

# Local anaesthetic toxicity

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## ABSTRACT

Local anaesthetic toxicity has been known since the introduction of local anaesthetic drugs into anaesthetic practice more than a hundred years ago. The aim of this review is to follow the history of the search for less toxic local anaesthetic drugs, to highlight molecular mechanisms thought to contribute to the clinical phenomenon of toxicity, and to finally discuss novel treatment strategies.

## Introduction

The clinical phenomenon of local anaesthetic toxicity has been known for more than a hundred years. Local anaesthesia as we know it today is the result of three events during 1850 to 1860. In 1852 Charles Gabriel Pravaz of Lyon invented a silver hollow needle, which he combined with a miniaturised glass syringe of approximately 1.5ml to use for intradermal injection. This was refined in 1853, when Alexander Woods of Scotland developed the metallic hollow needle. In 1859, two German chemists, Albert Niemann and Wilhelm Lossen, managed to isolate the alkaloid responsible for the stimulating effect of the coca plant. They called it *cocaine*.

The Austrian pharmacologist Karl Damian Ritter von Schorff was the first to think of cocaine as a narcotic. He noticed skin insensibility after the application of cocaine and postulated a central nervous system effect as mechanism of action. In 1884, Sigmund Freud proposed the use of cocaine as local anaesthetic to his friend Carl Koller, who went on to demonstrate the analgesic properties of cocaine in the eye.

Less than a year later the first reports of cocaine intoxication were described. In the following three decades, the incidence of respiratory depression and central nervous system and cardiovascular toxicity increased parallel to the more widespread use of cocaine. Severe and fatal intoxication was certainly much higher than the number of reported cases suggest. By 1928, the increasing body of evidence on mortality directly attributable to local anaesthetic use led the American Medical Association forming a Council to investigate this phenomenon. The Council concluded that, of 43 fatalities reported during that year, 40 were directly due to the action of local anaesthetics. Cocaine was responsible for 50% of these deaths, but other local anaesthetic agents used at the time (procaine, benzocaine) were also implicated. The medical and pharmaceutical industry was prompted to search for new, less toxic drugs.

At first, development concentrated on the analysis of natural products and the manipulation of existing molecular structures. It became clear that development of the ester group did not return the desired results. The main concern was the short duration of action because of the instability of the ester bonds. To increase the duration of action, the drugs were prepared in an oily formulation (which proved neurotoxic locally), or by enhancing the lipophilicity of the molecule (which made it more central nervous system- and cardiotoxic).

Lignocaine, synthesised in 1944, was the first amide local anaesthetic drug to be used clinically. It gave a dependable

block, but unfortunately was short acting. Attempts to increase its duration of action included adding vasoconstrictors, continuous administration via indwelling catheters, encapsulation in biodegradable polymers and binding to cyclodextrins, cyclising analogues and biotoxins. Of these, only the addition of a vasoconstrictor remains in clinical use.

In the quest for a still longer duration of action, a family of N-alkyl piperidine 2,6, xylydides was introduced in the 1950-'s. It was shown that increasing the N-n alkyl carbon chain length (to a maximum at C4 or C5) increased lipophilicity, which increased the duration of action but unfortunately also increased systemic toxicity. The derivatives developed for clinical use included mepivacaine (methyl group substitution on N-n), bupivacaine (butyl group substitution on N-n) and ropivacaine (propyl group substitution on N-n). Bupivacaine was discarded at first because it was about four times more toxic to the cardiovascular system than the methyl derivative mepivacaine. However, its long duration of action and the differentiation of sensory and motor blockade with low dosage have made bupivacaine (trials in 1965) the *de facto* standard long-acting local anaesthetic.<sup>1</sup>

## Local anaesthetic toxicity

Local anaesthetic intoxication is a rare but catastrophic occurrence. Local anaesthetic toxicity can be divided into three categories: local toxicity, systemic toxicity, and allergic reactions. Local toxicity may manifest in neurotoxicity, transient neurological symptoms, or myotoxicity, while systemic toxicity includes central nervous system (CNS) and cardiovascular (CVS) toxicity.

