Survival after local anaesthetic overdose:

a comparison of the success of resuscitation after established cardiotoxicity caused by ropivacaine or bupivacaine.

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DECLARATION

I, Paul Neville Whitehead, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Index

Introduction.

Ropivacaine, S-(-)-1-propyl-2'6'-pipecholoxylidide hydrochloride monohydrate, is the latest in the series of amide local anaesthetic agents, the development of which has been spurred by the need for an agent that would be effective and long lasting but have minimal toxic effects.

Bupivacaine has been the local anaesthetic of choice for many years but the serious, albeit rare, cardiac toxicity associated with its use has prompted research for a safer agent. The toxic effects of the long acting local anaesthetics were reported by Albright in 1979, in an editorial in Anesthesiology (1). He reported 6 cases of presumed accidental intravascular injection of either etidocaine or bupivacaine, which caused convulsions and ventricular arrhythmia. Three cases were attempted brachial plexus blockade with 0.5% bupivacaine, one was an intravenous regional anaesthetic with 0.5% bupivacaine and chloroprocaine, one was a caudal extradural anaesthetic with etidocaine and one was an extradural block with 0.75% bupivacaine.

Subsequently, sporadic cases of maternal death after extradural anaesthesia for Caesarean section were reported (2). In the UK there were 5 deaths after intravenous

regional anaesthesia administered by trainee casualty officers. Tourniquet malfunction and bupivacaine were involved in all of these cases (3).

In response to Albright's findings, the United States Food and Drug administration issued a statement that 0.75% bupivacaine was no longer recommended for obstetric anaesthesia.

This adverse attention provided the impetus for the development of a local anaesthetic with the efficacy of bupivacaine but with lower toxicity. Ropivacaine has been developed as the drug with these required characteristics.

The purpose of this thesis is to review the pharmacology and toxicity of local anaesthetics, particularly highlighting the differences between bupivacaine and ropivacaine and to present an experiment attempting to establish whether ropivacaine is a safer drug, once cardiotoxicity has occurred.

Mechanism of Action of Local Anaesthetics.

Local anaesthetics are tertiary bases and are supplied as the hydrochloride to ensure water solubility for ease of administration. After administration, tissue buffering raises the pH and a percentage of the drug dissociates to become free base. The free base is lipid soluble and able to penetrate the nerve sheath and lipid cell membrane to enter the axoplasm where it partially re-ionises again. The ionised form then enters the sodium channel and prevents the flow of sodium ions into the cell. As a result, action potentials are neither generated nor propagated and conduction blockade has occurred.

Sodium channels.

The sodium channels are postulated to exist in 3 different forms (4).

1. A resting state R, in which sodium activation and inactivation gates are closed and which predominates before nerve stimulation.

2. An open state O, in which both gates are open, allowing passage of sodium ions during stimulation. This state is present during depolarisation of the membrane.

3. An inactive state I, in which the activation gate remains open but the inactivation gate is closed immediately following stimulation. This state is associated with the initial phase of repolarisation and the refractory period.

Local anaesthetics have a high affinity for channels in the open or inactivated states but a very low affinity for channels in the rested state. Consequently, in cardiac muscle,

block of sodium channels develops during the upstroke and plateau of the action potential and dissipates during the diastolic interval between beats (4).

Cardiotoxicity of Local Anaesthetic Agents.

In order to understand the effects exerted on the heart by local anaesthetics, one must first understand normal cardiac electrophysiology.

The resting membrane potential of cardiac muscle cells is about -90mV (interior negative to exterior). Stimulation produces a propagated action potential that is responsible for initiating contraction. Rapid depolarisation occurs followed by a plateau phase before the membrane potential returns to the baseline. The depolarisation lasts for about 2ms but the plateau phase and repolarisation last 200ms or more, so that repolarisation is not complete until the contraction is half over. Recorded extracellularly, the summed electrical activity of all the cardiac muscle fibres is the electrocardiogram. The electrical events include a spike and a later wave that resemble the QRS complex and T wave of the ECG. As in all excitable tissues, changes in the potassium ion concentration affect the resting membrane potential of cardiac muscle, whereas changes in the sodium ion concentration affect the magnitude of the action potential. The initial rapid depolarisation and the overshoot phase (phase 0/Vmax) are due to a rapid increase in sodium conductance similar to that occurring in nerve and skeletal muscle. The accumulated upstrokes of the ventricular action potentials account for the QRS complex on the ECG. The maximal rate of rise (Vmax) is a major determinant of the conduction velocity and duration of the QRS complex on the ECG. The initial rapid repolarisation (phase 1) is due to closure of sodium channels and chloride influx. The subsequent prolonged plateau (phase 2) is due to a slower but

prolonged opening of voltage gated calcium channels. This plateau is reflected on the body surface ECG as the ST segment.

Final repolarisation (phase 3) is due to closure of the calcium channels and potassium efflux through 2 types of potassium channels and is responsible for the T wave of the ECG. This restores the resting potential (phase 4).

The fast sodium channel probably has 2 gates, an outer gate that opens at the start of depolarisation, at a membrane potential of -70 to -80mV, and a second inner gate that then closes and precludes further influx until the action potential is over (sodium channel inactivation).

Local anaesthetics manifest their toxicity at a local and systemic level. Neurotoxicity has been attributed to antioxidants or preservative agents but it seems that local toxicity is related to the concentration of agent used (5). Muscles are also damaged by local anaesthetics (6), but it is the dramatic central nervous system and cardiac effects that are probably the most important side effects of these agents.

Most of the work on local anaesthetic toxicity has involved comparisons between bupivacaine and other agents.

Studies on isolated myocardial tissue.

Electrophysiological studies have shown that local anaesthetics depress the maximal rate of increase of the cardiac action potential (Vmax) in a dose dependent manner depending on membrane potential and rate of stimulation (7). Vmax is dependent on the sodium ion influx via sodium channels. Local anaesthetics depress the cardiac sodium channels in a time and a voltage manner by binding to specific sites within the sodium channel. Highly lipid soluble compounds reach their site of action throughout the membrane whereas the binding site is only accessible to polar compounds when the channel is open. Drug affinity for the receptor site is dependent on the state of the sodium channel with local anaesthetics having high affinity for the open or inactivated channel and low affinity for the resting channel. Inhibition of sodium channel by local anaesthetics includes both voltage dependant and frequency dependant components. The block is enhanced by rapid stimulation and depolarisation and dissipates with hyperpolarisation and increase in cycle length. Thus, changes in heart rate and diastolic membrane potential may alter drug action.

Clarkson and Hondeghem (8) studied the effect of lignocaine and bupivacaine at various concentrations and stimulation rates on guinea pig ventricular muscle Vmax. In high concentrations, lignocaine blocked sodium channels in a fast in fast out manner. In low concentrations, bupivacaine blocked sodium channels in a slow in slow out manner, whereas in high concentrations the bupivacaine block was of a fast in slow out

type. Therefore recovery from bupivacaine induced block is always slow and the block can accumulate even at low heart rates, making bupivacaine a more potent depressor of Vmax than lignocaine.

In the intact heart, reduction in Vmax which results in slowed conduction of the cardiac action potential, is manifested by prolongation of the PR interval and QRS complex (7). Slowed conduction may also result in re-entrant phenomena (9), which may account for the sudden onset of ventricular arrhythmia after toxic doses of bupivacaine.

Dose dependant depression of cardiac conduction and contractility by local anaesthetics has been demonstrated in the isolated rabbit heart preparation (10). The effect of bupivacaine was apparent at a lower dose than that of lignocaine.

Feldman et al investigated the effect of local anaesthetics on the chronotropy and inotropy of the isolated guinea pig atrium. They showed that the relative potency of the various agents in depressing cardiac contractility is similar to the anaesthetic potency of the drug (11).

Moller et al looked at the effect of bupivacaine and lignocaine on the action potential of the right bundle of the rabbit heart. They found that bupivacaine was a far more potent depressor of membrane potential, Vmax, action potential duration, and conduction time. The agents appeared to block the entrance of sodium through fast sodium channels (12).

Calcium is important in the conduction of the action potential in the atrio-ventricular pathway especially the SA and AV nodes. Calcium influx initiates and controls the force of contraction in the process of excitation contraction coupling. Therefore the effect of local anaesthetics, especially bupivacaine, may be important in the pathophysiology of local anaesthetic toxicity. Arlock showed that bupivacaine causes attenuation and block of automaticity at potentials where calcium conductance is high. This may indicate that bupivacaine affects the transmembrane calcium current which is responsible for triggering the contractile apparatus (13).

Coyle studied the effect of bupivacaine on calcium channels in the guinea pig heart. Blockade of sodium channels was achieved by perfusing the hearts with high levels of potassium. Pharmacological concentrations of bupivacaine depressed Vmax by 50% suggesting that bupivacaine inhibits the slow inward calcium current (14).

