THE PHARMACOLOGY OF LOCAL ANAESTHETIC AGENTS

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Classification

Local anaesthetic agents can be defined as drugs which are used clinically to produce reversible loss of sensation in a circumscribed area of the body. At high concentrations, many drugs that are used for other purposes possess local anaesthetic or membrane stabilising properties. These include Beta-adrenoceptor antagonists, opioid analgesics, anticonvulsants and antihistamines. Most of the clinically useful local anaesthetic agents consist of an aromatic ring linked by a carbonyl containing moiety through a carbon chain to a substituted amino group.

There are 2 classes of local anaesthetic drugs defined by the nature of the carbonyl-containing linkage group. The ester agents include cocaine, procaine, amethocaine and chloroprocaine, whilst the amides include lignocaine, prilocaine, mepivacaine and bupivacaine. There are important practical differences between these two groups of local anaesthetic agents. Esters are relatively unstable in solution and are rapidly hydrolysed in the body by plasma cholinesterase (and other esterases). One of the main breakdown products is para-amino benzoate (PABA) which is associated with allergic phenomena and hypersensitivity reactions. In contrast, amides are relatively stable in solution, are slowly metabolised by hepatic amidases and hypersensitivity reactions to amide local anaesthetics are extremely rare. In current clinical practice esters have largely been superseded by the amides.

Mode of Action

Local anaesthetics cause reversible interruption of the conduction of impulses in peripheral nerves. The primary electrophysiological effect of these compounds is to cause a local decrease in the rate and degree of depolarisation of the nerve membrane

such that the threshold potential for transmission is not reached and the electrical impulse is not propagated down the nerve. There is no effect on the resting or threshold potential, although the refractory period and repolarisation may be prolonged. These effects are due to blockade of sodium channels, thereby impairing sodium ion flux, across the membrane.

Most local anaesthetic agents are tertiary amine bases (B) that are administered as water soluble hydrochlorides (B.HCl). After injection, the tertiary amine base is liberated by the relatively alkaline pH of tissue fluids:

$$B.HCl + HCO_3 \rightleftharpoons B + H_2CO_3 + Cl^-$$
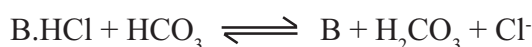
In tissue fluid the local anaesthetic will be present in both an ionised (BH$^+$) and non-ionised form (B); their relative proportions will depend on the pH of the solution and the pKa of the individual drug. The non-ionised base (B) then diffuses through the nerve sheath, perineuronal tissues and the neuronal membrane, to reach the axoplasm where it partially ionises again:

$$B + H^+ \rightleftharpoons BH^+$$

In the ionised form BH$^+$, the local anaesthetic enters the sodium channel (from the interior of the nerve fibre) and either occludes the channel or combines with a specific receptor within the channel that results in channel blockade.

In clinical practice, local anaesthesia may be influenced by the local availability of free base (B), as only the unionised portion can diffuse through the neuronal membrane. Thus, local anaesthetics are relatively inactive when injected into tissues with an acid pH (e.g. pyogenic abscess) which is presumably due to reduced release of free base.

Preparations of Local Anaesthetics

Most local anaesthetics are bases that are almost insoluble in water. Solubility is greatly increased by preparation of their hydrochloride salts which are usually dissolved in modified isotonic Ringer solutions. Dilute preparations of local anaesthetics are usually acid (pH range 4.0-5.5), and contain a reducing agent (e.g. sodium metabisulphite) to enhance the stability of added vasoconstrictors.

They also contain a preservative and a fungicide. The dilute preparations are presented as percentage solutions of local anaesthetic. For example lignocaine is available in 0.5, 1.0, 1.5 and 2% solutions for injection (with or without adrenaline). A solution expressed as 1% contains 1g of substance in each 100mls. The number of mg/ml can easily be calculated by multiplying the percentage strength by 10. Therefore a 1% solution of lignocaine contains 10mg/ml of solution. A 0.25% solution of bupivacaine has 2.5mg/ml.

Most local anaesthetics produce some degree of vasodilation, and they may be rapidly absorbed after local injection. Consequently, vasoconstrictors are frequently added, to enhance their potency and prolong their duration of action by localising them in tissues. In addition, vasoconstrictors decrease the systemic toxicity and increase the safety margin of local anaesthetics by reducing their rate of absorption (which is mainly dependent on local blood flow). Adrenaline is the most commonly used vasoconstrictor, it is added to local anaesthetic solutions in concentrations ranging from 1 in 80,000 to 1 in 300,000, although most are usually prepared to contain a 1 in 200,000 (5 microgram/ml) concentration of adrenaline.

