Local anaesthetic and additive drugs

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Local anaesthetics reversibly block nerve impulses and are the mainstays of regional anaesthesia. Local anaesthetics can be divided into two main groups, esters (e.g. cocaine, procaine, chloroprocaine, tetracaine) and the more commonly used amides (e.g. lidocaine, prilocaine, bupivacaine). The newer amides, ropivacaine and levobupivacaine, are single enantiomers. For each agent, the onset, potency and duration of action are determined by its physical properties, in particular its pK_a, lipid solubility, protein binding and intrinsic vasodilatory activity.

pK_a of a chemical compound represents the pH at which its ionized and non-ionized forms are in equilibrium. The pK_a of a local anaesthetic determines its speed of onset of action because only the uncharged form is lipid soluble and is able to diffuse quickly across the myelin layers of nerve fibres. Local anaesthetics are weak bases but are injected in acidic solutions as hydrochloric salts. The tertiary amine (hydrophobic or water insoluble) becomes quarternary and is thus soluble in water and suitable for injection. At physiological pH, the proportion of the drug that dissociates into a free base (which is lipid soluble) is determined by its pK_a. This non-ionized portion passes through the lipid cell membrane to the inner axon where re-ionization takes place. The re-ionized portion of the local anaesthetic blocks the sodium channels. The closer the pK_a of the drug is to physiological pH (7.4), the greater the amount of free base or non-ionized drug present and the faster the onset of the block. The higher the pK_a, the less non-ionized drug is available and the slower the onset of block. For example, at pH 7.4, lidocaine (pK_a 7.7) is 35% non-ionized and bupivacaine (pK_a 8.4) is 12–13% non-ionized, therefore lidocaine has a faster onset of action than bupivacaine in equipotent doses.

Lipid solubility determines the potency of a local anaesthetic. Potency is the minimum amount of a drug required to produce a given effect. A local anaesthetic that is more lipid soluble will have more of its molecules penetrate the nerves; therefore less drug is required to give the same blockade.

Protein binding affects the duration of action of a local anaesthetic. The sites of action for local anaesthetics are sodium channels, which are protein molecules, therefore highly bound drugs have a long duration of action. The intrinsic vascular effects of the drug and the total dose given also influence its duration of action.

Local vascular effects: all local anaesthetics are vasodilators, except cocaine, ropivacaine and levobupivacaine, which are vasoconstrictors. The degree of vasodilatation influences the toxicity and potency of local anaesthetics because a higher degree of vasodilatation causes more systemic absorption of the drug, particularly in vascular sites and thus less drug is available for neural blockade.

Differential block: ropivacaine produces more selective blockade for sensory fibres when used in lower concentrations than bupivacaine. Ropivacaine has lower lipid solubility and a similar high pK_a, which reduces its affinity and penetration of the myelin sheath. Therefore, blockade of C fibres is greater than blockade of larger myelinated A fibres.

Additives

Additives are used in conjunction with local anaesthetics for regional anaesthesia to quicken onset, to prolong duration and to enhance analgesia. Additives to local anaesthetics for regional anaesthesia are listed in Figure 1.

Mode of action, sites and side-effects of additives

Drug	Action	Neuraxial use	Peripheral use	Potential problems
Vasoconstrictors	Reduce systemic uptake Direct action on α_1- and α_2-receptors	Yes	Yes	Arrhythmias Increase blood pressure Ischaemia
Opioids	Bind opioid receptors Synergistic with local anaesthetic	Yes	Insufficient evidence	Respiratory depression CNS depression Nausea Pruritus Constipation Urinary retention
Clonidine (α_2-agonist)	Decreases catecholamine release by negative feedback	Yes	Yes	Sedation Hypotension Bradycardia Dry mouth
Bicarbonate	Increases non-ionized component of drug allowing faster onset of local anaesthetic	Yes	Yes	Precipitation
Neostigmine	Increases availability of acetylcholine	Not recommended Many side-effects	Insufficient evidence	Nausea Vomiting
Hyaluronidase	Enzyme. Depolymerizes polysaccharide hyaluronic acid in connective tissue	No	Yes	Allergic reactions reported
Ketamine (NMDA antagonist)	Blocks NMDA receptor May act on opioid receptors	Yes, particularly in caudals in children	No	Neurotoxic concerns about preservative in preparation (use preservative-free preparations) Psychomimetic effects Nausea
Midazolam	Via GABA benzodiazepine receptors in lamina 2 of the dorsal horn May act on opioid receptors	Controversial	No	Sedation Respiratory depression
Dextrose	Increases baricity for intrathecal anaesthesia	Intrathecal	No	Safe intrathecally up to concentration of 7.5%

Abbreviations: GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate

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Vasoconstrictors

Vasoconstrictors increase the duration and intensity of the block by two mechanisms. First, vasoconstriction of epidural vessels reduces systemic uptake so more of the drug becomes available to the nerves. Second, vasoconstrictors may exert a direct antinociceptive effect by acting on α_1- and α_2-receptors, thus modulating dorsal horn action, which has a dose-dependent analgesic effect. Local anaesthetics with intrinsic vasodilatory properties (e.g. lidocaine and prilocaine) benefit most from this additive.