The duration of the cardiac action potential is mainly controlled by potassium currents flowing through several different voltage dependent potassium channels. Prolongation of the action potential by potassium channel block may contribute to local anaesthetic toxicity because of an increased number of open or inactivated sodium channels. It has been shown that in dogs that are normally ventilated but hyperkalaemic, bupivacaine toxicity occurred at a lower dose than when the dogs were normokalaemic (15).

Significant blockade of the delayed rectifier potassium current and the inward rectifier potassium current potassium channels in the frog heart, has been produced by bupivacaine in concentrations that cause sodium channel block (16). Castle showed that bupivacaine was a potent blocker of the delayed rectifier potassium current and the transient outward potassium channel. This results in prolongation of the action potentials as the duration of the action potential is controlled by potassium flow through several potassium channels. Prolongation of the action potential results in an increase in the time that the sodium channels spend in the inactivated state which is the state in which they are most vulnerable to the effect of bupivacaine

In summary, the in vitro effect of local anaesthetic agents seems to be related to their affinity for and duration of binding to sodium channels. Bupivacaine also has an effect on calcium channels and potassium channels.

Studies on intact animals.

Liu has investigated the effect of an intravenous bolus of amide local anaesthetics administered to anaesthetised ventilated dogs (17). He found that bupivacaine caused profound hypotension compared to mild cardiac depression with the same dose of lignocaine and prilocaine. The cardiodepressant effect was proportional to their in vivo anaesthetic potency. Death occurred as a result of progressive cardiac depression and no arrhythmias were recorded.

Nath (18) infused bupivacaine and lignocaine into the left anterior descending artery in pigs in order to study the effect on the heart while eliminating any possible effects mediated by the central nervous system. He noted a dose dependant depression of the left ventricle in the ratio of anaesthetic potency. Bupivacaine was 4 times more potent than lignocaine in depressing contractility but 16 times more potent in prolonging the QRS interval. 50% of the animals given bupivacaine died of sudden ventricular fibrillation.

Thigpen (19) studied sheep rendered acidotic and hypoxaemic by ventilation with a mixture of air and 12% carbon dioxide. 100% of these sheep died as a result of bupivacaine infusion. This was in contrast to a study by Kotelko (20) in which hypoxia was avoided during treatment with bupivacaine. All the animals developed serious arrhythmias but the mortality was very low. Kotelko postulated that under conditions of hypoxia and acidosis, bupivacaine toxicity is potentiated.

Mets demonstrated in rats that respiratory depression occurs before serious cardiac depression due to bupivacaine toxicity (21). This was confirmed in a study by Nancarrow (22).

Mallampati et al reported a case of bupivacaine toxicity in which successful resuscitation was achieved. This was attributed by them to early aggressive

cardiorespiratory support and they commented that there was mounting evidence that prevention of hypoxia was associated with a good outcome (23).

In summary, at toxic concentrations, bupivacaine alters cardiac function by decreasing the myocardial contractile force, and creating dysrhythmias, high degree blocks, major QRS widening and ventricular tachycardias of the re-entrant type (24).

A) Inotropy.

Multiple studies both in vitro and in vivo have shown that bupivacaine has a strongly negative inotropic action (25,26,27,28).

B) Electrophysiology.

Depression of cardiac conduction is one of the main mechanisms of the cardiac effects of bupivacaine. This is mainly on the basis of cardiac sodium channels but block of transient and delayed potassium channels (29), and block of calcium channels are postulated also to have an effect (14).

Severe ventricular arrhythmias after large doses of bupivacaine are the result of re-entrant phenomena (24,30). A multitude of arrhythmias have been described due to bupivacaine including broad QRS complexes, ventricular ectopic beats, ventricular tachycardias, Torsade de Pointes, ventricular fibrillation, electromechanical dissociation and asystole.

Studies of the cardiac actions of Ropivacaine.

Reiz et al studied the cardiotoxicity of ropivacaine (31). At doses adjusted to anaesthetic potency, lignocaine, bupivacaine or ropivacaine was infused into the left anterior descending artery of anaesthetised pigs. At high doses (16mg, 4mg or 5.33mg respectively), all 3 drugs significantly reduced by similar amounts the mean arterial pressure (approximately 10%) and left ventricular dP/dT (approximately 30%). The effects were seen 5 seconds after injection and were short lived, haemodynamics were back to control values within 60 seconds. Ropivacaine produced an increase of 30% in the great cardiac venous blood flow, suggesting that it is a coronary vasodilator. This effect was not seen with lignocaine or bupivacaine. The QRS interval was prolonged by 75% due to the action of ropivacaine 5.33mg and by 155% after bupivacaine 4mg. Lignocaine did not affect the ventricular depolarisation time. None of the drugs had any significant effect on heart rate or cardiac output. They concluded on the basis of their results, that ropivacaine should be expected to have a 70% greater margin of safety than bupivacaine. They felt that the lower toxicity of ropivacaine is due not to the slightly shortened exposure to the myocardium, but to its lower lipid solubility.

Arlock studied the effect of local anaesthetics on sodium channels in the guinea pig papillary muscle (13). He showed a more rapid dissipation after ropivacaine induced blockade, compared with bupivacaine blockade at equimolar concentrations. The

difference was however not sufficient to prevent accumulation of blockade although the block was lower with ropivacaine.

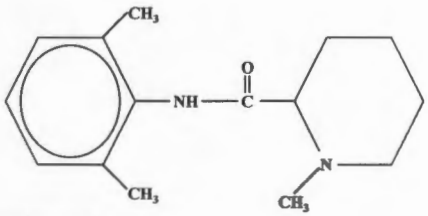
Ropivacaine blocks open human delayed rectifier potassium channels in a concentration dependant manner. It seems however that ropivacaine has a lower affinity for these channels than bupivacaine (32). This may contribute to a lowered cardiac toxicity of ropivacaine as prolongation of the cardiac action potential is not as pronounced with ropivacaine compared to bupivacaine on the basis of potassium channel blockade.

Moller and Covino compared the electrophysiologic properties of bupivacaine, lignocaine and ropivacaine (33). They used an isolated rabbit Purkinje fibre-ventricular muscle preparation. Only bupivacaine significantly decreased Purkinje fibre maximum diastolic potential. Action potential amplitude and maximal rate of depolarisation (Vmax), were significantly decreased by all agents in the order bupivacaine → ropivacaine → lignocaine. All three agents produced Purkinje fibre inexitability and Purkinje fibre-ventricular muscle conduction block. However, the duration of Purkinje fibre inexcitability after exposure to lignocaine and ropivacaine was significantly shorter than in the bupivacaine exposed group. Duration of the Purkinje fibre-ventriclular muscle conduction block was shorter for ropivacaine than bupivacaine. They concluded that ropivacaine is less potent than bupivacaine but more potent than lignocaine in terms of its depressant effect on cardiac excitation and conduction.

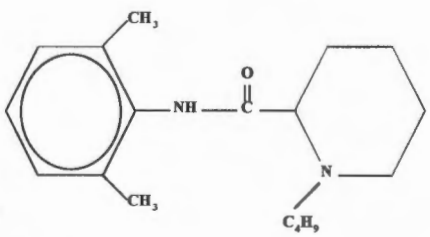
The Pharmacology of Bupivacaine and Ropivacaine.

The pharmacological effects of the two drugs are similar. Equal volumes and concentrations of ropivacaine and bupivacaine provide similar onset, quality and duration of sensory block when used for infiltration anaesthesia or peripheral nerve, brachial plexus or extradural block (34).

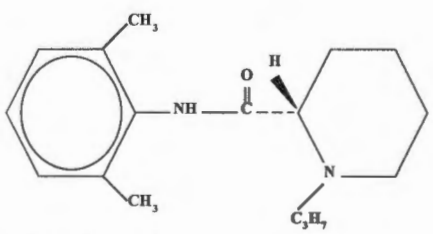
However there are significant pharmacokinetic differences between the two drugs. Both bupivacaine and ropivacaine are amide local anaesthetics and are derived from the parent compound mepivacaine. Both consist of a lipophilic aromatic group linked to a hydrophilic tertiary amine by an intermediate amide chain.



Mepivacaine



Bupivacaine



Ropivacaine

As can be seen from the above diagrams, the structures are similar, ropivacaine having a propyl group on the piperidine nitrogen atom compared to the butyl group of bupivacaine. The centre of asymmetry for ropivacaine is shown.

Differences in the 3 dimensional structure confer differences in the activity of enantiomers in the complex biological environment of the receptor (35). This property of the pipecoloxylidides was known in the late 1960's because the different enantiomers had different durations of action at the target receptor in neural tissue (36). These differences in biological activity are not surprising because individual enantiomers bind to receptors or enzymes, which are chiral amino acids with stereoselective properties.