Practical Point

Adrenaline 1:1000 contains 1 gram of adrenaline per 1000mls solution i.e. 1mg/ml.

To prepare a 1 in 200,000 solution the 1:1000 must be diluted 200 times. This is achieved by taking 0.1ml (= 0.1mg) and adding 19.9 mls of local anaesthetic solution.

The vasoconstrictor felypressin is added to some local anaesthetics (i.e. prilocaine) in a concentration of 0.003 i.u./ml. Felypressin is a non catecholamine vasoconstrictor that is chemically related to vasopressin, the posterior pituitary hormone.

The effect of vasoconstrictors on prolonging the duration of anaesthesia varies according to the local anaesthetic employed and the site of the injection. For example the duration of action of all agents is prolonged by the addition of adrenaline when used for infiltration anaesthesia and peripheral nerve blocks. Adrenaline also increases the duration of extradural anaesthesia when added to procaine,

mepivacaine and lignocaine but does not alter markedly the duration of action of extradural prilocaine, bupivacaine or etidocaine.

Adrenaline containing solutions should **never** be used for infiltration around end-arteries i.e. penis, ring block of fingers or other areas with a terminal vascular supply as the intense vasoconstriction may lead to severe ischaemia and necrosis. Maximum safe dosages are often quoted for local anaesthetics with and without vasoconstrictors (table 1), but such recommendations should be treated with caution as they ignore variations caused by factors such as the site of injection, the patient's general condition and the concomitant use of a general anaesthetic. For example if one assumes that a plasma concentration of lignocaine of 5 microgram/ml is required for the development of toxic symptoms, this would be achieved by the administration of approximately 300mg in the intercostal area, 500mg extradurally, 600mg in the region of the brachial plexus and 1000mg subcutaneously. Thus recommendation of a single maximum dose without regard to the site of injection is meaningless.

Table 1. Upper dose limits for commonly used local anaesthetic agents

	Plain solution mg/kg	**With adrenaline mg/kg**
Prilocaine	6	9
Lignocaine	3	7
Bupivacaine	2	2

The addition of adrenaline reduces the peak concentration in blood, but the degree of this reduction again depends on the site of injection and the specific local anaesthetic agent.

Clinical Uses of Local Anaesthetics

Local anaesthetic requirements and activity vary considerably. Selection of an appropriate agent in a specific situation requires knowledge of the clinical needs and pharmacological properties of the various anaesthetic drugs currently available (table 2).

Topical Anaesthesia

Local anaesthetics may be applied to the skin, the eye, the ear, the nose and the mouth as well as other mucous membranes. In general, cocaine, amethocaine, lignocaine and prilocaine are the most useful and effective local anaesthetics for this purpose. When used to produce topical anaesthesia, they usually have a rapid onset of action (5-10mins) and a moderate duration of action (30-60 mins). Cocaine is a potent vasoconstrictor and is useful in the reduction of bleeding as well as topical anaesthesia. Other local anaesthetic agents may be absorbed in significant amounts particularly after topical application to the more vascular areas, and fatalities have occurred after application of these agents to mucosal surfaces.

Absorption of local anaesthetics through intact skin is usually slow and unreliable and high concentrations (e.g. 20% benzocaine or 40% lignocaine) are required.

EMLA cream is a eutectic mixture of local anaesthetics which may be used to provide surface anaesthesia of the skin (particularly in paediatric practice). It is a mixture of the base forms of lignocaine and prilocaine in equal proportions in an emulsion. Cutaneous contact (usually under an occlusive dressing) should be maintained for at least 60 minutes prior to venepuncture.

Infiltration Anaesthesia

Infiltration techniques are used to provide anaesthesia for minor surgical procedures. Amide anaesthetics with a moderate duration of action are commonly used (lignocaine, prilocaine and mepivacaine). The site of action is at unmyelinated nerve endings and onset is almost immediate. The duration of local anaesthesia is variable. Procaine has a short duration of action (15-30 min), while lignocaine, mepivacaine and prilocaine have a moderate duration of action (70-140 min). Bupivacaine has the longest duration of action (approximately 200 min). The addition of adrenaline (1 in 200,000) will increase the quality and prolong the duration of anaesthesia.