## Local toxicity

Intrathecal anaesthesia has developed into a safe, widely accepted method of anaesthesia. However, in the past two decades, case reports and incidence studies have focused attention on the direct neurotoxic effects of local anaesthetics. Most of them seem to indicate lignocaine as having more direct toxic effects than the longer-acting bupivacaine. Two syndromes have thus far been described. The first is a persistent neurological injury from spinal local anaesthetic, while the second is a transient neurological symptom complex.<sup>2</sup>

Persistent neurological injury after intrathecal anaesthesia is associated with the patients receiving lignocaine in high concentration (5% solution) as a spinal anaesthetic.<sup>3</sup> For various reasons, the use of micro-catheters for continuous administration is a contributing factor. The small diameter of the catheter prevents a high flow rate of local anaesthetic agent in the catheter. Therefore no turbulent flow can be achieved as the local

anaesthetic leaves the catheter orifice. The resultant poor mixing of local anaesthetic with the cerebrospinal fluid causes pooling of the agent in the sacral area. The *Cauda Equina* is therefore subjected to high concentrations of local anaesthetic.

The neurotoxic effects of the local anaesthetics are probably mediated by a mechanism other than Na<sup>+</sup> channel blockade. The proposed models of neuronal injury (e.g. glutamate excitotoxicity, the production of reactive oxygen species)<sup>4</sup> include depletion of ATP, mitochondrial injury and prolonged elevation of cytosol Ca<sup>++</sup>. Na<sup>+</sup> channel blockade and the resultant electrical inactivity will preserve ATP levels and decrease neuronal metabolism. Furthermore, the level of cytosol Ca<sup>++</sup> is expected to be low not only as a result of blockade of the Na<sup>+</sup>/Ca<sup>++</sup> exchanger, but also because of the ability of local anaesthetics to block Ca<sup>++</sup> channels as well.<sup>5</sup>

Transient neurological symptoms (TNS) comprise a syndrome of pain or dyesthesia in the buttocks or legs after recovery from spinal anaesthesia, often accompanied by lower back pain.<sup>6</sup> It is worsened by early ambulation, and there is a pain free period after resolution of the neuraxial blockade. The pain usually resolves within one week, but as many as 30% of patients will be severely debilitated, needing readmission to hospital and requiring analgesic therapy beyond that of surgery. It is thought that TNS might be a mild transient form of direct neurotoxicity. This train of thought is controversial since TNS is not associated with high concentrations of lignocaine or sacral pooling as is the case with *Cauda Equina* syndrome. Explanations of TNS other than neurotoxicity remain problematic.<sup>7</sup>

TNS has been ignored as a pure neurological lesion because patients often have no localising pain or sensory or motor impairment other than radicular pain. It is known however that the predominant presenting symptom (70%) of early primary cauda equina lesions (eg. tumour) is low back pain without any localising signs. Secondly, TNS has also been dismissed as non-specific back pain. The definition now states that buttock/ leg pain is to be viewed as part of the syndrome. Thirdly, it is argued that positioning of the patient in lithotomy position or for arthroscopy *per se* may be responsible for nerve injury. As lignocaine is more frequently associated with TNS in these cases than bupivacaine, it shows lignocaine to have an additive toxic effect to the mechanical neuronal stress of positioning.<sup>8</sup>

### **Local anaesthetic myotoxicity**

Skeletal muscle toxicity appears to be an uncommon side effect of local anaesthetics. Fortunately it remains clinically unnoticed in most cases.<sup>9</sup> Intramuscular injection of these agents causes reversible myonecrosis.<sup>10</sup> The extent of damage is dependent on the dose used, the concentration of the drug used, and whether or not the local anaesthetic is applied as a continuous infusion. Bupivacaine seems to induce the most damage, and tetracaine and prilocaine the least.

Histological changes in striated muscle fibres following the application of these drugs were noted as far back as 1959.<sup>11</sup> The injury follows a uniform pattern and time course, starting as a hyper contraction of the myofibrils directly after injection. This is followed by lytic degeneration of the sarcoplasmic reticulum (SR), myocyte oedema and necrosis over the next one to two days. In most cases the myoblasts, basal laminae and connective

tissue structure remains intact, resulting in regeneration of the muscle fibres within three to four weeks.

