

# LOCAL ANAESTHETIC AGENT TOXICITY

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## 1 Pharmacodynamics of local anaesthetic agents:

Local anaesthetic agents reversibly block the action potentials responsible for nerve conduction. This action is demonstrable in any part of the nervous system and on every type of nerve fibre.

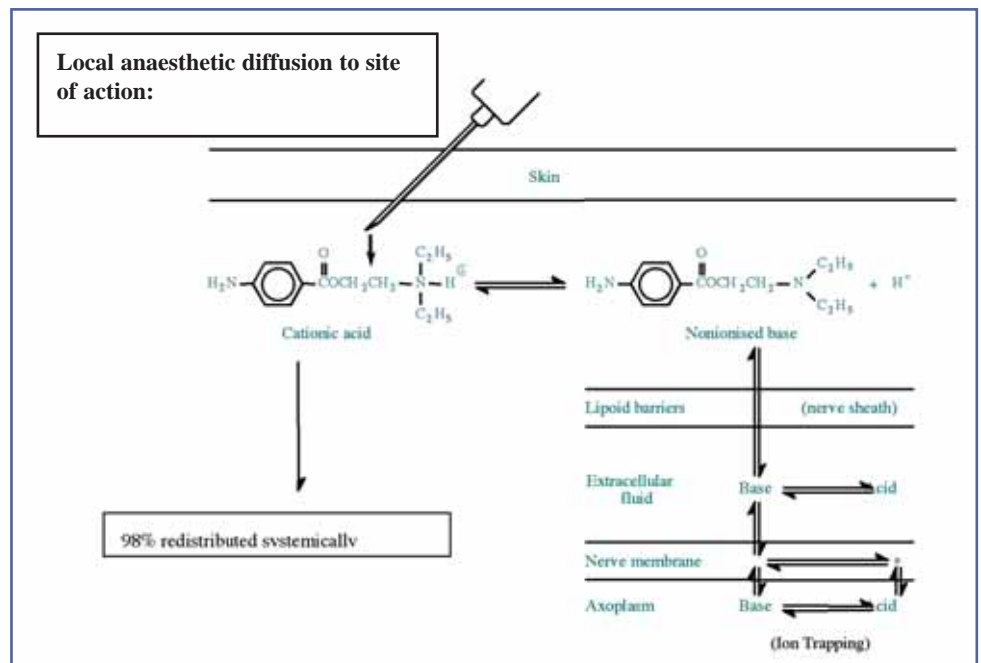
The Na<sup>+</sup> selective transmembrane pore of the channel is presumed to reside in the centre of a nearly symmetrical structure formed by the four homologous domains of a 300KDa protein complex. A change in the transmembrane potential towards the threshold value induces conformational changes in the molecule, which cause the Na<sup>+</sup> channel to open. This gives rise to a rapid influx of Na<sup>+</sup> with further depolarisation of the cell membrane. After it opens, the Na<sup>+</sup> channel inactivates within a few milliseconds due to closure of an inactivation gate.

Local anaesthetic agents produce conduction blockade by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na<sup>+</sup> that normally is produced by a slight depolarization of the membrane. This seems to occur via an interaction of the local anaesthetic molecule with a binding site inside the (open) voltage-gated Na<sup>+</sup> channels. Binding of the local anaesthetic agent stabilises the inactive state of the channel. This binding site is only accessible from the intracellular side of the cell membrane. In order to reach this site the delivered (water soluble) cationic acid first needs to dissociate into its lipid soluble nonionised base form.

Dissociation of the local anaesthetic molecule from its binding site within the channel may occur

either via the lipid phase or through the open pore. Dissociation via the lipid phase appears to occur 20-50 times as rapidly as via the channel, but requires that the molecule be in the unionised base form. Extracellular protons may bind to the amine portion of the local anaesthetic in the channel and tend to trap it there. The clinical implication of this is that a decrease in pH increases the binding of local anaesthetic molecules to Na<sup>+</sup> channels, increasing toxic potential.