Epinephrine is the most common vasoconstrictor added to local anaesthetic solutions for regional anaesthesia. Epinephrine, 5 μg/ml, is used for epidurals and is said to have no β-mimetic effects. Epinephrine can also be added to the epidural 'test dose' to detect inadvertent intravascular injection of local anaesthetic; this is more popular in the USA than in the UK. A test dose containing epinephrine injected intravascularly may increase the heart rate by 20% within 30–60 seconds. However, this may be difficult to detect in patients who are already tachycardic for other reasons or who are taking β-blockers, and it is unreliable in children. Epinephrine can also be added to local anaesthetics for peripheral nerve blocks (e.g. brachial or lumbar plexus). When interscalene blocks are used for shoulder surgery in the sitting position, sudden hypotensive and/or bradycardic events have been reported in 13–28% of patients. The Bezold–Jarisch reflex occurs when venous pooling and increased levels of epinephrine induce a low volume ventricle that is in a hypercontractile state. Recently, exogenous epinephrine administered with local anaesthetic for interscalene block has been implicated.[1]

Felypressin, 0.03 IU/ml, is added to prilocaine for dental blocks. It is a synthetic octapeptide chemically related to vasopressin. Felypressin does not cause arrhythmias but may increase blood pressure.

Contraindications – care should be taken when using vasoconstrictors in certain patients, in particular, those with cardiovascular disease. Concentrations of epinephrine above 5 µg/ml are not of benefit in prolonging the local anaesthetic effect. Patients taking tricyclic antidepressants (which inhibit the process of reuptake of noradrenaline into neurons) may have an increased response to vasoconstrictors. This is also the case with patients who use cocaine. Traditionally, vasoconstrictors should not be used with local anaesthetics for digital nerve blocks, but this has been challenged recently.[2]

Clonidine

Clonidine, an α_2-adrenergic agonist, has been shown to prolong the action of local anaesthetics especially when used in the intrathecal or epidural space. It activates a negative-feedback mechanism via its action on α_2-receptors, which decreases catecholamine release. This modulates input at the dorsal horn. Clonidine also has cholinergic effects and increases the amount of acetylcholine available centrally. Its main adverse effects are hypotension, bradycardia and sedation. When combined with ropivacaine 0.1%, as little as 25 µg of clonidine in the epidural space has been associated with bradycardia and sedation. However, hypotension was significant only with doses of more than 75 µg epidurally.

Clonidine has also been shown to prolong local anaesthesia in peripheral blocks, probably by direct peripheral action. A recent study using only clonidine for interscalene blocks showed significantly longer analgesia when compared with a group receiving clonidine subcutaneously.[3] The exact mechanism of peripheral action is unknown. Clonidine may act on peripheral α_2-receptors or reduce the vascular uptake of local anaesthetic by its vascular adrenergic effects. Clonidine may exert a peripheral analgesic action by causing the release of enkephalin-like compounds. Doses up to 150 µg administered peripherally have minimal side-effects.

Bicarbonate

Local anaesthetic solutions are weak bases in an acidic solution. Alkalinization of local anaesthetics increases the non-ionized component and allows faster penetration of nerves. This should make the onset of the block quicker, but the literature is controversial, with some studies unable to demonstrate a difference when bicarbonate is added to bupivacaine 0.5% or lidocaine 2% for epidurals. However, other studies have found this technique to be effective. A recent study has shown alkalinization of ropivacaine 0.75% with sodium bicarbonate 1.26%, 0.012 mEq, significantly increased the duration of epidural blockade.[4] There is a risk of precipitation when bicarbonate solutions with concentrations of 1–8.4% are used.

Opioids

The addition of opioids to local anaesthetics in epidurals or spinals enhances and prolongs the duration of block. Opioid receptors are found in the dorsal horn and the brainstem. Binding of opioid receptors causes hyperpolarization of nerve membranes, which decreases nerve impulse transmission. Substance P and glutamate release are also inhibited. Animal experiments suggest that opioids and local anaesthetic have a synergistic effect, but the mechanism is unknown. The addition of an opioid to a local anaesthetic for epidural or intrathecal use allows more dilute solutions of local anaesthetic to be used.

Many types of opioids are used in neuraxial blockade. Their onset and duration of action depends on their physicochemical properties. For example, morphine, which has relatively low lipid solubility, has a delayed onset and prolonged duration of action up to 24 hours. Fentanyl is more lipid soluble than morphine and therefore produces quicker onset of analgesia, but it has a shorter duration of action because it is subject to higher vascular uptake than less lipid-soluble opioids. The properties of diamorphine lie between the two. A drug that is less lipophilic could remain in the cerebrospinal fluid (CSF) for some time allowing it to spread to the brainstem. Only 4% of epidurally administered morphine reaches the CSF. Most of the morphine is taken up by the epidural fat where it is absorbed rapidly by the vertebral venous plexus.