The exact mechanism of myotoxicity remains unclear. Abolition of the nerve impulses by chemical or anatomical denervation, inhibition of sarcolemmal Na<sup>+</sup> channels by tetrodotoxin (TTX, a selective inhibitor of fast Na<sup>+</sup> channels), needle injury and direct toxic effect on the myofibrils have been excluded as mechanisms of injury. Toxicity is closely related to the dysregulation of intracellular free Ca<sup>++</sup> homeostasis rather than to the disturbance of sarcolemma conductance. It is these high levels of free Ca<sup>++</sup> that initiate the hyper contracted state of the myofibrils which then leads to subsequent necrosis.

An increased level of free Ca<sup>++</sup> level is the result of direct interaction of the local anaesthetic drug with the ryanodine receptor (RYR).<sup>12</sup> In high concentrations, local anaesthetics (>1mmol/L) activate the receptor and causes the release of Ca<sup>++</sup> from the SR, whereas lower concentrations (<1mmol/L) inhibit these channels.<sup>13</sup> This biphasic effect is noticed when local anaesthetics fail to induce muscle damage after IV blockade or systemic administration, due to the serum concentration seldom reaching levels higher than 1 mmol/L. The receptor interaction is also pH dependent, as only the free bases induce Ca<sup>++</sup> release, while protonated local anaesthetic molecules inhibit Ca<sup>++</sup> conduction across the membrane. The extent of muscle damage closely correlates with the amount of free protonated molecules reaching the SR, and myotoxicity is potentiated at high pH.<sup>14</sup>

Bupivacaine and ropivacaine has been shown to not only cause the release of Ca<sup>++</sup> from the SR, but, by inhibiting Ca<sup>++</sup> ATPase activity they also decreases the reuptake of Ca<sup>++</sup> from the sarcoplasm back into the SR in a dose-dependent manner.<sup>15</sup> In equivalent concentrations bupivacaine disturbs the Ca<sup>++</sup> homeostases much more than does ropivacaine. It is thought that bupivacaine, because of its high lipophilicity, accumulates rapidly in the sarcoplasm, whereas ropivacaine crosses the barrier more slowly and deranges the Ca<sup>++</sup> homeostasis only moderately. Whether stereoselective effects are involved is not known at this stage.

Several studies indicate that disturbances in SR function may not be the only etiological pathway in myotoxicity. Local anaesthetics have the ability to uncouple oxidative phosphorylation in the mitochondria in dose-dependent fashion. The depletion of ATP that follows is believed to contribute to the Ca<sup>++</sup> dysregulation. It has recently been shown that bupivacaine may cause contraction-dependent mitochondrial depolarisation by inducing the opening of the so-called mitochondrial permeability transition pore (MPTP).<sup>16</sup> The MPTPs are located on the inner membrane of the mitochondria and play a key role in converting the organelle from a structure that supports life to one that actively induce apoptosis and cell necrosis. Opening of the MPTP causes two major events. Firstly, it enables large molecules such as proteins to enter the mitochondria. Proteins exert colloidal osmotic pressure and cause the mitochondria to swell. The subsequent unfolding of the cristae allows the matrix to expand but the outer membrane will eventually rupture, releasing cytochrome c, apoptosis-inducing factor and endonuclease G. Apoptosis is induced and cell death follows. Secondly, the membrane now becomes freely permeable to H<sup>+</sup>. This uncouples oxidative phosphorylation (with the resultant decreased production of ATP), and it activates the proton-translocating ATPase to reverse direction and actively hydrolyse ATP. The dramatic decrease in

ATP levels leads to the disruption of ionic homeostasis and the activation of degradation enzymes culminating in cell necrosis.<sup>17</sup>

It is argued that oxidative stress within the affected muscle fibres may be involved in the pathogenesis of myotoxicity. The formation of highly reactive hydroxyl radicals and superoxides amplifies the myocyte damage. The extent and influence of this mechanism still needs to be investigated further.<sup>18</sup>

The clinical impact of this myotoxicity remains controversial. Few case reports of myotoxic complications have been published. The only extensive and systematic studies into the incidence of anaesthesia-related muscle dysfunction relate to the extraocular muscles after ophthalmic surgery. Anaesthetic-related persistent diplopia has an overall incidence of 0.25%. In their series (of 3 587 patients) damage was predominantly due to direct damage of the inferior rectus muscle. For the retrobulbar block alone, the incidence was 0.39%. One patient out of 98 who received peribulbar blockade had permanent damage. Bupivacaine (alone or in combination with lignocaine) was used in all of the cases.<sup>19</sup>