Phasic inhibition (Frequency dependent blockade) refers to the phenomenon of increased impulse blockade due to repetitive stimulation of a nerve fibre. This is thought to occur because the local anaesthetic molecule in its charged form gains access to the binding site only when the Na<sup>+</sup> channel is in its open state. After binding, the channel is then stabilised in the inactive state. Because binding therefore takes place only during depolarisation and dissociation occurs between action potentials, rapid stimulation of a nerve fibre leads to accumulation of inactivated (bound) channels at rapid stimulation rates. As mentioned before, in order for the local anaesthetic molecule to dissociate from the channel (via the open channel



pore) it should preferably be in its water soluble state - more hydrophobic drugs tend to dissociate slowly from the pore (dissociation constant for bupivacaine typically up to 2 seconds). Smaller and more hydrophilic drugs dissociate more rapidly, so a higher frequency of stimulation is needed with these drugs to yield frequency-dependent block. A clinical correlate of this is the reduced therapeutic index of the more hydrophobic drugs (e.g. bupivacaine).

## 2 Pharmacokinetics of local anaesthetic agents:

Absorption from the GI tract is rapid, with peak plasma levels occurring within 30-60 minutes. There is significant first-pass hepatic metabolism of amide-type agents. Bioavailability of orally ingested lignocaine is only about 35%.

Ester type agents are rapidly metabolized in the plasma by pseudocholinesterases, with minimal liver esterase metabolism. Amide type agents are metabolized by hepatic microsomal enzymes. Their elimination is prolonged by liver disease, immaturity, and decreased hepatic blood flow. Only small amounts of either type of drug are excreted unchanged in the urine.

### 2.1 Blood levels according to administration site:

The following lists some sites of administration in approximate order of their associated blood levels:

- Intercostal nerve blocks (highest level),
- Paracervical nerve blocks,
- Brachial plexus anaesthesia,
- Epidural anaesthesia.
- Spinal anaesthesia, on the other hand, requires very little drug and is associated with very low blood levels of anaesthetic.

### 2.2 Reproductive system redistribution:

Local anaesthetic agents readily cross the placenta. Foetal or neonatal poisoning may occur as a result of maternal poisoning. Bupivacaine foetal toxicity after maternal administration may be lower than that of lignocaine, most probably related to higher maternal protein binding. Although local anaesthetics are pres-

ent in breast milk, the concentrations found (40% of serum levels) would not be expected to produce detectable effects.

### 2.3 Serum elimination half-lives:

Lignocaine: 1.5-2 hours. Active metabolites MEGX = 2 hrs, GX= 7-10 hrs

Bupivacaine: 1.3-5.5 hours.

Ropivacaine: 1.6-5.5 hours.

Levobupivacaine: 2.06-2.6 hours.

### 2.4 Attempts at enhancement of local anaesthetic elimination:

- Diuresis: less than 5-10% of a dose is excreted in the urine as unchanged drug. Although acidification of the urine will enhance the excretion, the contribution to overall elimination is small and the risk outweighs the benefit.
- Both haemodialysis and haemofiltration are ineffective
- Exchange transfusion is ineffective

Local anaesthetic toxicity may be classified into systemic and local toxicity:

## 3 Systemic toxicity:

The following additional mechanisms of action may play a role in toxicity:

- Calcium ion channels:  
Inhibition of voltage gated  $Ca^{2+}$  currents across the neuronal cell membrane leads to diminished neurotransmitter release, contributing to analgesia in neuraxial administration. As far as cardiotoxicity is concerned, it has been shown that the sensitivity of myocardial  $Ca^{2+}$  channels to bupivacaine is comparable to that of the voltage gated  $Na^{+}$  channels.
- Inhibition of  $K^{+}$  channels:  
Local anaesthetic agents block neuronal  $K^{+}$  channels in high concentrations - probably not of any clinical significance in therapeutic doses, but may be of importance in the development of cardiotoxicity.
- Inhibition of mitochondrial oxidative metabolism:  
Implicated in cardiac toxicity as well as myotoxicity:

- 'Mitochondrial uncoupling' at low concentrations.
- Respiratory inhibition at higher concentrations.
- Interference with ATP synthase.
- Interference with:
  - G-protein modulation of Ca<sup>2+</sup> and K<sup>+</sup> channels.
  - Substance P binding to its neuronal receptor.
  - Binding of muscarinic agonists to their receptor.
  - Beta-adrenergic pathways.
  - Lysophosphatidate signalling.

