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Toxicity of local anaesthetics

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The complications of failure, neural injury and local anaesthetic toxicity are common to all regional anaesthetic techniques, and individual techniques are associated with specific complications. All potential candidates for regional anaesthesia should be thoroughly evaluated and informed of potential complications. Central neural blockades still account for more than 70% of regional anaesthesia procedures.

Permanent neurological injury is 0.02–0.07%. Pain on injection and paraesthesias while performing regional anaesthesia are danger signals of potential injury and must not be ignored. The incidence of systemic toxicity to local anaesthetics has significantly decreased in the past 30 years, from 0.2 to 0.01%. Peripheral nerve blocks are associated with the highest incidence of systemic toxicity (7.5 per 10 000) and the lowest incidence of serious neural injury (1.9 per 10 000).

Key words: local anaesthetics; cardiac toxicity; neurotoxicity; allergy; treatment.

Effective and reversible regional block is not possible without the use of local anaesthetics, but the administration of local anaesthetics carries the potential hazard of intravascular injection, inducing life-threatening central nervous system (CNS) and cardiovascular toxicity. The introduction of the new local anaesthetics levobupivacaine and ropivacaine, and the increasing interest in transient radicular syndrome, cauda equina syndrome and apoptosis, stimulated us to write this chapter.

We present and summarize literature on the toxicity of local anaesthetics, starting with a brief overview of the toxicity to the individual organ systems of the CNS and cardiovascular system. A description of the toxicity of each drug is then provided; this includes allergy, toxicity of additives and possible treatment of local anaesthetic toxicity.

LOCAL ANAESTHETICS IN GENERAL

The use of chemical substances for preventing or treating local pain had its origin in South America. It was known that CNS stimulation occurred among the natives of

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Peru who chewed the leaves of an indigenous plant (*Erythroxylon coca*). Attempts to isolate the active principle from the leaves finally resulted in the isolation of the alkaloid, cocaine, by Nieman in 1860. The clinical usefulness of cocaine was not appreciated until 1884, when Koller reported upon topical anaesthesia of the eye. The chemical identification of cocaine as a benzoic acid ester led to the synthesis of numerous drugs, which were basically benzoic ester derivates. In 1905, Einhorn reported the synthesis of procaine. Tetracaine, the most potent ester of the benzoic acid series, appeared in 1930. A major breakthrough in the chemistry of local anaesthetic agents occurred in 1943 when Loefgren synthesized lidocaine; this was not an ester but an amide derivate of diethylamino acetic acid. Concerning structure–activity relationships, local anaesthetic agents, in general, have the chemical arrangement: aromatic portion—intermediate chain-amide portion. Changes in the aromatic or amide portion of a local anaesthetic will alter its lipid/water distribution coefficient and its protein-binding characteristics, which, in turn, will markedly alter the anaesthetic profile.

The toxic effect of long-acting local anaesthetics on brain and heart, first reported by Albright, provided the initial stimulus to develop new amide-like local anaesthetics. The first of these drugs, which has come into clinical practice, was ropivacaine, the S-enantiomer of two possible optical isomers. It is structurally related to bupivacaine and mepivacaine, exerting a different pharmacodynamic profile, specifically on cardiac electrophysiology (less arrhythmogenic than bupivacaine). Studies on the anaesthetic activity and toxicity of the individual enantiomers of bupivacaine and mepivacaine generally indicate that the S-enantiomers are longer acting and less toxic than the R-enantiomers.[1]

MECHANISMS OF ACTION

When local anaesthetics reach and enter the sodium channels of nerves, they are able to interrupt nerve activity and a conduction block, occurs. For an effective conduction block, an estimated 75% of the sodium channels have to be inactivated.

Sodium channels exist in activated-open, inactivated-closed and rested-closed states during various phases of the action potential. In an activated or opened state, sodium channels are able to propagate impulses. Local anaesthetics bind to open channels and convert these into an inactivated or closed state.

The speed of entry and exit of local anaesthetics is agent-specific. Intermediate-acting agents (lidocaine, mepivacaine) have a short-in and short-out profile, and long-acting agents (bupivacaine) have a fast-in and slow-out profile.

Local anaesthetics can also bind to sodium channels which are in an inactivated state, but in this case binding is weaker.

In the case of myelinated nerve fibres, neural block can occur at the nodes of Ranvier by interrupting the propagation of a signal that occurs by depolarization jumping between adjacent nodes of Ranvier. Myelinated fibres are more susceptible to conduction block than are unmyelinated fibres because the blocking of two nodes increases the probability of impulse extinction, while blocking of three or more gives an almost certain extinction of impulses. Extinction of impulses in unmyelinated nerve fibres increases with the length of the fibre exposed to the agent.

Smaller fibres are more susceptible to blockade by local anaesthetic because, when myelinated, there is a shorter distance between the nodes, and, when unmyelinated, the length exposure is greater than with larger nerves.

MAXIMUM RECOMMENDED DOSES FOR LOCAL ANAESTHETICS

The maximum recommended doses of local anaesthetics presently applicable are as old as the drugs themselves and are based on observed or assumed toxic peak plasma concentrations. The main purpose of stating such doses is to prevent the administration of excessive amounts of drug, which could result in systemic toxicity.

The maximum doses recommended at present usually do not take into consideration the site of injection and factors which may influence tissue re-distribution, metabolism or excretion. Moreover, the recommended maximum dose also differs according to the technique used for local anaesthesia: (a) subcutaneous injection, (b) injections in regions of high absorption, (c) single injection (perineural, e.g. plexus), (d) protracted injection (catheter, combined techniques), (e) injection into vasoactive regions (near the spinal cord, spinal, epidural, sympathetic). This sequential categorization also underscores the need to select appropriate techniques as well as concomitant monitoring according to the technique of administration and to the expected and possible plasma level. Thus, the 'maximum recommended doses' by Niesel are low for zones of raised absorption and higher for techniques of protracted injection.[2]

In many recent textbooks, maximum recommended doses of local anaesthetics are avoided and recommended effective doses are given. On the other hand, leading textbooks contain recommended doses for local anaesthetics (Table 1).

In Europe, the most recent recommendations for bupivacaine have been cautious, and this is also reflected in the recommended doses for the newest local anaesthetics (Table 2).

The rate of local anaesthetic absorption in the circulation will be influenced by the vascularity of the injection site. This will conclusively influence the peak plasma concentration. Regardless of the local anaesthetic used, the rate of vascular absorption decreases in the order: interpleural, intercostal, caudal, epidural, brachial plexus, sciatic/femoral, spinal. Accordingly, the recommended dose of local anaesthetic will vary—with the exception of the subarachnoid space owing to its lack of vascularization. Injection in highly vascularized regions (e.g. scalp, trachea and bronchi) can involve a high risk of systemic toxicity—even after administration of the recommended doses—because of fast absorption.

In the elderly, deteriorating blood flow and organ function usually decrease the clearance of local anaesthetics.[4,5]

Peak plasma concentrations and plasma protein binding of local anaesthetics are similar in elderly people and young adults.[6,7] In the elderly, nerve axons are more

Table 1. Maximum doses of local anaesthetics in adults.

