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Adverse Effects and Drug Interactions Associated with Local and Regional Anaesthesia

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Summary

Systemic and localised adverse effects of local anaesthetic drugs usually occur because of excessive dosage, rapid absorption or inadvertent intravascular injection.

Small children are more prone than adults to methaemoglobinaemia, and the combination of sulfonamides and prilocaine, even when correctly administered, should be avoided in this age group. The incidence of true allergy to local anaesthetics is rare.

All local anaesthetics can cause CNS toxicity and cardiovascular toxicity if their plasma concentrations are increased by accidental intravenous injection or an absolute overdose. Excitation of the CNS may be manifested by numbness of the tongue and perioral area, and restlessness, which may progress to seizures, respiratory failure and coma. Bupivacaine is the local anaesthetic most frequently associated with seizures. Treatment of CNS toxicity includes maintaining ade-

quate ventilation and oxygenation, and controlling seizures with the administration of thiopental sodium or benzodiazepines.

Cardiovascular toxicity generally begins after signs of CNS toxicity have occurred. Bupivacaine and etidocaine appear to be more cardiotoxic than most other commonly used local anaesthetics. Sudden onset of profound bradycardia and asystole during neuraxial blockade is of great concern and the mechanism(s) remains largely unknown. Treatment of cardiovascular toxicity depends on the severity of effects. Cardiac arrest caused by local anaesthetics should be treated with cardiopulmonary resuscitation procedures, but bupivacaine-induced dysrhythmias may be refractory to treatment.

Many recent reports of permanent neurological complications involved patients who had received continuous spinal anaesthesia through a microcatheter. Injection of local anaesthetic through microcatheters and possibly small-gauge spinal needles results in poor CSF mixing and accumulation of high concentrations of local anaesthetic in the areas of the lumbosacral nerve roots. In contrast to bupivacaine, the hyperbaric lidocaine (lignocaine) formulation carries a substantial risk of neurotoxicity when given intrathecally.

Drugs altering plasma cholinesterase activity have the potential to decrease hydrolysis of ester-type local anaesthetics. Drugs inhibiting hepatic microsomal enzymes, such as cimetidine, may allow the accumulation of unexpectedly high (possibly toxic) blood concentrations of lidocaine. Reduction of hepatic blood flow by drugs or hypotension will decrease the hepatic clearance of amide local anaesthetics. Special caution must be exercised in patients taking digoxin, calcium antagonists and/or β-blockers.

Local anaesthetics are compounds that, when applied to nervous tissue, produce reversible loss of sensation. They interfere with the conduction process of nervous tissue by preventing the voltage-dependent increase in Na^+ conductance and, therefore, block the initiation and propagation of action potentials.[1] Local anaesthetics could also be termed 'local analgesics' as they are commonly used to produce loss of pain without loss of nervous control.

The notion of providing analgesia by applying a solution directly to a wound or a surgical area is very old. Approximately 1000 years ago, the Arab scholars Avicenna and Al Razi used opium and other drugs, such as mandrake, papaveris, henbane or hyoscyamus, as local anaesthetics in patients with dental pain, eye pain, earache or joint pain.[2] Cocaine, the first local anaesthetic discovered, was isolated from the leaves of the shrub *Erythroxylon coca* in 1860. Anrep in 1880 was the first to describe the local anaesthetic properties of cocaine in the skin, while Koller[3] in 1884 demonstrated its usefulness as a topical anaesthetic for the eye. Koller stated: 'Perhaps it is not too daring to hope that cocaine will be able to be used successfully as an anaesthetic when removing foreign objects from the cornea or for more major operations, or as a narcotic for retinal or conjunctival diseases'.[3]

All of the agents used by anaesthetists are known to have potentially toxic effects depending on the dosage, the pharmacological characteristics of the drug, site of injection and specific patient characteristics. Local anaesthetics differ from other drugs in that they are usually applied to the specific areas where they are to exert their primary pharmacological actions. Since sodium channels are an essential feature not only of nerve fibres, but also of all excitable tissues, local anaesthetics tend to exert a generalised effect on all excitable membranes.[1] Systemic absorption or inadvertent intravascular injection of these drugs will particularly affect the cardiovascular system and CNS.

Clinically useful local anaesthetics have the same general chemical configuration of an amine portion (hydrophilic component) joined to an aromatic residue (lipophilic component) by an ester or amide link. The type of linkage is important in determining the properties of the drug. The ester-type local anaesthetics are hydrolysed in plasma by plasma cholinesterase. The amide-type anaesthetics are metabolised mainly in the liver, and renal clearance of unchanged amide local anaesthetic is low; for example, it has been estimated that 70% of injected lidocaine is metabolised in the liver.[4] While little protein binding occurs with most ester-type anaesthetics, the amide types are considerably protein-bound.

This review focuses on the adverse effects of local anaesthetic drugs *per se* (and not on errors or complications of techniques) as well as the interactions of these drugs with other drugs commonly used in anaesthesia.

We began with a systematic review of published material on adverse effects and drug interactions of local anaesthetics using a computerised bibliographical database (MEDLINE), then searched the reference lists of identified studies; we also hand-searched journals in which relevant material tended to appear. In the Medline search strategy (from 1966 to 1997), we used the following MeSH headings: anesthesia (anaesthesia); side effects; adverse effects; drug interaction; lidocaine (lignocaine); bupivacaine; procaine; chloroprocaine procainamide; prilocaine; cocaine; etidocaine; mepivacaine; tetracaine (amethocaine); dibucaine (cinchocaine); benzocaine. We limited the search to English language papers. A separate search was carried out for each local anaesthetic drug. In addition, a search for adverse effects was carried out separately from that of drug interactions.

1. Mechanisms of Toxicity

Systemic and localised adverse effects of local anaesthetic drugs usually occur because of excessive dosage, rapid absorption or inadvertent intravascular injection; the latter being the commonest cause of local anaesthetic toxicity. Less commonly, retrograde passage of a local anaesthetic injected under pressure (reverse intracarotid flow) and transarterial diffusion of local anaesthetics during stellate ganglion block may lead to CNS intoxication.[5-7]

The rate of absorption of local anaesthetics varies with the site of administration and the presence or absence of a vasoconstrictor. Exposure of a local anaesthetic solution to a larger vascular area results in a greater rate and degree of absorption. The most rapid absorption occurs from mucous membranes, or after deep tracheal, intercostal or epidural injection. Less rapid absorption was reported with plexus blocks, but this still produced significant blood concentrations of the local anaesthetic. For example, the use of lidocaine 400mg without epinephrine (adrenaline) for intercostal nerve block or for brachial plexus block results in average peak venous plasma concentrations of approximately 7 mg/ml and 3 mg/ml, respectively.[8] In addition, peak plasma concentrations occur about 5 minutes after pharyngeal instillation, 10 minutes after intercostal block, and 20 to 30 minutes after epidural injection; the peak concentration occurs after various plexus blocks somewhat later.[9] The use of epinephrine (5 μg/ml) with local anaesthetics decreases the rate of absorption and delays the onset of peak plasma concentrations and thus lowers their potential toxicity.[10] However, when absorption is retarded by a vasoconstrictor agent, the potential toxicity of the vasoconstrictor agent must also be considered.[11]

The UK Committee on Safety of Medicines reported that 27.8% of all adverse drug reactions (561 out of 2014) and 6.6% of deaths (19 out of 286) were attributable to local anaesthetics.[12] The distribution is given in table I.

The definition and mechanisms of drug interactions have been discussed elsewhere.[13] Briefly, a drug-drug interaction is an *in vivo* phenomenon that occurs when the prior or concurrent administration of one drug alters the effects or kinetics of another drug. Drug interactions with local anaesthetics can be divided into those that are pharmacokinetic and those that are pharmacodynamic in

Table I. Adverse reactions to local anaesthetics (including syncope, palpitations, apnoea, cardiac arrest, seizures and application-site reactions) reported to the UK Committee on Safety of Medicines (1964 to 1985)[12]

Local anaesthetics	Number of adverse reactions	Number of deaths
Lidocaine (lignocaine)	329	9
Prilocaine	88	0
Bupivacaine	68	10
Mepivacaine	27	0
Tetracaine (amethocaine)	20	0
Dibucaine (cinchocaine)	14	0
Oxethazaine	15	0
Total	**561**	**19**

nature. Pharmacokinetic interactions occur when the absorption, distribution, metabolism or excretion of a drug is altered by the coadministration of a second drug. Pharmacodynamic interactions involve a change in the pharmacological effect of a drug as a result of the action of a second drug at receptor sites.

2. Adverse Effects

2.1 Haematological Effects

2.1.1 Methaemoglobinaemia

Methaemoglobinaemia has been reported following the use of several local anaesthetics, including benzocaine, tetracaine, prilocaine and lidocaine.[14] Methaemoglobin is haemoglobin with the iron oxidised to the ferric state, rather than the normal (reduced) ferrous state, and methaemoglobin is incapable of transporting oxygen. Methaemoglobinaemia refers to the presence of greater than the normal physiological level of 1 to 2% methaemoglobin in erythrocytes.