It is important to note that toxicity of anaesthetics may be potentiated in patients with renal or hepatic compromise, respiratory acidosis, pre-existing heart block, or heart conditions. Toxicity may be potentiated during pregnancy, at the extremes of age, or in those with hypoxia. However, the most common cause of local anaesthetic toxicity is inadvertent intravascular injection. In this respect the degree of protein binding a drug exhibits may play a role: It is thought that the high degree of protein binding by bupivacaine causes free drug levels to suddenly rise disproportionately when available binding sites become saturated - underlining the importance of fractionated injection techniques.

Systemic toxic reactions to local anaesthetics are manifested by a progressive spectrum of neurological symptoms as blood levels rise. Initial symptoms suggest some form of central nervous system excitation and are often described as a ringing in the ears, a metallic taste in the mouth, or a circumoral tingling. With increasing blood levels of local anaesthetics, there is progression to motor twitching in the periphery followed by grand mal seizures. These higher blood levels are associated with coma and eventually respiratory arrest. At extremely high levels, cardiac arrhythmia or hypotension and cardiovascular collapse occur.

### 3.1 Cardiovascular

The most dreaded form of toxicity to local anaesthetics is cardiovascular toxicity. There is a positive correlation between the cardiotoxic potency of a local anaesthetic agent, its lipid solubility and nerve block-

ing potency. The rank order of toxicity is as follows (low to high toxicity): Prilocaine < Lignocaine < Mepivacaine < Ropivacaine < Levobupivacaine < racemic Bupivacaine < R-Bupivacaine < Etidocaine < Tetracaine. The dissociation time constant for bupivacaine from sodium channels is approximately 2 seconds - this is at least tenfold longer than that of lignocaine. The pharmacodynamics of lignocaine at the sodium receptor are commonly referred to as being "fast-in-fast-out," in contrast with bupivacaine being "fast-in-slow-out". This timing results in greater cardiac depression by bupivacaine, which is out of proportion to its potency at sodium channels. Overdose is therefore more likely to result in cardiovascular collapse with bupivacaine than with other agents. For example, the dose needed for cardiovascular collapse divided by the dose needed for convulsions is 3.7 for bupivacaine compared with 7.1 for lignocaine. When bupivacaine toxicity occurs, it is also more likely to result in ventricular arrhythmias than with other agents. Pregnant women appear to be more sensitive to bupivacaine cardiac toxicity.

The two most important components of local anaesthetic cardiac toxicity are arrhythmias and contractile depression. Peripheral vasodilatation also occurs, worsening the hypotension. Furthermore, local anaesthetic overdose is likely to cause seizures, hypoxia, or acidosis, all of which may exacerbate cardiotoxicity. The resulting cycle of systemic and myocardial hypoperfusion, tissue acidosis, and worsening cardiac performance can lead to failed resuscitation.

#### 3.1.1 Manifestation:

The circulatory effects of local anaesthetic agents may be summarised as follows:

##### 3.1.1.1 Vasomotor:

Direct effects of local anaesthetic agents on blood vessels are highly variable, with some studies showing vasoconstriction and others vasodilatation. This discrepancy may reflect dose-dependent effects as well as the confounding effects of the sympathetic nervous system in the intact animal. In the initial phase or in mild intoxication, catecholamine release and vasoconstriction may cause hypertension and tachycardia. Late hypotension and cardiovascular collapse may be due to sympathetic blockade (neuraxial

block), depression of the medullary vasomotor centre, hypoxia, acidosis or vasodilatation.

### 3.1.1.2 Myocardial contractility:

Local anaesthetic agents produce a dose dependent decrease in myocardial contractile force, probably via interference with myocardial energetics. At higher doses, they may also act via reduction of intracellular  $Ca^{2+}$ :

- Blockade of  $Ca^{2+}$  channels leads to diminished inward  $Ca^{2+}$  current
- Reduced myoplasmic  $Ca^{2+}$  reduces  $Ca^{2+}$ -induced  $Ca^{2+}$  release
- Local anaesthetic agents seem to inhibit the function of the sarcoplasmic  $Ca^{2+}$  release channel

### 3.1.1.3 Arrhythmias:

Local anaesthetic agents depress cardiac automaticity. Phase 4 depolarisation of pacemaker cells during diastole is slowed due to  $Ca^{2+}$ -channel blockade. Cardiac impulse conduction is slowed due to diminished inward  $Na^{+}$  current. This leads to a prolonged PR interval, widened QRS complex and AV block. Slowed conduction predisposes to unidirectional block and re-entry, which may cause ventricular tachycardia and fibrillation. A CNS mechanism may also contribute to cardiotoxicity: Intracranial (and cervical intra-arterial) administration of bupivacaine is followed by ventricular arrhythmias, probably via sympathetic nervous system activation.