Bupivacaine is supplied as the racemic mixture of its S and R forms, although recently isomeric S-bupivacaine has become available and studies into its use are being undertaken.

Ropivacaine is supplied as the S enantiomer, having an enantiomeric purity of 99.5%. It is prepared by the alkylation of the S-enantiomer of dibenzoyl-L-tartaric acid.

Bupivacaine is 95% protein bound, mainly to alpha-1-acid glycoprotein but also to albumin (38). The protein binding of ropivacaine is similar at 90%. Although highly

protein bound, the ratio of free to bound drug increases rapidly as the concentration increases (39). This has importance in situations where a large dose is given rapidly.

The pKa of both bupivacaine and ropivacaine is 8.1 at 25°, which means that significant changes in the ratio of ionised to unionised drug may occur with changes in body pH (40).

The partition coefficient of bupivacaine (octanol/phosphate buffer pH 7.4) is 309. It is therefore highly lipid soluble and this increases the potency, increases the speed of onset and prolongs the duration of its effect. The lipid solubility of ropivacaine is significantly less than that of bupivacaine and this is the main cause of the differing degree of motor block seen with these two agents (41).

Aδ and C fibres transmit pain sensation whereas large Aα fibres transmit motor impulses. In vitro most local anaesthetic drugs block C fibres at approximately the same rate. The rate of A fibre block depends on the physicochemical properties of the individual drugs with high pKa and low lipid solubility favouring block of C fibres before A fibres.

The high lipid solubility of bupivacaine confers benefit by reducing absorption from the intended site of action e.g. the extradural space. However, this property is not relevant if this site is bypassed when the drug is injected directly into the circulation, as when a large dose is injected intravenously. In this situation it is transported directly to the heart and brain, where it presents a high concentration of free drug available to cross

the lipoprotein membrane (42). In addition, after accidental intravenous injection the mass of plasma protein in the volume of blood exposed to the drug is quickly saturated, leaving a significant amount of unbound drug available for diffusion into the conducting tissue of the heart and into the brain. Diffusion will obviously be faster with bupivacaine, possibly resulting in worse toxicity than with the less lipid soluble ropivacaine.

	Molecular Weight	pKa(25°C)	Distribution Coefficient	Protein Binding
Bupivacaine	288	8.1	346	95%
Ropivacaine	274	8.1	115	90%

Table 1. (43)

	Volume of distribution (litres)	Clearance (l/min)	Hepatic extraction ratio	Terminal elimination half life (h)	Mean body residence time (h)
Bupivacaine	73	0.58	0.38	2.7	2.1
Ropivacaine	61	0.73	0.49	1.9	1.4

Table 2. (42)

The clearance of the amide local anaesthetics is mainly by liver metabolism and renal excretion of the metabolic products. The major metabolic reactions are aromatic hydroxylation, *N*-dealkylation and amide hydrolysis. The pharmacokinetics of ropivacaine and bupivacaine after intravenous and extradural administration have been determined in the dog and the Rhesus monkey (44,45). The concentration of ropivacaine decreases more rapidly than bupivacaine during the elimination phase after intravenous infusion. Mean clearance for ropivacaine in the dog was 41.1 ± 8.2 ml/min/kg and for bupivacaine it was 32.3 ± 4.8 ml/min/kg. This was similar after extradural dosage.

The pharmacokinetics of ropivacaine in human volunteers after intravenous infusion have been determined (46). Clearance was found to be 0.82 ± 0.16 l/min. This is higher than the value for bupivacaine which is 0.58 l/min.

The higher clearance of ropivacaine compared with bupivacaine may offer an advantage in terms of systemic toxicity.

From the foregoing it can be seen that ropivacaine is likely to be less toxic than bupivacaine on the pharmacokinetic basis of lower fat solubility and increased clearance. In addition the fact that ropivacaine is a pure enantiomer has been shown to be important.

Chirality.

The observation that differences in drug pharmacology may be due to chirality has gained importance in recent years (47). This is due in part to the fact that modern technology allows the separation of or the optically pure synthesis of many drugs that were previously administered as racemic mixtures. Several reviews have appeared in recent years concerning chirality and local anaesthetics (48,49,50,34,51).

Definitions:

Isomers: Two or more different substances that have the same molecular formula, may be structural or stereoisomers.

Structural Isomers: These have the same chemical formula but the atoms are not arranged with the same configuration so they have distinct chemical and physical properties (e.g. isoflurane and enflurane).

Stereoisomers: These have the same chemical structure as each other but a different 3-dimensional spatial configuration. There are right and left forms which are non-superimposable mirror images.

Geometric isomers: Are a form of stereoisomers but not always true mirror images of each other. They occur when two different groups are attached to each other by rigid covalent bonds that cannot rotate (e.g. cis trans isomerism).

Chiral compounds: Chiral means having 'handedness'. A chiral compound is a substance with a centre of molecular asymmetry, such as a carbon atom with four different atoms or groups linked to it. Due to this asymmetry it is possible to have

different 3 dimensional spatial configurations of the molecule, which are mirror images of each other. These are known as stereoisomers, optical isomers or enantiomers.

Optical isomers have the property of rotating plane polarised light giving rise to the system of nomenclature based upon the relative direction of rotation (clockwise: d/ dextro/ +, counterclockwise: l/ laevo/-)

Further nomenclature is confusing, as there are at least three different naming systems. In addition to the optical rotation the absolute configuration can be defined according to a set of rules (Cahn-Ingold-Prelog system). This is based on the groups of the molecule and each centre of chirality is given a name R, rectus or S, sinister. The relative configuration implies a comparison to D (+) glutaraldehyde denoted as D or L and should not be confused with d or l, which have a different meaning.

Racemic mixture: A mixture of equal concentrations of each isomer. A solution of a racemic mixture does not rotate plane, polarised light. A single stereoisomer, free from its enantiomer is referred to as enantiopure. A racemic mixture consists of equal amounts of both enantiomers. Natural chiral drugs are usually enantiopure as they are synthesised enzymatically and enzymatic reactions usually produce one enantiomer only e.g. atropine or morphine.

Most synthetic chiral drugs are racemes because chemical reactions have an equal probability of producing both enantiomers.

Enantiomers often differ in their pharmacological actions. This is due to the body being a chiral environment. Enantioselective pharmacology occurs where a chiral drug

interacts with an endogenous chiral centre, e.g. a receptor binding protein, metabolising enzyme or biomembrane.

The ultimate action of the raceme is a weighted mean of the actions of the components.

Ropivacaine is a single enantiomer, the S-(-)-N-n-propyl homologue of the S-(-) enantiomer of the mepivacaine/bupivacaine series. Laevobupivacaine, S-(-) bupivacaine, is a newly released form of bupivacaine and has been investigated regarding its efficacy and toxicity.

Bupivacaine enantiomers differ in their properties at the site of action (52). The same enantiomers exert different effects on the heart. Some studies have shown that S(-) bupivacaine is less cardiotoxic than R(+) bupivacaine (37,53). It seems that the S(-) enantiomer binds less tightly than the R(+) enantiomer to serum proteins but this may have two different effects. An increased free fraction leads to an increased hepatic clearance of bupivacaine so increasing safety, but in the case of massive overdose the increased level of free bupivacaine may in fact contribute to worse toxicity. However, the balance seems to be in favour of the use of the S(-)enantiomer.

In neural sodium channels, R-bupivacaine associates 3 times as firmly as S-bupivacaine and dissociates 4.4 times as slowly, with the net effect that R-bupivacaine has a cardiac sodium channel dwell time 3 times as long as that of S-bupivacaine (52). Gristwood et

al have shown that R-bupivacaine prolongs ventricular conduction 4.6 times as much as S-bupivacaine, which renders R-bupivacaine severalfold more proarrhythmic than S-bupivacaine (54). These observations suggest that the potential cardiotoxicity of R-bupivacaine is far greater than that of S-bupivacaine.

Heavner in 1986 made an important discovery when he noted that as little as 300μg of bupivacaine injected into the cerebral ventricle has distant cardiac effects and it suddenly became evident that bupivacaine cardiotoxicity was a dual phenomenon of direct cardiac toxicity plus some kind of neurogenic action (55). Shortly after this Thomas et al (56) performed a study where they injected lignocaine or bupivacaine directly into the C1 region or the intermediolateral column or the nucleus tractus solitarius of the rat medulla. They showed that both drugs into the C1 area decreased mean arterial blood pressure, and at the intermediolateral column resulted in significant bradycardia and hypotension. At the nucleus tractus solitarius both caused bradycardia and hypotension, which was accompanied by ventricular arrhythmias. All animals receiving lignocaine survived, but 50% of the animals developing arrhythmias in the bupivacaine group died. In addition, R-bupivacaine has a more potent depressant effect on brainstem cardiorespiratory neurones, than the S enantiomer. The toxic effect of bupivacaine on electrical conduction through the heart is therefore compounded by an effect on indirect control, mediated by excited proarrhythmic and apneustic medullary command centres. This effect is strongly stereoselective for the R enantiomer and was established by Denson et al (57). They inserted electrodes into the nucleus tractus

solitarius and measured the cell-firing rate, after infusion of either isomer of bupivacaine. This was much lower after R bupivacaine and the incidence of hypotension, bradycardia and death was much higher in this group.