	Plain	+Adrenalin
2-Cloroprocaine	800 mg (11 mg/kg)	1000 mg (14 mg/kg)
Lidocaine	300 mg (4–5 mg/kg)	500 mg (7 mg/kg)
Prilocaine	500 mg (7 mg/kg)	600 mg (8.5 mg/kg)
Mepivacaine	300 mg (4–5 mg/kg)	500 mg (7 mg/kg)
Bupivacaine	175 mg (2.5 mg/kg)	225 mg (3 mg/kg)

Reproduced from Miller R (*Anesthesia*, 5th edn, 2000, Churchill Livingstone, Philadelphia).[3]

Table 2. Maximum dose of bupivacaine, levobupivacaine and ropivacaine in adults.

	Single dose[a]	Total dose in 24 hours
Bupivacaine	150 mg (2 mg/kg)	400 mg (5.5 mg/kg)
Levobupivacaine	150 mg (2 mg/kg)	400 mg (5.5 mg/kg)
Ropivacaine	225 mg (3 mg/kg)	800 mg (11 mg/kg)

Data from Pharmacia Fennica 2002, Finland.
[a]With or without adrenalin (epinephrine).

sensitive to the blocking action and smaller doses are required to achieve a sufficient block.[8] In very small children, toxicity related to continuous blocks may result from a less rapid clearance and less binding by plasma proteins.[9]

The clearance of local anaesthetics is not diminished in renal failure because they are inactivated in the liver (amides) or hydrolysed in the plasma (esters).

Synthesis of the local anaesthetic binding protein—1-acid glycoprotein (AAG)—in the liver is stimulated in renal failure,[10] offering some protection against systemic toxicity diminishing the free plasma fraction.

Decreased cardiac output (haemorrhage, heart failure, etc.) decreases the action of hepatic enzymes on amide agents in direct proportion to the decrease in liver blood flow. Cirrhosis of the liver decreases hepatic extraction of amide agents in proportion to the extent of hepatic parenchymal tissue loss.[11]

In end-stage pregnant patients, initial plasma concentrations may be higher than normal.[12] When there is a greater risk of toxicity, the reasons for a greater risk of toxicity of local anaesthetics during pregnancy include enhanced penetration of drugs through tissue membranes (hormonal), reduced plasma protein binding and increased cardiotoxicity caused by progesterone.[13]

Additionally, drug interactions can potentiate the toxicity of local anaesthetics. It is very risky to use lidocaine to treat cardiac ventricular arrhythmia induced by a local anaesthetic. The amide-linked local anaesthetics potentiate each other's systemic toxicity in an additive way.[14] The recommended dose—as well as the maximum dose—of a local anaesthetic should be defined specifically in relation to the type of block and the state of the patient (age, size, diseases). Owing to the common use of very potent and toxic pipecolyl xylidine derivates (rac-bupivacaine, L-bupivacaine, ropivacaine), such definitions are certainly clinically relevant.[15]

SYSTEMIC TOXICITY

Accidental direct intravascular injection during performance of high-volume peripheral nerve block or epidural anaesthesia with a local anaesthetic causes systemic toxicity owing to an excess plasma concentration of the drug. Less often, absorption of the local anaesthetic from the injection site results in an excess plasma concentration. The extent of systemic absorption depends on: (1) the dose administered into the tissue, (2) the vascularity of the injection site, (3) the presence of adrenalin (epinephrine) in the solution, and (4) physiochemical properties of the drug.

The addition of 5 μg of adrenalin (epinephrine) to every millilitre of local anaesthetic solution (1 : 200 000 dilution) decreases the systemic absorption of local anaesthetics by approximately one-third.[16]

The CNS and cardiovascular systems are the most prominent ones involved owing to the systemic toxicity of local anaesthetics.

TOXICITY OF LOCAL ANAESTHETICS TO THE CNS

Local anaesthetics decrease the electrical activity of excitable cells by inhibiting the conductance of sodium channels. At low doses, all local anaesthetics are effective anticonvulsants, which also have sedative effects. As the plasma level rises, excitation of the CNS occurs. In conscious, unsedated humans, the signs include light-headedness, dizziness, drowsiness, paresthesia of sight and sound, and acute anxiety or even fear of death.[17] With further increases, uncontrolled muscle activity occurs, which can evolve into tonic–clonic seizure activity and complete depression of conscious activity.

Not all local anaesthetics produce signs of aura, such as drowsiness or excitement, before the onset of seizures. With the highly lipophilic, highly protein-bound agents, such as bupivacaine, the excitement phase can be brief and mild, and the first signs may be bradycardia, cyanosis and unconsciousness.[18] In contrast, cocaine rapidly induces euphoria and intense sensory stimulation. The extent of protein binding is related to the intensity of excitation: intensity is greater for agents which are less protein bound.

After a seizure most of the time CNS depression is followed. This can be with respiratory depression and cardio vascular depression. A possible explanation of seizures is the unopposed excitation of pathways due to depression of the inhibitory cortical neurones in the temporal lobe or the amygdala. Depolarization is facilitated by hyperkalaemia and thus markedly increases local anaesthetic toxicity. Conversely, hypokalaemia decreases local anaesthetic toxicity.

The long-acting local anaesthetics levobupivacaine and ropivacaine are less toxic than bupivacaine to the CNS judging by the larger doses tolerated before the onset of seizures.[19–22] This may be clinically important because CNS effects may be involved in the production of serious cardiotoxicity because of the onset of respiratory failure accompanied by hypoxia, bradycardia and acidosis.

NEUROTOXICITY

Placement of solutions containing local anaesthetics into the epidural or subarachnoidal space can cause neurotoxicity. This is increasingly recognized.[22] Local anaesthetics can induce growth cone collapse and neurite degeneration in the growing neurones.[22]

The ability of local anaesthetics to induce neuronal apoptosis (programmed cell death) has been shown in several models and with different local anaesthetics, especially cocaine.[23–25] Mepivacaine was safer than lidocaine, bupivacaine and ropivacaine for the primary cultured chicken neurones.[22]

Clinically, the spectrum of neurotoxicity of local anaesthetics may range from patchy groin numbness and persistent isolated myotomal weakness to cauda equina syndrome.[26]

Since the 1990s, subarachnoid administration of lidocaine has been the subject of controversy following its implication in numerous cases of neurological complications. The clinical pictures described in the literature are cauda equina syndrome, which is associated mainly with continuous subarachnoid anaesthesia through microcatheters, and transitory neurological symptoms, also termed radicular irritation syndrome and associated with single injections.[27]

Permanent neurological injury after regional anaesthesia is a very rare event.[28]

Transient radicular irritation

Moderate to severe pain in the lower back, buttocks and posterior thighs that appears within 24 hours after complete recovery from spinal anaesthesia can be a manifestation of transient radicular irritation of the lumbosacral nerves.[29] The symptoms will usually last for 5–7 days until full recovery.[30]