Therapeutic lignocaine concentrations have no effect on the QRS duration, although the QT time and AV refractory period may decrease. Lignocaine in progressively increasing doses leads to prolongation of the PR time, AV block (especially in patients with underlying bundle-branch disease), widening of the QRS complex (apparently uncommon) and eventual circulatory failure and hypotension. Sinus bradycardia is a common manifestation of toxicity. On the other hand, bupivacaine toxicity tends to present

with progressive widening of the QRS complex, ventricular arrhythmias, electromechanical dissociation and refractory asystole. These differences are thought to reflect the different binding characteristics of these drugs at the cardiac  $Na^{+}$  channel. Adrenaline used during resuscitation is more likely to cause tachyarrhythmias in the face of bupivacaine toxicity than with lignocaine.

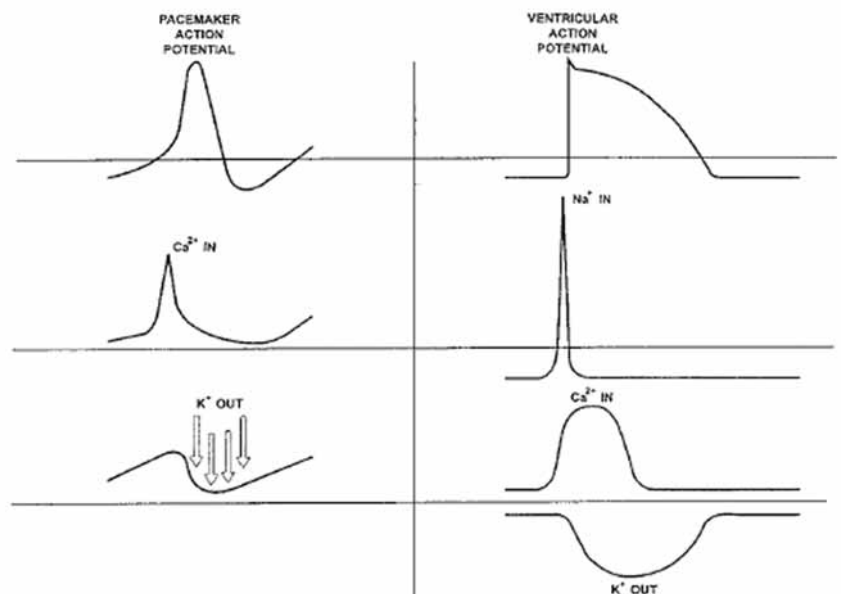
### 3.1.2 Management of cardiac toxicity:

Initial management of cardiac toxicity is according to ACLS guidelines. Because hypercapnia, hypoxia and acidosis exacerbate local anaesthetic toxicity, airway management and suppression of seizure activity are key therapeutic interventions. Ventilation should not be aimed at hypocapnia, but rather at the normalisation of arterial pH and oxygen delivery. Because of the strong binding of bupivacaine to cardiac receptors, resuscitation should be continued for "far longer than is usual". It may be worthwhile to plan for cardiopulmonary bypass early in the course of resuscitation.

#### 3.1.2.1 Specific therapy:

- Sympathomimetic agents improve outcome - probably by raising coronary perfusion pressure

Ionic currents forming pacemaker action potentials (left) and ventricular action potentials (right) in the heart. Note that the initial upstroke of pacemaker potentials is due to calcium flux and the initial upstroke of ventricular action potentials is due to sodium flux.



and thereby facilitating washout, but also by counteracting the low output state that is central to this condition. High doses of adrenaline - in the order of 2-3 times usual doses - should be used. Some authors point out that adrenaline may exacerbate arrhythmias without increasing cardiac output - this may be especially problematic in cases of bupivacaine toxicity. Vasopressin may have a theoretical advantage in these circumstances.

