Review of local anaesthetic agents

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The currently available local anaesthetic agents are capable of providing high quality nerve blockade in a wide variety of clinical circumstances. Our understanding of the mechanisms and consequences of toxicity is increasing rapidly. Knowledge of the chemistry of local anaesthetics has enabled clinicians to exploit the increased safety of single isomer agents. However, the extent, if any, of this improvement in toxicity has yet to be proven. Established toxicity may be very difficult to treat and no specific reversing therapy is yet available. Until this occurs it is essential that practitioners of regional anaesthesia maintain their knowledge base and skill in techniques of administration of local anaesthetic, are able to recognise impending disaster, and constantly update their skills in resuscitation.

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Local anaesthetic agents have a wide variety of applications. They are used as the backbone ingredients for local and regional anaesthetic techniques, in the treatment of acute pain during labour, and for analgesia in the operative and postoperative period. They are also used in the management of chronic pain where local anaesthetic injections may have a prolonged effect, and are used to aid diagnosis and management prior to neurolytic procedures. In addition to these well recognised analgesic nerve blocking functions, local anaesthetic agents also have a role in the diagnosis of suxamethonium apnoea (dibucaine test), the treatment of cardiac arrhythmias (lidocaine for ventricular arrhythmias), as mucosal vasoconstrictors of the upper airway (cocaine), to obtund the pressor response to tracheal intubation (intravenous lidocaine) and recreationally, as a drug of abuse (cocaine).

The origins of local anaesthesia date back to 1884 when Carl Koller, a young Viennese ophthalmologist, discovered that cocaine instilled into his own conjunctival fornix produced localised insensitivity to touch and injury.1 The subsequent evolution of use of local anaesthetics has seen a vast expansion in our knowledge of these drugs and in techniques of administration, although the agents themselves have changed comparatively less. Modern local anaesthetics are safer than their predecessors, but risks persist, and even the experienced practitioner using the correct dose may provoke a fatal reaction. The cornerstone of safe practice is a thorough understanding of the pharmacology and toxicity...
of the agents used, in particular, dose and concentration required, likely speed of onset and duration of action. Clinicians administering local anaesthetic agents must be capable of recognising impending toxicity, and have access to the equipment, current knowledge and skills to manage these events.

The physiology of nerve conduction

Impulses are conducted along nerves by the movement of sodium, potassium and calcium ions across the nerve membrane during a rapid event called an action potential. The altered distribution of these ions briefly reverses the electrical polarity of the membrane for 1-2 ms, generating small local electrical currents that are propagated along the nerve as a wave.

At rest, chemical and electrical gradients across the nerve membrane are established by ion channels, which may be passive, active or voltage-gated. Passive ion channels allow free leakage of ions across the membrane, although the movement is disproportionate with potassium moving more readily than sodium. Active Na/K ATPase channels pump sodium out of the cell in exchange for potassium, in a ratio of 3 sodium to 2 potassium ions. Consequently, chemical gradients are established with high extracellular sodium concentrations and high intracellular potassium concentrations. The active pumping of positively charged sodium ions out of the cell by Na/K ATPase, coupled with the rapid passive leak of positively charged potassium ions out of the cell along a concentration gradient, generates a resting electrical potential difference across the membrane, such that the inside of the cell is negatively charged (-70 to -90 mV) compared to the outside.

In addition to passive and active ion channels the membrane contains voltage-gated sodium channels, which may open or close depending on the membrane potential difference. Each consists of a pore forming $\alpha$-subunit and 1 or 2 $\beta$-subunits. The $\alpha$-subunit is composed of 4 domains (D1-4) which contain 6 helical trans-membrane segments (S1-6). When the nerve is stimulated this structure undergoes a series of conformational changes cycling through four functional states: resting, activated, inactivated and deactivated. Although highly complex the channel can be considered to have 2 functioning gates, an outer $m$ gate and an inner $h$ gate, whose state varies with the membrane potential. In the resting state (-70 mV to -90 mV) the outer $m$ gate is closed, but the inner $h$ gate is open. On stimulation of the nerve (activation) the outer $m$ gate opens. There is a rapid influx of sodium ions along an electro-chemical gradient and the membrane potential rises. If sufficient sodium channels open and the membrane potential rises above a threshold of around -60 mV, a widespread opening of sodium channels is triggered, resulting in a much more rapid influx of sodium ions such that the membrane potential may overshoot neutral to around +20 mV. This causes the inner $h$ gate to close, inactivating the sodium channel and preventing further sodium movement. The depolarisation of a section of membrane creates a potential difference relative to adjacent areas. This generates an electrical current and raises the membrane potential of these adjacent areas such that further depolarisation occurs. Consequently, a wave of depolarisation flows along the nerve propagating the original stimulus.

In the inactivated phase there is no inward movement of sodium through the voltage-gated channels, but continued active pumping of sodium out of the cell by the Na/K ATPase and leak of potassium through passive ion channels restores the membrane potential towards the polarised state. When the membrane potential reaches -60 mV the outer $m$ gate closes and the channel is deactivated. During the inactivated and deactivated state the nerve is refractory to further stimulation. This prevents rapid redepolarisation of that section of the axon and inhibits retrograde conduction of the impulse.