Early reports suggested that neurotoxicity is dose-dependent, but the incidence is similar after intrathecal placement of 1 ml/kg of either 5 or 2% lidocaine in 7.5% glucose.[31,32]

Mepivacaine 4% has also been associated with transient radicular irritation.[33,34] Spinal anaesthesia produced with 0.5% bupivacaine or 0.5% tetracaine is associated with a lower incidence of transient radicular irritation compared with lidocaine.[33,35–37]

Cauda equina syndrome

The literature reveals a clearly higher incidence of transitory neurological symptoms with lidocaine than with other local anaesthetics. Although the underlying mechanism remains unclear, the main hypothesis is that the neurotoxicity is due to lidocaine itself, or to the malpositioning of the paravertebral musculature resulting from extreme relaxation. The various factors that can lead to neuropathy have been widely described in the many articles reporting complications. Arthoscopy and lithotomy positions are significantly related to the appearance of symptoms, as are early ambulation or the use of small-gauge needles or pencil-point needles.[27] Symptoms can range from sensory anaesthesia, bowel and bladder sphincter dysfunction to paraplegia.

Anterior spinal artery syndrome

The combination of a sudden lancinating radicular pain, paresthesia, selective pain and temperature sensory loss, and preserved tactile sensation, followed by flaccid paralysis, is strongly suggestive of acute anterior spinal artery syndrome (ASAS).

First described by Spiller in 1909, thrombosis of the anterior spinal artery is often due to fracture of a cervical vertebra, or a cervical hyperextension injury. Pregnancy and the postpartum induce a hypercoagulable state, and Caesarean section increases the risk of venous thromboembolism. Occlusion of the anterior spinal artery by thrombosis has been reported.[38]

In the last 2 years, ASAS has been reported in two young women after Caesarean section.[38,39]

As this is a very rare event, it may be difficult to distinguish it from events caused by spinal cord compression produced by an epidural abscess or haematoma.

TOXICITY OF LOCAL ANAESTHETICS TO THE CARDIOVASCULAR SYSTEM

Toxic responses in the cardiovascular system occur when anaesthetics are at higher levels in the blood compared with the levels that cause toxic responses in the CNS.

Plasma concentrations of lidocaine <5 μg/ml have no toxic effects on the heart. However, plasma concentrations of 5–10 μg/ml of lidocaine, or equivalent concentrations of other local anaesthetics, may produce profound hypotension. This is caused by decreased systemic vascular resistance and cardiac output due to relaxation of arteriolar vascular smooth muscle and direct cardiac depression.

Local anaesthetics block cardiac sodium channels. In high concentrations, this causes cardiac toxicity, while at low concentrations an antidysrhythmic effect is produced.

The effects of local anaesthetics on calcium ion and potassium ion channels and local anaesthetic-induced inhibition of cyclic adenosine monophosphate (cAMP) production may also contribute to cardiac toxicity.[40] Local anaesthetics also demonstrate a rank of order of avidity for displacing ligands from beta2-adrenergic receptors such that larger molecules displace ligands at lower concentrations than do smaller local anaesthetic molecules. This relationship between molecular size and receptor avidity could explain the greater propensity for cardiovascular toxicity of local anaesthetics with relatively large molecules—such as bupivacaine.[40]

The recognition that long-acting local anaesthetics, particularly bupivacaine, were disproportionately more cardiotoxic than their shorter-acting counterparts stimulated the development of the bupivacaine congeners, ropivacaine and levobupivacaine. These agents, like all local anaesthetics, can produce cardiotoxic sequelae with direct and indirect mechanisms that derive from their mode of local anaesthetic actions, i.e. inhibition of voltage-gated ion channels.

While all local anaesthetics can cause direct negative ionotropic effects, ropivacaine and levobupivacaine are less cardiotoxic than bupivacaine judging by the larger doses tolerated in laboratory animal preparations and humans before the onset of serious cardiotoxicity (particularly electromechanical dissociation or malignant ventricular arrhythmias). Thus, compared with bupivacaine, the newer agents may be seen as 'safer' but they must not be regarded as 'safe'.[41]

Selective cardiac toxicity

Cardiac toxicity can occur after accidental intravascular injection of local anaesthetics, especially bupivacaine. Bupivacaine has an advantage over other local anaesthetics because of its long-acting sensory anaesthesia; however, because of its high affinity for the myocardial Na^+ channel, it can be cardiotoxic. Cardiac toxicity is related to a plasma concentration of 0.5–5 μg/ml that can depress cardiac conduction and contractility consequent to an accidental intravascular injection. Electrophysiological studies have shown that bupivacaine inhibits both Na^+ and L-type Ca^{2+} channels in cardiac cells, but the contribution of each component to cardiac arrhythmia or depressed contractility is still not completely understood. Electrophysiological studies have also demonstrated that the racemic mixture of bupivacaine induces alteration in the genesis and conduction of cardiac action potentials predisposing to re-entry ventricular arrhythmias.[42]

In the article of Zapata-Sudo et al.,[42] a significantly increased P–R interval and QRS duration was found for R(+) bupivacaine compared with S(−) bupivacaine. Also, a reduced recovery from complete AV block was found for R(+) bupivacaine compared with S(−) bupivacaine. Lack of total recovery from cardiotoxicity is one of the most important disadvantages of racemic bupivacaine in comparison of other amide-type local anaesthetics.[42]

Cardiac toxicity of local anaesthetics is more pronounced in some conditions. There is, for example, some discussion of whether pregnancy may increase sensitivity to the cardiotoxic effects of bupivacaine, more than ropivacaine, as emphasized by the occurrence of cardiopulmonary collapse with a smaller dose of bupivacaine in pregnant animals compared with non-pregnant animals.[43,44] However, in 1999, Santos et al. concluded that levobupivacaine was similar to bupivacaine and ropivacaine in causing haemodynamic changes in the pregnant ewe at the same plasma levels.[45] In 2001, they disagreed with their prior opinion, concluding that the risk of toxicity is greatest with bupivacaine and least with ropivacaine.[21]

The threshold for cardiac toxicity produced by bupivacaine may be decreased in patients being treated with drugs that inhibit myocardial impulse propagation (beta-adrenergic blockers, digitalis preparations, calcium channel blockers).[46] In the presence of propanolol, atrioventricular heart block and cardiac dysrhythmias occurred at plasma bupivacaine concentrations of 2 to 3 μg/ml.[47]

Caution must be exercised when bupivacaine is used for patients who are on antidysrhythmic drugs or other cardiac medications. Adrenalin (epinephrine) and phenylephrine may increase bupivacaine cardiotoxicity, reflecting bupivacaine-induced inhibition of catecholamine-stimulated production of cAMP.[48]

All local anaesthetics depress the maximal depolarization rate of the cardiac action potential (V_{max}) by virtue of their ability to inhibit sodium ion influx via sodium channels. In isolated papillary muscle preparations, bupivacaine depresses V_{max} considerably more than does lidocaine, whereas ropivacaine is intermediate in its depressant effect on V_{max}.[43,49]

The resulting slowed conduction of the cardiac action potential manifests on the electrocardiogram as prolongation of the P–R and QRS intervals and re-entry ventricular cardiac dysrhythmias. Dissociation of highly lipid-soluble bupivacaine from sodium channel receptor sites is slow, accounting for the drug's persistent depressant effect on V_{max} and subsequent cardiac toxicity.[50] In contrast, less lipid-soluble lidocaine dissociates rapidly from cardiac sodium channels and its cardiac toxicity is low. The critical point is that lidocaine molecules can unbind from the sodium-channel between action potentials, but bupivacaine cannot, resulting in accumulation.