In theory, muscle damage is possible after the systemic application of local anaesthetics. Nevertheless, most agents never induce damage, as the plasma concentration never reaches adequate levels. Long-term abuse of cocaine is known to cause lethal muscle damage and rhabdomyolysis. The cellular mechanism remains unclear.<sup>20</sup> Local anaesthetics have been extensively used in patients who are susceptible to malignant hyperthermia (MH) without any reported adverse reactions or MH episodes.<sup>21</sup>

The diagnosis of muscle injury after local anaesthetic application is complex. The signs are not uniform and depend on the site of injection and the regional technique used. The evaluation of extraocular muscle dysfunction appears easy, but the exact clinical evaluation of function and structural integrity after peripheral nerve block might be a serious problem. Therefore the definite diagnosis should include the clinical picture (tenderness, increased intensity on stretch, relief by shortening). The time course can help to elucidate more specific information. Although myonecrosis is not painful per se, the inflammatory response that follows is at its peak on day four. Clinical information should be supplemented by laboratory investigations (increased muscle type creatine kinase), electromyographic evaluation (for signs of necrotic myopathy), magnetic resonance imaging (increased protein, blood flow) and histology. Underlying congenital myopathies must be excluded as etiology for postoperative muscle dysfunction.<sup>11</sup>

### **Systemic toxicity**

As classic neuronal Na<sup>+</sup> channel inhibitors, these drugs have a particular high level of activity in the central nervous system and the cardiovascular system and their side effect profile remains remarkably consistent, differing only quantitatively between the agents in their doses (and blood and relevant tissue concentration).

Local anaesthetic agents exist in both ionised acid- and non-ionised base forms in the tissue after injection. The non-ionised form crosses the barrier of the myelin sheath and the axon membrane. Here it will dissociate to the ionised acid form due to the lower pH inside the cell. The ionised fraction binds to the activated Na<sup>+</sup> channel and produce blockade of the channel in the inactivated state. The development of symptoms and signs

related to local anaesthetic toxicity relates directly to the concentration of the drug in the plasma. The plasma concentration will depend on the rate of absorption from the injected site, as well as inadvertent intravascular injection.<sup>22</sup> It is appropriate to first review the physiology of the ion channels implicated in local anaesthetic toxicity.

### *Sodium channel blockade*

The Na<sup>+</sup> channel exists as a tetramer of 300 KD.<sup>23</sup> Each of the subunits is made up of an amino acid chain that crosses the membrane six times. The tetramers surround an aqueous pore of about 0.5 nm in diameter. The channel has an outer gate that opens at the start of depolarisation, and an inner gate that closes soon after. Thus the channel exists in three states, namely closed, activated and inactivated. An action potential being propagated down the membrane will open the outer gate and *activate* the closed channel if the threshold potential of -70mV is reached. Because of conformational changes, the activated channel opens and the ensuing influx of Na<sup>+</sup> causes depolarisation. Closure of the inner gate follows and leaves the channel open but physically obstructed, thus *inactivated*. During repolarisation, the original conformation of the channel is restored (the outer gate *closed*) and it is ready for the next action potential to activate it.

The initial rapid depolarisation and overshoot of the cardiac muscle action potential (phase 0) are due to Na<sup>+</sup> influx through the rapidly opening Na<sup>+</sup> channels. The plateau of phase 1 is the result, in part at least, of the closure of these channels. As local anaesthetics act as Na<sup>+</sup> channel-blocking agents, they slow down the initial depolarisation phase by blocking the inactivated channel. The clinical consequence of this is slowed cardiac conduction, widening of the QRS complex, prolongation of the PR interval, AV block and, eventually, ventricular fibrillation due to the unidirectional blockade and re-entry phenomenon.

Lignocaine is an anti-arrhythmic drug as it causes a fast blockade, but also a fast release of the Na<sup>+</sup> channel (lasting 0.15 sec). Bupivacaine and ropivacaine, on the other hand, causes a fast blockade but a slow release of the Na<sup>+</sup> channel (lasting longer than 1 sec). They cannot be used as anti-arrhythmic drugs.<sup>24</sup>

### *Potassium channel blockade*

K<sup>+</sup> channels are tetramer ion channels and are organised into three superfamilies according to the subunit membrane topology: (1) subunits with six membrane-spanning segments and one pore domain, (2) subunits with two membrane-spanning segments and one pore domain, and (3) subunits with four membrane-spanning segments and two pore domains arranged in tandem. The first and third group are of interest where local anaesthetic toxicity is concerned.

