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Pharmacology of Local Anaesthetics and Commonly Used Recipes in Clinical Practice

Jesse Musokota Mumba, Freddy Kasandji Kabambi and Christian Tshebeletso Ngaka

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Abstract

Local anaesthetics are commonly used drugs in clinical anaesthesia. The knowledge of their pharmacology is paramount for safe and optimal use of this group of drugs. This chapter consists of two sections. The first section will address the chemical and physical properties, pharmacokinetics and pharmacodynamics of the local anaesthetics. In the second section, examples of the commonly used doses and additives used for various peripheral and regional anaesthetics will be discussed. We will also address the treatment of toxicity as a result of inadvertent intravascular injection of the local anaesthetics.

Keywords: local anaesthetics, lidocaine, bupivacaine, ropivacaine, cocaine

Summary points

1. Local anaesthetics block the transmission of pain from the nerve endings into the central nervous system. Chemically, they are classified as esters and amides depending on the intermediate chain between the lipophilic aromatic ring and the hydrophilic amine group.

2. The primary mode of action is blockade of the fast voltage-gated sodium channels. To achieve this effect, the unionised fraction of the drug crosses the lipid bilayer of the axoplasm and blocks the channel intracellularly.

3. The duration and density of the block depend on both the volume and concentration of the agent used.
4. Factors that influence the efficacy of local anaesthetics are the pH, pKa, lipid solubility, protein binding and the length of the intermediate chain. Efficacy can be augmented by use of adjuncts such as adrenaline, opioids, alpha 2-adrenergic agonists (clonidine) and alkalisation.

5. Toxicity is related to the site of injection, the vascularity of the site and the injected dose. The use of vasoconstrictors may reduce toxicity due to reduction in systemic absorption.

6. From the local anaesthetics in clinical use, racemic bupivacaine has the highest affinity for the sodium channels and is the most difficult to manage in the event of systemic toxicity.

1. The neuron and pharmacology of local anaesthetics

1.1. Introduction

Local anaesthetics are drugs that block conduction of electrical impulses in excitable tissues. These tissues include the nerve cells and myocytes (both cardiac and skeletal muscles). Analgesia and anaesthesia occur as a result of the blockage of electrical impulses. Other local anaesthetics like lidocaine also possess Class I antiarrhythmic properties. Before a detailed venture into the physical-chemical properties and mechanism of action of this class of drugs, a brief overview of the nerve anatomy is discussed. This will aid in the overall understanding of how these agents work and how their efficacy and safety can be improved by the use of appropriate doses and adjuncts.

1.2. Nerve anatomy

Neurons are the primary cells in the nervous system. The nervous system is made up of the central and peripheral nervous system. It can also be looked at in terms of parasympathetic and sympathetic nervous system. A group of neurons bundled together make up peripheral nerves. The basic structure of a neuron is illustrated in Figure 1.

![Figure 1. Structure of a neuron. Source: http://www.vce.bioninja.com.au/aos-2-detecting-and-respond/coordination--regulation/nervous-system.html. Used with permission 05/11/2016.](image-url)
Peripheral nerves contain both afferent and efferent fibres, which are bundled into one or more fascicles as illustrated in Figure 2. Individual nerve fibres within the fascicle are surrounded by a layer of loose connective tissue called the endoneurium. The endoneurium houses the glial cells, fibroblasts and blood vessel capillaries, all of which are integral to the function of the nerve fibre. The fascicle is in turn surrounded by a dense layer of collagenous connective tissue called the perineurium. A cylindrical sheath called the epineurium forms the outermost layer of a peripheral nerve. The main function of these layers is to protect the nerve fibres and also act as barriers to agents acting on the nerves including local anaesthetics.

Figure 2. Peripheral nerve. Source: https://www.studyblue.com/t/f/flashcard/review/8819508.

1.3. Electrophysiology of nerve conduction

The resting membrane potential of a nerve cell is in the range of −60 to −70 mV. At rest, neurons are more permeable to potassium ions due to the presence of potassium leak channels. This explains why the resting neuronal membrane potential is closer to the equilibrium potential of potassium of −80 mV. The ionic disequilibria acts as the energy needed for propagation of action potentials on the cell surface [1]. The intracellular milieu of the nerve cell is negatively charged relative to the extracellular. Upon excitation of the nerve fibres, the electrical impulse propagates along the axon as a result of changes occurring in the adjacent membrane alternating from negative to positive values of about +50 mV due to rapid influx of sodium ions. At an electrical potential of +50 mV, there is rapid efflux...
of potassium ions in an attempt to maintain electrical neutrality of the cell. To restore the resting membrane potential, the sodium/potassium ATPase pumps sodium extracellularly, while the opposite happens to the potassium ions. The conduction of impulses along nerve fibres occurs as small brief, localised spikes of depolarisation on the surface of the cell membrane. Impulses travel in one direction as the axonal membrane that has just undergone depolarisation remains in the refractory state until the resting potential is restored by the Sodium/Potassium ATPase pumps on [2]. Figure 3 illustrates the sequence of events occurring during the propagation of the action potential.