However, this effect of direct cardiotoxicity plus indirect neurogenic cardiotoxicity is only apparent when the drug's free plasma level increases rapidly, as in accidental intravenous injection. In clinical practice, slow incremental injection has rendered bupivacaine extremely safe although mishaps occasionally occur.

The foregoing would seem to suggest that ropivacaine, being the S(-) enantiomer, should be a safer drug in terms of cardiovascular side effects.

Treatment of Local Anaesthetic Toxicity.

Resuscitation should take place along well-established management protocols, as for any case of cardiovascular or respiratory arrest, with attention to airway, ventilation and maintenance of cardiac output. Hypoxia and acidosis should be prevented or treated, as there is evidence that these are deleterious. Kotelko et al induced cardiotoxicity in tracheostomised sheep but was able to show a low mortality due, they thought, to avoidance of hypoxia or hyperkalaemia (20). Mets et al suggest that death in the rats studied was most likely due to respiratory arrest and circulatory arrest was due to a combination of hypoxia, acidosis and local anaesthetic toxicity (21). De Jong showed that in well ventilated and oxygenated cats, correction of hypotension by the use of ephedrine and maintenance of ventilation were important in the treatment of cardiovascular toxicity induced by bupivacaine. Mallampati suggests that prevention of hypoxia is associated with a successful resuscitation after bupivacaine toxicity, reporting a case in which bupivacaine toxicity was treated with aggressive cardiorespiratory support (23).

The use of drugs in the treatment of established local anaesthetic toxicity is controversial.

Although lignocaine has been used to treat ventricular arrhythmias induced by bupivacaine, Mets (21) et al showed an additive toxic effect when either bupivacaine

0.5%, or lignocaine 2% or a mixture of 1% lignocaine and 0.25% bupivacaine was infused into rats. De La Coussaye (58) questioned the wisdom of using a local anaesthetic to treat local anaesthetic toxicity as both have an effect on ventricular conduction causing re-entrant arrhythmias

The use of adrenaline is also controversial. Very high doses of adrenaline were used to successfully resuscitate rats after bupivacaine overdosage (59). Adrenaline was also successfully used to resuscitate dogs overdosed with bupivacaine (60), but was of no value in attempts to resuscitate sheep in another study (61). Feldman noted that multiple doses of adrenaline were not effective in resuscitating dogs with bupivacaine induced cardiotoxicity and that it caused ventricular tachycardia and hypertension in one dog with ropivacaine induced toxicity (62). He suggested that phenylephrine may be a better choice of vasopressor. In the absence of clear guidelines, it was decided that in this study, resuscitation would take place along standard protocols using adrenaline as the first line treatment for ventricular arrhythmias and severe hypotension.

Atropine, beta receptor antagonists, benzodiazepines and noradrenaline have all been studied as treatment for local anaesthetic induced toxicity but no firm recommendation can be made concerning their use. Likewise calcium channel blockers, clonidine, dobutamine, hexamethonium and pacemakers have been suggested (63).

Solomon (64) et al showed that magnesium sulphate given to establish therapeutic concentrations prior to bupivacaine infusion, raised the threshold for cardiotoxicity. Magnesium as the drug of choice for treatment of bupivacaine induced cardiotoxicity has been studied by Reed (63). He studied the effect of a bolus of magnesium on the electrophysiological abnormalities induced by an infusion of bupivacaine in rats. He was able to show that magnesium produces a more rapid resolution of bupivacaine induced electrophysiological changes than placebo. It was decided on the basis of this work, to use magnesium as the anti arrhythmic agent in this study, should adrenaline and DC cardioversion fail to restore sinus rhythm after local anaesthetic induced arrhythmias.

Studies Comparing the Toxicity of Ropivacaine and Bupivacaine.

Rutten et al studied the effect on the cardiovascular and central nervous systems of intravenous administration of lignocaine, bupivacaine and ropivacaine (65). They administered bolus doses of the local anaesthetics in sequentially increasing doses to 18 conscious, instrumented sheep. The doses were administered into a central vein over 5 seconds and the sheep were observed for CNS and CVS effects. After doses of local anaesthetic agents that did not cause convulsions, there were minimal cardiovascular effects. After doses that produced convulsions, there were marked increase in heart rate, mean arterial pressure, cardiac output, pulmonary artery pressure, systemic vascular resistance, left ventricular end diastolic pressure and dP/dt (left ventricular contractility). 2 sheep died after bupivacaine 80mg, one died after 90mg ropivacaine and one died after ropivacaine 120mg.

The same team then examined the mechanisms of death after fatal doses of the same agents (22). 4 awake, instrumented sheep were given lignocaine, 4 bupivacaine and 4 ropivacaine by infusion over 3 minutes. Fatal doses were established by treating the sheep with successive daily dose increments of each drug. The mean fatal dose of lignocaine was 30.7mg/kg, that of bupivacaine was 3.7mg/kg and that of ropivacaine was 7.3mg/kg. 3 of the bupivacaine group died after sudden onset of ventricular tachycardia/fibrillation without hypoxia or acidosis. The fourth died of respiratory depression with bradycardia and hypotension as did the lignocaine treated animals. The

ropivacaine treated animals died of a combination of these two mechanisms. When the fatal doses of bupivacaine was compared to those of ropivacaine divided by 1.5 to compensate for the lower anaesthetic potency of ropivacaine, there was no significant difference between the 2 groups. This is important in terms of potential recovery as if severe cardiac toxicity occurs, it would be useful to establish that resuscitation is likely to be more successful after a toxic dose of ropivacaine. The authors suggest that ropivacaine has electrophysiological effects intermediate to those of bupivacaine and lignocaine. The proportion of the administered dose found in the heart and brain were similar for all three agent implying that the observed differences in toxicity were due to qualitative differences with respect to the effects of the agents on cardiac electrophysiology.

The systemic toxicity of lignocaine, bupivacaine and ropivacaine has been studied in dogs (66). Feldman designed an experiment to mimic the accidental intravenous administration of a local anaesthetic and assessed the systemic toxicity, arrhythmogenicity and mode of death of convulsant and supraconvulsant doses of lignocaine, bupivacaine and ropivacaine. The experiment was performed on conscious dogs. Each dog was given a local anaesthetic on up to 3 consecutive days in increasing dosage. On the first day the drugs were infused until convulsions occurred. The average doses of each drug to cause convulsions, was 20.8mg/kg for lignocaine, 4.31mg/kg for bupivacaine and 4.88mg/kg for ropivacaine. The next day twice that dose was given and the response assessed. 2 dogs given lignocaine died due to progressive

hypotension, respiratory arrest and cardiovascular collapse. No ventricular arrhythmias were seen in this group. Ventricular arrhythmias were seen in 5 out of 6 dogs treated with bupivacaine and 4 died because of hypotension, respiratory arrest and cardiovascular collapse. A fifth dog died in ventricular fibrillation. In the ropivacaine group one animal died due to hypotension, respiratory arrest and cardiovascular collapse. Another dog had transient premature ventricular contractions. On the third day the surviving animals were given three times the convulsant dose i.e. for bupivacaine and ropivacaine the dose was 12.93mg/kg and 14.64mg/kg respectively. The remaining 3 dogs in the lignocaine group, the last dog in the bupivacaine group and four dogs in the ropivacaine group died. Deaths were due to hypotension, respiratory arrest and cardiovascular collapse.

The conclusions made were that the convulsive doses for ropivacaine and bupivacaine are similar but that ropivacaine has a greater margin of safety and is less arrhythmogenic than bupivacaine. The mean doses given in the study I am presenting were 21.2mg/kg for bupivacaine, and 20.1mg/kg for ropivacaine. These are significantly higher than those given by Feldman.

Feldman's group then looked at the treatment of acute systemic toxicity of the local anaesthetics (62). They again established the convulsant dose of bupivacaine (4.3mg/kg) and ropivacaine (4.9mg/kg) and followed this with twice this dose 2 days later. Seizures at this time were treated with thiamylal and the dogs were intubated and

ventilated with oxygen enriched air. Two dogs in the bupivacaine group developed hypotension, respiratory arrest, ventricular tachycardia and fibrillation, which was resistant to closed chest massage, treatment with adrenaline, bretylium and atropine and DC cardioversion. The 4 remaining dogs survived after being successfully resuscitated by treatment of seizures and ventilation alone. All 6 dogs given ropivacaine survived without requiring any major intervention apart from intubation and treatment of seizures. They concluded that the rapid aggressive treatment of CNS and CVS toxicity can reduce the mortality associated with rapid intravenous administration of a local anaesthetic agent. The difference in mortality rates was not statistically significant although all dogs in the ropivacaine group survived compared to 66% of the dogs treated with bupivacaine. In this study, severe cardiotoxicity was not seen in the majority of dogs studied, as the dose of local anaesthetic was not enough to cause arrhythmias and hypotension. In contrast, the study I am presenting deliberately ensures severe cardiac depression to the point of cardiac arrest before resuscitation is attempted.