There are at least 50 reports describing methaemoglobinaemia in association with benzocaine,[15] and most cases reported in the literature occurred in infants and young children.[16-20] In these cases, methaemoglobinaemia resulted from the topical application of benzocaine from skin, mucous or pulmonary membranes. Methaemoglobinaemia has also been reported in adult patients following topical application of benzocaine to the pharynx and trachea, and also to an endotracheal tube in order to facilitate intubation.[14,21,22] It has been estimated that benzocaine in doses of 15 to 25 mg/kg can produce recognisable cyanosis.[23]

The formation of methaemoglobinaemia from prilocaine is caused by 2 of its metabolites, 4-hydroxy-2-methylaniline and 2-methylaniline (*o*-toluidine) producing oxidation of normal haemoglobin. Methaemoglobinaemia was reported in a 12-week infant who became cyanosed after application of 5g of a eutectic preparation of prilocaine and lidocaine [eutectic mixture of local anaesthetics (EMLA®) cream] to the dorsum of the hands and in the antecubital area for a total of 5 hours. His methaemoglobin level was 28%, although this may have partly resulted from concomitant treatment with a sulfonamide drug.[24] In one study,[25] plasma lidocaine, prilocaine and methaemoglobin levels were measured in 22 infants aged 3 to 12 months after application of EMLA® 2g beneath an occlusive dressing; methaemoglobin levels all remained within the normal range. This phenomenon is dose-related, with detectable blood methaemoglobin levels usually appearing following prilocaine doses of 8 mg/kg or more.[26-30]

Methaemoglobinaemia has been noted after intravenous administration of lidocaine; however, it is probably not clinically significant in most cases.[14] One study reported statistically significant increases in methaemoglobin levels in patients with cardiac disorders who received intravenous lidocaine.[31]

Infants and children are more susceptible than adults to induced methaemoglobinaemia because (i): haemoglobin F is more susceptible to oxidation;[32] (ii) newborns have lower levels of reduced nicotinamide adenine dinucleotide (NADH)-methaemoglobin reductase, catalase and glutathione peroxidase; and (iii) the dose is usually greater per kilogram of bodyweight.[33] Concomitant administration of other agents such as sulfonamides[24] or antimalarials[34] may predispose to methaemoglobinaemia. Patients with haemoglobinopathies or glucose-6-phosphate dehydrogenase deficiency may also be at greater risk.[14]

Approximately 5 g/dl of deoxyhaemoglobin are necessary to produce visible cyanosis, but a similar skin colour is produced by 1.5 to 2 g/dl of methaemoglobin.[35] Clinical cyanosis becomes apparent at a methaemoglobin level of about 15%. A methaemoglobin level in excess of 30% is associated with obvious cyanosis, but a near normal oxygen tension, along with agitation and even coma.[36] The effect of partial oxidation of one haem group in the haemoglobin tetramer increases the oxygen affinity of the remaining haem groups. This causes the oxygen dissociation curve to be shifted to the left.

Because of the technical limitations of conventional dual-wavelength pulse oximetry, it cannot provide any useful information in the presence of methaemoglobinaemia. It underestimates the magnitude of methaemoglobinaemia by about 50% at low levels of methaemoglobin, and only indicates a saturation decrease to 80 to 85% with 70% methaemoglobinaemia.[37,38] However, methaemoglobin can be detected by using a multiwavelength oximeter.[39]

Treatment of methaemoglobinaemia consists of removing the causative agent, administration of 100% oxygen and intravenous methylene blue (methylthioninium chloride) 1 to 2 mg/kg, together with, occasionally, haemodialysis. Methylene blue acts as an exogenous electron acceptor and is converted to leukomethylene blue, which rapidly and nonenzymatically reduces methaemoglobin.[40]

2.1.2 Other Haematological Effects

Epidural bupivacaine has been reported to inhibit platelet aggregation *in vitro*.[41] *In vivo* studies have also shown a reduced incidence of postoperative thromboembolism in patients receiving epidural[42] or spinal[43] anaesthesia; this has been attributed to increased blood flow to the limbs[44] and altered coagulation and fibrinolysis.[45-47] Additional factors could be the inhibitory effects of local anaesthesia on platelets[47] and leucocyte function,[48] and the morphological change in erythrocytes induced by local anaesthetics.[49] Changes in blood rheology caused by local anaesthetics may also be important.[49] Recently, it has been suggested that these changes may to be caused by haemodilution, resulting from intravenous administration of fluids or the redistribution of body fluids associated with sympathetic blockade, or to a combination of these factors, rather than to the direct effect of bupivacaine in the blood.[50]

Amide local anaesthetics are known to interfere with various steps of the inflammatory response of leucocytes.[51-53] It has been shown that administration of lidocaine (and possibly other local anaesthetics) in the area of the surgical procedure reduces granulocyte migration and metabolic activation.[54] The effects of local anaesthetics on wound healing are controversial.[55,56]

Local anaesthetics may cause vasodilation,[57] and may increase the incidence of intraoperative and postoperative bleeding.[58] Local anaesthetics, however, can dilate or constrict vessels in a dose-dependent manner.[59] At lower concentrations, including those that occur in the plasma of patients during intravenous infusion or nerve blocks, dose-related vasoconstriction was shown to occur in animals.[59] Whereas, lidocaine in a concentration similar to that which occurs at the site of injection during infiltration, nerve block or epidural anaesthesia, produced vasoconstriction.[59] Toxic concentrations of bupivacaine have resulted in vasoconstriction and increases in systemic vascular resistance caused by increased efferent sympathetic activity.[60]

2.2 Cardiovascular Effects

2.2.1 Features and Mechanisms

Cardiovascular effects of local anaesthetics occurring after spinal or epidural administration are probably caused by an imbalance between sympathetic and parasympathetic nervous activity or because of supine hypotension in pregnant women.[61,62] However, all local anaesthetics can cause CNS toxicity (section 2.3) and cardiovascular toxicity if their plasma concentrations are increased by accidental intravenous injection or an absolute overdose.[63]

Cardiovascular toxicity generally begins after signs of CNS toxicity have occurred. The doses of lidocaine, bupivacaine, etidocaine and tetracaine that cause significant cardiovascular effects were found to be 3.5 to 6.7 times greater than those required for CNS toxicity.[64] Higher plasma concentrations of local anaesthetics impair myocardial contractility and decrease conduction velocity in the heart, which may progress to sinus bradycardia, dysrhythmias or asystole.[65] Vasodilation results from vasomotor-centre depression and a direct effect on the vascular system.

The contributing effect of acidosis, hypoxia or hyperkalaemia on the cardiac toxicity of local anaesthetics is significant (especially with bupivacaine).[66,67] Acidosis will decrease the plasma protein binding of local anaesthetics, thus increasing the free fraction of local anaesthetic in the plasma. Additionally, acidosis will increase the ionised and active fraction of a local anaesthetic within the neuron itself and increase plasma potassium levels.

Administration of progesterone to rabbits was found to increase the potency of bupivacaine, but not lidocaine, in depressing cardiac action potentials;[68] human pregnancy, however, does not increase bupivacaine cardiac toxicity.[69]

It has also been suggested that the CNS may play an important role in the development of cardiovascular toxicity, since direct application of bupivacaine within the medulla resulted in cardiovascular changes similar to those of cardiovascular toxicity.[70]

The degree of myocardial depression was found to be directly related to anaesthetic potency.[11,71] Bupivacaine[72,73] and etidocaine[73] appear to be more cardiotoxic than most other commonly used local anaesthetics. In contrast to other, less potent, local anaesthetics that depress cardiac contractility only at higher concentrations, bupivacaine depresses ventricular contractility *in vitro* at relatively low concentrations.[72,74-76] Furthermore, although lidocaine and bupivacaine have no direct myocardial effects at clinical concentrations (below 5 mg/ml and 1.25 mg/ml, respectively), they depress myocardial function at plasma concentrations near the cardiotoxic concentration. This effect was more pronounced with bupivacaine at concentrations >5 mg/ml than with lidocaine at concentrations >20 mg/ml.[77] Comparable prolongation of the QRS interval with bupivacaine and lidocaine were obtained at a dose ratio of 1 : 16.[78] Thus, bupivacaine is 4 times more potent than lidocaine in depressing cardiac contractility, but 16 times more potent in prolonging the QRS interval.

Furthermore, it has been shown that bupivacaine has greater potency than lidocaine or ropivacaine to induce serious cardiac dysrhythmias such as torsade de pointes, ventricular tachycardias, multiform premature ventricular contractions, ventricular fibrillation and refractory asystole.[79] The *S*-(–) enantiomer of bupivacaine has been shown to be less dysrhythmogenic than the *R*-(+) enantiomer or the racemic mixture, although the anaesthetic potency of the *S*-(–) enantiomer is the same or greater than that of the *R*-(+) enantiomer.[80]

These unique features of bupivacaine result from the kinetics of its binding to the cardiac sodium channels. It has been reported that the effects of lidocaine and bupivacaine on sodium channel blockade in the papillary muscles are different.[81] Lidocaine-induced blockade has fast on and off rates, whereas the bupivacaine-induced blockade is fast on, but slow off. Therefore, bupivacaine causes frequency-dependent blockade of sodium channels at lower heart rates than lidocaine, resulting in slowing or blockade of conduction at lower rates.