Mechanism of local anaesthetic action

Local anaesthetics block nerve conduction by reversibly binding with the D4-S6 part of the $\alpha$-subunit of the voltage-gated sodium
channels in the nerve membrane. This site of action is intracellular, requiring local anaesthetic to diffuse across the lipophilic lipoprotein membrane. Local anaesthetic is administered in an acidic solution that maintains the majority of the drug in the ionised soluble form. Once injected into the tissue it must be converted into the neutral unionised form in order to enter the nerve cell. The proportion of drug that is converted will depend upon the local anaesthetic pK_a and the tissue pH. Once inside the cell the lower intracellular pH regenerates the ionised form, which blocks the receptor within the sodium channel. Sodium influx is reduced and the upsurge in the membrane potential slows. If a sufficient number of sodium channels are blocked the threshold potential will not be reached and impulse conduction stops. The resting membrane and threshold potential remain the same, but the action potential is temporarily halted.

In addition to the action of ionised local anaesthetic on the intracellular portion of the sodium channel the unionised local anaesthetic also disrupts the intra-membrane portion of the channel. The local anaesthetic action is augmented by blockade of potassium channels, calcium channels and G-protein-coupled receptors. The degree of neuronal block is affected by the diameter of the nerve. Larger diameter fibres (touch/pressure/motor) require higher concentrations of local anaesthetic to achieve a given degree of block, compared with small myelinated fibres (pain afferents). As the block proceeds different sensory modalities are lost in the order of pain, temperature, touch, deep pressure then motor function.

The affinity of local anaesthetic for the sodium channel varies with the channel state, as conformational changes reveal or obscure the local anaesthetic binding sites. In general, affinity is highest when the sodium channel is open (activated or inactive), and least when the channel is closed (deactivated and resting). At very low frequencies of nerve stimulation low concentrations of local anaesthetic will produce a certain degree of block (termed tonic block). Increasing the frequency of stimulation allows greater amounts of local anaesthetic to access the binding sites so there is an increase in the degree of block (termed use-, phase- or frequency dependent-block). If the frequency of nerve stimulation is stopped the degree of block recedes. Currently, there is no evidence that this effect can be utilised to improve the quality of the block.

In addition to state-dependent differences in channel affinity there are differences in affinity between local anaesthetics. Lidocaine binds and dissociates rapidly from the channel, whereas bupivacaine binds rapidly, but dissociates more slowly. The stereo-isomers of bupivacaine have different dissociation rates with R-bupivacaine dissociating more slowly than the S-isomer. Clinically, these differences are relatively unimportant for neuronal block, but assume great significance for cardio-toxicity. Specialised excitable tissue in the heart initiates and conducts the electrical impulse that spreads through the myocardium and drives the cycle of contraction and relaxation. This process is mediated by voltage-gated sodium channels, which are blocked by local anaesthetics. Lidocaine binds and dissociates quickly so there is little chance of frequency-dependent block developing. However, bupivacaine, particularly R-bupivacaine, dissociates much more slowly allowing a more pronounced frequency-dependent block to develop. Cardiac impulse conduction is slowed and lethal arrhythmias, which are often refractory to treatment, may occur.

**Chemistry**

Local anaesthetic agents conform to a similar molecular configuration consisting of a lipophilic aromatic ring connected to a hydrophilic amine group (Figure 1). The linking chain may be used to classify the agents as an ester, amide, ketone or ether. Other molecules without this structure may also have local anaesthetic properties, but are not used clinically in this role (e.g. atropine, propranolol, amitryptiline, meperidine). Ester and amides have achieved popularity in clinical practice. Esters include cocaine, procaine,
Figure 1. — Local anaesthetic agents conform to a similar molecular configuration consisting of a lipophilic aromatic ring connected to a hydrophilic amine group.
2-chloroprocaine, tetracaine and benzocaine. Amides include lidocaine, bupivacaine, levobupivacaine, mepivacaine, etidocaine, prilocaine, ropivacaine and articaine.

Stereochemistry

Organic molecules containing a carbon atom connected to 4 different groups may exist in forms that are mirror images of each other. These 2 forms are called stereo-isomers. They may be differentiated according to the direction they deflect polarised light, and are labelled as either S-(−)-laevorotatory or R-(+)-dextrorotatory. Their physiochemical properties are usually identical but their effects on biological receptors can be dramatically different. Stereo-isomerism is found in bupivacaine, prilocaine, ropivacaine, etidocaine and mepivacaine. Most are marketed as racemic mixtures (equal proportions of each stereo-isomer), with the exception of levobupivacaine (S-bupivacaine) and ropivacaine (S-ropivacaine). These single isomer local anaesthetics have fairly similar local anaesthetic efficacy to their racemic mixtures, but possess useful differences in terms of their toxicity profiles. Using an animal model in 1972 Aberg showed that S-bupivacaine had reduced toxicity compared to R-bupivacaine.

Ionisation

Local anaesthetics are weak bases (pKₐ 7.6-8.9) with esters tending to have higher pKₐ values (Table I). They are poorly soluble in water and therefore constituted in acidic solutions (pH 3-6), where they exist as a mixture of charged cationic molecule and neutral base. The ratio of ionised to neutral base varies, following the Henderson-Hasselbach equation with the dissociation constant (pKₐ) of that local anaesthetic and the solution pH;

\[ \text{pH} = \text{pK}_a + \log [\text{base}]/[\text{acid}] \]

For a base pH=pKₐ+log [unionised]/ [ionised].

