Local anaesthetic agents

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Abstract

Local anaesthetics are weak bases and consist of a lipophilic aromatic ring, a link and a hydrophilic amine. The chemistry of the link classifies them as amides or esters. They act by blocking the sodium ionophore, especially in the activated state of the channel, and frequency dependence can be shown. The speed of onset is related to dose and proportion of drug in the unionized lipid-soluble form, which in turn is determined by the pK_a and the ambient pH. Local anaesthetic agents, being weak bases, are bound in the plasma to α_1-acid glycoproteins, influencing duration of action. Esters undergo hydrolysis by esterases in the plasma. Amides are subject to phase I and II hepatic cytochrome P450 metabolism. The development of the S-enantiomers, levobupivacaine and ropivacaine, has not been without some controversy with regards to therapeutic benefits when assessed by clinical potency models such as the minimum local analgesic concentration (MLAC). Drugs derived from biological toxins that target and bind to the sodium ionophore are gaining acceptance for use as analgesics in chronic pain.

Keywords Articaine; bupivacaine; chloroprocaine; levobupivacaine; lidocaine; local anaesthetics; pharmacology; ropivacaine; saxitoxin; tetrodotoxin

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Drugs that have 'membrane-stabilizing activity' have become widespread in clinical practice since Koller, an ophthalmologist, discovered the local anaesthetic properties of cocaine in 1884. They are now well established in many areas of clinical practice, including nerve blockade, neuropathic pain syndromes, obtunding the pressor response to laryngoscopy, treatment of cardiac arrhythmias, mucosal vasoconstrictors, epilepsy, as a diagnostic tool for suxamethonium apnoea and even for treatment of asthma. Significant milestones in the development of this class of drugs were procaine (1898), lidocaine (1943) and bupivacaine (1957). More recent advances have come through research into the cardiotoxicity of bupivacaine, and developments in stereochemistry, resulting in the introduction of the S-enantiomers: ropivacaine (1996) and levobupivacaine (1999). There have also been improvements in our understanding of dosing, particularly in combination with other analgesics such as opioids and α_2-adrenergic agonists.

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Chemistry

Local anaesthetics have a common chemical structure, consisting of a lipophilic aromatic ring, a link and a hydrophilic amine group (Figure 1); most are tertiary amines (three alkyl or aryl groups attached to the nitrogen atom). They can be classified into two groups based on the nature of the link: amides [−NH−CO−] and esters [−O−CO−]. The amide group is the most commonly used clinically and includes lidocaine, prilocaine, (levo-) bupivacaine and ropivacaine. The ester group includes cocaine, procaine, chloroprocaine, benzocaine and amethocaine. Being weak bases they are made soluble for injection by formulating them as strong conjugate acidic hydrochloride salts (pH 3−6).

$$\text{Lidocaine} + \text{HCl} = \text{Lidocaine-H}^+ + \text{Cl}^-$$

Mechanism of action

Local anaesthetics work by blocking the inward Na^+ current at the sodium ionophore during depolarization, which prevents propagation of the axonal action potential. However, research indicates that their mechanism of action is more complicated than this, with calcium, potassium and G-protein regulated channels also being blocked by local anaesthetics. When delivered by injection, the local anaesthetic is predominantly in the acidic ionized form (pH 3−6). This dissociates in the relatively alkaline perineural tissues (pH 7.4) to lipid-soluble free base. This crosses the axolemma and re-ionizes in the acidic axoplasm to the active moiety, which blocks the sodium ionophore from within the cell or from the membrane lipid bilayer. Therefore, the non-ionized form promotes delivery into the axon and the ammonium or ionized state provides activity.

When the nerve is stimulated, the sodium ionophore alters structurally. This initiates its cycle through four functional states: resting, activated, inactivated and deactivated (Figure 2). The complex ionophore can be considered to have two functioning gates, an outer m gate and an inner h gate. In its resting state, the outer m gate is closed and the inner h gate is open. On nerve stimulation, the ionophore enters its active state whereby opening of the outer m gate results in the rapid influx of sodium ions. As the membrane potential increases (to around 20 mV) this triggers the closure of the inner h gate and the ionophore enters an inactive state. The deactivated state is produced as a result of closure of the outer m gate once the membrane potential reaches −60 mV. Whilst in an inactivated or deactivated state, the nerve is resistant to further stimulation. Local anaesthetic block is more readily achieved when the ionophore is in the activated than in the inactivated state and least when in the deactivated or resting state (state-dependent block). When the sodium channel is closed, as is the case in the deactivated or resting states, the local anaesthetic can only gain access via the membrane as free base. However, when the sodium channel is open, as is the case in the activated, and to a lesser extent in the inactivated state, the ionized local anaesthetic can also gain access to the nerve via the channel. In addition to this, the ionized form may enter from outside if the ionophore is repeatedly activated or opened. This

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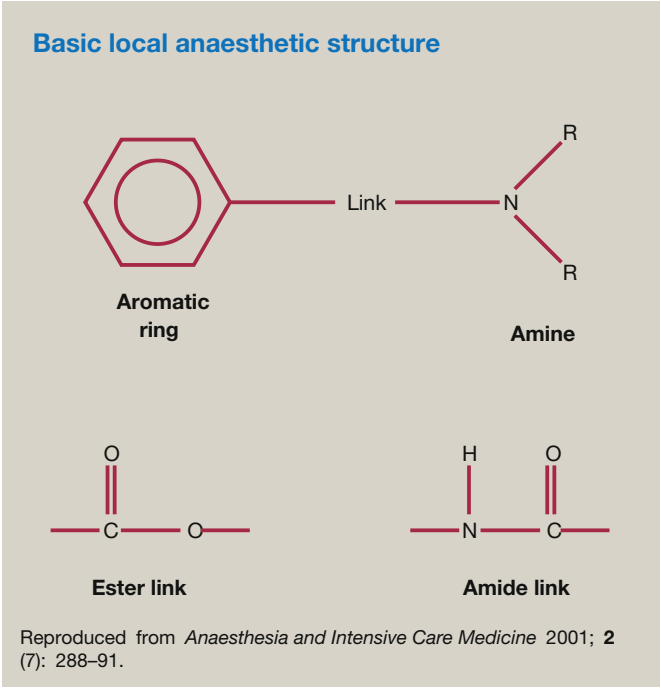