Table 2.   Pharmacological effects and clinical uses of local anaesthetics

	Ester or Amide	Onset of Action	Duration of Action	Clinical Use	Properties
Procaine	Ester	Slow	Short	Limited Vascular Spasm Diagnostic procedures	Vasodilatation Allergenic
Amethocaine	Ester	Slow	Long	Topical anaesthesia Spinal anaesthesia	High systemic toxicity
Chloroprocaine	Ester	Fast	Short	Peripheral anaesthesia Obstetric extradural blocks	Low systemic toxicity
Mepivacaine	Amide	Fast	Moderate	Infiltration Peripheral nerve blocks	Versatile Moderate vasodilatation
Prilocaine	Amide	Fast	Moderate	Infiltration IVRA Peripheral nerve blocks	Methaemoglobinaemia at high doses Least systemic toxicity of amides
Bupivacaine	Amide	Moderate	Long	Infiltration Peripheral nerve blocks Extradural & spinal blocks	Separation of sensory and motor blockades
Etidocaine	Amide	Fast	Long	Infiltration Peripheral nerve blocks Extradural blocks	Profound motor blockade
Lignocaine	Amide	Fast	Moderate	Infiltration/Topical IVRA Peripheral nerve blocks Extradural and spinal blocks	Most versatile agent Moderate vasodilatation

IVRA : Intravenous regional anaesthesia

Conduction Anaesthesia

Conduction anaesthesia can be divided into minor nerve blockade (e.g. ulnar, radial or intercostal), and major blockade of deeper nerves or trunks with a wide dermatomal distribution (e.g. brachial plexus blockade). For each individual agent the duration of anaesthesia will be determined more by the total dose of the drug rather than the volume or concentration of drug used.

When amide local anaesthetics are used to produce minor nerve blockade, they have a relatively rapid onset of action (5-10min). Lignocaine, mepivacaine and prilocaine have a moderate duration of action (1-2 hr), while bupivacaine and etidocaine produce local anaesthesia for 2-6 hrs.

In major nerve blockade the onset is more variable, mainly due to anatomical factors which can delay or restrict the access of the local anaesthetic to its site of action. In general lignocaine, mepivacaine and prilocaine have a faster onset of action (10-15 min) than bupivacaine (15-30 min). Analgesia persists for 3-4 hr with lignocaine, prilocaine and mepivacaine, but up to 10 hrs with bupivacaine.

Extradural Anaesthesia

Local anaesthetic solutions are deposited in the epidural space between the dura mater and the periosteum lining the vertebral canal. The epidural space contains adipose tissue, lymphatics and blood vessels. The injected local anaesthetic solution produces analgesia by blocking conduction at the intradural spinal nerve roots.

The quality and extent of the blockade produced by each agent is determined by the volume as well as the total dose of the drug. The spread of local anaesthetic solutions may be more extensive in pregnant women as the volume of the potential space is reduced by venous engorgement in the epidural space. Enhanced effects may also be seen in the elderly and in patients with arteriosclerosis due to impairment of vascular absorption from the epidural space.

Bupivacaine (0.5%) or lignocaine (1.5-2.0%) are usually used to produce extradural anaesthesia. Repeated administration of lignocaine or mepivacaine into the epidural space may result in a diminished response with each subsequent dose (tachyphylaxis). This may be due to local changes in pH due to the relative acidity of these solutions. The reduction in pH may reduce the amount of free base available for diffusion across the neuronal membrane.

Spinal Anaesthesia

The introduction of local anaesthetic solutions directly into the cerebrospinal fluid (CSF) produces spinal anaesthesia. The local anaesthetics do not have to cross tissue or diffusion barriers and also the central attachments of the ventral and dorsal nerve roots are unmyelinated, which allows rapid uptake of the free base. There is a faster onset of action and a smaller dose is required. Spinal anaesthesia produces a similar clinical effect with a dose approximately ten times smaller than that needed for extradural anaesthesia.

Solutions of amethocaine (0.2%), lignocaine (5%), prilocaine (5%) bupivacaine (0.5%) and mepivacaine (4%) are commonly used to produce spinal anaesthesia. Prilocaine and mepivacaine have a slightly longer duration of action than lignocaine; bupivacaine has the longest duration of action.

In pregnancy, compression of the inferior vena cava by the pregnant uterus leads to distension of the vertebral venous plexus and reduces the volume of the subarachnoid space. Consequently the degree of blockade is enhanced and reduced doses are required.

Intravenous Local Anaesthesia

Intravenous regional anaesthesia (IVRA) is a useful method of providing analgesia for minor surgical procedures. The local anaesthetic agent is injected into a vein of a limb that has been previously exsanguinated and occluded by a tourniquet. The site of action is probably the unmyelinated nerve fibres, reached by retrograde spread in the vascular bed. The onset of action is almost immediate.

Lignocaine or prilocaine are commonly used and systemic blood levels of these agents are unlikely to be significant if the tourniquet is released more than 15 min after injection.

Bupivacaine and etidocaine **should never be used for IVRA!** They are significantly protein bound and once the tourniquet is released there is a risk of cardiotoxicity. Several deaths have been reported during IVRA with bupivacaine.