The pKₐ is constant for any local anaesthetic. It is the ambient pH that dictates the amount of each species present. Most current local anaesthetic agents have a pKₐ greater than physiological pH (7.4), so on injection into tissue the new equilibrium favours the ionised species. Consequently, a reduced amount is available to block the nerve. Agents with a low pKₐ are less ionised, so there is an increased proportion of neutral base available to penetrate the cell and speed the onset of action. Inflamed tissue has a lower pH so there is a greater ionisation and a reduction in efficacy.

Lipid solubility

Lipid solubility is important in determining the ability of a local anaesthetic to diffuse across the lipid rich nerve membrane and access target receptors. It is quantified in the laboratory by measurement of the relative distribution of the local anaesthetic between a reference aqueous phase (e.g. water or buffer at physiological pH) and a non-aqueous solvent phase (e.g. octanol, η-heptane, hexane). The distribution of the substance between these 2 phases enables calculation of a solvent partition coefficient. The higher the partition coefficient, the higher the lipid solubility, and the greater the local anaesthetic potency. In clinical practice, local anaesthetics with high lipid solubilities require the use of lower concentration solutions to achieve the same neuronal block (e.g. bupivacaine 0.25-0.5% cf prilocaine 1-4%).

Protein binding

Local anaesthetics bind to plasma (albumin, α₁-acid glycoprotein) and tissue proteins. Albumin is considered to be a high volume, low affinity site whereas α₁-acid glycoprotein is high affinity, but low volume. Protein binding has been shown to correlate well with the duration of action of local anaesthetics, but other factors also have a significant effect such as potency, dose administered, addition of vasoconstrictors,
vascularity of the tissue and rate of metabolism. However, the latter effect is probably less important than the rate at which they are removed from their target receptors. Protein binding may vary, increasing in trauma, major surgery, chronic inflammation, cancer, and uraemia. Conversely, protein binding decreases during pregnancy, in the newborn and with use of the contraceptive pill. As local anaesthetics are systemically absorbed the plasma level rises slowly. However, once protein sites have become saturated, which may occur rapidly after accidental intravenous injection, there may be a precipitous increase in plasma levels. This can quickly lead to severe cardiovascular and central nervous system (CNS) toxicity with few warning premonitory signs. A similar situation occurs when plasma pH falls. Local anaesthetic dissociates from the protein molecules causing a sudden rise in the free fraction.

**Vaso-activity**

Most local anaesthetics exhibit a biphasic effect on blood vessels with vasoconstriction at very low concentrations and vasodilatation at concentrations that are used clinically. However, there are significant differences between agents. Cocaine has an intense vasoconstrictor effect, used therapeutically to prevent bleeding during instrumentation of the upper airway. In addition, ropivacaine has a pronounced vasoconstrictor effect at low concentrations which may reduce the requirement for added vasoconstrictors. Isomer-specific differences have also been noted with greater vasoconstriction with L-bupivacaine compared to R-bupivacaine. In theory, marked vasoconstriction may have deleterious consequences following infiltration around end arteries, although this has never been reported.

**Absorption and distribution**

Intravenously administered local anaesthetic is initially distributed to highly perfused organs such as brain, kidneys and heart, followed by less well perfused tissues such as skin, skeletal muscle and fat. Local absorption into those organs will be affected by lipid solubility, pKₐ, protein binding as well as binding to other blood born sites (e.g. erythrocytes), tissue binding affinity and clearance, as well as patient factors such as cardiac output and metabolic status. The site of inject-
ed local anaesthetic has a significant effect on plasma levels with the highest peak levels from intercostal and caudal injections followed by lumbar epidural, brachial plexus, sciatic and femoral injections.\textsuperscript{16}

**Lung extraction**

A large proportion of local anaesthetic is extracted temporarily during the first pass through the lungs.\textsuperscript{17} This effect may be due to the lower pH of lung tissue relative to plasma, resulting in a degree of ion trapping. Consequently, the lungs are able to attenuate the toxic sequelae of accidental intravascular injections of local anaesthetic.\textsuperscript{18} In patients with right to left cardiac shunts this safety net is absent and there is an increased risk of toxicity. Following lung absorption the local anaesthetic is more slowly washed back into the circulation.

**Placental transfer**

Local anaesthetics are able to diffuse across the placenta, although ester local anaesthetics are hydrolysed rapidly in the blood, so do not cross the placenta in significant amounts. Amide local anaesthetics vary considerably in their speed of placental transfer and degree of foetal retention. Increased protein binding in the mother reduces the amount of local anaesthetic that is free and able to diffuse across the placenta. Conversely, the foetus has low levels of α\textsubscript{1}-acid glycoprotein so has a reduced concentration of local anaesthetic binding sites. In addition, foetal pH is lower than maternal, resulting in ion trapping of agents with higher pK\textsubscript{a} values.\textsuperscript{19} The distribution of local anaesthetics across the placenta has been demonstrated by measuring the ratio of the concentration of local anaesthetic in umbilical vein versus maternal arterial blood (bupivacaine 0.32, lidocaine 0.73, prilocaine 0.85). Less is known about transfer of local anaesthetic into breast milk although lidocaine has been detected in the breast milk of a parturient.\textsuperscript{20}

**Clearance**

Ester local anaesthetics undergo rapid hydrolysis in the plasma by non-specific esterases. The metabolites are inactive as local anaesthetics, but derivatives (p-aminobenzoic acid, PABA) can be allergenic. The speed of degradation lends a degree of safety as plasma levels fall quickly. Patients with atypical plasma cholinesterases may be at higher risk of developing toxicity due to slower or absent plasma hydrolysis. The exception to plasma hydrolysis is cocaine which undergoes a slower process of metabolism in the liver. Cocaine metabolites may be present in the urine for 24-36 h after administration.