A study by Reiz (31) in pigs showed a greater margin of safety of ropivacaine compared to bupivacaine injected directly into the left anterior descending artery. Anaesthetised pigs were studied by administering lignocaine, bupivacaine and ropivacaine in equi-analgesic doses. The favourable cardiotoxic profile of ropivacaine was confirmed and the toxicity ratio based on the electrophysiological effect of

prolongation of the QRS complex was determined as 1: 6.7: 15 for lignocaine: ropivacaine: bupivacaine.

Bupivacaine has also been shown to be more cardiotoxic than an equivalent dose of ropivacaine, in the isolated perfused rabbit heart. It caused more severe arrhythmias than ropivacaine and the development of ECG changes and myocardial depression was more rapid with bupivacaine (67).

Several other studies have reported the safety of ropivacaine compared to bupivacaine both in animal studies and in humans. Santos et al compared the effect of infusing ropivacaine and bupivacaine into pregnant and non-pregnant sheep and concluded that toxicity was not worsened by gestation (68). The dose of ropivacaine required to produce circulatory collapse was 12.9mg/kg compared to 8.5mg/kg for bupivacaine.

Scott et al compared the acute toxicity of bupivacaine and ropivacaine (69). They studied 12 healthy male volunteers who received both drugs as an infusion at 10mg/min 7 days apart. The occurrence of CNS symptoms was the cue to terminating the infusion but a dose of 150mg of local anaesthetic was the maximum allowed by the protocol. The mean doses infused were 124mg of ropivacaine and 99mg of bupivacaine. Only 1 out of 12 subjects tolerated 150mg of bupivacaine compared to 7 out of 12 who tolerated 150mg of ropivacaine. Both drugs increased heart rate and arterial pressure

with a reduced stroke volume and ejection fraction, but cardiac output was maintained. Prolongation of the PR interval, QRS duration and QT interval was seen with bupivacaine but not ropivacaine.

Knudsen et al performed a similar experiment. They infused bupivacaine and ropivacaine into human volunteers until CNS toxicity occurred (70). The maximum tolerated dose was higher after ropivacaine in 9 subjects (mean 115mg) and higher after bupivacaine in 3 subjects (mean 103mg). The maximum tolerated unbound arterial plasma concentration was twice as high after ropivacaine but the time to disappearance of all symptoms was shorter after ropivacaine. At doses producing CNS symptoms cardiovascular changes were less significant with ropivacaine: the QRS width was increased more by bupivacaine and there was a greater effect on contractility from bupivacaine as assessed by echocardiography.

In summary, most studies comparing the toxicity of ropivacaine with that of bupivacaine have shown ropivacaine to be less toxic in terms of dosage and direct toxicity. There seems to be no doubt that ropivacaine is less likely than bupivacaine to cause problems with cardiovascular toxicity in clinical use. However, if severe cardiovascular depression does occur, there is no published evidence that resuscitation will be more successful after ropivacaine.

Method.

The aim of the experiment was to establish whether, after deliberately induced cardiac arrest by overdosage of a local anaesthetic agent, resuscitation was more successful after administration of ropivacaine compared to bupivacaine.

Male pigs were chosen as the model for the experiment. Ethical approval was granted by the Animal Research Review Committee, of the Faculty Medicine, of the University of Cape Town.

The study was performed in two parts. Experiment 1 was a pilot study, with the expectation that the survival in the pigs treated with ropivacaine would be far greater than in the bupivacaine treated group.

Power analysis indicated that a sample size of 12 pigs would be required to show a statistically significant difference if there were 4 deaths in the bupivacaine group and none in the ropivacaine group.

Experiment 2 was a modification of experiment 1, the difference being in the rate of infusion of the test drug, as it became apparent that the rate of infusion could have influenced the outcome of the experiment.

The investigators were blinded as to the identity of the infused drug.

In each experiment, the 12 pigs were randomised to receive either ropivacaine or bupivacaine, 6 in each group.

The pigs were anaesthetised by administration of ketamine 10mg/kg intramuscularly followed by atropine 0.5mg IM. Intravenous access was established and thiopentone 3mg/kg plus fentanyl 10μg/kg given intravenously. The pigs were intubated and a bolus of pancuronium 0.1mg/kg IV was given. Subsequent maintenance consisted of intermittent positive pressure ventilation with nitrous oxide, oxygen and halothane. The halothane was discontinued 20 minutes prior to administration of the local anaesthetic agent. All pigs had previously been tested for susceptibility to malignant hyperthermia.

Vascular access consisted of an arterial line in each carotid artery, one for monitoring of blood pressure and the other for blood sampling. A central venous line was inserted into the internal jugular vein for infusion of drugs and central venous pressure monitoring.

Monitoring consisted of an ECG, arterial blood gases and rectal temperature probe in addition to invasive blood pressure monitoring. The temperature was maintained between 36° and 38° by use of a warming fan.

Sodium chloride 0.9% with 5% dextrose was given intravenously at 2-5ml/kg/hr to maintain blood pressure as required.

Once vascular access was established, a bolus of fentanyl 10μg/kg was given IV and a left lateral thoracotomy was performed in order to expose the heart for internal cardiac massage. Once this was complete the halothane was discontinued and blood gases checked to confirm oxygenation and normocapnia. The ventilation was adjusted as required at this point.

In experiment 1, the local anaesthetic given consisted of either bupivacaine 0.5%, 5mg/kg bolus, followed by an infusion of 1mg/kg/min, or ropivacaine 1%, 10mg/kg bolus, followed by an infusion of 2mg/kg/min. These doses were calculated on the basis of work done by Feldman (62) and Nancarrow (22) and were felt to be sufficient to cause cardiac arrest shortly after the bolus dose was injected, with the subsequent infusion ensuring that the arrest occurred. The infusion was continued until cardiac arrest and was then stopped. At cardiac arrest, blood was taken for local anaesthetic levels, and resuscitation started. Cardiac arrest was defined as a systolic blood pressure

of less than 30mmHg, or pulseless ventricular tachycardia, or ventricular fibrillation, or asystole.

Resuscitation was performed according to the guidelines of the Resuscitation Council (UK) of 1997 (72).

Survival was defined as the maintenance of a spontaneous regular cardiac rhythm with a mean blood pressure of at least 50mmHg for the last 30 seconds of the 15 minute period.

Any pig deemed a survivor at the termination of the experiment was given a bolus of potassium chloride as euthanasia.

Resuscitation.

Ventricular fibrillation or pulseless ventricular tachycardia.

100% oxygen was given.

Immediate defibrillation with internal paddles was performed with 4 joules, repeated with 4 joules and again with 8 joules if the previous shock was unsuccessful at defibrillating.

Adrenaline 1mg IV was given and internal cardiac massage commenced at 80-100 compressions per minute.

DC cardioversion was repeated with 3 shocks at 8 joules after every minute of resuscitation or 60s after any intervention. Internal cardiac massage was continued as long as there was insufficient cardiac output.

Adrenaline 1 mg IV was given every 3 minutes.

Blood gases were checked at 8 minutes and acidosis corrected with sodium bicarbonate if the pH was less than 7.20 or the base excess greater than -10.

Magnesium sulphate 60mg/kg IV was given at 12 minutes if the rhythm was ventricular tachycardia with no cardiac output, or ventricular fibrillation.

The experiment was terminated at 15 minutes.

Blood was taken at 15 minutes for measurement of the plasma concentration of the local anaesthetic. In survivors, blood was taken for local anaesthetic plasma

concentrations at resumption of stable CVS parameters. The local anaesthetic levels were measured using Gas Chromatography with a Nitrogen Phosphorous Detector.

Non VF/VT.

100% oxygen was commenced.

Internal cardiac massage at 80-100 compressions per minute was performed.

Adrenaline 1mg was given IV every 3 minutes.

Blood gases were checked at 8 minutes and corrected as required (as in the VF protocol).

The experiment was terminated at 15 minutes and blood taken for plasma levels of local anaesthetic.

In survivors the local anaesthetic levels were measured at the resumption of stable cardiovascular parameters.

Results Experiment 1.

The mortality in the ropivacaine treated pigs was 16% versus 50% in the bupivacaine group.

The resuscitation of each pig followed the recommendations as above but the course of events during the arrest situation varied during each experiment.