![Figure 3](image-url) Sequence of events occurring during the propagation of the action potential. Source: http://www.vce.bioninja.com.au/aos-2-detecting-and-respond/coordination-regulation/nervous-system.html. Used with permission 05/11/2016.

1.4. Pharmacology of local anaesthetics

1.4.1. Structure-activity relationship of local anaesthetics

Local anaesthetics consist of a hydrophilic amine and a lipophilic aromatic ring connected by an intermediate chain. The structural bond in the intermediate chain determines whether the local anaesthetic will be classified as an ester or an amide. Furthermore, the bond in the intermediate chain determines the pathway of metabolism of the compound. Ester local anaesthetics are metabolised by plasma pseudocholinesterases, whereas the amides are metabolised in the liver by the cytochrome family of enzymes.

Figure 4 illustrates the structure of an ester and amide local anaesthetic showing clearly the bonds in the intermediate chains.
1.4.2. Mechanism of action of local anaesthetics

Local anaesthetic blocks the transmission of nerve impulses by reversibly blocking the fast voltage-gated sodium channels, thereby inducing analgesia and anaesthesia. Physicochemically, local anaesthetics are weak bases that are formulated in an acidic milieu, hence containing a larger proportion of the drug in the ionised state. However, it is the unionised fraction that is able to cross the lipid bilayer neuronal membrane and block the voltage-gated sodium channels from the inside of the axoplasm. This blockade renders the sodium channel inactive, and hence, no further conduction of impulses occurs. Diagramatically this is well demonstrated by Figure 5.
1.4.3. Determinants of physiological activities of local anaesthetics

The activity of local anaesthetics is influenced by a number of factors. These include the pH of the surrounding tissue, the lipid solubility of the local anaesthetic, pKa, the bond in the intermediate chain and its length and the protein binding of the particular local anaesthetic in question. Details of how each of these factors influence the activity of local anaesthetics is discussed below:

1. pKa: The pKa is the pH at which the number of ionised and unionised fractions of the drug is in equilibrium. The lower the pKa, the more the unionised fraction is present for any given pH and hence the faster the onset of action.

2. pH: The lower the pH, that is, acidic milieu, the less the potency because in acidic conditions the ionised fraction predominates, there is less of the unionised fraction, and there is less of the local anaesthetic available to cross the lipid bilayer and block the voltage-gated sodium channels. This explains why local anaesthetic does not have much efficacy in reducing pain in infected tissues like abscesses in which the pH of such tissues is much lower than the physiological pH of 7.4.

3. Lipid solubility: The more lipid soluble the local anaesthetic is, the higher the potency, the faster the onset of action and the longer the duration of action. This is because there are more drug molecules able to cross the lipid bilayer of the neuronal membrane and create a ‘depot’ of the drug from within the axoplasm.

4. Intermediate chain: The longer the intermediate chain, the more potent the local anaesthetic. Bupivacaine has a longer intermediate chain compared to lidocaine. Bupivacaine is three to four times more potent than lidocaine.

5. Protein binding: Local anaesthetics with higher degrees of protein binding have longer duration of action.

Depending on the type of nerves and their fibres, the sequence of blockade of the nerve fibres is illustrated in Table 1.

<table>
<thead>
<tr>
<th>Fibre type</th>
<th>Myelin</th>
<th>Diameter (μm)</th>
<th>Function</th>
<th>Conduction velocity</th>
<th>Onset of block</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-α</td>
<td>Yes</td>
<td>12–20</td>
<td>Somatic motor and proprioception</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>A-β</td>
<td>Yes</td>
<td>5–12</td>
<td>Light touch and pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-γ</td>
<td>Yes</td>
<td>3–6</td>
<td>Muscle spindle (stretch)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-δ</td>
<td>Yes</td>
<td>1–4</td>
<td>Firm touch, pain (fast-localising) and temperature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Yes</td>
<td>1–3</td>
<td>Preganglionic autonomic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>No</td>
<td>0.3–1.3</td>
<td>Pain (nonlocalising ache), temperature, touch, postganglionic autonomic</td>
<td>Slow</td>
<td>Fast</td>
</tr>
</tbody>
</table>

Table 1. Classification of nerve fibres and sequence of blockade.
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supplementation and possibly conversion to general anaesthesia [40]. The practice at our institution is to use 10 mg of hyperbaric bupivacaine plus 10 μg fentanyl with satisfactory results.

2. Labour epidural analgesia

The current policy at our institution is to draw up a mixture of 5 mL of 0.5% bupivacaine, 4 mL saline and 50 μg fentanyl, that is, a total of 10 mL of 0.25% bupivacaine with 5 μg/mL fentanyl, and to administer two 4 mL boluses of this mixture 3 min apart, with the patient in the left lateral position for the first bolus and the right lateral for the second. In early labour, an initial bolus of 8 mL of 0.125% bupivacaine may be given, followed by a repeat dose of a similar volume. The aim is to obtain levels of T8–T10 bilaterally, and this can take up to 20 min. Analgesia is maintained with an infusion of 0.125% bupivacaine plus 2 μg/mL fentanyl at the rate of 8–14 mL/h.