As noted, the first group of channels are tetramers with fourfold symmetry around a central pore in the form of an inverted teepee.<sup>25</sup> Both the N terminal and the C terminal are located intracellularly. The amino acids of the N terminal are shaped like a ball and chain, and conformational changes causes this ball to close the channel from inside the cell. These channels are known as the inward, outward and transient rectifier K<sup>+</sup> channels, and their resultant effect is partly responsible for the K<sup>+</sup> efflux during phases 2 and 3 of the cardiac muscle action potential.<sup>23</sup> A blockade of these channels will prolong the action potential (phase 2), delay

repolarisation (phase 3), and shift the resting membrane potential more positive (phase 4) to increase automaticity.<sup>26</sup>

The second group of K<sup>+</sup> channels of interest is the two pore domain K<sup>+</sup> channels (K<sub>2p</sub>). Previously known as the delayed rectifier channels, these channels are believed to be responsible for the background or "leak" K<sup>+</sup> currents. In this setting they control the resting membrane potential. A blockade of these channels shifts the resting membrane potential towards spontaneous depolarisation.<sup>27</sup>

K<sub>2p</sub> channels are wide spread in the body. In the CNS they are mainly located in the thalamo-cortical and striatal neurons, where blockade leads to increased neuroexcitability.<sup>28</sup> They are also present in high concentrations in the cerebral blood vessels, where blockade leads to vasoconstriction and decreased cerebral blood flow. K<sub>2p</sub> channels are also present in neurons of the auditory system, where blockade leads to tinnitus.<sup>24</sup> K<sub>2p</sub> channels are thought to mediate the stimulating effect of local anaesthetics on ventilation.<sup>29</sup> They are located in the brainstem, where they modulate the respiratory response to carbon dioxide via chemo sensing of the pH. They are also found in the carotid body, where they are expressed in the oxygen-sensing cells of the glomus body. K<sub>2p</sub> channels are sensitive to changes in O<sub>2</sub> tension and extracellular pH and are potentiated by volatile anaesthetic.<sup>28</sup>

In the CVS, K<sub>2p</sub> channels are spread throughout the conduction system of the heart, where blockade predisposes the patient to re-entry dysrhythmias. It is well known that hyperkalemia exacerbates local anaesthetic toxicity, and that K<sup>+</sup><sub>ATP</sub> openers (which effectively lowers intracellular K<sup>+</sup> levels) attenuate the toxic effects of bupivacaine.<sup>30</sup>

#### Ca<sup>++</sup> channel blockade

The latest research shows that all voltage-gated Ca<sup>++</sup> channels are comprised of two subunits. The  $\alpha$ -subunit consists of a tetramer that comprises four membrane-spanning domains.

**Table I.** Symptoms and signs of local anaesthetic overdose. (adapted from Hugo JM (ed). Anesthesiology, an undergraduate course. Pretoria: Pretoria University Press 2002.)

CENTRAL NERVOUS SYSTEM	CARDIOVASCULAR SYSTEM
<b>Initial phase</b>	<b>Initial phase</b>
Circumoral paresthesia	Hypertension
Tinnitus	Tachycardia during CNS excitatory phase
Confusion	
<b>Excitatory phase</b>	<b>Intermediary phase</b>
Convulsions	Myocardial depression
	Decreased cardiac output
	Hypotension
<b>Depressive phase</b>	<b>Terminal phase</b>
Loss of consciousness	Peripheral vasodilatation
Coma	Severe hypotension
Respiratory depression	Sinus bradycardia
	Conduction defects
	Dysrhythmias

Domains I, III and IV are critical in the opening of the channel.<sup>31</sup> This  $\alpha$ -subunit is the main pore-forming element of the channel, and its chemical structure remains fairly consistent for all voltage-gated Ca<sup>++</sup> channels. The second unit has a highly variable structure that depends on the location and function of the channel. In cardiac conduction tissue, it is the  $\beta_1$  subunit that completes the ion channel structure. The role of the  $\beta_1$  subunit seems to be the modulation of channel opening and membrane ion trafficking.<sup>32</sup> In terms of their physiological effect, the heart has two distinct types of channels namely the T- type (transient) and L-type (long lasting) channels. The T-type channel (also known as the low voltage activated channel -LVA) is mainly located in the pacemaker cells of the sino-atrial node, and the opening of these channels completes the prepotential required for the pacemaker potential. L-type channels (known as high voltage activated channels -HVA) are present on the surface of the myocytes of both atrium and ventricle, and are closely associated with the T-tubules. The opening of these L-type channels produces the impulse seen as the plateau phase (phase 2) of the cardiac muscle action potential. Local anaesthetic drugs bind to the L-type Ca<sup>++</sup> channels, predisposing them to an inactivated state. The consequence of this is prolongation of the action potential (phase 2) and depressed contractility.<sup>24</sup>