Amide local anaesthetics are much more stable in blood than esters (half-life of lidocaine=approximately 90 min, procaine=6 min). They are cleared by hepatic metabolism with a minimal fraction by renal mechanisms (less than 1-6\%).\textsuperscript{11} Within the liver they undergo a complex process of biotransformation by microsomal enzymes (CYP450) followed by renal excretion. Phase I involves hydroxylation, N-dealkylation and methylation, followed by Phase II where the metabolites are conjugated with amino acids into less active and inactive metabolites. The rate of metabolism is highly dependent on liver blood flow, and differs between agents with prilo-
caine and etidocaine being the most rapid, lidocaine and mepivacaine intermediate, and ropivacaine and bupivacaine the slowest. The clearance of prilocaine exceeds that which would be possible by the liver alone indicating other sites of metabolism, most probably the lung.

Ester local anaesthetics

Cocaine

Cocaine (2-β-carbomethoxy-3-β-benzoxytropane) is an ester of benzoic acid and is found naturally in the leaves of *Erythro-xylon coca* or of *Erythroxylon truxillense*, which are indigenous to Bolivia and Peru. It is a colourless crystalline compound only slightly soluble in water, but soluble in most organic solvents. It has been used medically and recreationally for hundreds of years. In addition to its local anaesthetic actions on nerve membranes it is also able to block the re-uptake of norepinephrine at sympathetic neurones, potentiating the effects of catecholamines and causing intense vasoconstriction. It is used as a topical anaesthetic, as it is well absorbed from all mucous membranes. Currently, concentrations of 1-10% are used for procedures involving the nasal mucosa. Traditionally, cocaine is combined with epinephrine and bicarbonate as Moffet's solution to provide a vasoconstrictor solution. In overdose it produces hypertension, tachy-arrhythmias, tachypnoea, nausea and a myriad of central nervous system effects. Toxicity is enhanced by slower metabolism compared to other ester local anaesthetics.

2-chloroprocaine (Nesacaine)

The low potency of procaine led to the development in 1952 of 2-chloroprocaine (2-diethylaminoethyl-4-amino-2-chlorobenzoate). This agent was more lipid soluble, more potent and so required lower concentrations (2-3%). Clinically it has a rapid onset and relatively short duration of action. The original formulation of 2-chloroprocaine was highly acidic (pH 3.3). Large doses accidentally injected into the cerebrospinal fluid produced significant neurotoxicity. To reduce these injuries future formulations did not contain the preservative sodium metabisulfite.

Tetracaine (Amethocaine, Pontocaine)

Syntheitized in 1928 by Eisleb, tetracaine has a moderate onset of action and a prolonged duration. However, it was found to be significantly more toxic than procaine and, although used for spinal anaesthesia in some areas, in modern practice it's use is restricted to topical anaesthesia for ophthalmic procedures, amethocaine lozenges for painful oropharyngeal conditions and as ametop for topical anaesthesia of the skin. Ametop (Smith & Nephew Healthcare Ltd) is an aqueous cream preparation containing 4% tetracaine. It penetrates skin rapidly, but can cause severe skin reddening.

Benzocaine (Americaine)

Benzocaine (ethyl p-aminobenzoate) is a procaine derivative with no amino terminus. It is very poorly soluble in water so is used topically where it is very slowly absorbed. It is formulated in a gel or lozenges and is used in dentistry or for mucosal irritation.
Topical agents

Topical agents may be used to provide surface anaesthesia of mucous membranes, the cornea or the skin. Unlike injection techniques where local anaesthetic is placed directly into the tissue around the nerve, topical anaesthetics must cross tissue barriers to have their effect. This may be achieved by either using a drug with a low pKₐ value, ensuring generous proportions of the unionised base form are present, or using much greater concentrations of local anaesthetic than would be injected. In the UK agents that are used exclusively for topical anaesthesia are all esters and include tetracaine (Amethocaine), oxybuprocaine (Benzoxinate), proxymetacaine (Proparacaine) and benzocaine (Dequacaine). All except benzocaine are used in ophthalmology where they produce excellent topical anaesthesia. Clinical differences are stinging when dropped onto the eye (proxymetacaine least, tetracaine worst, oxybuprocaine in between), and corneal toxicity, which is worst with tetracaine. Benzocaine has a very low pKₐ value so even in acidic conditions it exists almost entirely in the unionised form and is able to penetrate mucous membranes. It is highly toxic and consequently is used only for topical anaesthesia in patients with painful superficial oropharyngeal conditions.