Toxicity of Local Anaesthetic Agents

Local anaesthetic agents are relatively free from side effects if they are administered in an appropriate dosage and in the correct anatomical location. However, systemic and localised toxic reactions may occur, usually from the accidental intravascular or intrathecal injection, or the administration of an excessive dose of the local anaesthetic agent. Systemic reactions to local anaesthetics involve primarily the central nervous system (CNS) and the cardiovascular system.

The initial symptoms of CNS toxicity involve feelings of light- headedness, dizziness and circumoral paraesthesia which may precede visual and/or auditory disturbances such as difficulty focusing and tinnitus (ringing in the ears). Other subjective CNS symptoms include disorientation and feelings of drowsiness. Objective signs of CNS toxicity are usually excitatory in nature and include shivering, muscular twitching and tremors initially involving muscles of the face and distal parts of the extremities. Ultimately, generalised convulsions of a tonic-clonic nature occur. If a sufficiently large dose, or rapid intravenous injection of local anaesthetic is given, the initial signs of excitation may progress very rapidly to generalised CNS depression and coma. Respiratory depression may result in respiratory arrest. CNS toxicity is exacerbated by hypercarbia and acidosis.

Cardiovascular toxicity usually occurs at doses and blood concentrations which are higher than those required to produce CNS toxicity. Local anaesthetics can exert a direct effect both on the heart and the peripheral blood vessels.

Extremely high concentrations of local

anaesthetics depress spontaneous pacemaker activity in the sinus node resulting in sinus bradycardia and sinus arrest. They also exert a dose - dependent negative inotropic action on isolated cardiac tissue. The more potent local anaesthetics depress cardiac contractility at lower concentrations than the less potent drugs.

Local anaesthetic agents appear to exert a biphasic effect on peripheral vascular smooth muscle. In lower doses they may increase peripheral vascular resistance, and in higher doses, reduce it. Cocaine is the only anaesthetic that causes vasoconstriction consistently because of its ability to inhibit the re-uptake of noradrenaline by storage granules at the synapse. The excess concentration of free circulating noradrenaline is responsible for the vasoconstriction associated with the use of cocaine. In general, a direct relationship exists between the anaesthetic potency and cardiovascular depressant potential of the various agents. The more potent drugs e.g. bupivacaine and etidocaine, have been reported to cause rapid and profound cardiovascular depression in some patients following accidental intravascular injection. Severe cardiac arrhythmias such as resistant ventricular fibrillation may occur.

Management of Acute Toxicity

The airway is maintained and oxygen administered by facemask, using artificial ventilation if apnoea occurs. Convulsions should be treated with anticonvulsant drugs such as thiopentone (150-250mg I.V.) or diazepam (10-20 mg I.V.) repeated as necessary. Profound hypotension and brady-arrhythmias should be treated with intravenous atropine (0.5 - 1.5mg) and colloid or crystalloid infusions as plasma expanders may be necessary. Occasionally adrenaline may be required for severe hypotension or bradycardia.

In patients with ventricular fibrillation due to bupivacaine toxicity, cardiopulmonary resuscitation should be continued for at least 60mins. Bretyllium may facilitate cardioversion.

Practical Use of Local Anaesthetic Agents

Example 1

A 70 kg male is scheduled for axillary block. The anaesthetist decides to use 30 mls of solution. He only has 2% plain lignocaine available. What should he do?

A 2% solution contains 20mg/ml lignocaine. The toxic dose of lignocaine is 3mg/kg without adrenaline added and 7mg/kg with adrenaline.

The maximum safe dose of lignocaine for this patient is 210mg without and 490 mg with adrenaline.

30mls of 2% plain lignocaine gives 600mg. The anaesthetist must therefore dilute the lignocaine and add adrenaline to it.

20 mls of 2% plain lignocaine contains 400 mg lignocaine which can be made up to a 30 ml solution with 10 mls N. Saline.

The adrenaline is 1:1000 i.e. 1mg/ml and he requires 1:200,000 i.e. 5 microgram/ml. Therefore for every 20mls of local anaesthetic solution he should add 0.1ml of 1:1000 solution; a total of 0.15mls for his 30ml mixture.

Example 2

A 6 year old child weighing 20kg is scheduled for hernia repair. The anaesthetist wishes to supplement general anaesthesia with an ilioinguinal block. He only has 0.5% plain bupivacaine. What should he do? Ideally he would wish to use at least 10mls of solution. The maximum dose of bupivacaine which can be given is 2mg/kg ie. 40mg.

10 ml of 0.5% solution should be diluted with 10ml normal saline to give 20ml 0.25% solution. 10 ml of this solution should be used to produce an ilioinguinal block.