At the molecular level, local anaesthetics block not only voltage–dependent sodium channels but also calcium and potassium channels.[82,83] In addition, there might be a delay of activation because of either disturbance of conduction or excitation-contraction coupling. Local anaesthetic–induced inhibition of cyclic adenosine monophosphate (cAMP) production (most potently by bupivacaine) may also contribute to the negative inotropic effect and interfere with the effects of epinephrine.[84] The clinical implication of this finding is that a higher dose of epinephrine may be required during resuscitation in order to restore cardiac contractile function after bupivacaine intoxication.

It is important to distinguish the cardiovascular changes related to toxic concentrations of local anaesthetics and those secondary to the regional anaesthetic procedure itself.[85] For example, hypotension was reported to occur in 38 to 45% of patients after neuraxial blockade (spinal or epidural anaesthesia).[86-88] This hypotension is not usually associated with a significant increase in heart rate. In fact, bradycardia occurs only in about 9 to 13% of patients, and it has been accepted as a typical cardiovascular response to high spinal anaesthesia.[86-88] In addition, epidural anaesthesia extending to the first thoracic segment is associated with a fall in mean arterial blood pressure of 16.3%, a decrease in total peripheral resistance of 18.7%, but little change in cardiac output.[89]

The haemodynamic changes after epidural anaesthesia were also found to be related to effects of the β-adrenergic stimulating action of absorbed epinephrine. Epinephrine is used in the test dose for epidural anaesthesia and to potentiate the effects of epidurally administered lidocaine. A combination of epinephrine and lidocaine was found to produce a 49% increase in cardiac output, a 37% decrease in total peripheral resistance and a 10% decrease in mean arterial blood pressure.[90] Therefore, the addition of epinephrine to lidocaine resulted in a marked increase in cardiac output and significant decrease in total peripheral resistance.[89,90]

Anaesthetists are currently confronted with a plethora of case reports describing the phenomenon of abrupt, extreme bradycardia and/or asystole during spinal or epidural anaesthesia.[61,91-97] The American Society of Anesthesiologists' (ASA) Closed Claim study[98] reported 14 cases of sudden cardiac arrest during spinal anaesthesia in healthy patients undergoing minor surgical procedures. The highest block averaged T4. Despite apparently appropriate resuscitation procedures, 6 of the 14 patients died, and only 1 survivor had complete neurological recovery.[98] It was concluded that the potential for sudden cardiac arrest in the setting of apparent haemodynamic stability is present, yet poorly understood.[98]

Risk factors identified for the development of bradycardia during spinal anaesthesia include: baseline heart rate <60 beats/min, ASA physical status 1 versus 3 or 4,[99] regular use of β-blocking drugs, sensory block height at T5 or higher, age <50 years and prolonged PR interval on the preoperative ECG.[100,101] In addition, high spinal anaesthesia was found to alter susceptibility to the soporific effects of sedatives and hence increase the risk of hypoventilation and hypoxaemia.[98,102]

It has been suggested that the deafferentation caused by spinal anaesthesia and the loss of facilitatory proprioceptive input into the respiratory centre may alter the respiratory response to sedatives.[102] Nevertheless, the exact mechanism of the sudden onset of profound bradycardia and asystole during neuraxial blockade remains largely unknown, but it is probably multifactorial. The aetiology of this phenomenon could be attributed to inhibition of cardiac sympathetic fibres, enhanced vagal tone, decrease in central venous return and activation of Bezold-Jarisch reflex.[100-102] Another possible mechanism could be pre-existing autonomic imbalance or dysfunction.[103] Patients with conditions characterised by autonomic nervous system degeneration or dysfunction often have postural hypotension and high resting heart rate, which may be exaggerated or diminished by the expected effects of regional anaesthesia. Tests for autonomic dysfunction include measuring the degree of sinus dysrhythmia or beat-to-beat variaility, Valsalva manoeuvre with blood pressure monitoring, carotid sinus pressure, and vasopressor-challenge or atropine-challenge tests.

2.2.2 Treatment

Treatment of cardiovascular toxicity depends on the severity of the effects. Hypotension is treated by administration of crystalloids and/or colloids. A small dose of a vasopressor, such as ephedrine, may be required. Bradycardia and decreased myocardial contractility may require positive inotropic agents, such as ephedrine or epinephrine. The routine use of epinephrine in local anaesthetic solutions for regional blockade may prophylactically provide inotropic agents, as well

as giving warning of intravascular injections when it is associated with an increase in heart rate of approximately ≥ 10 beats/min. Furthermore, adding vasoconstrictors, such as epinephrine, norepinephrine (noradrenaline) and phenylephrine, to local anaesthetics for regional anaesthesia may provide several beneficial effects, such as decreasing the peak plasma concentrations of local anaesthetics, increasing the duration of the blockade and decreasing toxicity.[104,105]

Cardiac arrest caused by local anaesthetics should be treated by cardiopulmonary resuscitation, along with hyperventilation with oxygen and pharmacological interventions (e.g. epinephrine, bretylium, atropine). Defibrillation should be instituted when indicated. The rapid production of acidosis and hypoxia after local anaesthetic–induced toxicity are well documented in humans and animals[106-108] and should be promptly corrected. Nevertheless, little information exists regarding the best treatment of cardiovascular toxicity of local anaesthetics in humans.[108,109] Animal data indicate that early aggressive treatment of CNS and cardiovascular toxicity is capable of reducing the incidence of mortality associated with the rapid intravenous administration of excessive doses of local anaesthetics.[106] Animal data also suggest that: (i) high doses of epinephrine may be necessary to support the heart rate and blood pressure; (ii) atropine may be useful for bradycardia; (iii) direct current (DC) cardioversion is often successful; and (iv) ventricular dysrhythmias are probably better treated with bretylium than with lidocaine.[110]

The effectiveness of epinephrine in treating cardiovascular collapse after bupivacaine overdose is controversial. Vasopressor drugs with less-direct cardiac effects than epinephrine, e.g. phenylephrine, may be more beneficial in the treatment of local anaesthetic-induced hypotension,[111] since the ability of epinephrine to stimulate cAMP formation may be inhibited by bupivacaine.[84] Amrinone can augment intracellular Ca^{++} concentrations and was found to be superior to epinephrine in the treatment of bupivacaine-induced cardiovascular depression.[112,113] A drug such as norepinephrine, which has both cardiostimulator (β_1 receptor agonist) and peripheral vasoconstrictor (α_1 receptor agonist) activity, may be the drug of choice for treating asystole induced by bupivacaine.[114] In addition, isoprenaline (isoproterenol) was found to partially or completely correct all bupivacaine-induced abnormalities and to decrease sinus cycle length.[115] Therefore, isoprenaline may have potential therapeutic value in the treatment of bupivacaine intoxication.[115] Cardiac pacing can be difficult in the presence of toxic bupivacaine concentrations, and high-frequency pacing should be avoided;[116] it was noted that the higher heart rates generated by the physiological pacemakers of the heart also increase the cardiocirculatory toxicity of bupivacaine.[116]

Bupivacaine-induced dysrhythmias have been refractory to treatment. Lidocaine, bretylium, magnesium, calcium antagonists and amiodarone have been used experimentally, with variable results.[79,117-120] By binding to the same receptor, lidocaine (at high doses) may displace bupivacaine from cardiac sodium channels,[121] and has on occasions been successful in the resuscitation of humans.[109] However, lidocaine is ineffective in treating haemodynamic changes, and can worsen dysrhythmias.[119] Bretylium has been more effective than lidocaine in animals with experimental bupivacaine-induced dysrhythmias.[79,119] The unique antidysrhythmic mechanism of bretylium is related to blockade of catecholamine reuptake as well as blockade of potassium channels, which together prolong repolarisation.[119] Phenytoin was also reported to be effective in treating bupivacaine-induced cardiac toxicity in 2 full-term neonates after other therapies, including bretylium, had been unsuccessful.[122] The initial dose of phenytoin should be 5 mg/kg; second and third doses may be administered as necessary at 5-minute intervals, to a maximum dose of 15 mg/kg.[123] Combined administration of clonidine and dobutamine has been effective in dogs; however, clonidine alone can enhance the bradycardia and haemodynamic depression induced by local anaesthetics.[124]

An algorithm for treatment of local anaesthetic-induced acute cardiovascular toxicity and seizures is shown in figure 1.