- Arrhythmias are probably best managed with amiodarone. Although there may be theoretical reasons to use lignocaine in cases of bupivacaine toxicity, this is not consistently supported by studies.
- Lipid emulsion: Pre-treatment with lipid emulsion has been shown to increase the toxic dose of bupivacaine, and the use of lipid emulsion during resuscitation has similarly been shown to improve outcome. There are two possible mechanisms:
  - Bupivacaine severely impairs transport of fatty acid molecules in cardiac mitochondria, where they are the dominant fuel for aerobic metabolism. Increased concentrations of fatty acids may overcome this bupivacaine-induced blockade.
    - An artificially induced lipid phase in blood may decrease the effective plasma concentration of lipophilic local anaesthetic molecules.
- Propofol: It seems as if propofol reduces lignocaine- or bupivacaine-induced hypotension independent of the effects of the lipid carrier. In addition to this, propofol may be useful by:
  - Suppressing seizures
  - Aiding in the recovery from tissue hypoxia via antioxidant effects
- Insulin/Glucose/K: Insulin treatment (with or without Potassium) has been shown to improve outcome of resuscitation in laboratory animals. This may be due to two mechanisms:
  - Insulin increases the amount of K<sup>+</sup> entering cells, which may counteract the bupivacaine-induced inhibition K<sup>+</sup> channels, allowing for improved myocardial repolarisation.
  - Insulin/Glucose may improve intracellular availability of alternative substrates in the presence of Bupivacaine induced inhibition of lipid substrate utilisation.

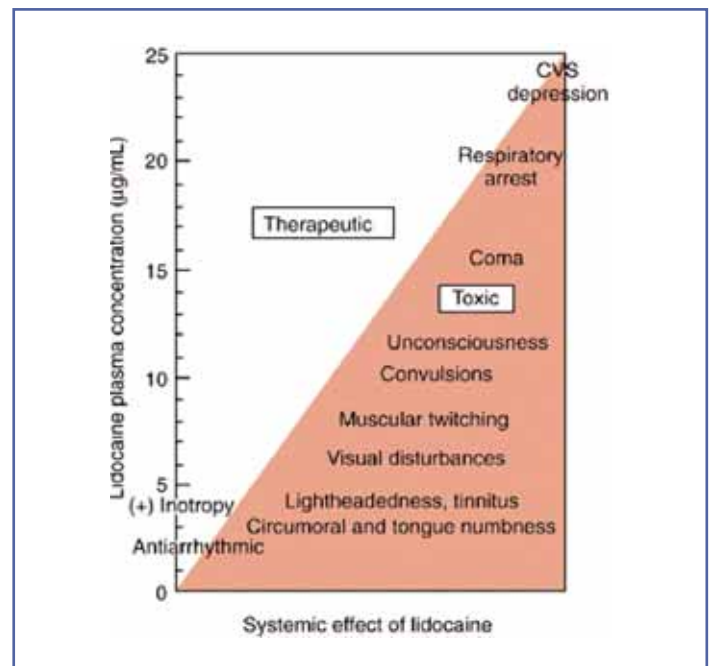
The potential effects of induced hyperglycaemia on neurological outcome merit consideration when this technique is used in more severe cases of local anaesthetic toxicity. Also, it is worth noting that hyperkalaemia potentiates local anaesthetic cardiotoxicity.

### 3.1.2.2 Drugs not to use:

- Calcium channel blockers: Additive toxicity and increased mortality has been shown in mice.
- Phenytoin: Increases toxicity due to Na<sup>+</sup> channel blocking effects.
- Bretylium: "Not supported"

### 3.2 Central Nervous System:

Although local anaesthetics are anticonvulsant at low concentrations (probably mediated by potentiation of inhibitory GABA-ergic neurotransmission - lignocaine 1.5-2 mg/kg has been recommended for the management of refractory status epilepticus), they are convulsant at toxic concentrations. The proconvulsant effects of local anaesthetic agents are additive. A rapid rise in blood concentration leads to CNS manifestations at lower blood levels than would be evident with slower administration. Hyponatraemia, possibly secondary to SIADH, has been reported after lignocaine toxicity.



### 3.2.1.1 Interactions:

- Prophylactic administration of benzodiazepines reduce the likelihood of CNS manifestations of toxicity without affecting that of cardiovascular toxicity, thereby potentially abolishing early warning signs of potential toxicity.
- Systemic hypercarbia decreases lignocaine seizure threshold, probably via effects on pH as well as cerebral blood flow.
- Muscle paralysis prevents systemic acidosis and hypoxia, but does not prevent cerebral lactic acidosis. This results in further cerebral ion trapping of local anaesthetic agent. Increased blood-brain barrier permeability secondary to ongoing convulsions may increase CNS uptake even further, leading to CNS-mediated inotropic and chronotropic suppression of the myocardium.
- Co-administration of local anaesthetic agents with adrenaline may lead to hypertension with consequent lowering of the seizure threshold.