Top-up of labour epidural for caesarean delivery step-by-step

- Draw up 17 mL 2% lignocaine, plus 50 μg fentanyl, 1 mL 8.4% sodium bicarbonate and 1 mL 1/10,000 adrenaline (i.e. 1 mL of an ampoule which has been diluted 10 times). This makes a total of 20 mL, with approximately 1/200,000 adrenaline.
- Administer 5 mL boluses after a test dose.
- Unless the initial dose of epidural bupivacaine has been administered within the previous hour, treat as though the patient has no block at all. Most patients will require between 16 and 22 mL for an effective block to T4.
- Conversion to spinal anaesthesia may result in a high block if there has been an unsuccessful attempt at a top-up with a large volume of local anaesthetic.
- A poorly functioning epidural catheter is best re-sited, or spinal anaesthesia may be performed using a reduced dose (unpredictable), or general anaesthesia may be preferred.

3. Local anaesthetics for regional intravenous anaesthesia

Regional intravenous anaesthesia is indicated for short operative procedures for extremities and sometimes for pain therapy (e.g. treatment of complex regional pain syndromes). This is a very basic technique, and it requires 12–15 mL of 2% lidocaine or 30–40 mL of 0.5% lidocaine for upper extremity regional anaesthesia. Other local anaesthetics such as bupivacaine are contraindicated for IV injection for reasons discussed in the toxicity section. Some evidence exits supporting a better quality of the block by use if additives such as ketamine and alpha-2 agonists are added to local anaesthetics for peripheral nerve blocks [41, 42].

Equipment required includes:

- Lidocaine
- IV cannulae
- Double pneumatic tourniquet
- Esmarch bandage
- Syringes
Technique:

- An IV cannula is inserted in the extremity opposite the block side.
- A double pneumatic tourniquet is placed with proximal cuff high on the upper arm.
- A peripheral IV cannula is placed on the limbs on which surgery is to be done as distal as feasible.
- The block arm is elevated for 1–2 min to allow passive exsanguination, and then, Esmarch bandage is wrapped around the arm to exsanguinate the extremity completely.
- The distal cuff is inflated to 50–100 mmHg above systolic BP after which the proximal cuff is inflated followed by deflation the distal cuff.
- Inject preservative-free local anaesthetic (recommended maximum dose is 3 mg/kg).
- After injection IV cannula is removed from anaesthetised hand and pressure is quickly applied to puncture site.
- Anaesthesia onset is almost immediate.
- When the patient reports tourniquet pain inflate the distal cuff and deflate the proximal cuff.

4. Local anaesthetics for peripheral nerve blocks

There are a wide variety of local anaesthetic agents available for peripheral nerve blocks. Important points to consider when making the choice are onset and duration of action, duration of the surgical procedure and anticipated degree of pain. Caution is to be used if one decided to use additives to local anaesthetics for peripheral nerve blocks to prolong their effect as none of the additives discussed in this chapter have got the Food and Drug Administration (FDA) approval for this purpose [43].

5. Topical anaesthetics

Topical anaesthetics are used for procedures such as vein cannulation, laceration repair to avoid infiltrative local anaesthesia injections and associated pain. They are widely used in the paediatric population. There are many dosage forms in clinical use, for example, gels, sprays, creams, ointments, patches. Skin absorption is variable and accounts for the systemic toxicity. This complication is rare provided the skin is intact with the exception of 5% EMLA cream, a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine. Commonly available forms are Ametop (4% tetracaine) and EMLA, and more recently, a 4% lidocaine topical cream has been introduced. It is better tolerated on the skin while having flexible application times. Onset of action for Ametop is between 30 and 40 min and has a duration of action of about 4–5 h. EMLA on the other hand has a slower onset of about 60 min with a short duration of action of about 2 h. Toxicity is largely related to the age of the patients and possible damage in the skin. It is recommended that in those below 3 months, duration of application should not be more than 1 h, while for age group between 3 and 12 months maximum duration of application does not exceed 4 h [44].
6. Neuraxial techniques in paediatrics

Caudal anaesthesia is a popular technique to provide analgesia in paediatric patients. The single-shot technique is often adequate for most urological, lower extremity and lower abdominal procedures. An indwelling catheter can extend its use to upper abdomen and thoracic procedures and offers the added benefit of continuous post-operative analgesia. The LA dose depends on the operative site that ranges from 0.5 to 2 mL/kg of 0.25% bupivacaine, that is, the level of the block is proportional to the dose.

Spinal and epidural anaesthesia are safe and effective ways to provide anaesthesia for infants [45]. For spinal anaesthesia, bupivacaine 0.5% at a dose 0.5–1 mg/kg is commonly used with the dose decreasing with increasing age.

Local anaesthetics add to the armament that is at the disposal of anaesthetists. Understanding of their pharmacology increases the safety with which these drugs can be used. Early recognition of toxicity is core to avoiding central nervous system and cardiorespiratory collapse.

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References