Pig 1. A wide complex bradycardia developed and after 450mg of drug the systolic blood pressure was <30mmHg. Adrenaline 1mg was given and after 30 seconds of internal cardiac massage a good cardiac output had resumed. No further resuscitation was required. Survivor. Drug: ropivacaine.

Pig 2. A wide complex bradycardia occurred followed by ventricular fibrillation after 380mg of drug. The protocol was followed with 3 DC cardioversion attempts and a total of 5mg of adrenaline. There was no need to correct the acid base status. At 12 minutes magnesium sulphate was given. 60 seconds later resumption of sinus rhythm occurred with a rate of 42 beats per minute and blood pressure of 118/68.

Survivor. Drug: ropivacaine.

Pig 3. A bradycardia with normal complexes developed which evolved into asystole after 730mg of drug. Adrenaline 1mg was given with simultaneous internal cardiac massage. Within 30 seconds a regular rhythm was established followed by the recovery of the blood pressure. No further resuscitation was required. During the completion of the 15 minute study period, multiple ectopic beats developed which although not causing haemodynamic instability were treated twice with a bolus of magnesium sulphate. Survivor. Drug: ropivacaine.

Pig 4. A wide complex bradycardia progressed to asystole after 430mg of drug. Cardiac massage was commenced and adrenaline 1mg given. There was a good initial recovery, which developed after 3 minutes into ventricular fibrillation. DC cardioversion was unsuccessful and further adrenaline was given to a total of 4 mg. Cardiac massage and further attempts at cardioversion were unsuccessful. The acid base status remained normal. Magnesium sulphate was given at 12 minutes. The cardiac rhythm degenerated to fine ventricular fibrillation and then asystole and was unresponsive to further resuscitation attempts. Non-survivor. Drug: ropivacaine.

Pig 5. A wide complex bradycardia developed with hypotension and after 490mg of drug, when the systolic blood pressure was 30mmHg, adrenaline was given and cardiac massage commenced. There was a good response initially with regular wide complexes

at a rate of 97 and a blood pressure of 97/78. No correction of blood gases was required and at 12 minutes there was sinus rhythm with a BP of 120/70. In spite of the satisfactory parameters magnesium was given and caused hypotension with wide complexes requiring 2 doses of adrenaline and DC cardioversion. There was a good response and this animal was alive at and beyond 15 minutes. Survivor. Drug: bupivacaine.

Pig 6. There was initial hypotension with a wide complex bradycardia and a systolic BP <30mmHg after 540mg of drug. Adrenaline and cardiac massage were commenced and after 60 seconds there was resumption of a regular rhythm. At 6 minutes atropine 0.5mg was given for bradycardia followed 2 minutes later by adrenaline 1 mg for hypotension. This was followed by ventricular fibrillation so DC cardioversion at 4J, 4J then 8J was performed. The rhythm remained VF and magnesium was given. A further 3 DC shocks were given followed by adrenaline 1mg and atropine 0.5mg given to treat a sinus bradycardia. This animal maintained an adequate spontaneous cardiac output at 15 minutes. Survivor. Drug: bupivacaine.

Pig 7. A wide complex bradycardia developed associated with hypotension until after 700mg of drug the systolic blood pressure was <30mm Hg. After the initial adrenaline there was a good response but the pulse slowed and atropine 0.5mg was given. The blood pressure fell so another dose of adrenaline was given which was followed by

ventricular fibrillation. Further resuscitation consisted of DC shocks, adrenaline and magnesium. The acid base status remained satisfactory. This animal remained in VF until termination of the experiment. Non-survivor. Drug: bupivacaine.

Pig 8. A sinus bradycardia developed with associated hypotension until 450mg of drug had been given when the BP fell to 30mm Hg. Cardiac massage was commenced followed by 3 doses of adrenaline and DC cardioversion at 9 minutes for VF. This was unsuccessful so another dose of adrenaline, and DC shock were given. At 12 minutes magnesium was given and this was followed by the resumption of sinus rhythm. There was no cardiac output associated with this rhythm so adrenaline was again given followed by brief cardiac massage. At 15 minutes the blood pressure was 126/86 and pulse in sinus rhythm at a rate of 59. (This animal was observed for a further 15 minutes after the experiment was terminated, remaining stable throughout). Survivor. Drug: ropivacaine.

Pig 9. Asystole occurred after 350mg of drug. Cardiac massage was commenced and adrenaline 1mg given. There was an immediate resumption of cardiac output and no further treatment was required. Survivor. Drug: ropivacaine.

Pig 10. Arrest in asystole occurred after 330mg of drug. Cardiac massage and adrenaline resulted in an immediate resumption of good cardiac output and no further treatment was required. Survivor. Drug: bupivacaine.

Pig 11. Asystole occurred after 635mg of drug. After several doses of adrenaline, ventricular fibrillation occurred and this remained refractory to further treatment by DC shock and magnesium. The rhythm at 15 minutes was asystole.

Non-survivor. Drug: bupivacaine.

Pig 12. Bradycardia occurred evolving to asystole after 335mg of drug. Adrenaline initially restored the rhythm and blood pressure briefly, but this was followed by VF. This was unresponsive to further treatment with adrenaline, magnesium and DC shock and the rhythm was asystole at 15 minutes. Non-survivor. Drug: bupivacaine.

The results are presented in Table 3 overleaf.

Pig number	Weight(kg)	Test Drug	Dose(mg)	Vol(ml)	Dose(mg/kg)	Outcome
1	24.5	ropivacaine	450	45	18.4	survived
2	22.0	ropivacaine	380	38	17.3	survived
3	23.0	ropivacaine	730	73	31.7	survived
4	23.0	ropivacaine	430	43	18.7	died
5	23.0	bupivacaine	490	98	21.3	survived
6	23.0	bupivacaine	540	108	23.5	survived
7	25.0	bupivacaine	700	140	28.0	died
8	22.0	ropivacaine	450	45	20.5	survived
9	25.0	ropivacaine	350	35	14.0	survived
10	23.0	bupivacaine	330	66	14.3	survived
11	25.0	bupivacaine	635	127	25.4	died
12	23.0	bupivacaine	335	67	14.6	died

Table 3

Local anaesthetic levels were measured at arrest and at 15 minutes or at recovery of stable cardiovascular parameters.

Pig No.	Drug	L.A. at arrest (μg/ml)	L.A. at recovery/death (μg/ml)	Outcome
1	ropivacaine	87.7	14.9	survived
2	ropivacaine	178.7	13.6	survived
3	ropivacaine	80.6	12.4	survived
4	ropivacaine	102.1	35.8	died
5	bupivacaine	128.4	21.2	survived
6	bupivacaine	29.5	19.1	survived
7	bupivacaine	53.0	18.2	died
8	ropivacaine	54.6	16.4	survived
9	ropivacaine	47.1	7.6	survived
10	bupivacaine	32.7	17.6	survived
11	bupivacaine	78.0	28.0	died
12	bupivacaine	33.4	21.3	died

Table 4.

The times to arrest and recovery are shown in table 5.

Pig Number	1	2	3	4	5	6	7	8	9	10	11	12
T to arrest(min)	4.7	4.1	11.4	5.0	16.8	18.9	23.5	4.7	2.7	9.8	20.9	10.0
T to recov.(min)	1	13	1	15	1	14	15	15	1	1	15	15

Table 5.

A summary of the results is presented in table 6.

Drug	Mean weight (kg)	Mean dose (mg)	Mean dose/kg (mg)	Mean time to arrest (min)	Mean time to recovery (min)	Mean blood level at arrest (μg/ml)	Mean blood level at end (μg/ml)
Ropivacaine	23.25	465	20.1	5.4 ± 3.0	7.7 ± 7.3	91.8 ± 47.3	16.8 ± 9.8
Bupivacaine	23.67	505	21.2	16.6 ± 5.7	10.2 ± 7.1	59.2 ± 38.5	20.9 ± 3.8

Table 6.

There was no statistically significant difference between the 2 groups regarding the weights of the pigs, mean dose of local anaesthetic or mean dose per kilogram. The time to cardiac arrest was longer with bupivacaine and this was highly statistically significant ($p = 0.002$). However the time to recovery/death was not significantly different. There was no statistically significant difference in the blood levels of local

anaesthetic at arrest or at recovery. The difference in mortality (16% versus 50%) did not reach statistical significance.