### 3.2.1.2 Management of seizures:

- Initial control should be attempted with a benzodiazepine.
- Persistent convulsions should be treated with phenobarbital.
- Phenytoin should be avoided as it may worsen cardiac arrhythmias.

### 3.3 Haematological:

Methaemoglobinemia has been reported primarily with prilocaine toxicity (even after use of EMLA cream). Lignocaine and benzocaine have also been implicated, although co-administered drugs may have been predisposing factors.

### 3.4 Allergic reactions:

Amino esters are derivatives of para-aminobenzoic acid (PABA), which has been associated with acute allergic reactions. Previous studies indicate a 30% rate of allergic reactions to procaine, tetracaine, and chlorprocaine. Amino amides are not associated with PABA and do not produce allergic reactions with the same frequency. However, it has been noted that preparations of amide anaesthetics may sometimes contain methylparaben, which structurally is similar to PABA and thus may give rise to allergic reactions.

### Treatment of lignocaine overdose:

(From Haddad: Clinical Management of Poisoning and Drug Overdose, 3rd ed.)

1. General management:
  - a. Discontinue further administration
  - b. Oral ingestion: Administer charcoal and possibly lavage
  - c. Seizures: Administer diazepam, up to 5-10 mg IV
2. Impaired Myocardial Conduction:
  - a. Sodium bicarbonate: 0.5-1 mEq/kg IV. Repeat every 5-10 minutes to maintain arterial pH of 7.4-7.5
3. Arrhythmias:
  - a. Bradyarrhythmias:
    - i. Isoproterenol
    - ii. Cardiac pacemaker
  - b. Ventricular tachycardia:
    - i. Overdrive pacing  
(avoid using other type Ib antiarrhythmic drugs)
4. Hypotension:
  - a. Administer normal saline, 2-3 ml/kg every 10 minutes until response, 15-30 ml/kg has been given, or evidence of pulmonary oedema demonstrated.
  - b. If patient is still hypotensive, consider pulmonary arterial catheter:
    - i. If low SVR, administer dopamine or norepinephrine
    - ii. If low cardiac output, administer isoproterenol, dobutamine, or adrenaline
  - c. If patient has intractable cardiogenic shock, consider intra-aortic balloon pump assistance or cardiopulmonary bypass
  - d. Methaemoglobinemia: Consider administering 1-2 mg/kg of 1% methylene blue if the patient is cyanotic or symptomatic, or has a methaemoglobin level > 30%
5. Accelerated drug removal:
  - a. Consider hemoperfusion in patients with massive poisonings with circulatory and / or liver failure (possibly combined with cardiopulmonary bypass)

## 4 Local toxicity:

### 4.1 Neurovascular

Other than numbness and paraesthesia, which is expected in the normal range of anaesthetic application, very high doses of anaesthetics (e.g. 5% lignocaine) administered directly onto a desheathed nerve can produce irreversible conduction block within 5 minutes. This toxicity has been shown to be concentration-dependent between 40 and 80mM (1-2%). The mechanism of this neurotoxicity remains uncertain, but is probably related to increased intracellular calcium levels. Of the currently available drugs, lignocaine appears to have the greatest potential for neurotoxicity.

With placement of anesthetic inside the perineurium, axonal degeneration and barrier changes are unequivocal and often severe. This is probably due largely to the violation of the protective perineurial barrier, but pressure and compression may play a role - intra-fascicular injections may result in compressive nerve sheath pressures exceeding 600 mmHg. Local anaesthetic agents themselves may decrease neural blood flow: 2% lignocaine can decrease neural blood flow by 39%. More substantial decrease is noted when adrenaline is added. Bupivacaine 0.25% plain decreases flow 30%, but much less with higher concentrations. Although this is an unlikely primary mechanism of injury, compromised nerves (e.g., diabetes, chemotherapy) may be more susceptible.

