LEADING ARTICLE

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Cardiac and CNS Toxicity of Levobupivacaine

Strength of Evidence for Advantage Over Bupivacaine

Robert W. Gristwood

Arachnova Limited, St John's Innovation Centre, Cambridge, United Kingdom

Abstract

Bupivacaine is currently the most widely used long-acting local anaesthetic. Its uses include surgery and obstetrics; however, it has been associated with potentially fatal cardiotoxicity, particularly when given intravascularly by accident. Levobupivacaine, a single enantiomer of bupivacaine, has recently been introduced as a new long-acting local anaesthetic with a potentially reduced toxicity compared with bupivacaine. Numerous preclinical and clinical studies have compared levobupivacaine with bupivacaine and in most but not all studies there is evidence that levobupivacaine is less toxic. Advantages for levobupivacaine are seen on cardiac sodium and potassium channels, on isolated animal hearts and in whole animals, anaesthetised or awake. In particular the intravascular dose of levobupivacaine required to cause lethality in animals is consistently higher compared with bupivacaine. In awake sheep, for example, almost 78% more levobupivacaine was required to cause death. In contrast, in anaesthetised dogs no differences were seen in the incidence of spontaneous or electrical stimulation-induced ventricular tachycardia and fibrillations among animals exposed to levobupivacaine or bupivacaine. The reversibility of levobupivacaine-induced cardiotoxicity has also been assessed. Some data point to an advantage of levobupivacaine over bupivacaine but this potential advantage was not confirmed in a recent study in anaesthetised dogs. Three clinical studies have been conducted using surrogate markers of both cardiac and CNS toxicity. In these studies levobupivacaine or bupivacaine were given by intravascular injection to healthy volunteers. Levobupivacaine was found to cause smaller changes in indices of cardiac contractility and the QTc interval of the electrocardiogram and also to have less depressant effect on the electroencephalogram. Assuming that levobupivacaine has the same local anaesthetic potency as bupivacaine, then, all things being equal, it is difficult to argue that levobupivacaine should not displace bupivacaine as the long-acting local anaesthetic of choice. It would appear, however, that levobupivacaine has not yet significantly displaced bupivacaine from the markets in which it is sold. This may be due to a lack of perceived safety benefit and/or consideration of the additional costs that are associated with switching to levobupivacaine, which is approximately 57% more expensive than bupivacaine. If the price of levobupivacaine were closer to bupivacaine then the argument to switch to levobupivacaine would undoubtedly be much stronger. With the continued clinical use of levobupivacaine the database available to make comparisons will increase and this may allow cost-benefit arguments to be made more forcefully for levobupivacaine in the future.

A number of local anaesthetic agents are used clinically. Lidocaine (lignocaine), the best known example, has been used for many years; it has a rapid onset of action but its duration of action is short. Bupivacaine was, until the recent introduction of levobupivacaine, the longest acting local anaesthetic used clinically; its sustained action reducing the requirement for repeated administrations, for example, in childbirth where a long duration of anaesthesia is usually required. Bupivacaine has had a good safety record over 30 years of clinical use. However, there have been reports of serious CNS and cardiovascular adverse reactions and even deaths, following accidental intravascular injection[1] or cuff deflation during Biers block procedure.[2] The occurrence of irreversible fatal ventricular fibrillation, without previous warning symptoms, has been of particular concern in the clinical use of bupivacaine. CNS symptoms associated with all modern local anaesthetics are dose-limiting.[3] However, bupivacaine appears to be relatively more cardiotoxic compared with shorter acting anaesthetic agents.[3]

Levobupivacaine was recently developed as a long acting local anaesthetic with a potentially reduced toxicity compared with bupivacaine.[4] Levobupivacaine was approved by the US Food and Drug Administration (FDA) in March 1999. It is now commercially available in a number of countries (table I). Sales volume figures for levobupivacaine are not available to the author, but it would appear that levobupivacaine has not yet significantly displaced bupivacaine from the markets in which it is sold. The reasons for this may be related to a lack of perceived safety benefit of levobupivacaine over bupivacaine and/or consideration of the additional costs that are associated with switching from bupivacaine to levobupivacaine. In a recent review, D'Angelo[5] concluded that the new local anaesthetics including ropivacaine and levobupivacaine were not worth their higher costs based on available safety data and price considerations. D'Angelo[5] conceded that levobupivacaine and ropivacaine may be less cardiotoxic than bupivacaine, but concluded that bupivacaine-induced cardiac arrest is an exceedingly rare event, especially where dilute concentrations of bupivacaine are used to produce anaesthesia. Indeed, the risks associated with bupivacaine administration have been reduced by changes in clinical practice e.g. administration of incremental doses as opposed to a single bolus administration.[6] This appears to question whether there actually is a safety issue with the use of bupivacaine.