2.3 CNS Effects

2.3.1 CNS Excitation and Depression

Features and Mechanisms

Local anaesthetics cause concentration-dependent CNS toxicity, characterised by excitation and seizures.[64,125] Excitation of the CNS may be manifested by restlessness, excitement, nervousness, dizziness, tinnitus, blurred vision, nausea and vomiting, muscle twitching, tremors and seizures.[126-130] Numbness of the tongue and perioral region may appear as an early sign of systemic toxicity. CNS excitation may be transient and followed by CNS depression, with drowsiness, respiratory failure and coma. However, CNS depression may be the first manifestation of CNS toxicity in some patients. There may be simultaneous effects on the cardiovascular system, with myocardial depression and peripheral vasodilatation resulting in hypotension and bradycardia; dysrhythmias and cardiac arrest may also occur (section 2.2). Severe tissue hypoxia and acidosis were shown to decrease seizure threshold and enhance the CNS toxicity of local anaesthetics.[66]

The mechanism of initial CNS excitation and subsequent depression has been attributed to the selective blockade of inhibitory cortical synapses by local anaesthetics.[131-133] This allows facilitatory neurons to function unopposed and thus leads to an increase in excitation of the CNS, ultimately manifested as seizures. Further increases in local anaesthetic dose produce a depression of both inhibitory and facilitatory neurons, leading to a generalised state of CNS depression.[131] EEG changes after intravenous administration of local anaesthetics in humans included a decrease in α activity, and a simultaneous increase in δ-θ activity.[125] In animals, dose-related changes were observed, particularly in the amygdaloid nuclear complexes, including rhythmic spindling progressing to spike-spindle complexes and ictal episodes, which could become generalised and were correlated behaviourally with clonic seizures.[134] Evoked-potential studies demonstrated that the electrical activity of the brain stem auditory pathway is suppressed even when the cerebral cortex is in the excitatory state during the convulsive stage of procaine toxicity.[135]

In one study, CNS adverse effects of ropivacaine and bupivacaine (such as tinnitus, lightheadedness, dizziness and circumoral paraesthesia) were compared in 12 volunteers, who received intravenous infusions of either drug at a rate of 10 mg/min up to a maximal dose of 150mg.[136] Ropivacaine caused fewer CNS symptoms and the maximum tolerated dose of ropivacaine was 25% higher than that of bupivacaine.[136] In clinical trials using epidural ropivacaine, or comparing epidural ropivacaine with bupivacaine, CNS symptoms have been too rare to assess a singular or comparative incidence.

Systemic toxicity from excessive continuous infusions of local anaesthetics has been reported in children.[127,130,137] Although adults frequently report symptoms of minor CNS toxicity, younger children may not report these symptoms, and restlessness or agitation caused by minor CNS toxicity in infants and toddlers may be misinterpreted as pain or 'difficulty in adjusting to the hospital environment'.[138]

The earlier concept that pregnancy might be associated with increased sensitivity to local anaesthetics[69] has not been confirmed by recent studies.[139,140] It has been shown that the plasma lidocaine concentration necessary to induce seizure activity, as well as circulatory collapse, were very similar in pregnant and nonpregnant sheep.[139] In another study, the seizure threshold for lidocaine was prospectively assessed in male, nonpregnant female and pregnant female rats;[140] mean lidocaine doses, as well as plasma and brain concentrations of the drug, at the onset of EEG seizure activity were not different among the 3 groups.[140]

In animals, prophylactic benzodiazepine administration reduced the likelihood of seizures after intravenous local anaesthetic administra-

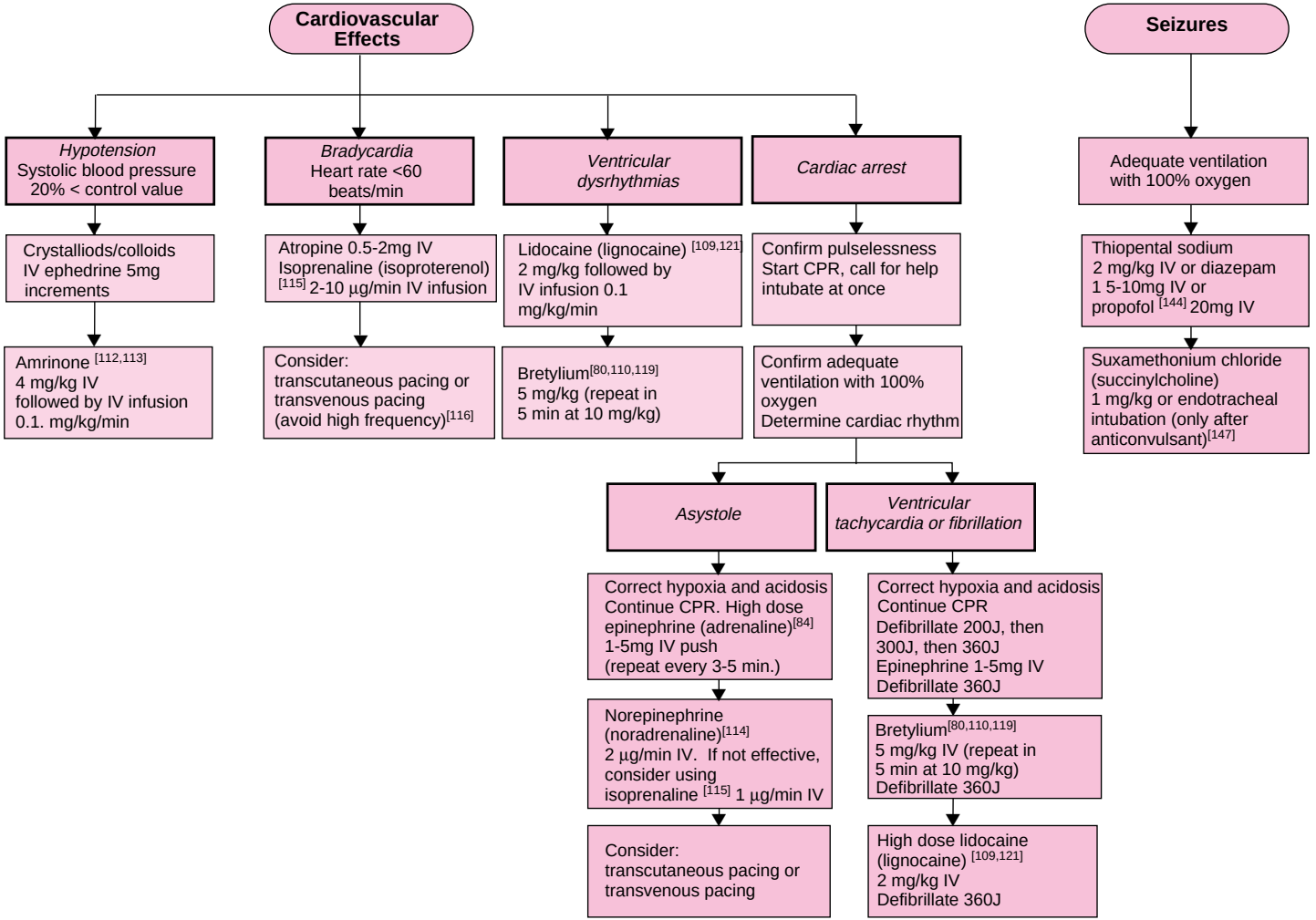

Fig. 1. Algorithm showing treatment of local anaesthetic–induced acute cardiovascular toxicity and seizures.[79,84,109,110,112-116,119,121,144,147] *Abbreviations:* CPR = cardiopulmonary resuscitation; IV = intravenously.

tion.[141,142] However, the use of benzodiazepines may make toxic responses more dangerous by removing a treatable warning sign, since the animals proceeded to circulatory failure directly without seizures.

Treatment

Treatment of CNS toxicity includes maintaining adequate ventilation and oxygenation, and controlling seizures (figure 1). Circulatory collapse may follow if plasma concentrations of local anaesthetics continue to increase. Pharmacological treatment of seizures includes intravenous administration of thiopental sodium or benzodiazepines.[143] However, the administration of an anticonvulsant should never take precedence over oxygen administration.

A recent study demonstrated the effectiveness of propofol in stopping lidocaine-induced seizures.[144] The CNS toxicity of local anaesthetics may result from depression of subcortical inhibitory control of γ-aminobutyric acid (GABA) over normally occurring excitatory activity.[125,132] Propofol may specifically reverse this deficiency by acting as a GABA-mimetic drug.[145] Lidocaine-induced seizure activity can be modulated by antagonism of glutamatergic receptors.[146]

Suxamethonium chloride (succinylcholine) may also be needed for skeletal muscle relaxation and to aid intubation. However, administration of neuromuscular blockers *alone* (without an anticonvulsant) is not recommended, because it only prevents systemic, not cerebral, acidosis. It has been shown that cerebral lidocaine concentrations were higher – 10-fold over control – in animals paralysed during seizures compared to nonparalysed animals,[147] which probably reflects an ion-trapping mechanism resulting from a fall in the pH of the brain.[147] It has also been suggested that acute hypertension induced by vasoconstrictive agents [epinephrine, norepinephrine and phenylephrine] added to local anaesthetics may play a role in reducing the threshold of lidocaine-induced seizures in rats.[148]

2.3.2 Other Effects

Peripheral Neurological Complications

Adverse neurological effects, such as numbness, tingling, heaviness or burning sensations, have been noted by patients following spinal or epidural administration of local anaesthetics.[149-154] In most cases, these symptoms were restricted to the lumbar and sacral dermatomes, and disappeared within 6 months.

