusion and the drug/blood partition coefficient, which is influenced by protein binding and lipid solubility.[3]

Metabolism

Esters are metabolised by plasma cholinesterase whilst amides undergo hepatic metabolism via the microsomal hepatic.[1] The administration of other drugs that use the same hepatic system along with a decrease in hepatic blood flow may affect the metabolism of a LA.[8]

Excretion

Ester metabolites are renally excreted and amides excrete very little renally unchanged.[1,2]

Adjuvants

Substances may be added to a LA to:

- preserve the molecules;
- prevent microbial growth;
- prevent systematic absorption;
- prolong or enhance the LA's action; and
- enhance the speed of the LA.[4]

The commonly used adjuvants are adrenaline, dexamethasone, clonidine, opioids, dexmedetomidine, ketamine, and midazolam.[2]

Table II: Physiochemical properties of LAs

Property	Definition	Effect
pKa	The pH where the ionised and un-ionised form of the LA is in equal concentration; also known as the dissociation constant.[3]	The closer the pKa is to serum pH, the greater the concentration of the drug intracellularly binding to the sodium-channels, resulting in a faster onset of action.[3]
Lipid solubility	The ratio of concentrations when LAs are dissolved in a mixture of lipid and aqueous solvents.[2]	The greater the lipid solubility of the drug, the better it can penetrate the cell membrane and have an effect, making it more potent.[1]
Protein binding	This defines the degree of attachment of drugs to the proteins in blood plasma.[6]	The more highly protein-bound, the lower the bioavailability of the LA, and the longer the duration of effect.[2]
Isomerism	Stereoisomers are molecules with identical atomic composition and chemical properties but different spatial arrangements of atoms.[7]	The R-enantiomer seems to be more potent and more toxic compared to the L-enantiomer.[3]

Complications

LA complications include neurotoxicity, muscle damage where they infiltrate, anaphylactic reactions, and local anaesthetic systematic toxicity (LAST). LAST may be due to either an accidental intravascular injection or secondary to a high plasma LA concentration. For this reason, it is important to know the toxic doses of LAs. Table III mentions the maximum doses of some LAs.[3]

Table III: Maximum doses of LAs[3]

Drug	Toxic dose without adrenaline	Toxic dose with adrenaline
Lignocaine	IV: 1–1.5 mg/kg	IM: 7 mg/kg
	S/C or IM: 3–5 mg/kg	
	Topical: 5 mg/kg	
	IVRA: Use 0.5% Upper limb: 0.5 ml/kg Lower limb: 1 ml/kg	Not applicable
Bupivacaine	2 mg/kg (maximum 150 mg)	No benefit
L-bupivacaine	2 mg/kg (maximum 150 mg)	No benefit
Ropivacaine	2 mg/kg (maximum 150 mg)	No benefit

LAST can present with symptoms that either predominantly affect the central nervous system (CNS) or cerebrovascular system (CVS).[3] CNS symptoms arise from the selective inhibition of excitatory CNS pathways.[9] This may manifest as vertigo, tinnitus, circumoral paresthesias, confusion, tremors, myoclonus jerks, convulsions, loss of consciousness, and coma.[9]

CVS toxicity may be from direct or indirect mechanisms. The direct mechanisms are from negative inotropy driven by decreased calcium release from the sarcoplasmic reticulum, disturbances of sodium-calcium pumps, alteration of mitochondrial energy transduction, and delays in impulse conduction through the cardiac conduction tissue. The indirect mechanisms arise centrally from the blockage of outflow impulses of the nucleus tractus solitarius, inhibition of baroreflex sensitivity, and inhibition of the cardiac centre in the midbrain. These will initially manifest as hypertension, tachycardia, decreased cardiac output, hypotension, severe hypotension, sinus bradycardia, ventricular dysrhythmias, and ultimately cardiac arrest.[3]

Treatment of LAST

Intravenous lipid emulsion therapy can either be intralipid or linoleic. Intralipid is a 20% lipid solution that works as a lipid sink, which draws the drug out and binds it, thereby decreasing the amount of LA available to bind receptors. Furthermore, it has a high lipid concentration and acts as a source of energy via long-chain fatty acids; the dose is 1 ml/kg intravenous STAT, and the STAT dose can be repeated twice, followed by an infusion of 0.25 ml/kg/min. Other treatments such as amiodarone, glucose, insulin and potassium infusions, bretylium tosylate, and potassium-channel openers have also been used.[3]

Reversal for LAs

Phentolamine mesylate is a non-selective alpha antagonist and has been used to reverse LA post-dental surgery. It functions by causing vasodilatation, which increases blood flow and increases clearance time.[2]

Resistance to LAs

There are a few reasons why the block performed may fail resulting in inadequate analgesia. These include factors such as:

- wrong expectations or fears by the patient;
- incorrect mode of application;
- errors in dosage;
- product preparation; and
- tissue inflammation.[10]

There are some conditions where true LA resistance may occur:[10]

- Gene mutations associated with the VGSC are suspected to cause LA resistance with possible alteration of nociception and perception of temperature.
- Scorpion stings. The poison is believed to induce antibodies that interact with the LA binding site of the VGSC.
- Ehlers-Danlos syndrome of the hypermobility type, causing altered LA spread.
- Regular opioid use. This is due to multiple mechanisms including changes in the shape, function, and concentration of opioid receptors. The interaction and cross-tolerance between LA and opioid consumers needed higher doses of lidocaine to experience sufficient analgesia during surgical wound treatment.
- Natural red hair. The hypothesis is that there is an increase in central nociception and that the melanocortin 1 receptor gene mutation upregulates central melanocortin, which in turn increases baseline pain.

Other uses of LAs

LAs may also be used to treat acute and chronic pain, inflammation, cancer, and postoperative ileus.[4] However, the evidence for some of these uses is still conflicting.[2]

Conclusion

Given the variety of situations in which one can use LA drugs, it is imperative to have a full understanding of their pharmacology to use them safely and effectively.

ORCID

K Mogotsi https://orcid.org/0000-0003-1038-1890

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