Arterial blood gases were also analysed for statistical significance. There was no difference in any of the parameters except the mean pO_2 was lower in the ropivacaine group, and this was statistically significant. However, the pO_2 was above normal at all times and not felt to be clinically important. The blood gas results and mean results are presented in table 7 and 8 respectively.

	pH	pCO_2	pO_2	Std Bicarb	Base Excess
Pig 1 pre infusion	7.54	3.52	24.92	25.9	+0.2
Pig 1 post arrest	7.40	5.48	20.71	25.0	+0.7
Pig 2 pre infusion	7.48	4.80	13.36	27.4	+2.9
Pig 2 post arrest	7.55	3.17	50.11	25.1	-1.1
Pig 3 pre infusion	7.47	4.73	16.89	27.1	+2.5
Pig 3 post arrest	7.43	5.35	16.72	26.2	+1.9
Pig 4 pre infusion	7.49	4.44	14.52	25.2	+2.8
Pig 4 post arrest	7.62	1.93	45.90	21.8	-6.1
Pig 5 pre infusion	7.57	4.03	29.90	31.0	+5.8
Pig 5 post arrest	7.74	2.11	65.30	29.6	+1.8
Pig 6 pre infusion	7.51	4.60	38.40	27.6	+4.5
Pig 6 post arrest	7.65	2.29	69.60	25.6	-1.5
Pig 7 pre infusion	7.52	4.12	34.78	27.8	+2.8
Pig 7 post arrest	7.54	2.95	67.31	23.3	-3.4
Pig 8 pre infusion	7.45	4.96	29.01	26.6	+2.1
Pig 8 post arrest	7.51	3.53	41.94	24.7	-1.2
Pig 9 pre infusion	7.42	6.16	24.40	28.5	+5.0
Pig 9 post arrest	7.32	7.04	42.93	24.5	+1.1
Pig 10 pre infusion	7.41	5.73	32.58	26.5	+2.6
Pig 10 post arrest	7.25	7.74	32.80	21.8	-1.6
Pig 11 pre infusion	7.45	4.09	35.83	23.5	-2.1
Pig 11 post arrest	7.54	4.06	25.04	28.0	+2.9
Pig 12 pre infusion	7.49	4.89	17.95	29.0	+4.7
Pig 12 post arrest	7.64	2.59	54.12	26.9	+0.3

Table 7.

Mean blood gas results.

	pH	pCO_2	pO_2	Std Bicarb	Base excess
Ropivacaine pre infusion	7.48	4.76	20.52	26.8	+2.6
Bupivacaine pre infusion	7.49	4.57	31.56	27.6	+3.0
Ropivacaine post arrest	7.47	4.41	36.38	24.6	-0.8
Bupivacaine post arrest	7.57	3.62	52.36	25.9	-0.3

Table 8.

Discussion Experiment 1.

There was a statistically significant difference in the time of infusion to cause cardiac arrest (16.6 minutes for bupivacaine versus 5.4 minutes for ropivacaine). This was felt to be contributory to the improved survival in the ropivacaine group, as it would have taken longer for cardiac levels of bupivacaine to reach toxic levels, during which time peripheral compartment would have become saturated with the drug. Despite the mean dose of drug being similar, the plasma level of bupivacaine was much lower than that of ropivacaine at arrest (59.2μg/ml compared to 91.8μg/ml). This was probably due firstly to the larger volume of distribution of bupivacaine (73l versus 61l), and secondly to the longer infusion time, allowing for a greater degree of redistribution to occur. This implies less facility for redistribution from the myocardium for bupivacaine, whereas the recovery from ropivacaine induced cardiac arrest could have been mainly due to redistribution

Accordingly, Experiment 2 was a modification of Experiment 1.

The bolus of drug given was unchanged, 5mg/kg for bupivacaine, and 10mg/kg for ropivacaine, these being the commercially available concentrations.

The infusion was altered. Bupivacaine was given as in Experiment 1, at a concentration of 0.5%. The ropivacaine was diluted with saline to give a concentration of 0.5%. The infusion rate of both drugs was 10ml/minute of this 0.5% solution, therefore 50mg of each drug was given per minute.

Results Experiment 2.

The mortality in the bupivacaine group was 50%, unchanged from Experiment 1.

The mortality in the ropivacaine group was also 50%, up from 16% in Experiment 1.

The sequence of events during the process of cardiac arrest and resuscitation during Experiment 2 was similar to the events of Experiment 1. The animals developed a wide complex bradycardia with hypotension to a systolic blood pressure of less than 30mmHg. No animal developed ventricular tachycardia or fibrillation prior to the administration of adrenaline, although ventricular fibrillation was seen sometimes after adrenaline was given. The sequence of events for each animal will not be described further.

Table 9 overleaf shows the results of Experiment 2.

Pig Number	Weight(kg)	Test Drug	Dose(mg)	Vol(ml)	Dose (mg/kg)	Outcome
13	25	ropivacaine	510	77	20.4	survived
14	23	ropivacaine	400	57	17.4	died
15	25	bupivacaine	335	67	13.4	survived
16	23	bupivacaine	390	78	17.0	died
17	26	bupivacaine	380	76	14.6	died
18	21	ropivacaine	375	54	17.8	survived
19	22	bupivacaine	400	80	18.2	died
20	21	ropivacaine	420	63	20.0	died
21	27	ropivacaine	355	46	13.2	died
22	24	bupivacaine	285	57	11.9	survived
23	23	bupivacaine	325	65	14.1	survived
24	26	ropivacaine	450	64	17.3	survived

Table 9.

The plasma levels of local anaesthetic at arrest and recovery/death are shown in table 10.

Pig number	Drug	L.A. at arrest (μg/ml)	L.A. at recovery/death (μg/ml)	Outcome
13	ropivacaine	94.o	14.1	survived
14	ropivacaine	168.3	16.7	died
15	bupivacaine	140.4	13.2	survived
16	bupivacaine	113.3	22.8	died
17	bupivacaine	68.3	25.6	died
18	ropivacaine	77.6	14.0	survived
19	bupivacaine	105.3	33.0	died
20	ropivacaine	131.8	33.9	died
21	ropivacaine	19.9	15.5	died
22	bupivacaine	173.4	16.3	survived
23	bupivacaine	86.0	10.7	survived
24	ropivacaine	33.5	5.6	survived

Table 10.

Times to arrest and recovery are shown in table 11.

Pig number	13	14	15	16	17	18	19	20	21	22	23	24
T to arrest(min)	5.2	3.4	4.2	5.5	2.5	3.3	5.8	4.2	1.9	3.3	4.2	3.8
T to recovery(min)	13	15	1	15	15	2	15	15	15	11	1	1

Table 11.

A summary of the results of Experiment 2 is presented in table 12.

Drug	Mean weight(kg)	Mean dose (mg)	Mean dose/kg (mg)	Mean time to arrest (min)	Mean time to recovery (min)	Mean blood level at arrest (μg/ml)	Mean blood level at end (μg/ml)
ropivacaine	23.8	418	17.6	3.6 ± 1.1	10.16 ± 6.8	101.0 ± 51.6	16.7 ± 10.4
bupivacaine	23.8	353	14.9	4.2 ± 1.3	9.66 ± 6.9	114.5 ± 37.9	20.3 ± 8.4

Table 12.

There were no statistically significant differences in the weight of the pigs, mean doses, mean time to arrest or recovery, or mean plasma levels at arrest or recovery. The mortality was 50% for both groups.

The blood gas results are shown in table 13.

	pH	pCO_2	pO_2	Std Bicarb	Base Excess
Pig 13 pre infusion	7.42	5.41	14.12	26.9	+2.7
Pig 13 post arrest	7.30	6.75	13.14	26.6	-1.4
Pig 14 pre infusion	7.42	5.89	13.72	28.6	+4.6
Pig 14 post arrest	7.76	1.78	53.90	28.0	+3.9
Pig 15 pre infusion	7.38	6.45	20.15	27.4	+3.2
Pig 15 post arrest	7.66	2.26	78.26	26.7	+2.5
Pig 16 pre infusion	7.63	2.47	20.30	26.3	+2.0
Pig 16 post arrest	7.64	1.64	56.58	22.0	-3.0
Pig 17 pre infusion	7.51	2.60	19.77	20.5	-4.9
Pig 17 post arrest	7.52	2.93	39.16	22.5	-2.3
Pig 18 pre infusion	7.59	2.90	15.53	25.8	+1.5
Pig 18 post arrest	7.41	3.88	62.10	20.9	-4.4
Pig 19 pre infusion	7.60	3.60	11.20	30.0	+6.2
Pig 19 post arrest	7.59	2.39	59.20	23.0	-1.7
Pig 20 pre infusion	7.65	2.29	13.88	29.2	+5.3
Pig 20 post arrest	7.50	3.68	40.08	24.8	+0.4
Pig 21pre infusion	7.52	4.76	11.20	30.3	+6.6
Pig 21 post arrest	7.44	4.48	7.62	23.8	-0.5
Pig 22 pre infusion	7.53	4.13	15.85	28.2	+4.2
Pig 22 post arrest	7.58	3.13	72.13	26.6	+2.4
Pig 23 pre infusion	7.49	4.20	33.86	25.8	+1.6
Pig 23 post arrest	7.38	4.99	64.40	22.5	-2.4
Pig 24 pre infusion	7.47	4.90	16.13	26.8	+3.7
Pig 24 post arrest	7.29	6.61	17.33	23.5	-3.0

Table 13.