Cauda equina syndrome is a very rare and serious neurological complication of neuraxial blockade.[151,155] It is an acute neuropathy that, by affecting the smaller nerve fibres or autonomic fibres, leads to varying degrees of urinary and faecal incontinence, localised sensory loss in the perineal area and varying degrees of leg weakness. The onset of symptoms is rapid and is usually detected immediately after regression of the nerve block. In an extensive review of complications of neuraxial blockade in 32 718 patients, transient paralysis was reported in 48 patients (0.1%), whereas 7 patients experienced permanent paralysis (0.02%).[154] In a more recent survey, the incidence of paraesthesiae and motor dysfunction associated with 23 827 deliveries was 18.9/10 000 deliveries. All symptoms resolved within 72 hours, after supportive therapy only.[152]

In another study, 17 733 consecutive neuraxial blocks (8501 spinal and 9232 epidural anaesthetics) performed during a 3-year period were analysed.[153] Neurological complications related to anaesthesia were noted in 17 patients, of whom 13 had persistent lesions (3 spinal and 10 epidural blocks). In 5 of these cases, polyneuropathy or nonspecific neurological symptoms were present. In 3 cases, occurring after epidural blocks, paraplegia was caused by epidural haematoma that developed in the presence of anticoagulant therapy.[153]

Recently, there were some alarming reports of devastating neurological complications following continuous subarachnoid anaesthesia.[155-159] In one report, 4 cases of cauda equina syndrome were reported, 3 of which occurred after repetitive injection of a hyperbaric solution of lidocaine 5% through a 28-gauge catheter[156] In another, 2 cases

of persistent sacral nerve root deficits after continuous subarachnoid anaesthesia were reported; both had been performed using an identical hyperbaric solution of lidocaine 5% for incremental injection through a 28-gauge catheter.[157] Other authors reported a patient in whom cauda equina syndrome may have resulted from the subarachnoid administration of an intended epidural injection of pH-adjusted solution of lidocaine 2%.[155]

The technique of continuous spinal anaesthesia, particularly with small-bore catheters, might have partially contributed to the development of these neurological sequelae.[160,161] A recent US Food and Drug Administration safety alert regarding cauda equina syndrome described 11 patients with cauda equina syndrome after continuous spinal anaesthesia with small-bore 28-gauge catheters and lidocaine 5% in a glucose 7.5% solution.[162] Eventually, microcatheters were withdrawn from the North American market. However, clinicians can use continuous spinal anaesthesia, but with large-bore catheters. It appears that microcatheters might have contributed to nonuniform distribution of the local anaesthetic in the CSF, along with drug overdose. These factors might have resulted in a potentially harmful or neurotoxic local anaesthetic concentration that contributed to the cauda equina syndrome or persistent sacral nerve root deficits.[156-158,163] In fact, restricted distribution of local anaesthetics has been shown to induce sensory impairment in rats.[155,161] Not surprisingly, pencil-point spinal needles, which may result in maldistribution of local anaesthetics, have also been incriminated.[164]

In addition, significant differences exist in the neurotoxic potential of different local anaesthetics.[161] Infusion of lidocaine solution was associated with a persistent increase in tail-flick latency in the rat when compared with bupivacaine, tetracaine and saline solutions. In a clinical study in which patients received either lidocaine 5% in glucose 7.5% or bupivacaine 0.5% in glucose 8.5%, neurological symptoms occurred in 44/120 patients (37%) receiving lidocaine, but only 1/150 patients (0.7%) receiving bupivacaine.[165] The authors concluded that this difference in incidence suggests 'that symptoms were the result of a specific drug effect',[165] and that glucose *per se* was not an important factor. The presence of 7.5% glucose does not affect the potential of intrathecally administered 5% lidocaine to induce sensory impairment.[166] These findings provide further support for the hypothesis that recent injuries after spinal anaesthesia resulted from a direct neurotoxic effect of the local anaesthetic.[166]

Local anaesthetic-induced myelotoxicity (in rabbits) was found to be related to water solubility.[167] Highly water-soluble drugs such as lidocaine and tetracaine could be prepared in concentrations sufficiently potent to cause neural damage, whereas less water-soluble drugs, such as bupivacaine, could not.

Local anaesthetics seem capable of inducing long-lasting structural and functional changes in neural tissue when administered at a large enough dose or concentration.[156] Exposing amphibian myelinated nerves to the high concentrations of lidocaine and tetracaine used for spinal anaesthesia caused irreversible impulse blockade.[168] This loss of electrical activity was not a result of residual local anaesthetic, irreversible membrane lysis or depolarisation, nor was it caused by the high dextrose concentration added to certain commercial formulations of lidocaine.[168] In rats, repetitive lidocaine exposure of the tibial nerve may be neurotoxic if a 4% drug concentration is used.[169] Exposing rat sciatic nerves to a 2.5% lidocaine concentration has been shown to cause selective vulnerability of unmyelinated fibre Schwann cells.[170] The addition of epinephrine to the local anaesthetic was also suggested as being responsible for localised vasoconstriction, resulting in a compromise of blood flow to the lumbosacral cord.[171]

The lithotomy position may predispose patients to develop radicular symptoms. This concept is supported by case reports, in which radicular symptoms predominantly occurred in patients having surgery in the lithotomy position[158,172] and by cadaveric dissection, suggesting that the lithotomy

position stretches the nerve roots in the cauda equina.[158] Other factors that may predispose the patient to neurological deficits are: arterial hypotension; the condition of the patient; performing the block during general anaesthesia (the patient is rendered unable to report pain); or the existence of poor systems of communication between the operating team, and nursing and medical staff.[151,170,173]

It seems that the hyperbaric lidocaine formulation carries a substantial risk of neurotoxicity when administered intrathecally. In a recent editorial, de Jong[174] recommends that hyperbaric lidocaine be used with caution, if at all. Astra USA has revised the prescribing information for lidocaine, recommending: (i) dilution of lidocaine 5% with an equal volume of CSF or preservative-free saline; (ii) a maximum dose of 100mg; (iii) removal and replacement of the needle if inadequate spread of anaesthesia requires an additional dose; and (iv) use of a spinal needle of sufficient gauge to ensure adequate withdrawal of cerebrospinal fluid through the needle before and after anaesthetic administration. Whether these recommendations will reduce the incidence of transient radicular symptoms after lidocaine spinal anaesthesia remains to be established. It may be prudent to substitute bupivacaine or ropivacaine for lidocaine when performing operations during which lidocaine with epinephrine would normally be used.[175] Bupivacaine is clearly less likely than lidocaine to produce permanent neurological deficit in a variety of animal models.[155,161,167]

Meningitis

The risk of infective sequelae after neuraxial blockade is low with a strict aseptic technique, as evidenced by the few anecdotal reports in the literature. Such sequelae were noted in only 2 cases in 2 reviews of 27 000 and 505 000 patients who received epidural block during labour.[176,177] The frequency of meningitis after spinal anaesthesia was found to be similar to that in the ordinary population.[178] Most of the reported cases of meningitis after dural puncture were aseptic in origin,[179-183] with an incidence of 0.26%.[184,185] Aseptic meningitis could result from meningeal irritation, or may be drug-induced after administration of ranitidine, antimicrobials, carbamazepine or nonsteroidal anti-inflammatory agents and immunoglobulins.[186-188]

Bacterial and viral meningitis can also occur after neuraxial blockade.[189-191] Bacterial meningitis was found to occur in 2.1% of patients with bacteraemia,[178] and is probably much rarer in patients with negative blood cultures. The possible causes of post–lumbar puncture meningitis are concomitant systemic infection (with entrance of bacteria through a break in the blood-brain barrier produced by the spinal needle), equipment and anaesthetic drug contamination, and improper technique.[192] It is, therefore, essential that meticulous attention is paid to aseptic technique, and that a facemask is always worn during the performance of central neural block.[190]

2.4 Endocrine and Metabolic Effects

Spinal or extradural administration of local anaesthetics has been shown to prevent a major part of the classical endocrine-metabolic response of surgical procedures.[193-197] Although there is little evidence that the stress response *per se* results in morbidity, several potentially detrimental physiological effects are modulated through the stress response. For example, stress response mediators are potent inhibitors of the immune system and may contribute to postoperative immunosuppression and infection.[198] Furthermore, cardiac morbidity may be increased through release of neuroendocrine hormones, with resultant reductions in myocardial oxygen supply or increases in demand.[199]

Hypoglycaemia progressing to coma was described in a 69-year-old patient with type 1 (insulin-dependent) diabetes mellitus following epidural analgesia with 6ml of bupivacaine 0.5%.[200] In contrast, an intravenous infusion of bupivacaine (2 mg/min for 3 hours) had no significant effect on blood glucose levels in a group of 8 healthy individuals.[201]

Local anaesthetics, including lidocaine and bupivacaine, do not appear to trigger porphyric reactions,[202,203] and no clinical exacerbations of

porphyria have been reported after the administration of ester or amide local anaesthetics.[204,205] Procaine, however, decreases the activity of δ-amino levulinic acid (ALA) synthase, which catalyses the rate-limiting step in the biosynthesis of porphyrins in the rat-liver experimental model;[205] such inhibition can precipitate acute attacks of porphyria in humans. It has been suggested that regional anaesthesia should probably be avoided in the setting of acute porphyric crisis.[206] Associated neuropathy may be rapid in onset, clouding the differentiation between the onset of regional anaesthesia and progressive porphyric neuropathy.[206] In addition, mental-status changes often make patients with porphyria uncooperative.[206]

Epidural anaesthesia is associated with several thermoregulatory changes that lead to hypothermia, such as increased cutaneous blood flow, decreased input from cutaneous thermal receptors and redistribution of central heat.[207-209] It has been suggested that regional anaesthesia blocks all thermal sensations; however, cold signals are disproportionately affected because cold receptor activity is predominant at typical skin temperatures.[210] Hence, regional anaesthesia would cause thermoregulatory control centres to detect a higher temperature in the legs.[210] This higher apparent leg temperature would consequently decrease the core temperature threshold for shivering.[210] Thermoregulatory changes are augmented with concomitant administration of general anaesthesia with epidural anaesthesia.[211] Surprisingly, epidural analgesia has also been associated with otherwise unexplained hyperthermia in women during labour.[212] It appears that the effects of epidural analgesia on human thermoregulation are complex and incompletely understood.