Ropivacaine is a pure S-enantiomer that is less lipid-soluble and less cardiotoxic than bupivacaine but more cardiotoxic than lidocaine.[51]

Tachycardia can enhance frequency-dependent blockade of cardiac sodium channels by bupivacaine, further contributing to the selective cardiac toxicity of this local anaesthetic.[52]

Recent studies showed that direct cardiac myocyte toxicity by apoptotic cell death in the adult and fetal heart muscle and coronary artery endothelial cells can be caused by cocaine.[53–55] This could be a possible explanation for heart failure and ischaemic myocardial infarction especially when cocaine is used.

In addition, the local anaesthetic's toxic CNS effects may be involved in the production of serious cardiotoxicity because of the onset of respiratory failure accompanied by hypoxia, bradycardia, hypercarbia and acidosis.

ALLERGY TO LOCAL ANAESTHETICS

A true immunological reaction to a local anaesthetic is rare. Although there is an unfortunately large number of patients presenting to anaesthesiologists with a history of 'allergy to local anaesthetics', this is frequently due to the systemic effects of absorbed adrenalin (epinephrine) that are falsely interpreted as 'allergy'.

It is estimated that less than 1% of all adverse reactions to local anaesthetics are due to an allergic mechanism.[56]

Systemic and cellular reactions are the most important reactions of the body. Systemic exposure can create circulating antibodies, and repeat exposure can cause anaphylaxis, which is a reaction to a substance mediated by the immune system (IgE). This is usually related to repeated exposure to a particular agent or to another agent with chemical similarity.

Some cross-reactivity exists between procaine, penicillin and the ester group. Cell-mediated immunity occurs with the sensitization of cells and leads to a localized response to exposure known as contact hypersensitivity. The great majority (80%) of allergic events involving systemic or contact hypersensitivity to local anaesthetics involve contact hypersensitivity.[57]

Local anaesthetic molecules are too small to be antigenic. However, they readily bind to proteins, and the protein–local anaesthetic complex can behave as an antigen.

Contact hypersensitivity to a eutectic mixture of lidocaine and prilocaine (EMLA) has also been reported.[58]

Cutaneous manifestations, including erythema and urticaria, can precede the systemic signs, causing diagnostic problems of anaphylaxis during neuraxial anaesthesia by the similarity of the initial presentation of anaphylaxis to the onset of sympathetic blockade during central axis regional anaesthesia.[59]

The differential diagnosis for allergy to local anaesthetics is complex. Atopic individuals may be more likely to have a true allergy to local anaesthetics.

Additives, preservatives and compounds can create an allergy that is not caused by the primary local anaesthetic.

Esters are associated with a higher incidence of allergic reactions, due to a *p*-aminobenzoic acid (PABA) metabolite. Amide agents do not undergo such metabolism. However, preservative compounds (methylparaben) used in the preparation of amide-type agents are metabolized to PABA. Patients who are allergic to ester local anaesthetics should be treated with a preservative-free amide local anaesthetic. If the patient is not allergic to ester local anaesthetics, these agents may be used in amide-sensitive patients. In the rare instance of hypersensitivity to *both* ester and amide local anaesthetics, or if skin testing cannot be performed, then alternative therapies—including diphenhydramine, opioids, general analgesia or hypnosis—can be used.[60]

COCAINE

In addition to blocking sodium channels, cocaine produces sympathetic nervous system stimulation by blocking the presynaptic re-uptake of noradrenalin (norepinephrine) and dopamine, thus increasing their synaptic concentrations. Due to this blocking effect, dopamine remains at high concentrations in the synapse and continues to affect adjacent neurones, producing the characteristic cocaine 'high'.[61,62] Chronic exposure to cocaine is postulated to affect adversely dopaminergic function in the brain due to dopamine depletion.

Acute cocaine administration is known to cause coronary vasospasm, myocardial ischaemia, myocardial infarction and ventricular cardiac dysrhythmias, including ventricular fibrillation.[63] Associated hypertension and tachycardia further increase myocardial oxygen requirements at a time when coronary oxygen delivery is decreased by the effects of cocaine on coronary blood flow. Even incidental cocaine use can result in myocardial ischaemia and hypotension for as long as 6 weeks after discontinuing cocaine use.[64,65]

Presumably, even delayed episodes of myocardial ischaemia are due to cocaine-induced coronary arterial vasospasm. In animals, chronic cocaine exposure sensitizes the left anterior descending coronary artery to catecholamines, even in the absence of circulating cocaine, resulting in vasoconstriction.

Cocaine-abusing parturients are at higher risk for interim peripartum events such as hypertension, hypotension and wheezing episodes.[66]

Halothane synthesizes the myocardium to the effects of catecholamines. Cocaine and amphetamines cause sympathetic hyperstimulation, and there is a risk of both cardiovascular and CNS effects, including cardiovascular collapse and convulsions.

Cocaine produces dose-dependent decreases in uterine blood flow that result in fetal hypoxaemia.[67] Cocaine may produce hyperpyrexia, which could contribute to seizures. Unexpected patient agitation in the perioperative period may reflect the effects of cocaine ingestion.[68] There is a relationship between the recreational use of cocaine and cerebrovascular accidents.[69]

The most commonly cited maximum dosage for cocaine is 200 mg for an average adult (about 3 mg/kg). Reported lethal doses range from 22 mg (sublingual) to 2500 mg (subcutaneously) in various case reports.[70] The toxicity of cocaine is related to the local anaesthetic action in the CNS, the vasoconstrictive properties and its action on catecholamine metabolism. The excitation and euphoria evolve into dysphoria, tremor and seizure activity in a dose-dependent manner.

In contrast to other local anaesthetic agents that cause sedation before toxicity, cocaine increases acetylcholine use in the animal cerebral cortex and causes agitation and increased motor activity.[71] Concentrations exceeding 20% may be excessively toxic and should be avoided for all applications.[70]

The range between the clinical dose and the toxic range is narrow. Peak plasma levels after intranasal application can be expected to occur within 30–60 minutes from application.[72] The plasma levels can be decreased if the agent is applied in increments, separated in time, as opposed to all at once,[73] taking advantage of the rapid plasma hydrolysis of the ester agent.