Amide local anaesthetics

Lidocaine (lignocaine, xylocaine, dalcaine, octocaine)

Synthesized by Lofgren and Lundqvist in Sweden in 1943, then introduced clinically in 1947, lidocaine (diethylaminoacetyl-2-6-xylidine) is a tertiary amide derivative of diethylamino-acetic acid. It has become one of the most widely used local anaesthetics across the world. In concentrations of 0.5-2% it produces a rapid onset of intense motor and sensory nerve blockade. Higher concentrations (5%) were used for spinal anaesthesia until reports of transient radicular irritation suggested these concentrations may be neurotoxic. However, there is laboratory data suggesting that even lower concentrations may result in neurotoxicity, although there are no data to support this in humans. Protein binding is relatively low so the duration of action is intermediate, and repeated injection may reveal tachyphylaxis. It is also used intravenously as a class 1b anti-arrhythmic agent. As a marker of its impressive safety intravenous lidocaine is often used in volunteer studies to familiarise the subjects with the symptoms of local anaesthetic toxicity, although even in the controlled environment of clinical research this safe local anaesthetic has resulted in a fatality.

Mepivacaine (carbocaine, polocaine, scandicaine, meaverin)

Mepivacaine [1-methyl-2-(2,6-xylylcarbamoyl)-piperidine] is the methyl derivative of N-alkyl pipercoloxylidine, and is structurally related to bupivacaine and ropivacaine. It was synthesized in 1956 by Ekenstam and Egner and was the second amide local anaesthetic to be introduced. Clinically, it has a fast onset, similar to that of lidocaine, but a longer duration due to a lack of vasodilator activity. Systemic toxicity is very low, but slow neonatal clearance rates have limited its use in obstetrics. The reliable safety record has ensured that mepivacaine in concentrations of 0.5-2% is a popular choice for a wide range of regional anaesthetic procedures including intravenous regional anaesthesia (IVRA).

Bupivacaine (marcaine, sensorcaine, carboslerin)

Bupivacaine [1-butyl-2-(2,6-xylylcarbamoyl)-piperidine] was introduced in 1963. It is the butyl derivative of N-alkyl piperoxylidine and is structurally related to mepivacaine and ropivacaine. It is a potent agent (commercial preparation concentrations 0.1-0.75%) with a slow onset, but despite this, is a popular choice due to its prolonged duration of action. Concerns about toxicity and difficulties in resuscitation with the higher concentrations of bupivacaine...
have led to the removal of 0.75% bupivacaine from obstetric anaesthesia. Similarly, the use of bupivacaine for IVRA is inadvisable.

**Levobupivacaine (chirocaine)**

Standard bupivacaine is a racemic mixture of two isomers. Both isomers have similar local anaesthetic efficacy, but the S-isomer has a safer side effect profile. There are animal and human volunteer data to show a reduction in central nervous system and cardiovascular toxicity with levobupivacaine, although in some studies the difference is relatively modest and much less than the difference between racemic bupivacaine and lidocaine. Despite the improved toxicity profile there have been reports of severe adverse reactions, and it is yet to be established whether these differences will be significant in clinical practice where toxicity often occurs though intravascular injection and massive overdose. Of note, European legislation states that the percentage w/v should be expressed in terms of the free base alone rather than the hydrochloride salt, which is the case with Marcaine. This difference in expressed formulation means that similar concentrations of levobupivacaine contain 11% more molecules than are found in the racemate. This may offset some of the measured advantages in terms of toxicity.

**Ropivacaine (Naropin)**

Synthesized in the 1950s, but not introduced clinically until 1996, ropivacaine (N-n-propyl-2,6-pipecoloxylidide) is the propyl derivative of N-alkyl pipecoloxylidine, the 3rd in the mepivacaine, bupivacaine series. It has a similar onset and duration of action as bupivacaine, but is less potent requiring concentrations of up to 1%. In low concentrations ropivacaine appears to have a differential sensory/motor block with a degree of motor sparing, although this disappears with the higher concentrations that are capable of providing a dense motor block. The preservation of motor function is appealing in areas where ambulation is desirable, such as on the labour ward or following surgery. The dual effect may be due to reduced lipid solubility, preventing ropivacaine from penetrating the larger Aβ fibres. However, the full explanation is likely to be more complex as the motor sparing differential block is not seen with other less lipid soluble agents.

Structurally, ropivacaine has an asymmetric carbon so forms racemic mixtures, although the commercial preparation is the purified S-isomer. This single isomer preparation has reduced cardiovascular and central nervous system toxicity compared to racemic bupivacaine, and adverse events following accidental intravascular injection may be easier to treat. Relative to other agents the toxicity of ropivacaine is intermediate between bupivacaine and lidocaine, although the toxicity advantage over bupivacaine is offset by reduced potency. Despite encouraging laboratory reports of improved safety, systemic toxicity has occurred.

**Etidocaine (Duranest)**

Etidocaine [2-(N-ethylpropylamino)-butyro-2,6-xylidine], was first described by Adams in 1972. It has a similar structure to lidocaine. Clinically, it has an equally rapid onset of action, but a much more prolonged duration. It produces a very intense motor block, thought to be due to high lipid solubility. Predictably, this confers high potency and concentrations of 0.25-1.5% are used. The profound motor block has prevented etidocaine from gaining popularity in obstetric analgesia where maintained ambulation is currently desirable.