2.5 Gastrointestinal and Hepatic Effects

Local anaesthetics have been associated with taste disturbances and paraesthesiae. Although the actual incidence is unknown, it is suggested that this is a rare complication.[213] In addition, nasal irritation and transient gagging sensations have been observed following topical application of 20% benzocaine spray to the pharynx.[214]

Nausea and vomiting are relatively common adverse effects associated with neuraxial block and its resultant hypotension.[215-219] A rapid decline in systolic arterial blood pressure (to <80mm Hg) during spinal anaesthesia is often associated with the onset of nausea.[215,216] Incidences of nausea relating to spinal anaesthesia range from 14 to 45%.[215-221] In one study, the incidence of nausea and vomiting following a 21-hour epidural infusion of ropivacaine 0.5% for postoperative analgesia after orthopaedic surgery did not significantly differ from that observed in a control group who were treated with saline.[222] The reported incidences of nausea and vomiting following brachial plexus block were lower, being 8% and 4%, respectively.[223] The incidence of nausea and vomiting during spinal anaesthesia may be decreased by the administration of 100% oxygen and intravenous administration of atropine, suggesting that hypoxaemia and vagal stimulation may play a role.[215,216,218] Prophylactic administration of metoclopramide or other antiemetics can decrease the incidence of this complication.[224,225]

Acute mesenteric ischaemia and intestinal infarction were reported in a 38-year-old male following the administration of intravenous cocaine 4g.[226]

2.6 Respiratory Effects

It should be noted that intravenous administration of local anaesthetics, such as lidocaine, is an effective treatment of intraoperative bronchospasm.[227] *In vitro* studies have demonstrated that lidocaine exerts a direct relaxant effect on smooth muscles[228] and can inhibit mediator release.[229] However, there are reports of bronchospasm after interscalene brachial plexus block and spinal anaesthesia, which may have resulted from blockade of the sympathetic supply to the lung via blockade of the sympathetic chain;[230,231] the histochemical fluorescent technique has shown an extensive network of catecholamine-containing nerves throughout the tracheobronchial tree.[232]

Respiratory arrest has also been reported following caudal, intercostal and retrobulbar blocks, possibly caused by inadvertent intravenous or intrathecal injection.[233-235] In one report, respiratory arrest developed nearly 3 hours after the epidural administration of bupivacaine.[236] Respiratory arrest associated with unconsciousness and hypotension was reported after total spinal anaesthesia.[237] Adult respiratory distress syndrome has also been reported following administration of lidocaine.[238] The relative bioavailability of lidocaine has been found to be higher when applied to the upper respiratory tract than after administration to the lower respiratory tract.[239]

Lidocaine jelly has been reported to obstruct an endotracheal tube during surgery.[240] It was determined that lidocaine jelly, when exposed to nitrous oxide and oxygen, forms a sheet-like substance on the inner surface of the tube. This may cause a narrowing of the lumen or a complete obstruction. Therefore, lidocaine jelly should be avoided as a lubricant for both endotracheal tubes and stylets.[240]

2.7 Ocular Effects

Retrobulbar anaesthesia with local anaesthetics may result in a transient and marked reduction in visual acuity. However total blindness has never been reported.[241,242] In general, the longer the globe axial length, the greater the decrease in visual acuity following retrobulbar block.[241] In a patient with diabetic retinopathy, retrobulbar lidocaine injection resulted in a retinal vascular occlusion.[243] This was believed to be caused by vasospasm, because of the absence of retrobulbar haemorrhage, presence of a normal optic nerve on CT scanning and reversibility by paracentesis, sublingual nitroglycerin (glyceryl trinitrate) and carbon dioxide rebreathing.

With the exception of stellate-ganglion block, Horner's syndrome (miosis, ptosis, enophthalmos and anhidrosis) can result from blockade of the oculosympathetic pathway as a result of spread of local anaesthetics administered by various routes. The incidence of this complication was reported to be approximately 60% to 75% after supraclavicular techniques of brachial plexus blockade,[244,245] 12% after brachial plexus block,[223] and 0.5 to 4% after lumbar epidural block during labour.[246-248] Topical application to the eye of directly acting sympathomimetics, such as phenylephrine, could effectively reverse unpleasant ocular manifestations (e.g. ptosis and miosis) associated with Horner's syndrome.[249] It should be remembered, however, that blurred vision and diplopia are 2 of the early signs of CNS toxicity (section 2.3).

Extraocular muscle palsies have been described following administration of local anaesthetics for ophthalmic surgery,[250,251] most frequently affecting the inferior rectus muscle.[252-254] The highest concentrations of local anaesthetic should not be used, as these have been shown to be myotoxic.[255,256]

2.8 Musculoskeletal Effects

It has been shown that injection of local anaesthetics intramuscularly or into adjacent subcutaneous tissue can result in myonecrosis.[257-261] This is characterised by localised muscle dysfunction and tenderness following local anaesthetic injection. The extent of muscle injury from local anaesthetics is dose-dependent.[259,261] Bupivacaine was found to produce a greater tissue reaction than procaine, and the addition of corticosteroid to bupivacaine increased the initial tissue damage and prolonged the healing phase.[262] Furthermore, epinephrine alone, in concentrations higher than 1 : 200 000, caused similar, but less extensive, damage.[263] With all local anaesthetics, the initial damage to muscle fibres was restored by regeneration; complete regeneration occurred within 3 to 4 weeks, with relatively few long term effects of damage.[258,264]

The molecular event triggering local anaesthetic myotoxicity points to pathological efflux of intracellular Ca^{++} from the sarcoplasmic reticulum of mature multinucleated myocytes.[265,266] Therefore, high concentrations of bupivacaine, repeated administration and the use of epinephrine should

be avoided if injections are to be made into or adjacent to muscle.

All local anaesthetic drugs (amide and ester) appear to be suitable for use in patients susceptible to malignant hyperthermia.[267] Amide local anaesthetics were originally avoided in such patients on theoretical grounds, based on their *in vitro* ability to increase Ca^{++} efflux from sarcoplasmic reticulum. However, this class of drugs has been used extensively in these patients without demonstrable adverse reactions.[268] In fact, extensive search of the literature has revealed no reference to malignant hyperthermia being triggered by local anaesthetics.

Back pain is not infrequently observed after epidural anaesthesia.[269-272] Patients who have had epidural anaesthesia have twice the incidence of back pain compared with those who did not undergo this procedure (18.9% *vs* 10.5%).[269] Epidural administration of chloroprocaine, with or without epinephrine, has been associated with severe back pain, with a higher incidence than lidocaine.[273,274] Proposed factors contributing to back pain include the preservative disodium ethylene diamine tetra-acetate (EDTA), low pH, large injected volumes and local irritation of muscle tissue.[274] EDTA is the active agent producing pain, probably by chelation of Ca^{++} in the paraspinous muscle, which causes spasm.[274]

2.9 Allergic Reactions

Allergic reactions to local anaesthetics have been reported,[275-283] and have been documented by intradermal testing[275,282,283] and decreased serum complement C4 level with unchanged immunoglobulin E levels.[280] The incidence of true allergy to local anaesthetics is not known, but it has been widely quoted that <1% of all reactions to local anaesthetics are allergic in nature.[34,284] The National Adverse Anaesthetic Reactions Advisory Service in the UK noted that 5 to 10% of all reported anaphylactoid reactions were caused by local anaesthetics (table II).[285]

Ester derivatives of para-aminobenzoic acid (benzocaine, procaine, tetracaine) cause most of the allergic reactions. Allergic reactions to amide local anaesthetics are unusual and may be related to the preservative, which is a para-aminobenzoic acid derivative. In contrast to amide local anaesthetics, ester local anaesthetics are generally considered to show cross-sensitivity.[286]

Some patients diagnosed as being hypersensitive to local anaesthetics may have reacted to preservatives in the preparations.[234] In such patients, preservative-free local anaesthetic preparations should be used for subsequent anaesthesia. Several reviews have addressed in detail the different mechanisms and investigation of allergic reactions.[287-289]

The goals of treatment of allergic reactions are: (i) correction of arterial hypoxaemia; (ii) inhibition of further release of chemical mediators; and (iii) restoration of intravascular volume. 100% oxygen and intravenous epinephrine 10 to 20 μg/kg should be immediately administered. Early tracheal intubation with a cuffed tracheal tube should be considered in patients with rapidly developing angioedema. Fluids (crystalloid and/or colloid solutions) must be concurrently administered. Norepinephrine or a sympathomimetic drug (e.g. metaraminol, phenylephrine) may also be necessary to maintain perfusion pressure until intravascular fluid volume can be restored. Dysrhythmias should be treated.