Transient radicular irritation (TRI) was first reported in 1993 as short-lived neurologic symptoms after spinal anaesthesia with 5% lignocaine. The symptoms are described as a continuous bilateral burning radicular pain in the buttocks, thighs, and knees (without sensory or motor deficit), typically have an abrupt onset (within 12 to 24 hours), last from 45 minutes to 48 hours (rarely up to 5 days), and then completely resolve without intervention or sequelae. Prospective studies reveal an incidence of 4-33% after lignocaine spinal anaesthesia. The incidence of TRI is unrelated to either the baricity of the solution administered or the dilution (down to 0.5%), although the addition of adrenaline may potentiate toxicity. The majority of reported cases have occurred in where more than

75mg lignocaine was administered. Peculiarly, the incidence can be related to the type of surgery performed (knee arthroscopy), outpatient status and patient positioning (lithotomy). Reports of cauda equina syndrome after continuous lignocaine spinal anaesthesia and the potential concentration-dependent neurotoxicity of lignocaine have led several authors to label TRI as a manifestation of subclinical neurotoxicity. On the other hand, concentrations of lignocaine <40 mM (equivalent to 1%) have been shown not to be neurotoxic to desheathed peripheral nerves - this argues against a concentration-dependent neurotoxic mechanism.

Only 1% of patients treated with hyperbaric bupivacaine 0.5% develop TRI after spinal anaesthesia. TRI has been reported after both epidural and spinal ropivacaine administration

### 4.2 Myotoxicity

Local anaesthetic myotoxicity was first described in 1959 and has since been associated with high incidences of muscular dysfunction after peri- and retrobulbar block for ophthalmologic procedures. Recent increases in the use of catheter nerve block techniques have added further relevance to this problem. All clinically used anaesthetic agents may cause skeletal muscle injury and even myonecrosis. This toxicity is dose-dependent, and worsens with continuous and serial administration. Tetracaine and procaine are the least, and bupivacaine the most myotoxic (Bupivacaine is established as an agent used to induce muscle degeneration in certain animal models). The clinical presentation is one of localised muscle dysfunction, tenderness and swelling. The histological presentation is that of hypercontracted myofibrils with degeneration of the sarcoplasmic reticulum and myocyte oedema and necrosis. The structural elements (basal laminae, blood vessels, neurones, connective tissue) and myoblasts remain intact, allowing for regeneration of muscle within 4-6 weeks. Co-administration of steroids or adrenaline potentiates the myotoxicity and may lead to destruction of other tissue elements, thereby predisposing towards permanent muscle damage.

The mechanism, although incompletely understood, is thought to be via increased levels of intracellular

Ca<sup>2+</sup>. Bupivacaine and ropivacaine induce release of Ca<sup>2+</sup> from as well as inhibiting reuptake into the sarcoplasmic reticulum, whereas tetracaine only inhibits Ca<sup>2+</sup> release. Further support of this theory is found in the fact that myoblasts (which remain unaffected by local anaesthetic infiltration) are unable to store large amounts of Ca<sup>2+</sup> intracellularly. The effects of local anaesthetic agents on the mitochondria - uncoupling of oxidative phosphorylation and depletion of ATP - may ultimately exacerbate the rise in intracellular Ca<sup>2+</sup> levels. Interestingly, local anaesthetic agents have been proven safe to use in patients who are susceptible to malignant hyperthermia.

The clinical significance of local anaesthetic myotoxicity is controversial. In spite of unequivocal and reproducible laboratory evidence of myotoxicity, the clinical sequelae of this condition seem to be rare. On the other hand diplopia after cataract surgery is increasingly being recognized as a complication of regional techniques - current data indicates an incidence of 0.25-0.39%. Bupivacaine seems to be responsible for the vast majority of clinically significant complications.

### 5 Summary:

Although the toxicity of local anaesthetic agents is unequivocal and often impressive, it should be kept in mind that these drugs have a long track record of safety when used correctly, and may even confer benefits to the patient beyond their immediately apparent pharmacological actions. All local anaesthetic agents should however be assumed to have extreme toxic potential. In order to prevent complications arising from the use of these agents, the following guidelines have been proposed

- Careful consideration of indications and contraindications
- Do not administer more local anaesthetic agent than is necessary:
  - Lowest effective concentration
  - Lowest effective volume
  - Limit duration of infusion
- Fractionate doses where possible
- Maintain contact with your patient during administration

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