The vasoactive property of cocaine induces peripheral vasoconstriction at minimal plasma levels. This can cause hypertension. The first effect of cocaine on the coronary circulation is weak vasodilation when injected into the canine coronary circulation.[74] A direct effect on coronary smooth muscle after this vasodilation can result in coronary vasospasm,[75] and this can cause myocardial ischaemia and infarction even in very young patients.[76,77] Cocaine-induced cardial infarction can occur in patients with normal coronary anatomy and probably involves a combination of vasospasm, increased myocardial oxygen demand and coronary thrombosis.[78] When angiography was performed after a cocaine-induced myocardial infarction in a young adult, the finding was coronary thrombosis not amenable to angioplasty.[79] Even therapeutic levels used for topical nasal anaesthesia are associated with decreased coronary blood flow, mediated by α-adrenergic stimulation, which is accompanied by increases in myocardial oxygen demand and increases in a dose-dependent manner.[75] In contrast with bupivacaine-induced cardiac toxicity, lidocaine may reverse the sodium channel blocking properties of cocaine, and could be therapeutic during cocaine toxicity.[80]

Apoptosis (programmed cell death) has been shown to play an important role in the pathogenesis of several diseases in the heart, including heart failure and ischaemic myocardial infarction. The role of apoptosis in the toxic effect of cocaine has been investigated and recent studies indicate that cocaine causes apoptotic cell death in both adult and fetal heart muscle, suggesting a new way of understanding the cardiotoxic effects of cocaine.[53]

Adjunctive catecholamine sensitivity has been associated with the combination of ketamine and topical cocaine, which should probably be avoided.[76] Coronary vasospasm induced by cocaine is maximal at sites of coronary anatomy with narrowing by arteriosclerosis, because of increased sensitivity at these sites, further increasing the risk of myocardium in these vessel distribution, which are already at risk.[81] Acute vasculitis can result from cocaine abuse, and cerebral vasculitis has resulted in cerebral infarction or cerebral haemorrhage.[82] The vasoconstrictive properties of cocaine can cause damage to nasal mucosa and cartilage, but chronic use is probably required for this degree of cytotoxicity to occur.[83]

Clouding of the cornea by repeated use of cocaine eye solutions has been reported, which is probably related to vasoconstriction.[84] Severe corneal ulceration has been reported as a consequence of combined topical and intravenous cocaine abuse.[85] Cocaine abuse has been associated with rhabdomyolysis and renal failure, presumably from the extreme vasoconstriction that can occur with large doses.[86]

Further toxicity from cocaine results from its prevention of re-uptake of catecholamines into peripheral storage vessels. Progressive increases in plasma catecholamines can cause hypertension, tachycardia and arrhythmia. In addition to increases in circulating catecholamines, cocaine predisposes to arrhythmia by sodium channel blockade within the myocardium, which predisposes to re-entrant arrhythmia.[87] Increased aortic baroreceptor sensitivity also occurs.[88] The hypertensive response to significant blood levels was not as strong when the cocaine was administered with an opioid base during deep general anaesthesia.[89] This is not true with halothane as the primary general anaesthetic agent because halothane sensitizes the myocardium to the effects of catecholamines, and cocaine causes increased catecholamine levels for an extended interval.[72] In animals receiving halothane anaesthesia, plasma levels of cocaine reduced the arrhythmogenic dose of adrenalin (epinephrine) by as much as 50%.[90] Drug interactions with antidepressants also confuse this issue, with increased arrhythmogenicity and hyperdynamic response possible in patients taking tricyclic antidepressants and monoamine oxidase inhibitors.[72,91] The hyperdynamic state and the massive stimulation of the sympathetic nervous system can result in cardiogenic pulmonary oedema.[92]

Seizures associated with cocaine intoxication are serious clinical problems requiring immediate and adequate treatment; however, their mechanism has not been fully elucidated. In contrast to early views, in which convulsion properties of cocaine were ascribed predominantly to the effect of this drug on voltage-dependent sodium channels, recent reports put much emphasis on the interaction of cocaine with GABAergic and glutamatergic systems. Accordingly, pharmacological studies demonstrated that cocaine-induced seizures were efficiently inhibited by GABA-A receptor agonists and *N*-methyl-D-aspartate (NMDA) receptor antagonists, whereas sodium and calcium channel blockers were ineffective. An involvement of serotonin 5-HT2, dopamine and sigma receptors in cocaine-induced seizures has also been proposed. Furthermore, adaptive changes in various neuronal systems following cocaine-induced seizures have been vigorously investigated. Some of those changes, such as expression of immediate early genes and an increase in neuropeptide biosynthesis, may play a compensatory anticonvulsive role. However, other alterations, for example, up-regulation of NMDA receptors, may increase susceptibility to seizures.[93]

An additional problem to the toxic response of high systemic levels of cocaine is a potent respiratory depressant effect.[94]

On the basis of previously reported co-localizations and the relationship between cannaboid and dopamine receptors, Hayase et al. examined the effects of cannaboid receptor agonists against cocaine-induced toxic behavioural symptoms, including seizures. Their data support the previously reported close correlation between dopamine and cannaboid receptors, and between cannaboid agonists, especially amandamide, and glutamate (NMDA) receptors. Furthermore, their results suggest a potential therapeutic role for cannaboid agonists against toxicity induced by cocaine and other types of convulsant.[95]

MEPIVACAINE

Pharmacological features of mepivacaine are: its amide structure (therefore not detoxified by circulating plasma esterases); its rapid metabolism, which takes place in the liver; and its rapid excretion via the kidneys. Clinically, mepivacaine shows: short onset time (very similar to that of lidocaine); intermediate duration and low toxicity. Mepivacaine can therefore be considered as a first-choice agent for peripheral nerve blocks, particularly in high-risk cardiac patients.[96]

In a pilot study, even patients with end-stage chronic renal failure were able to receive brachial plexus anaesthesia with 650 mg plain mepivacaine without manifestations of serious systemic toxicity despite high concentrations of mepivacaine in the plasma.[97] With regard to toxicity, mepivacaine has often been compared with lidocaine. Comparable volumes and concentrations for achieving epidural or peripheral conduction block are desirable, but published reference sources suggest that mepivacaine has higher toxicity on an mg/kg basis. Maximum recommended doses are as much as 20% less for mepivacaine; suggested maximum doses are 400 mg without adrenalin (epinephrine) and 500 mg with adrenalin.

On the other hand, most reported doses of mepivacaine used for conduction block reach or exceed the maximum recommended doses, without apparent toxicity.[98–103]

High levels of mepivacaine in plasma (like those of lidocaine) cause a depression of heart rate and mean arterial pressure by direct effects on the myocardium.[104] As with all local anaesthetics, addition of vasoconstrictor reduces the peak plasma level.[105] Also, the direct myotoxic effect of mepivacaine—which leads to cellular destruction in rats[106]—is shared with other local anaesthetics. Moreover, bupivacaine appears to create myelotoxicity by suppressing muscle protein synthesis through inhibition of amino acylation of RNA.[107,108] Lack of a human correlate or other evidence of mepivacaine cytotoxicity above and beyond any local anaesthetic in clinical concentrations makes these data difficult to interpret.