2.10 Effects in Pregnancy

Local anaesthetics rapidly cross the placenta by passive diffusion. The placental transfer of basic drugs by passive diffusion is governed by their molecular weight, lipid solubility, pKa and protein binding. For example, a base such as lidocaine (molecular weight = 234; oil-water distribution ra-

Table II. Incidence of serious anaphylactoid reactions with various local anaesthetics from 1985 to 1987 (after Watkins,[285] with permission)

Year	Bupivacaine	Prilocaine	Lidocaine (lignocaine)
1985	3	0	2
1986	3	2	0
1987	8	1	1

tio at pH 7.20 = 30.2; pKa = 7.86) easily and rapidly crosses the placenta.[290] Furthermore, spinal or extradural anaesthesia for caesarean section and vaginal delivery may lead to maternal hypotension.[291] This may reduce uteroplacental blood flow and intervillous perfusion and cause fetal hypoxia, acidosis and bradycardia, and neonatal CNS and respiratory depression.[290,292-294]

Recently, however, numerous reports attest to the fetal and neonatal safety of maternal obstetric anaesthesia with various local anaesthetics.[295-299] However, administration of a large dose of local anaesthetics may produce excessive fetal and neonatal serum concentrations, leading to fetal acidosis, and CNS and cardiac toxicity, presumably because of ion trapping of local anaesthetics.[300] In one report, the administration of lidocaine either into the paracervical tissues or directly into the uterine cavity precipitated fetal heart-rate decelerations.[301]

3. Drug Interactions

3.1 Pharmacokinetic Interactions

3.1.1 Drugs Added to the Local Anaesthetic Preparation

Epinephrine (5 μg/ml) is frequently added to local anaesthetic solutions to prolong the duration of analgesia,[302,303] to serve as a marker for inadvertent intravascular injection and to delay vascular absorption of local anaesthetics, thus minimising plasma concentrations and systemic toxicity. However, the effect of adding epinephrine to bupivacaine or etidocaine is controversial.[302-305] Some reports[302,303] indicate that the addition of epinephrine enhances the quality of analgesia produced by neuraxial administration of bupivaaine or etidocaine, whereas others demonstrated that the action of these agents is not markedly affected by epinephrine.[306]

Several experimental and clinical studies have shown that clonidine was able to prolong the duration of action of local anaesthetics.[307-310] It has been reported that the analgesia obtained with clonidine lasts longer than that obtained with epinephrine.[308] The influence of clonidine on plasma concentrations of local anaesthetics is controversial. In some studies, clonidine was found to increase plasma concentrations of lidocaine[310] and bupivacaine,[311] while in another, it resulted in a greater than 50% reduction of peak plasma lidocaine concentrations.[312] Clonidine, however, was found to alter hepatic metabolism of bupivacaine, leading to increased plasma concentrations of bupivacaine.[311] Intrathecally, clonidine does not appear to alter spinal cord blood flow or cause neurotoxicity. Clonidine did not augment bupivacaine or lidocaine-induced toxicity.[313,314]

Hyaluronidase is used to improve the spread of local anaesthetic solutions through tissue planes.[315] Many combinations of local anaesthetics and hyaluronidase have been used, mainly for ocular anaesthesia, to enhance akinesia,[315,316] to speed the onset of surgical anaesthesia,[317] and to reduce the requirements for supplemental injections prior to surgery, compared with the situation if it was not used.[318] The addition of hyaluronidase, with or without epinephrine, to bupivacaine 0.75% was found to provide a better and faster globe akinesia compared with the addition of epinephrine.[304] In contrast to the effects of epinephrine, hyaluronidase had no significant effect on peak plasma concentrations of lidocaine or bupivacaine.[319]

Although the addition of low–molecular-weight dextran has been reported in some studies to prolong the duration of local anaesthetic action,[320] the consensus of opinion indicates that dextran does not affect the kinetics or enhance the action of local anaesthetics.[321]

3.1.2 Other Drugs

Ephedrine is one of the commonly used agents to treat systemic hypotension. It has been reported to increase plasma lidocaine concentrations following epidural administration, possibly because of the increased uptake of lidocaine from the epidural space, secondary to the increase in cardiac output. Other contributory factors might include a reduction in the volume of distribution as a result of peripheral vasoconstriction and, possibly, reduced hepatic clearance because of splanchnic

vasoconstriction.[322] However, no reports of serious adverse reactions to ephedrine have been found.

Since local anaesthetics not only block voltage–dependent sodium channels, but also calcium and potassium channels, interactions might be expected to occur with pharmacological agents, such as antidysrhythmic drugs (sodium-channel blockers), sulfonylureas (potassium-channel blockers) and calcium antagonists.[323]

Concomitant administration of oral viscous lidocaine 2% and mexiletine resulted in a significant increase in serum lidocaine concentrations and subsequent lidocaine toxicity;[324,325] similar observations of adverse effects were reported with disopyramide[326] and procainamide.[327] Although there are reports suggestive of interference with lidocaine clearance by amiodarone,[328] a study of the effects of combined therapy on lidocaine pharmacokinetics found no change in clearance or any other pharmacokinetic parameter.[329] There is evidence that phenytoin may stimulate the hepatic metabolism of lidocaine, resulting in reduced serum lidocaine concentrations.[330,331]

Combinations of calcium antagonists and local anaesthetics exert pronounced negative inotropic effects in animals. The effects of some local anaesthetics, on cardiac contractility are enhanced in the presence of calcium antagonists.[323] In animals, local anaesthetic–induced mortality was significantly increased by different calcium antagonists (diltiazem, verapamil and bepridil).[332] This was probably related to the increased free fraction of bupivacaine, resulting in enhanced toxicity.[333] In contrast, nimodipine was found to reduce the toxicity of intravenous bupivacaine in rats.[334] Nimodipine is usually used to improve the neurological deficits caused by cerebral artery spasm following subarachnoid haemorrhage.

Concomitant lidocaine and β-blocker therapy may reduce the clearance of local anaesthetics from the plasma.[335-337] This effect may be attributed to a β-blocker–induced reduction in cardiac output and hepatic blood flow, and inhibition of hepatic microsomal enzymes. A 30% increase in mean steady-state concentrations of lidocaine has been observed during concomitant propranolol therapy. This difference is of clinical significance and lidocaine doses should be adjusted accordingly. Additionally, the negative inotropic effect of propranolol and possibly other β-blockers, may be enhanced by lidocaine.[335-337] However, long term β-blocker therapy does not need to be discontinued before the use of local anaesthetics.[338,339]

In vitro studies have shown that bupivacaine dramatically reduces the binding of mepivacaine to α1-acid-glycoprotein. Concomitant administration of both drugs would be expected to produce higher than expected free concentrations of mepivacaine and increase the risk of systemic toxicity.[340] Other *in vitro* studies have demonstrated that pethidine (meperidine), phenytoin, quinidine and desipramine can displace bupivacaine from plasma proteins.[341] Extrapolation of this effect to patients receiving these drugs would result in an increase of 300 to 500% in the free fraction of bupivacaine. It should be noted, however, that drug interactions of this type have yet not been reported to be of great clinical or toxicological concern.[341]

Although ranitidine and nizatidine were found not to alter lidocaine pharmacokinetics,[342-344] cimetidine was reported to the significantly affect the pharmacokinetics of this local anaesthetic.[343] The effects of cimetidine on a lidocaine infusion included a 25 to 30% reduction in clearance, a decreased volume of distribution, reduced protein binding, increased peak plasma concentration and prolonged half-life. An increased incidence of neurotoxicity, cardiac dysrhythmias and seizures was also reported.[345] Cimetidine did not alter the pharmacokinetics or metabolism of bupivacaine.[346] Single doses of oral cimetidine 400mg or ranitidine 150mg, administered 90 to 120 minutes before epidural block with bupivacaine resulted in no significant effect on the disposition of bupivacaine.[347]

Prolonged use of ecothiopate could impair hydrolysis of ester-type local anaesthetics, secondary to reduced plasma cholinesterase activity.[348] However, in one report, a patient who had been receiving ecothiopate 0.125% eye drops twice daily for several years underwent epidural anaes-