#### Central nervous system toxicity

Central nervous system toxicity is presumed to be a two-stage process. Initial blockade of Na<sup>+</sup> channels in the inhibitory neurons entering the limbs allows the excitatory neurons to act unopposed, thereby creating an excitatory state. This culminates in generalised convulsions. Higher concentrations of local anaesthetic affect all neurons, leading to global CNS depression, slowing and ultimately silence on EEG, clinically seen as coma, and the eventual collapse of the cardiovascular system. In most cases, convulsions, although an impressive clinical entity, can be handled safely without permanent damage.

#### Cardiovascular system toxicity

All of the clinical effects due to local anaesthetic overdose are the result of the blockade of various ion channels. The normal pharmacological effects of local anaesthetic drugs are produced via their blockade of sodium (Na<sup>+</sup>) channels. However, these drugs also have the ability to block potassium (K<sup>+</sup>) as well as calcium (Ca<sup>++</sup>) channels. The whole picture of cardiovascular toxicity is the effect of the blockade of all these ion channels.

Ion channel blockade displays enantiomeric selectivity, with the R isomer having twice the potency at the Na<sup>+</sup> channels, seventy times the potency at K<sup>+</sup> channels and three times the potency at Ca<sup>++</sup> channels. Furthermore, channel blockade is dependent on the state of the channel. Levo-bupivacaine and ropivacaine interacts with both the activated and inactivated Na<sup>+</sup> channels, where as R bupivacaine is a more potent blocking agent of the inactivated Na<sup>+</sup> channels.

The mechanism of cardiovascular toxicity relies on the direct as well as indirect effects of the local anaesthetic drugs on the myocardium.<sup>33</sup> (See Figure 1) Direct effects include negative inotropy and delayed conduction of the impulse through the cardiac conduction tissue. Indirect effects have to do with the local anaesthetic effect on the autonomic outflow and the direct effect on the cardiac centre in the midbrain.

Negative inotropy due to local anesthetic overdose is the result of four main mechanisms. Firstly, local anaesthetics (LA) cause decreased  $\text{Ca}^{++}$  release from the sarcoplasmic reticulum in the cardiac myocyte. This, in turn, decreases excitation-contraction coupling and thus decreases contractility. Secondly, there is disturbance of the membrane  $\text{Na}^+/\text{Ca}^{++}$  pump function. This also decreases  $\text{Ca}^{++}$  levels in the cytosol and decreases contractility.

Thirdly, LA alters mitochondrial energy transduction. By binding to the inner mitochondrial membrane, LA agents cause the uncoupling of oxidative phosphorylation at complexes II and I. This leads to decreased levels of ATP and a low energy state in the myocyte. The binding of LA to the inner membrane further inhibits the function of L-carnitine acyl transferase. This enzyme is important in the transfer of long free fatty acids (FFA) across the cell - and mitochondrial membrane. The decreased availability of FFAs as substrate for oxidation leads to decreased ATP levels.

Fourthly, LA causes decreased cAMP production. This impairs second messenger function in the myocyte and disrupts cell homeostasis.

The second direct cardiovascular effect is perhaps the more well known. LA by their nature cause blockade of the ion channels, therefore causing conduction blockade of the impulse generated in the SA node. Abnormal conduction predisposes to re-entry phenomena and unidirectional conduction dysrhythmias.