The free plasma fraction of mepivacaine is increased by coincident lidocaine infusion by competition for binding sites.[109]

CHLOROPROCAINE

Chloroprocaine is one of the most rapidly metabolized local anaesthetics. It is metabolized by ester hydrolysis with a very short plasma half-life (less than 30 seconds). Therefore, high concentrations can be used with large volumes and minimal risk of toxicity. Doses of chloroprocaine in the 800–1000 mg range are reported to be without evidence of toxicity. Caution should be exerted when such doses are accidentally injected intravascularly. Owing to the very short half-life, slow and incremental dosing has even less toxicity. Exaggerated toxicity has been reported in a patient with a deficiency in plasma cholinesterase.[110]

Some direct cytotoxic effect is suggested, but only with very high doses.[111] A high percentage of patients treated with intravenous chloroprocaine reported venous irritation and urticaria after release of the tourniquet. This could be explained by the pH of the substance.[108,112]

TETRACAINE

Tetracaine is a chemical derivative of procaine with a lower pK_a and considerably higher lipid solubility, potency and duration of anaesthesia. It is used as a local anaesthetic for topical and spinal application. Arbitrary dose limits of 100 mg of tetracaine for the average-sized adult have a historical basis.

Campbell and Adriani investigated the application of tetracaine to mucous membranes. Application to the mucous membrane of the trachea resulted in the most rapid and highest peak level of anaesthesia, with levels approaching those of direct intravenous injection.[73]

Carmeliet et al. showed a dose-dependent depression of myocardial contractility, which occurs at very high plasma levels of tetracaine.[113]

Several investigators have shown the nerve injury in association with intrathecal injection of tetracaine. Adams et al. showed that intrathecal 2% tetracaine in rabbits caused small foci of degeneration in the nerve roots and superficial white matter of the spinal cord in two of four rabbits when they injected the drug through a needle inserted between the last lumbar and first sacral vertebrae.[114] Ready et al. showed that only high concentrations of tetracaine (8%) caused central necrosis within the spinal cord in rabbits, as well as subpial vacuolation at the surface of the spinal cord, whereas 1, 2, 4 and 8% tetracaine caused damage to the cauda equina with axonal degeneration when they injected the drug at the S1/S2 interspace.[115]

However, the precise lesions and pathological characteristics produced by neurotoxicity of tetracaine are not well demonstrated. The study of Takenami et al.[116] showed that intrathecal tetracaine induced histopathological changes in the spinal cord in rats, which were characterized by axonal degeneration with macrophage infiltration at the posterior roots near their entry into the spinal cord. They emphasized that their results cannot be extrapolated directly to clinical settings. Neurotoxic lesions in the present study were produced by much higher concentrations of tetracaine compared with the doses used clinically. Tetracaine is used clinically at a concentration $< 1\%$, and this concentration did not cause any damage in these rats. Therefore, tetracaine seems to be safe at the concentrations used clinically. However, toxic effects may appear under certain conditions, such as pooling of tetracaine in a restricted area.

In addition, rats and humans may have differences in sensitivity or vulnerability of the nervous system to tetracaine. For example, rats injected with 0.5% tetracaine showed a spontaneous recovery and were able to move within 1 hour after administration, whereas patients receiving the same concentration of tetracaine typically did not recover for at least 2 hours. Therefore, one may hypothesize that neurotoxic changes observed in rats injected with $>3\%$ tetracaine might also appear in humans treated with clinical concentrations.[116]

Saito et al. reported that slow-term exposure to tetracaine produced irreversible changes in growing neurones. Growth cones were quickly affected, and neurones subsequently degenerated.[117]

LIDOCAINE

The site of injection influences the absolute amount, as with other agents, but maximum doses of 500–600 mg or 7–8 mg/kg are considered safe.

Blood levels lower than 5 μg/ml are unlikely to result in toxicity. Obviously, absorbance of lidocaine decreases when adrenalin (epinephrine) is added to the local anaesthetic. Concentrations as low as 1/450 000 are effective in decreasing blood levels of lidocaine from epidural administration.[118] Protein binding of lidocaine is intermediate, and toxicity is slightly increased when plasma proteins are decreased. Toxicity is also increased in the presence of acidosis, which decreases plasma protein binding.[108,119] Liver disease increases the potential for toxicity. Hepatic dysfunction decreases its metabolism, therefore increasing the potential for toxicity.

Higher plasma levels result after comparable doses in patients with chronic renal failure. Fortunately, in these patients, clinical doses for conduction block do not routinely cause CNS toxicity.[120] Toxicity with lidocaine is reduced during the use of nitrous oxide and further reduced by concomitant use of benzodiazepine, which raises the seizure threshold.[121]

Cardiac toxicity with lidocaine is possible, but it is uncommon at clinically used doses. At levels toxic for the dog's CNS, lidocaine is a stimulant of the cardiovascular system.[122]

In significant plasma doses, lidocaine has a direct myocardial effect.[123] Due to the relaxation of arteriolar smooth muscle, lidocaine also has a peripheral vasodilatory effect.[124] In dogs, very high levels of lidocaine in the plasma induces pulmonary vasoconstriction, which accentuates the cardiac depression that occurs at these levels.[108,125] In a recent case report, Sawyer and von Schroeder presented an unknown side-effect of lidocaine. These authors described a case of temporary bilateral blindness in an otherwise healthy young female patient as a result of an acute toxic overdose of lidocaine. Fortunately, no long-term neurological or visual sequelae were seen.[126]

PRILOCAINE

Prilocaine is in contrast to lidocaine, rapidly hydrolysed so that its toxicity should be reduced. The allowable dose to avoid toxicity to the CNS is 20–30% higher with prilocaine than with lidocaine.

With its equipotency to lidocaine, and its virtual lack of vasodilator action, one could suggest that prilocaine is an underestimated drug.

Metabolism of prilocaine produces *o*-toluidine, which is able to reduce haemoglobin and can therefore produce methaemaglobin if maximum doses of 600 mg are exceeded. Spontaneous reversal of this process occurs by the action of reduced nicotinamide adenine dinucleotide-dependent methaemoglobin reductase within erythrocytes (red blood cells).[127]

A possible cyanosis can be effectively treated with methylene blue (1 mg/kg), although the therapeutic effect could be too short for all the methaemaglobin to be converted to haemaglobin because of the quick clearance of methylene blue.

Fetal haemaglobin is more sensitive to oxidation, and prilocaine should therefore not be used for epidural block during labour.

ETIDOCAINE

Etidocaine is an amide derived from lidocaine. It may be even longer acting than bupivacaine and its most characteristic difference from other agents is its ability to produce intense motor blockade.