Figure 1

gives rise to frequency dependent (or phasic) block. The onset of block with agents that have more ionized molecules outside the membrane can therefore be accelerated by stimulation. Thus, frequency dependent block is better demonstrated for bupivacaine than for lidocaine. Different local anaesthetics also have varying channel affinity. Lidocaine binds and dissociates rapidly from the channel, whereas bupivacaine binds rapidly but dissociates more slowly. This has little effect on neuronal block but assumes greater importance when referring to effects on cardiac toxicity. The S-enantiomer of bupivacaine dissociates more quickly thus reducing cardiotoxicity.

The speed of onset of block is related to the concentration of molecules of local anaesthetic that are in the free base or non-ionized state. This depends on the initial dose, the dissociation constant (pK_a) and the pH of the tissues. By convention, dissociation constants are applied to the acidic forms and this sometimes causes confusion as inversions of the Henderson −Hasselbach equation (1) are often used depending on whether an acid or base is involved.

$$pH = pK_a + \log([\text{base}]/[\text{acid}]) \quad (1)$$

$$\text{For an acid: } pH = pK_a + \log([\text{ionized}]/[\text{non-ionized}]) \quad (2)$$

$$\text{For a base: } pH = pK_a + \log([\text{non-ionized}]/[\text{ionized}]) \quad (3)$$

It is simpler to use equation 1 or a modification for all substances and consider only the acidic version:

$$pH = pK_a + \log([\text{dissociated}]/[\text{associated}]) \quad (4)$$

It is then helpful when looking at the pK_a for 'bases' to consider them in the acidic ionised form.

Equations (1) and (4) can be further modified to:

$$pK_a - pH = \log([\text{acid}]/[\text{base}]) \quad (5)$$

$$pK_a - pH = \log([\text{associated}]/[\text{dissociated}]) \quad (6)$$

Using either equation, and given that physiological pH is 7.4, it can be seen that more molecules of bupivacaine (86%) remain in the associated (ionized) form compared with lidocaine (72%) and therefore onset is slower (Table 1).

$0.8 = \log([BH^+]/[B])$ versus $0.4 = \log([LH^+]/[L])$

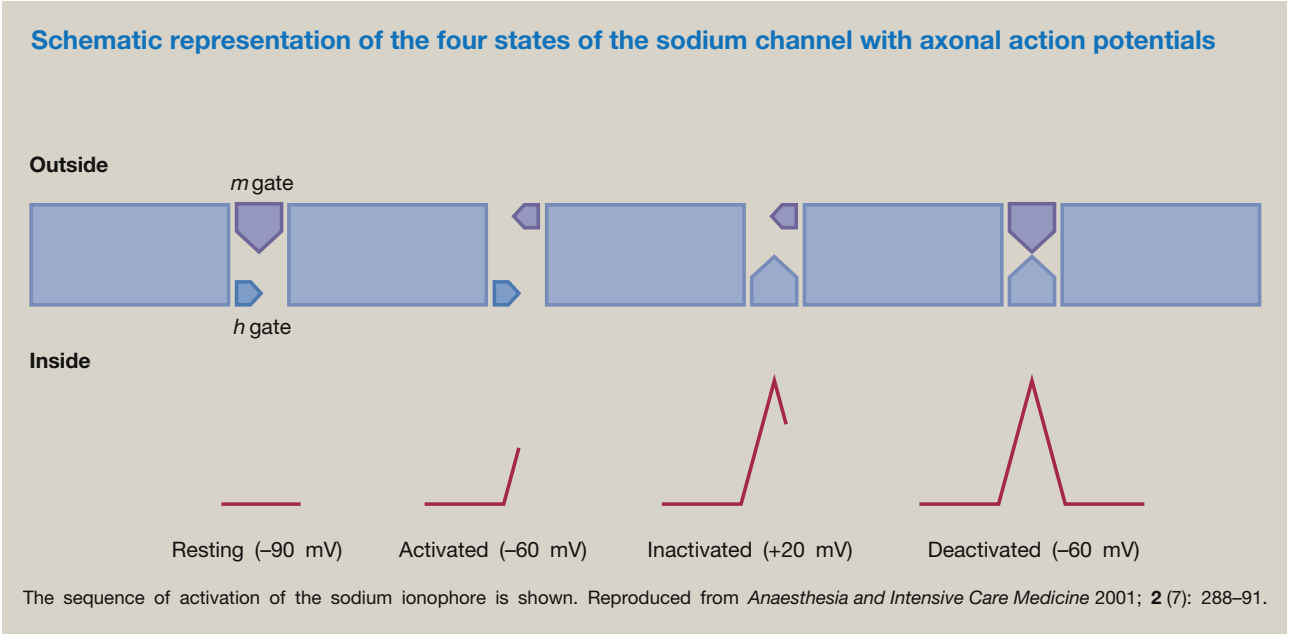

Figure 2

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