Table III. Pharmacokinetic interactions of local anaesthetics

Interacting drug	Effect	Mechanism	Management
Epinephrine (adrenaline)[302-305]	↓ Plasma concentrations → prolonged duration of analgesia and ↓ systemic toxicity of local anaesthetics. The effect of adding epinephrine to bupivacaine or etidocaine is controversial	Delayed vascular absorption of local anaesthetics	Clinically useful
Clonidine[307-314]	Prolongs the duration of action of local anaesthetics	1. Clonidine-induced reduction in local blood flow → reduction of local anaesthetic systemic absorption. 2. ? Inhibition of hepatic metabolism of local anaesthetics	Clinically useful
Hyaluronidase[315-319]	Improves the quality of local anaesthetic–induced block in ocular surgery. No significant effect on peak plasma concentrations of local anaesthetics	Improved spread of local anaesthetics through tissue planes	Clinically useful
Ephedrine[322]	↑ Plasma lidocaine (lignocaine) concentrations following epidural administration → lidocaine toxicity	↑ Uptake of lidocaine from epidural space secondary to: (i) ↑ cardiac output; (ii) ↓ volume of distribution and; (iii) ↓ hepatic clearance	Monitor the patient (CNS, CVS and respiratory system)
Antiarrythmic drugs:			
mexiletine,[324,325] disopyramide,[326] procainamide,[327] amiodarone,[328]	↑ Plasma lidocaine concentrations → lidocaine toxicity	? ↓ Clearance of local anaesthetics	Monitor patients receiving antidysrhythmic drugs and local anaesthetics. If possible, avoid such combinations in patients with known heart disease
phenytoin[330,331]	↓ Plasma concentrations of local anaesthetics	Hepatic enzyme induction → ↑ metabolism of amide-type local anaesthetics	
Calcium antagonists (diltiazem, verapamil and bepridil)[323,332-334]	Pronounced negative inotropic effects and significant increases in local anesthetic–induced mortality in animals	↓ Protein binding → ↑ free fraction of local anaesthetics	Avoid combination, if possible. If used, monitor for local anaesthetic toxicity and adjust dose accordingly. Intravenous calcium gluconate may be beneficial
β-Blockers[335-339]	↓ Clearance of local anaesthetics → ↑ adverse effects of both β-blocker and local anaesthetic drugs	Inhibition of hepatic microsomal enzymes	Decrease local anaesthetic dose. Long term β-blocker therapy does not need to be discontinued before the use of local anaesthetics
Bupivacaine and mepivacaine[340]	Concomitant administration of both drugs could produce higher than expected free concentration of mepivacaine and increase the risk of systemic toxicity	Bupivacaine reduces the binding of mepivacaine to α-1-acid glycoprotein	Avoid combination
Pethidine (meperidine), diphenylhydantoin, quinidine and desipramine[341]	↑ Free fraction of bupivacaine (and possibly other local anaesthetics) in animal studies	Displaces bupivacaine from plasma proteins	Monitor for local anaesthetic toxicity and adjust dose accordingly

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Table III. Contd

Interacting drug	Effect	Mechanism	Management
Cimetidine[343-347]	↑ Toxicity of lidocaine. No effect on bupivacaine	↓ Lidocaine metabolism, clearance, volume of distribution and protein binding → ↑ peak concentrations and prolonged half-life. Cimetidine does not alter the pharmacokinetics or metabolism of bupivacaine	Monitor for lidocaine toxicity and adjust dose accordingly. Consider another H_2-antagonist (e.g. ranitidine or famotidine) with less potential to alter lidocaine metabolism
Acetazolamide[348]	? ↑ Toxicity of procaine and possibly other ester-type local anaesthetics	Prolonged half-life of procaine	If possible, avoid this combination
Ecothiopate[349]	? ↓ Hydrolysis of ester-type local anaesthetics → ? ↑ toxicity	↓ Plasma cholinesterase activity	If possible, avoid this combination

Abbreviation and symbols: CVS = cardiovascular system; ↓ = decreased; ↑ = increased; → = leading to; ? = possible.

thesia with chloroprocaine without any signs of extended or enhanced action of chloroprocaine.[349] Administration of acetazolamide prolonged the half-life of procaine.[348]

The pharmacokinetic drug interactions involving local anaesthetics are summarised in table III.

3.2 Pharmacodynamic Interactions

α-Adrenergic receptors in the spinal cord are known to mediate endogenous analgesic mechanisms, and the potentiation of analgesia produced by epinephrine and clonidine with both epidural and intrathecal local anaesthetics may arise both from pharmacodynamic[350,351] and pharmacokinetic (vasoconstrictive) mechanisms.[302,303,307-310]

Intrathecal administration of cholinergic agonists decreased the hypotension observed after bupivacaine spinal block in rats. This vasopressor effect of cholinergic agonists is probably mediated by muscarinic M_2 receptors.[352]

Concomitant use of β-blockers and local anaesthetics, especially those containing epinephrine, may result in enhanced sympathomimetic adverse effects, including hypertensive crisis.[353,354] However, malignant hypertension is probably uncommon in patients receiving low doses of epinephrine. Long term β-blocker therapy does not need to be discontinued before the use of local anaesthetics.[338,339] Concomitant use of phenytoin and lidocaine (both are class IB antidysrhythmics) has resulted in additive cardiac depression.[355]

Local anaesthetics interfere with the release of acetylcholine and, in high concentrations, can produce neuromuscular blockade.[356] In clinical practice, local anaesthetics can potentiate neuromuscular blockade induced by either depolarising or nondepolarising neuromuscular blockers.[356-358] Hence, local anaesthetics given intraoperatively as antidysrhythmic agents or postoperatively may augment a residual neuromuscular blockade.

Plasma lidocaine concentrations of 3 to 6 mg/L decreased inhalational anaesthetic requirements by about 10 to 28%.[359] At clinically useful concentrations of lidocaine, significant decreases in anaesthetic requirements should be anticipated.

The convulsant activity and mortality associated with the bupivacaine were increased by flumazenil in animals.[360,361]

Animal studies have demonstrated antinociceptive synergism between intrathecal opioids and local anaesthetics during visceral and somatic nociception.[362,363] In humans, neuraxial administration of opioids in conjunction with local anaesthetics improves the quality, and prolongs the duration, of analgesia.[364]

Local anaesthetics that are para-aminobenzoic acid derivatives (benzocaine, procaine and tetracaine) can antagonise the antibacterial activity of sulfonamides. It is suggested that local anaesthetics that are not para-aminobenzoic acid derivatives

Table IV. Pharmacodynamic interactions of local anaesthetics

Interacting drug	Effect	Management
Epinephrine (adrenaline) and clonidine[350,351]	↑ Analgesia produced by epidural and intrathecal local anaesthetics	Clinically useful
Intrathecal administration of cholinergic agonists[352]	↓ Hypotension observed after local anaesthetic spinal block	? Clinically useful
β-Blockers[353,354]	Malignant hypertension in patients receiving local anaesthetics containing epinephrine	Probably uncommon in patients receiving low doses of epinephrine. Long term β-blocker therapy does not need to be discontinued before the use of local anaesthetics. Whenever possible, avoid epinephrine-containing anesthetics in patients receiving nonselective β-blockers
Phenytoin[355]	Additive cardiac depressive effects	If possible, avoid this combination in patients with known heart disease
Depolarizing and nondepolarizing neuromuscular blockers[356-358]	↑ Neuromuscular blockade	Monitor neuromuscular function
Volatile anaesthetics[359]	↓ Volatile anaesthetic requirements	Titrate volatile anaesthetic concentrations. May be clinically useful
Flumazenil[360,361]	↑ Convulsant activity and bupivacaine-induced mortality in animals	Avoid combination
Opioids[362-365]	Antinociceptive synergism between neuraxial opioids and local anaesthetics → improved quality and prolonged the duration of analgesia induced by local anaesthetics	Clinically useful
Sulfonamides[366]	↓Antibacterial effects when combined with local anaesthetics derived from para-aminobenzoic acid [benzocaine, procaine, tetracaine (amethocaine)]	Consider using local anesthetics that are not para-aminobenzoic acid derivatives in patients receiving sulfonamides

Symbols: ↓ = decreased; ↑ = increased/potentiation; → = leading to; ? = possible.

be used in patients receiving these antibacterials or that higher doses of sulfonamides are administered in case para-aminobenzoic acid derivatives are to be used.[366]

Pharmacodynamic drug interactions with local anaesthetics are summarised in table IV.

4. Conclusions

It is now evident that multiple mechanisms and receptor affinities contribute to the toxicity of local anaesthetic agents. The best form of management of toxic reactions is prevention. Meticulous technique should be used, along with test doses whenever possible, and the local anaesthetic solution should be administered slowly in small and divided doses. It is also necessary to have knowledge of those doses of local anaesthetic that should not be exceeded. The maximum allowed doses of local anaesthetics are listed in table V. Proper documentation of the technical procedures and postoperative follow-up are integral components of patients' care.

If systemic toxic reactions occur, early detection and prompt support of ventilation and circulation are necessary. Aggressive standard Advanced Cardiac Life Support[108,109,111,114,122] techniques

Table V. Maximum allowed doses of local anaesthetics

Drug	Maximum dose (mg/kg)	
	without epinephrine (adrenaline)	with epinephrine
Procaine	10	14
Chloroprocaine	10	14
Tetracaine (amethocaine)	2	2
Dibucaine (cinchocaine)	2	2
Lidocaine (lignocaine)	5	7
Prilocaine	7	10
Bupivacaine	2.5	3
Etidocaine	4.5	6.5
Mepivacaine	6	8
Ropivacaine	3.5	Not defined yet

should be sustained for a prolonged period. Recent studies, however, have demonstrated that the incidence of cardiovascular collapse from local anaesthetic injection is very low (none of 25 697 brachial/caudal/lumbar epidural block procedures,[367] and 1 in 40 010 epidural block procedures).[368]

Local anaesthetics interact with other classes of drugs. It is, therefore, essential that careful scrutiny of the patient's drug history should be an integral part of the preoperative assessment.

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