The mean arterial blood gas results are shown in table 14.

	pH	pCO2	pO2	Std Bicarb	Base Excess
Ropivacaine pre infusion	7.51	4.36	14.09	27.9	+4.0
Bupivacaine pre infusion	7.46	3.91	20.18	26.4	+2.1
Ropivacaine post arrest	7.44	4.24	32.36	24.6	-0.8
Bupivacaine post arrest	7.56	2.89	61.62	23.9	-0.8

Table 14.

There was a statistically significant difference in the post arrest pO_2 but other parameters were similar. This difference was not felt to be clinically significant.

Discussion.

For both pharmacokinetic and pharmacodynamic reasons, ropivacaine may be expected to have a more benign effect on the heart than bupivacaine, and resuscitation from local anaesthetic overdose could be expected to be more successful with ropivacaine.

In terms of pharmacokinetics, firstly, the clearance of ropivacaine is greater than that of bupivacaine so the effect of ropivacaine on the myocardium could be expected to dissipate more rapidly than that of bupivacaine (46). Secondly, as the fat solubility of bupivacaine is much greater than that of ropivacaine, it will more rapidly cross lipoprotein membranes to enter the myocardial cells to a greater extent than ropivacaine, thus gaining access to ion channels which can then be blocked, resulting in toxicity (42).

In terms of pharmacodynamics, ropivacaine has a more favourable profile compared to bupivacaine. There is less block of sodium channels (13), less block of potassium channels (32), and less block of calcium channels with ropivacaine compared to bupivacaine (14). This suggests that the effect on Vmax of ropivacaine is less than ropivacaine and that this effect is less amplified by blockade of calcium and potassium channels. The R isomer of bupivacaine has a much higher affinity for neural sodium channels than the S isomer and prolongs ventricular conduction 4.6 times as much as S-bupivacaine (54), thus the S isomer ropivacaine may be suspected of having similar

properties, thus being more benign. R-bupivacaine also has a greater effect on brainstem cardiorespiratory neurones than the S isomer (57), and R-ropivacaine has been shown to be more cardiotoxic than S-ropivacaine (71). Ropivacaine has also been shown to be a coronary vasodilator (31), increasing great cardiac venous blood flow, thus hastening its clearance from myocardial cells.

In each of the two experiments performed, the doses of drug infused to cause cardiotoxicity were similar on a mg/kg basis. However, in Experiment 1, on a ml/kg basis the volume of bupivacaine infused was more than twice that of ropivacaine (a mean of 101mls for bupivacaine versus 46.5ml for ropivacaine). This poses several questions regarding the experiment. It was initially thought that the bolus of each drug would be sufficient in terms of cardiotoxicity to necessitate only a short infusion prior to cardiac arrest. This calculation was based on the work of Feldman (62) and Nancarrow (22). Feldman studied the toxic doses of bupivacaine and ropivacaine and found that cardiovascular collapse occurred after an infusion of 8.62mg/kg of bupivacaine resulting in 4 deaths out of 6 dogs, and 22.8mg/kg of ropivacaine resulting similarly in 4 deaths out of six dogs. Nancarrow established the mean fatal dose of bupivacaine in sheep as 3.7mg/kg and of ropivacaine as 7.3mg/kg.

The pigs in the first experiment of this study were given either 5mg/kg of bupivacaine or 10mg/kg of ropivacaine as a bolus followed by an infusion of 1mg/kg/min or 2mg/kg/min for bupivacaine and ropivacaine respectively. The time to arrest was

approximately three times longer in the bupivacaine group once the infusion had started. This implies that significant redistribution of drug had already occurred by the time cardiac arrest occurred, which implies less facility for redistribution once resuscitation had started, as peripheral compartments can be considered as virtually saturated. The blood level of bupivacaine fell from 59.2μg/ml to 0.35 of that level, 20.9μg/ml. For ropivacaine, toxicity occurred sooner, and some of the success in resuscitation may be due to rapid redistribution from the heart whereas this mechanism may not have been available to the bupivacaine treated pigs. The ropivacaine plasma levels fell from 91.8 to 20.9μg/ml, 0.18 of the arrest values implying a very much greater clearance from the blood than bupivacaine. This difference was statistically significant ($p = 0.019$). In Experiment 2, this difference was eliminated, both falling to approximately one fifth of the arrest level. This enabled a more direct comparison of the two drugs.

In Experiment 1 the cardiovascular parameters may have been influenced by the effect of the volume alone. Based on a blood volume of 70ml/kg, the mean volume of drug infused represents approximately 6% of blood volume for bupivacaine and only 3% for ropivacaine. A rapid infusion of such magnitude may have had deleterious effects on a heart being subjected to negative inotropism and arrhythmias, and may also have contributed to a worse outcome in the bupivacaine group. Experiment 2 corrected for this, and similar volumes of local anaesthetic were given to cause cardiac arrest.

An interesting observation was that in none of the 24 pigs studied, did an acidosis develop during the arrest period, as shown by the blood gas results at 8 minutes. The cardiac output was maintained by internal cardiac massage and was seen to be effective in maintaining a mean blood pressure of approximately 30 - 40mmHg during the arrest period. As mentioned previously it has been noted that avoidance of hypoxia and acidosis is important for a successful resuscitation post bupivacaine cardiotoxicity (61,23). A contributing factor in the reported high mortality due to local anaesthetic toxicity, is that it is likely that in some cases, airway management problems with ineffective external chest compressions resulting in a low cardiac output may have led to a persistent metabolic acidosis due to hypoxia. In this study, the maintenance of an adequate cardiac output has avoided this problem. The extrapolation of animal model results to the situation in humans may not be valid but as a general principal of resuscitation, oxygen delivery must be maintained, and if cardiac output cannot be assured by external cardiac massage, consideration of internal cardiac massage is warranted.

Another interesting finding was that in each experiment, the dose to cause cardiovascular collapse was similar for both drugs (the doses in Experiment 2 were lower due to a more rapid infusion of the test drug resulting in earlier toxicity). This is in contrast to most studies, which show cardiovascular collapse at a lower dose for bupivacaine. This may be due to the fact that the effect on the heart alone was studied here while providing ventilatory support throughout the drug infusion period during

which cardiac toxicity was developing. There has been no study comparing the cardiac toxicity of ropivacaine and bupivacaine in ventilated animals. Previous studies have looked at the effect of these agents in spontaneously breathing animals, which develop CNS symptoms followed by CVS symptoms. Ropivacaine tends to be used in similar or slightly higher concentrations than bupivacaine, implying that the dose required to achieve an effect is similar for both agents. Most studies show cardiac complications after a higher dose of ropivacaine compared to bupivacaine.

The local anaesthetic levels of all 24 pigs were examined as a combined group. There was a highly statistically significant difference in the plasma level of local anaesthetic in survivors compared to non-survivors ($14.3 \pm 4.2\mu g/ml$ compared to $26.8 \pm 7.0\mu g/ml$, $p = 0.001$). The local anaesthetic levels at arrest for all 24 pigs were not significantly different ($86.8\mu g/ml$ for bupivacaine and $107.9\mu g/ml$ for ropivacaine). The arrest levels for survivors and non-survivors were also not significantly different ($90.1\mu g/ml$ compared to $104.6\mu g/ml$).

It seems therefore, that in pigs that survived, survival was due to redistribution of local anaesthetic resulting in rapidly falling plasma concentrations, which would enable the myocardial concentration of local anaesthetic to decrease, and that within the 15 minute study period, those pigs that achieved sufficient redistribution were the pigs that survived. This has implications for the treatment of local anaesthetic induced cardiac

arrest, in that resuscitation should continue for a prolonged period to allow for drug redistribution away from the heart.

The mortality in the ropivacaine treated pigs was substantially different in Experiment 1 compared to Experiment 2 (16% versus 50%). The initial result was the expected result, and it was surprising to note the substantially worse mortality in Experiment 2. However, the higher survival rate in Experiment 1 is felt to be due purely to chance, a consequence of the small numbers of pigs studied.

When taken as one large group of 24 pigs, the rate of survival between the pigs treated with ropivacaine was 67% compared to 50% for the bupivacaine treated pigs. This difference does not reach statistical significance. In order to show statistical significance, power analysis shows that a total of 56 pigs would need to be studied. However, the clinical relevance of a 67% survival compared to a 50% survival is questionable, as both rates are extremely poor. Local anaesthetic toxicity should be avoided.

The conclusion to be drawn from this study is that a statistically significant difference in the mortality due to overdose of ropivacaine or bupivacaine has not been shown. The mortality from cardiac arrest induced by local anaesthetic overdose is extremely high. Most evidence concerning cardiac toxicity of local anaesthetics however suggests that ropivacaine is less likely than bupivacaine to cause cardiac arrest.

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