**Prilocaine (Citanest, Xylonest, Distanest)**

Originally described by Lofgren and Tegner in 1960 prilocaine [N-(2-propylaminopropionyl)-O-toluidine] is a secondary amide analogue of lidocaine, with a similarly rapid onset, but longer duration. The O-toluidine structure lacks an aromatic methyl group, which are present on most other amides. Tissue uptake and metabolism are rapid so plasma levels fall quickly. This feature increases the safety profile of prilocaine, making it a popular choice for IVRA. Toxicity may be
manifest by the usual signs and symptoms of local anaesthetic overdose. In addition, ortho-toluidine, one of the breakdown products of prilocaine metabolism, is able to convert ferrous iron to ferric iron in haemoglobin, causing methaemoglobinaemia. Treatment is with high concentrations of oxygen and intravenous methylene blue (1 mg/kg). Neonates are particularly at risk because their red cells are deficient in methaemoglobin reductase. Interestingly, high doses of methylene blue (>7 mg/kg) may also cause methaemoglobinaemia.

Prilocaine is also found in EMLA (Eutectic Mixture of Local Anaesthetics), an oil/water emulsion containing 2.5% prilocaine and 2.5% lidocaine. Both constituents have a melting point considerably higher than body temperature, yet combined as a eutectic mixture they have a lower melting point (18 °C) than either substance separately. Room temperature is cool enough for EMLA to exist as a cream, which then liquefies slightly in contact with the skin. EMLA is able to penetrate the skin easily so is used extensively in pediatrics to reduce the pain of venepuncture. Caution must be exercised when using large amounts as methaemoglobinaemia has been described. Broken or inflamed skin should be avoided as absorption may greatly exceed that intended.

Articaine (Carticaine, Ultracaine, Septaneast, Astracaine)

Articaine [4-methyl-3-[2-(propylamino)propionamido]-2-thiophenecarboxylate], was synthesized in 1969 by Rusching, but not used clinically until the mid-1970s in Germany. Unlike other amide local anaesthetics articaine has a thiophene ring. This increases its lipid solubility to a value close to that of prilocaine and not surprisingly it is used in similar concentrations (2-4%). It has a low pKₐ and clinical studies have confirmed a rapid onset of action. Protein binding is high and a prolonged duration might be expected. However, unlike other amide local anaesthetics articaine contains an additional ester group, so that metabolism occurs in the plasma by non-specific cholinesterases as well as in the liver. The rapid offset of articaine has been demonstrated by Allman in ophthalmic blocks, where it may prove useful as ocular movement returns rapidly after the completion of surgery. In addition, the rapid fall in plasma levels will also reduce the risks of toxicity. However, in patients with known deficiency of plasma cholinesterases an alternative choice would be appropriate.

Toxicity

Local anaesthetics are safe drugs, but they have the potential to cause serious harm if used without caution. In 1979 Albright's editorial drew the attention of the anaesthetic community to the risks of intravascular injection of etidocaine and bupivacaine. He highlighted the unreliability of the aspiration test, the fact that cardiovascular collapse could occur without preceding hypoxia and that resuscitation may be difficult. Such severe reactions are rare, but can follow absorption of an inappropriately high dose, or accidental intravascular injection of an appropriate dose. The magnitude of the effect will depend on the toxicity of the drug, the dose administered, the speed and site of administration, as well as the physical status of the patient in terms of age, medical conditions and pregnancy. Methods to reduce the incidence of these events include careful techniques of needle placement, aspiration prior to every slow injection, the use of a test dose, fractionated doses, adequate time between doses, the use of a less toxic local anaesthetic, awareness of maximum doses in different settings, and the addition of other agents (opioids, clonidine, hyaluronidase, bicarbonate, epinephrine) to reduce the amount of local anaesthetic required.

When toxicity occurs the sequence of system involvement depends upon the route of administration and the speed at which toxic plasma levels occur. If plasma levels rise slowly the central nervous system (CNS) is affected first. Symptoms are generally excitatory, possibly due to inhibition of inhibitory neurons via GABA receptors. Patients may
report perioral and tongue paraesthesia, a metallic taste, and dizziness, then develop slurred speech, diplopia, tinnitus, confusion, restlessness, muscle twitching and convulsions. At higher plasma levels there is widespread sodium channel blockade with more generalised neuronal depression leading to coma. Treatment should be relatively straightforward and is aimed at maintaining oxygenation, fluids, vasopressors, inotropes with the use of anticonvulsants where appropriate.

Cardiovascular toxicity can be difficult to treat and usually follows CNS symptoms, unless the overdose has occurred by intravascular injection, when cardiovascular collapse may occur almost immediately. Imminent toxicity may be heralded by development of bradycardia, with a long PR interval and widened QRS complex. Increasing blood levels lead to varying degrees of block, the appearance of multi-focal ectopic beats, re-entrant arrhythmias, tachycardia and ventricular fibrillation. Similarly to CNS toxicity, treatment is supportive, relying on the use of oxygen, fluids, vasopressors, inotropes and anti-arrhythmics where needed. Amiodarone and bretylium may be useful, and there is evidence suggesting lipid emulsion infusions and clonidine may have a role. Circulatory arrest due to bupivacaine and etidocaine may be refractory to treatment, and as depression of neurological function induced by the local anaesthetic may have a neuro-protective role, resuscitation should be prolonged.