Respiratory depression with neuraxial opioids occurs because of rostral spread to the brainstem. Therefore there could be some delay before respiratory depression is seen. This side-effect is more likely with the less lipid-soluble agents. Other side-effects associated with rostral migration are pruritus, urinary retention and vomiting.

Opioid receptors have been found on peripheral nerves. It is thought that during an inflammatory condition, opioid receptors are transported from the dorsal root ganglia

towards peripheral sensory nerve endings. Concurrently, there is an accumulation of endogenous opioid peptides in immune cells within inflamed tissue. These peptides can be released by environmental stimuli such as stress or corticotropin-releasing factor. Interaction between opioid peptides and peripheral receptors causes local analgesia. It therefore seems logical to add opioids to local anaesthetic solutions for peripheral nerve blockade. However, there is insufficient evidence to recommend the use of opioid analgesia in peripheral nerve blockade. Studies involving the addition of fentanyl, tramadol, morphine or alfentanil are inconclusive. Several studies using a systemic opioid control do not demonstrate that peripherally administered opioids have a significant benefit. Adverse effects of opioid administration are not avoided by using them in peripheral nerve blockade.

Neostigmine
Neostigmine, an acetylcholinesterase inhibitor, increases the availability of endogenous acetylcholine. Activation of acetylcholine receptors is thought to contribute to an endogenous form of analgesia and the administration of systemic neostigmine has been shown to display a dose-dependent analgesic effect. Doses of 50–100 µg administered intrathecally provide analgesia comparable to morphine for 24 hours. However, it is not recommended for the treatment of acute pain because the incidence of nausea and vomiting is high.

In the periphery, muscarinic receptors have been found on peripheral nerves. Studies using neostigmine, up to 500 µg, as an adjunct to peripheral nerve blockade have not been convincing. Further studies are required and should include a systemic control.

Hyaluronidase
Hyaluronidase is an enzyme used in combination with local anaesthetics for eye blocks. It increases the speed of onset and quality of block by enhancing penetration through fascial planes. It is manufactured as a powder for reconstitution and the dose for ophthalmology is 15 IU/ml. Allergic reactions to hyaluronidase have been reported but are rare.

N-methyl-D-aspartate (NMDA) antagonists
The NMDA receptor is activated by glutamate, an excitatory neurotransmitter that plays a key role in central transmission of pain signals. Ketamine blocks the open calcium channel on the NMDA receptor complex. Ketamine also acts on opioid receptors and may have a local anaesthetic effect. Ketamine, 0.7 mg/kg, has been used intrathecally but is often associated with a high incidence (up to 30%) of psychomimetic effects. This dose produces inadequate analgesia (though sufficient motor blockade) and should not be used as the sole anaesthetic agent. There have been reports of ketamine, 1 mg/kg, being used caudally as a sole analgesic, producing surgical and postoperative analgesia equivalent to that of bupivacaine. However, this dose was associated with more behavioural side-effects. The optimal dose of ketamine, when combined with local anaesthetics caudally, is 0.5 mg/kg. When used in combination with bupivacaine, ketamine prolongs the mean duration of postoperative analgesia up to 12 hours in children. However, the use of additives to caudals for paediatric day-care anaesthesia remains controversial and routine use is not recommended.

There have been some concerns about the neurotoxicity of intrathecal ketamine but this could be due to the preservatives (e.g. benzethonium chloride) used in commercial preparations. Ketamine is not readily available in the UK without preservatives.

Midazolam
Studies combining bupivacaine and midazolam in the epidural or caudal space have shown prolongation of the mean duration of analgesia in children and adults. Midazolam acts via the γ-amino-butyric acid (GABA)-benzodiazepine system in lamina 2 of the dorsal horn. Its analgesic properties may involve opioid receptors because its analgesic actions are antagonized by naloxone. In adults, midazolam, up to 50 µg/kg epidurally, provides significant postoperative analgesia for upper abdominal surgery. In children, midazolam combined with caudal bupivacaine in children significantly increases the duration of analgesia. This is not associated with prolonged sedation, respiratory depression or motor blockade, but its use is controversial.

Glucose
Glucose is added to local anaesthetic solutions to increase baricity. 'Heavy' bupivacaine contains dextrose, 80 mg/ml. There have been concerns that glucose makes solutions hyperosmolar, which may be neurotoxic. Hyperbaric local anaesthetic

delivered by a catheter may cause sacral pooling and be associated with cauda equina syndrome. However, glucose has not been implicated as the cause of transient neurological symptoms after spinal anaesthesia. Most animal and human studies show that intrathecal glucose is safe in concentrations up to 7.5%.[5] ◆

KEY REFERENCES

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FURTHER READING

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