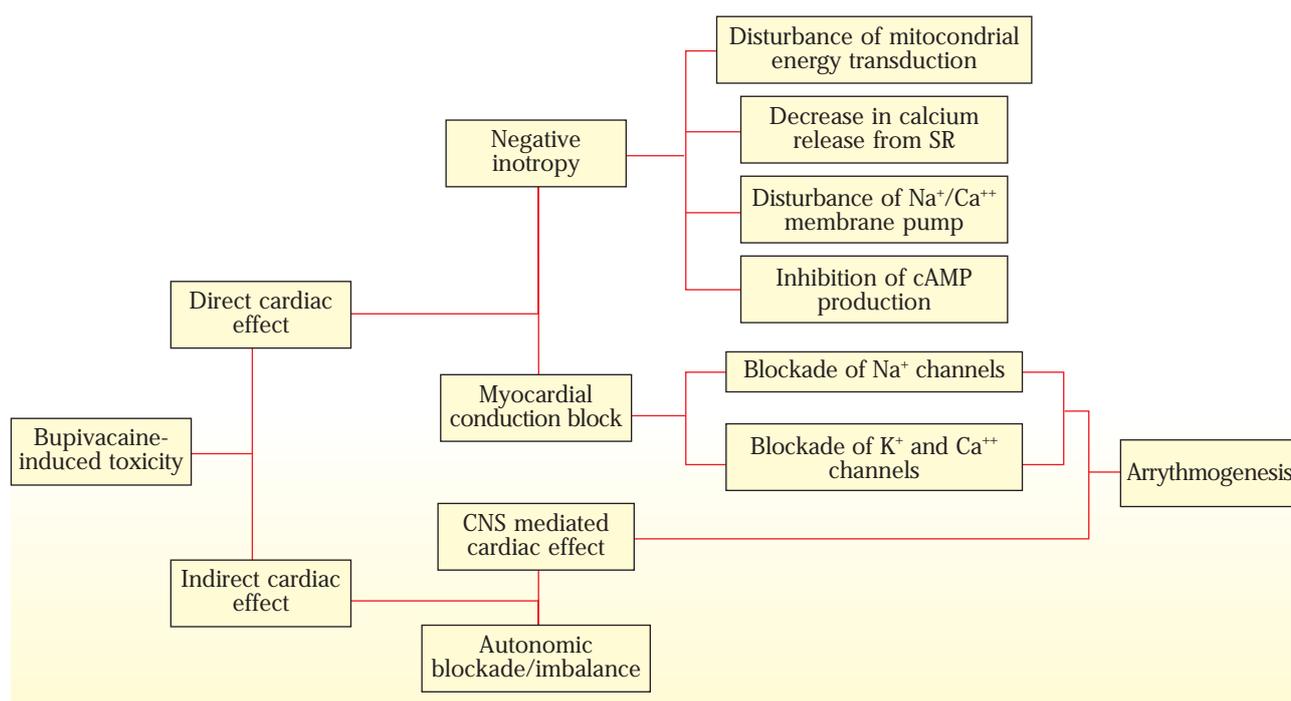
The indirect effects on the cardiovascular system are due to the blockade of impulse outflow from the *nucleus tractus solitarius* (NTS) located in the medulla oblongata. Afferent fibres from the baroreceptors in the carotid body and aortic arch reach the NTS via *N glossopharyngeus* (XI) and *N vagus* (X) where they secrete glutamate as neurotransmitter. From the NTS, projections reach the caudal and intermediate ventrolateral medulla, where they stimulate GABA-secreting neurons. These in turn project to the rostral ventrolateral medulla from where they course down the thoracic cord to eventually become the preganglionic sympathetic neurons that form the cardiac sympathetic innervation. Excitatory projections from the NTS also reach the vagal motor neurons, the nucleus ambiguus and dorsal motor neurons. Baroreceptor stimulation thus inhibits tonic discharge to the vasoconstrictor nerves and excites vagal innervation of the heart with its sequelae.<sup>23</sup> LA alters the spontaneous impulse production in the NTS and depresses cardiac output.<sup>24</sup> The blockade also leaves the sympathetic outflow relatively unopposed, which in turn leads to increased automaticity and dysrhythmias. The overall effect of the conduction block and CNS-mediated effects is the refractory ventricular fibrillation, for which bupivacaine is well known.

#### Treatment of refractory VF

Cardiac arrest after LA overdose is probably the worst nightmare an anesthetist must be able to deal with. Previously, bretylium tosylate was hailed as the magic bullet for the treatment of refractory ventricular fibrillation due to bupivacaine overdose. Bretylium is a class III antidysrhythmic drug. It slows down phase III repolarisation and thereby prolongs the refractory period. It decreases the release of noradrenaline. Unfortunately, the manufacture of this drug has ceased and it is not available for clinical use.