There is an increasing amount of laboratory data confirming the improved safety of the new single isomer local anaesthetics. Care must be taken in interpretation of some of these comparative studies as equal doses of drugs with differing potencies are administered. Nancarrow et al. administered toxic intravenous doses of bupivacaine, ropivacaine and lidocaine to sheep, and found a ratio of lethal doses of 1:2:9. Lidocaine treated sheep died with respiratory depression, bradycardia and hypotension, but without arrhythmias, whereas 3 of 4 bupivacaine treated sheep died after sudden onset of ventricular arrhythmias in the absence of hypoxia or acidosis. The ropivacaine treated sheep died in a similar way to the lidocaine treated sheep, but with the addition of ventricular arrhythmias, or as a result of the sudden onset of ventricular arrhythmias alone. The arrhythmias precipitated by local anaesthetics are a result of depression of the rapid depolarisation phase ($V_{\text{max}}$) of the cardiac action potential. This leads to slowed conduction with prolongation of the PR and QRS interval, allowing re-entrant rhythms and predisposing to ventricular tachycardia. Arlock quantified this effect by measuring $V_{\text{max}}$ in a guinea pig models, showing that bupivacaine depressed $V_{\text{max}}$ more than lidocaine, with ropivacaine intermediate.

The effects of arrhythmias on cardiac output are augmented by myocardial depression. The precise effects of different local anaesthetics on myocardial function may be confounded in whole animal models as local anaesthetic-induced convulsions are associated with cardiovascular stimulation. In an attempt to isolate the cardiovascular effects Chang et al. infused bupivacaine, levobupivacaine and ropivacaine directly into the coronary arteries of conscious sheep. No significant differences were found in survival or fatal doses, indicating that, unlike with intravenous infusions, when these agents are infused directly into coronary arteries they may have equal cardiac toxicity. Groban used an anaesthetised dog model to compare the arrhythmogenicity of bupivacaine, levobupivacaine, lidocaine and ropivacaine. No difference was found between bupivacaine or either of the single isomeric forms. In a similar experiment Morrison compared intracoronary injections of bupivacaine, levobupivacaine and ropivacaine in anaesthetised swine. Unlike Chang they found little difference in fatal dose between levobupivacaine and ropivacaine, but greater cardiotoxicity with racemic bupivacaine. Feldman et al. showed that similar doses of ropivacaine and bupivacaine caused convulsions in dogs, but that the mortality rate was lower in the ropivacaine treated animals. Isolated organ experiments have linked local anaesthetic toxicity in the brain with disturbances in the heart.
in results noted in these studies may be a result of species-specific differences in response or may be a reflection of the complex interplay between the CNS, the myocardium, and general anaesthesia during local anaesthetic toxicity.

The results from animal studies sometimes conflict, and translating these results to human subjects may not be appropriate. Consequently, healthy volunteer studies have compared the cardiovascular and CNS effects of intravenously infused local anaesthetics. Scott administered a maximum of 150 mg of ropivacaine and racemic bupivacaine to volunteers. Of the 12 subjects, seven tolerated the maximum dose of ropivacaine, whereas only 1 subject was able to tolerate 150 mg of bupivacaine. Plasma levels showed that CNS and cardiovascular symptoms occurred at lower plasma levels with bupivacaine than ropivacaine. In addition, myocardial depression and prolongation of the QRS interval were reduced with ropivacaine. Bardsley et al. used intravenous infusions of lidocaine to familiarise 12 healthy volunteers with the CNS effects of local anaesthetic toxicity. A few days later the volunteers received intravenous infusions of levobupivacaine or bupivacaine at a rate of 10 mg/min until they had received 150 mg, or had begun to experience CNS toxic effects. Cardiovascular monitoring demonstrated that, despite higher plasma levels, levobupivacaine depressed myocardial function significantly less than bupivacaine (mean [SD] stroke index –5.2 [7.4] ml · m⁻² · s⁻¹, 9.1 [8.4] ml · m⁻², p=0.001). Equal doses of intravenous levobupivacaine were compared with ropivacaine by Stewart et al. No differences were found in terms of CNS symptoms or cardiovascular effects. Animal and human volunteer studies have shown improved safety with levobupivacaine and ropivacaine in terms of convulsive threshold, arrhythmogenicity, myocardial depression and ease of resuscitation in comparison with racemic bupivacaine. Despite these advantages they may still provoke severe toxic reactions. In addition, the improved safety margin may be offset by reduced local anaesthetic potency, particularly with ropivacaine.

Allergy

Monk reported the first case of allergy to local anaesthetics in 1920. He described the development of contact dermatitis in the hands of a dentist who was repeatedly exposed to apothesin, an ester local anaesthetic. Further reports of mild hypersensitivity reactions followed, but very few patients developed anaphylaxis. The allergenic trigger was found to be para-aminobenzoic acid (PABA), which is generated as an intermediate metabolite on ester hydrolysis. Sensitivity to PABA may occur through exposure to ester local anaesthetics, or to cosmetics and foodstuffs that contain preservatives that are antigenically similar. In addition, sulphonamide substances structurally resemble PABA so cross reactivity may occur when sulphonamide sensitive patients are then exposed to ester local anaesthetics.