Due to its high plasma protein binding (94%), the small portion which is unbound to protein may limit the amount that will cross the placenta. Therefore, there is a possible use in Caesarean section. On the other hand, the free fraction (non-protein bound) of etidocaine increases during labour, and this could be the explanation for serious cardiac toxicity with etidocaine, as with bupivacaine, reported in labour and delivery.[128]

Etidocaine has, like bupivacaine, a high lipid solubility, and potential selective cardiac toxicity could be comparable due to equal fast-in, slow-out sodium-channel kinetics. The maximum doses of etidocaine are 2–3 mg/kg or 200–300 mg. It has a high degree of lipid solubility[122] and therefore a high potential for CNS toxicity. In a volunteer study, etidocaine was compared with bupivacaine and was found to be less likely to create CNS aura, even at maximum infused doses.[129]

In a study with dogs, the interval between a convulsive dose and a lethal dose was slightly higher with etidocaine than with bupivacaine.[130]

Reported cases of cardiotoxicity with etidocaine, compared with bupivacaine, are much fewer, but symptoms are similar, showing re-entrant arrhythmias (ventricular tachycardia, fibrillation) requiring prolonged resuscitation.

BUPIVACAINE

Bupivacaine is still the most widely used long-acting local anaesthetic in surgery and obstetrics. It has been associated with potential fatal cardiotoxicity, particularly when accidentally given intravascularly.

According to recent literature, bupivacaine is less safe than other long-acting local anaesthetics, especially with regard to cardiac toxicity. This literature will be discussed later in the chapter in relation to the newer long-acting local anaesthetics.

The maximum recommended dose for bupivacaine is the lowest of all available local anaesthetics at 1–2 mg/kg (150 mg).

Decreasing plasma levels and increasing the time interval to maximum levels is achieved by the addition of adrenalin (epinephrine).[131]

Bupivacaine has selective cardiac toxicity within the sodium channels of the myocardium. Like etidocaine, bupivacaine enters the sodium channel rapidly during the action potential (systole) but exits from the sodium channel slowly during recovery (diastole), with the potential for accumulation. This mechanism is called fast-in, slow-out kinetics.

Recovery during repolarization is not long enough for the exit of bupivacaine.[49] Accumulation increases if heart rate increases because diastolic time decreases. The net effect is a delay in conduction within the primary cardiac conduction system, most evident at the atrioventricular node.[132]

In case of a re-entrant arrhythmia, as serious manifestation of bupivacaine cardiac toxicity, resuscitation can be difficult. Prolonged advanced cardiac life support measures are required.[133]

In many patients, the aura of CNS toxicity, as a clinical sign of accumulation in the plasma, does not occur at all with bupivacaine.[134,135]

Although convulsion was found to precede cardiovascular collapse with intravenous bupivacaine in dogs[136] and monkeys,[137] this may not be the case in all humans—especially if pre-medicated. The systemic signs are related to the free plasma fraction, which remains extremely low until the binding sites are fully occupied. When no more sites for protein binding are available, the free fraction in the plasma rises rapidly, and toxicity can occur. When benzodiazepines are used to raise the seizure threshold, or for anxiolysis, they can displace bupivacaine from protein-binding sites and abruptly increase the free plasma fraction, suddenly increasing the potential for CNS toxicity.[108]

Accentuation of bupivacaine cardiotoxicity must also be considered in patients taking chronic medications that depress cardiac function, such as beta blockers, calcium channel blockers[138] and cardiac glycosides.[46]

Lidocaine, phenytoin and bupivacaine are sodium-channel blockers. Lidocaine displaces bupivacaine from its receptor on the sodium channel. However, lidocaine does not seem to decrease bupivacaine toxicity because QRS duration was significantly increased by adding phenytoin or lidocaine to bupivacaine. These drugs should not be used to treat the manifestations of bupivacaine toxicity.[139]

Adrenalin (epinephrine) or noradrenalin (norepinephrine), as strong, direct-acting inotropes with cardiostimulant and peripheral vasoconstrictive properties, may be the most effective treatment for mechanical depression of the myocardium.[140]

Recent studies have found that insulin and glucose rapidly reversed haemodynamic abnormality in dogs with bupivacaine-induced cardiac depression. This implies a possible clinical application of insulin treatment for bupivacaine-induced cardiac depression.[141] Decreased protein binding, and therefore increased free fraction, as physiological changes in pregnancy in the last trimester, enhances the cardiac toxicity in the parturient.

LEVOBUPIVACAINE

In the early 1970s, it had already been shown that L-bupivacaine was considerably less toxic, both intravenously and subcutaneously, than its opposite enantiomer in the mouse, rat and rabbit, without any apparent loss of local anaesthetic potency.[142] According to these models, levobupivacaine was, therefore, shown to have a superior safety margin over dextrobupivacaine.

Since then, a wide range of studies have been conducted with levobupivacaine. Investigation of the occurrence of atrioventricular block and ventricular fibrillation or cardiac arrest during infusion of racemic bupivacaine or its isomers in equal doses in the isolated, perfused rabbit heart, showed that the R-isomer appeared to be the most toxic, the S-isomer had the lowest toxicity and the racemate had intermediate toxicity.[143] These findings were analogous to those for prolonged AV conduction in isolated guinea-pig hearts.[132] The R-isomer reduces the rate of depolarization and recovery in guinea-pig papillary muscle more readily than does the S-isomer.[144]

Further studies compared the in-vitro effects of levobupivacaine, ropivacaine and racemic bupivacaine on guinea-pig papillary muscle and human ventricular myocytes. All three agents produced similar negative inotropic effects, but bupivacaine had a greater excitatory effect than the other two.[145]

Direct injection of levobupivacaine, ropivacine and racemic bupivacaine into the coronary arteries of pigs found only few differences between levobupivacaine and ropivacaine, but greater toxicity with bupivacaine.[146]

Studies on sheep showed that levobupivacaine produced fewer and less severe arrhythmias and convulsions than bupivacaine at the same dose.[147] Direct intravascular injection of levobupivacaine in conscious sheep produced fatal cardiac toxicity at doses significantly greater than those found in previous studies with bupivacaine.[148] Fetal toxicity is relatively low, as infusion of small doses (2.6 mg/kg as total dose over 1 hour) of bupivacaine, levobupivacaine and ropivacaine at equal rates into pregnant ewes showed no adverse fetal effects or any significant pharmacokinetic differences between drugs, although only racemic bupivacaine caused a significant maternal bradycardia.[45]

Thus, there is evidence from multiple sources that ropivacaine and levobupivacaine have similar cardiac toxicity, while both produce less toxicity to the CNS and heart than does racemic bupivacaine.[149]

Clinical studies have been conducted using surrogate markers of both cardiac and CNS toxicity. In these studies, levobupivacaine or bupivacaine was given by intravascular injection to healthy volunteers. Levobupivacaine was found to cause smaller changes in indices of cardiac contractility and the QRS interval of the electrocardiogram, and also to have less depressant effect on the electroencephalogram.[150]

Pre-clinical studies in humans are a 'blunt instrument' in their ability to distinguish significant differences between these drugs because of the relatively small doses that can be used. Nevertheless, available evidence from human studies corroborates the pre-clinical studies on laboratory animals.[41]

ROPIVACAINE

Ropivacaine is the newest long-acting, enantiomerically pure (S-enantiomer) amide local anaesthetic, designed by modification of an existing one. Chemically, it is very similar to bupivacaine and mepivacaine. All of these three anaesthetics come from the family of molecules known as pipecolyl xylidines, which combine the piperidine ring of cocaine with xylidine from lidocaine. Substitution of methyl, butyl and propyl groups on the piperidine ring give rise to mepivacaine, bupivacaine and ropivacaine, respectively.