The next group of drugs that shows promise are the  $\text{K}^+$  channel openers, of which pinacidil and bimakalim are examples. By

**Figure 1:** Mechanisms involved in local anaesthetic induced cardiotoxicity.



(Mather LE, Chang D H-T. cardiotoxicity with modern local anesthetics. Is there a safer choice? *Drugs* 2001;61(3): 333-42)

opening the  $K^+_{ATP}$  channels they shorten the action potential in the Purkinje fibres and ventricular cells. This prolongs the plateau phase and hyperpolarizes the resting membrane potential. It has been shown that pinacidil and bimakalim attenuates the bupivacaine induced AV block significantly, and that they can even partially reverse the induced block.<sup>24</sup> Unfortunately, the  $K^+_{ATP}$  channel openers have serious disadvantages. They are negatively inotropic because of their pharmacological action. As they shorten the action potential duration, they cause decreased  $Ca^{++}$  influx and therefore reduce contractility. They also cause excessive coronary vasodilatation that may lead to the "coronary steal" phenomenon in patients with "steal prone" anatomy.  $K^+_{ATP}$  channel openers can therefore be advantageous as they improve AV conduction, but their myocardial depression effect make them less suitable in the resuscitation scenario.

A more suitable alternative for treatment of refractory fibrillation caused by bupivacaine overdose may exist in the form of Intralipid®.<sup>34</sup> Intralipid® is a lipid emulsion consisting of soya oil, glycerol and egg phospholipids. It is most commonly used as the lipid substance of total parenteral nutrition (TPN) and as the solute for propofol. It has been shown to be an effective antidote to cardiovascular collapse caused by bupivacaine in rats and dogs.<sup>35, 36</sup>

There are a few theories as to the mechanism of action of Intralipid® as antidote for fatal bupivacaine overdose. It is thought that Intralipid® acts as a circulating lipid sink, drawing bupivacaine out of the plasma and binding it so that no more free fraction exist to bind to the receptors. Alternatively, the high lipid concentration forces lipid influx into the cardiac myocyte with the lipid rush simply overwhelming the LA blockade of the L-CAT enzyme, increasing the FFA supply to the mitochondria and thus increasing the production of ATP, which makes myocardium more susceptible to resuscitation.

The protocol suggests starting with Intralipid® 1ml/kg stat IV, repeated twice at intervals of three to five minutes. This is followed by a constant infusion of 0.25mg/kg/min until the patient is stable. According to the studies, exceeding a dose of 8 mg/kg is of no benefit at all.<sup>37</sup>

There remains a number of questions to answer before the use of Intralipid® as resuscitation aid can be condoned. In all the studies, racemic mixtures of bupivacaine were used. As yet there is no evidence to the effectiveness of Intralipid® in overdose with LA isomers.<sup>38</sup> It is well known that sustained high doses of lipid-containing solution have detrimental effects on the heart and lungs, for instance causing pulmonary vasoconstriction.<sup>39</sup> The long-term effects of the use of high doses of lipid-containing solution are not known. The resuscitation protocols to which the animal experiments adhered did not make use of adrenaline at any time during the resuscitation process. The benefit of adding adrenaline to the lipid regimen remains unknown. It further more is highly unlikely that high quality human data will ever be obtained for a treatment option that only benefits patients *in extremis*, as it is unethical to intoxicate subjects to the point of collapse.

Other therapies studied include a regimen that utilises glucose, insulin and potassium.<sup>40</sup> The dose of insulin found to be effective is in the order of 2 iu/kg stat. It is a massive dose, and very few anesthetists will even consider giving such a large dose to a normal patient, let alone a collapsed patient with an ischemic brain. Amiodarone has also been considered, but evidence to its effectiveness still eludes investigators.<sup>41</sup>

## Conclusion

Local anaesthetic toxicity encompasses much more than the seizures and cardiovascular collapse. These catastrophic events can be managed, especially now that Intralipid® is advocated as emergency treatment for the cardiac toxicity of bupivacaine. It is unwise to presume that because the patient does not suffer clinical sequelae of myotoxicity, it is not important to take note of the phenomenon. Direct neuronal toxicity may be rare, but is severely debilitating should it occur. SAJAA

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