The development of amide local anaesthetics in the 1940s reduced reporting of allergic reactions. Allergy to amides is now recognised as being extremely rare, with some specialists estimating that less than 1% of reported allergic reactions to amide local anaesthetics represent true immune system mediated responses. Local anaesthetics are too small (<300 daltons) to be antigenic, but may bind to plasma or tissue proteins as a hapten that possesses antigenic properties. Reports of allergic reactions are commonly reported to have occurred in the dental chair following a local anaesthetic injection. In reality this is likely to have been a vasovagal response in a highly anxious patient in an upright dental chair. Alternatively, they may have received an intra-vascular injection of local anaesthetic containing epinephrine with surprising and unpleasant cardiovascular effects. However, although allergy to amide local anaesthetics is rare these reports must be taken seriously and appropriate investigations or referral organised. Allergists may perform skin prick testing for those with a history of mild allergy, or use laboratory in vitro tests (lymphocyte proliferation test) in patients with a history of anaphylaxis.
Local toxicity

Localised toxicity occurs following injection of local anaesthetic directly into a structure or when a structure is exposed to a high concentration for a prolonged period. Direct injection into a muscle provokes an intense inflammatory reaction resulting in areas of muscle necrosis, which is worsened by added vasoconstrictors. Healing may be accompanied by fibrosis and localised contracture, which is rarely significant, except in ophthalmic local anaesthesia where damage to delicate extra-ocular muscles may produce restrictive muscle defects resulting in symptomatic diplopia and the need for corrective strabismus surgery.

Reports of transient radicular irritation and conus medullaris syndrome following spinal anaesthesia with the use of 5% lidocaine, or where microcatheters were used for continuous spinal analgesia, have alerted anaesthetists to the potential problems of local anaesthetic-induced neurotoxicity. Although attributed to the use of highly concentrated local anaesthetic there is laboratory evidence that even clinically useful concentrations of lidocaine (2%) are able to cause neurotoxicity. Despite this unsettling evidence, neurotoxicity is rarely a clinical problem.

Future developments

Liposomes

None of the available local anaesthetics, in their current formulation, have a duration beyond a few hours. A slightly more prolonged action may be achieved by adding a vasoconstrictor, which reduces washout of the local anaesthetic. Where local anaesthetic action is required for days or weeks, an infusion device using a catheter and mechanical pump are required. However, the local anaesthetic reservoir and pump are often bulky devices, prone to technical problems, and the catheter and connections may be a significant source of infection. A possible solution is the development of liposomal preparations. Liposomes are small (0.03-10 µm) hollow spheres with a phospholipid bilayer wall. High concentrations of local anaesthetic solution in an aqueous medium can be encapsulated within the liposome. They are biocompatible, non-immunogenic and degrade slowly allowing gradual release of their contents. In addition, their relatively large size prevents dispersal away from the site of injection. The slow release of local anaesthetic prevents high peak plasma levels reducing the chances of systemic toxicity. Clinical studies with a variety of agents have shown promising prolongation of the duration of local anaesthetic action. The technology of liposomal local anaesthetics is exciting, with the prospect of a preparation comprised of a solution of fast acting local anaesthetic containing liposomes filled with long acting local anaesthetic agent ie fast onset and very prolonged duration. However, at present there are significant problems to be overcome to achieve a stable formulation, without batch to batch variations in physiochemical properties, and there is still relatively little data on the safety of these compounds in humans.

Butyl amino-benzoate

A new agent for nerve blockade is butyl amino-benzoate (BAB). Originally discovered in 1923 BAB has interesting properties. Unlike most current local anaesthetics it has a very low pKₐ and is poorly soluble in both aqueous and lipid mediums. Myelin and dural permeability is very limited. It appears to be selective for Aδ- and C- fibres so that it produces minimal motor block. It undergoes rapid hydrolysis, although the duration of block may be exceedingly prolonged (weeks). This is probably related to the formulation which has a slow release effect. It is suspended in polyethylene glycol and polysorbate-80 (Butamben) and has been demonstrated to produce a prolonged effect when administered via the epidural route in oncology patients. Consequently, it may provide a useful alternative to phenol or alcohol neurolysis.
Riassunto

Gli anestetici ad azione locale. Una review

Gli anestetici ad azione locale attualmente disponibili sono in grado di garantire un blocco nervoso di alta qualità in un’ampia gamma di circostanze cliniche. La nostra comprensione dei meccanismi e delle conseguenze della tossicità sta aumentando rapidamente. La comprensione della struttura chimica degli anestetici ad azione locale ha reso i clinici in grado di sfruttare l’aumentata sicurezza di singoli isomeri. Tuttavia, l’ampiezza, se esiste, di questo miglioramento della tossicità deve ancora essere provata. La tossicità nota può essere molto difficile da trattare e non è ancora disponibile alcuna terapia specifica invertente. Sino a che questo non accadrà è essenziale che i somministratori di anestesia regionale siano preparati ed abili circa le tecniche di somministrazione di anestetici ad azione locale, che siano in grado di riconoscere i disastri imminenti e che aggiornino costantemente la loro abilità nella rianimazione.

Parole chiave: Agenti anestetici - Anestetici locali - loro abilità nella rianimazione.

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