The high level of potency and lipid solubility of ropivacaine suggests a CNS toxicity profile similar to that of bupivacaine.

Studies on anaesthetized rats showed that the cumulative doses of levobupivacaine and ropivacaine that produced seizures were similar and were larger than those of bupivacaine.[19]

The predicted cardiac toxicity profile of ropivacaine has been extensively studied, and animal studies confirm an arrhythmogenicity of ropivacaine that is intermediate between that of mepivacaine and bupivacaine.[151]

The cumulative doses of levobupivacaine that produced dysrhythmias and asystole were smaller than the corresponding doses of ropivacaine, but they were larger than those of bupivacaine. Ropivacaine-induced cardiac arrest was more susceptible to treatment than that induced by bupivacaine or levobupivacaine.[19]

Another study on rats concluded that ropivacaine, even at equipotent dose, is less toxic than bupivacaine.[20]

In rabbits and pigs, an indication was found that ropivacaine is less cardiodepressive and arrhythmogenic than bupivacaine.[152,153]

In a comparative study on pregnant and non-pregnant ewes, the conclusion was made that pregnancy increases the risk of convulsions, but not of more advanced manifestations of local anaesthetic toxicity, and that the risk of toxicity is greatest with bupivacaine and least with ropivacaine.[21]

Thus, ropivacaine, according to animal data, is less neurotoxic and cardiotoxic than bupivacaine. Based on available clinical data, ropivacaine appears to be as effective and well tolerated as bupivacaine, when equianalgesic doses are compared, and to block nerve fibres involved in pain transmission (A delta and C fibres) to a greater degree than those controlling motor function (A beta fibres).[154–156] The greater degree of separation between motor and sensory blockade seen with ropivacaine relative to bupivacaine at lower concentrations (approximately 5 mg/kg) will be advantageous in certain applications.[157]

COMPLICATIONS OF ADDITIVES

Vasoconstrictors

Adrenalin (epinephrine) and other vasoconstrictors have been added to local anaesthetics in order to prolong the duration of action. This was initially designed for spinal anaesthesia, where it prolonged the duration of anaesthesia by 30–50%, but after a while it was also used for other sites of regional anaesthesia. Other benefits of adding vasoconstrictors are their role as marker for intravasal injection and their ability to decrease vascular absorbance of highly toxic agents or high volumes of less toxic agents. Decreased blood loss during use in highly vascularized regions of skin or mucus membranes is another frequently used side-effect of vasoconstrictors during local anaesthesia.

Conclusively, the most important reason for adding vasoconstrictors to local anaesthetics is prolongation of their duration of action and, simultaneously, a reduction in their toxicity.

Miyabe et al. have investigated the effect of adrenalin (epinephrine) on the absorption of lidocaine and the accumulation of monoethylglycinexylidide (MEGX) during continuous epidural anaesthesia in children. They concluded that the reduction in potential for systemic toxicity by the addition of adrenalin to lidocaine is limited because the reduction of the sum of the plasma concentrations of lidocaine and its active metabolite MEGX is small and is limited to the initial phase of infusion.[158]

Preservatives

Preservatives are structurally similar to *p*-aminobenzoic acid, the common metabolite of the ester class, and a known allergen.

An allergic reaction after the use of a local anaesthetic may be due to methylparaben or similar substances used as preservatives in commercial preparations of ester and amide local anaesthetics.

Most cases of true allergy involve agents from the ester class. Cross-reaction with the amide group is very rare, and preservatives such as methylparaben should be suspected.

TREATMENT OF SYSTEMIC TOXICITY DUE TO LOCAL ANAESTHETICS

The best treatment for toxicity due to local anaesthetics is prevention, because most of such systemic reactions result from unintentional intravascular injection. Aspiration via the needle before injection, and addition of adrenalin (epinephrine) as an intravascular marker, can increase the safety of local anaesthesia.

When adrenalin (epinephrine) is added to the solution, heart rate increases after injection and the total dose administered can be minimized. This is the rationale behind the epidural test dose advocated by Moore and Batra.[159]

Toxic response in the CNS always precedes possible cardiovascular collapse, so most anaesthesiologists focus on managing seizures as an indication of toxic response in the CNS during the treatment of systemic toxic reactions. Many anaesthesiologists reflexly reach for sedatives or hypnotics at the onset of seizure activity, and it is known that barbiturates as well as benzodiazepines effectively treat many seizures induced by local anaesthetics.[133,160–164]

Doses of these sedatives and hypnotics are important because their associated myocardial depression appears to add to that induced by the local anaesthetic.[164]

Some authors have suggested that a key to successful treatment of CNS toxicity induced by local anaesthetic is the provision of oxygen and the use of succinylcholine, if needed, to allow adequate oxygenation.[165] Critics of this approach suggest that the succinylcholine simply masks local-anaesthetic-induced seizures, whereas Moore et al. emphasized that one of the reasons for using succinylcholine is to minimize the rapid development of acidosis that results from motor seizures which accompany CNS excitation induced by the local anaesthetic.[166,167]

Hypoxaemia, acidosis and hyperkalaemia are among the first physiological problems needing correction.

Despite sufficient information about the best treatment of cardiovascular toxicity, the use of either adrenalin (epinephrine) or noradrenalin (norepinephrine) could be used to sustain heart rate and blood pressure.

One study implied a possible clinical application of insulin treatment for bupivacaine-induced cardiac depression. The authors found that insulin and glucose rapidly reversed haemodynamic abnormality in dogs with bupivacaine-induced cardiac depression.[141] Furthermore, atropine may be useful for treating bradycardia; direct current cardioversion is often successful, and ventricular arrhythmias are probably better treated with bretylium than with lidocaine. Cardiopulmonary bypass may be a useful adjunct to resuscitation. Amiodarone has been recently classified as a level II b (alternative intervention) therapeutic intervention for VF and VT arrhythmias by the American Heart Association and the European Resuscitation Council.[168] Therefore, it could be a useful alternative for the treatment of therapy-resistant tachyarrhythmias—also caused by toxicity of local anaesthetics. Some recently published case reports demonstrate that it is effective for the treatment of tachyarrhythmias caused by other agents and causes.[169–171]

Practice points

- what are the highest dosages of local anaesthetics that you can use for peripheral nerve block, epidural anaesthesia and spinal anaesthesia?
- which local anaesthetic has specific cardiac toxicity?
- what is the recommended treatment of cardio- and neurotoxicity?

Research agenda

- it is still not totally clear how high we can go in giving local anaesthetics, e.g. for peripheral block; because of the rarity of real toxicity in humans caused by local anaesthetics, the best treatment is still theoretical

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