Although rare, deaths do occur following the administration of bupivacaine. One recent case made national headlines in the UK. In February 2001, a patient at the Royal Sussex County Hospital in Brighton, England, died when bupivacaine was wrongly injected into a vein, rather than into the spine. The BBC report on this incidence[7] stated that 'if this happens, the large amount of anaesthetic involved can stop the heart'. Levobupivacaine was commercially available in the UK at the time of the incident, and yet the hospital administered bupivacaine to the patient. It is perhaps valid to ask if this incident would have had a fatal outcome if levobupivacaine was used, rather than bupivacaine?

This review evaluates the strength of evidence for the claim that levobupivacaine is less cardiac and CNS toxic than bupivacaine. For the purposes of this review, an equal local anaesthetic potency

Table I. Countries in which levobupivacaine is currently marketed

Europe	Austria
	Belgium
	Finland
	Greece
	Ireland
	Italy
	Luxembourg
	The Netherlands
	Portugal
	Spain (registered and launch imminent)
	Sweden
	Switzerland (registered and launch imminent)
	UK
Rest of World	Australia
	Hong Kong
	Most of South America except Brazil
	New Zealand
	Saudi Arabia
	Singapore
	US

is assumed[4] and although prices are considered, no attempt is made to substantiate cost differentials between bupivacaine and levobupivacaine.

1. Mode of Action and Toxicity

Bupivacaine and levobupivacaine are members of the amino amide class of local anaesthetics. Bupivacaine is manufactured and used as a racemic mixture containing equal amounts of dexbupivacaine [R(+)bupivacaine] and levobupivacaine [S(−)bupivacaine]. Levobupivacaine is the single S-enantiomer of bupivacaine.

The amino amides produce their local anaesthetic action by interacting with voltage-sensitive ion channels on excitable membranes, thereby blocking impulse transmission. The interaction at the sodium channel is thought to be largely responsible for blockade of impulse transmission in the nerves involved in sensory perception and motor co-ordination, resulting in anaesthesia and decreased muscle control.[3] Adverse effects of local anaesthetics can be due to blockade of sodium channels in other tissue and also to the blockade of other ion channels such as potassium and calcium.[8] The clinical manifestations of CNS effects are light-headedness, tinnitus, numbness of tongue and convulsions.[9] Cardiac exposure may result in a decrease in contractile function and arrhythmogenic effects including ventricular tachycardia (VT) and ventricular fibrillation (VF), possibly leading to cardiovascular collapse and death.[10]

Comparisons are made between levobupivacaine and racemic bupivacaine where data are available. Some comparisons are between levo- and dexbupivacaine and since bupivacaine is a 50 : 50 mixture of the enantiomers this should be taken into consideration when extrapolating any differences between the individual enantiomers to a theoretical difference between one enantiomer and the racemate.

2. Cardiotoxicity

2.1 Effects on Cardiac Sodium Channels

Studies in guinea-pig heart have shown that levobupivacaine is significantly less potent at blocking cardiac sodium channels than bupivacaine.[11] Using the whole cell voltage clamp technique in isolated ventricular myocytes, the apparent affinities for the inactivated state of the sodium channel were 4.8 and 2.9 μmol/L for levobupivacaine and dexbupivacaine, respectively.[11] Against the maximum upstroke velocity of the ventricular action potential V_{max}, a parameter which reflects sodium current, the calculated K_d was 39 μmol/L for levobupivacaine compared with 16 μmol/L for dexbupivacaine.[12] Levobupivacaine was less potent than bupivacaine at inhibiting V_{max} and after drug washout, V_{max} was fully restored with levobupivacaine, but not bupivacaine.[13]

Recent data from human myocardial sodium channels support the above animal data. The effects of bupivacaine enantiomers were studied on cloned human heart sodium channels (hH1 Na) expressed in HEK293t cells.[14] Inactivated sodium channels displayed a stereoselectivity for bupivacaine with 50% more levobupivacaine than dexbupivacaine being required to produce the same degree of block [50% inhibitory concentration (IC_{50}) 4.45 versus 3.03 μmol/L]. Blocking kinetics were also studied.[14] Whereas, block developed at similar time constants with both bupivacaine enantiomers, the recovery from block, assessed in terms of slow time constant, was increased 35-fold by a dexbupivacaine concentration of 10 μmol/L and 22-fold by a levobupivacaine concentration of 10 μmol/L. These data clearly favour levobupivacaine.

2.2 Effects on Cardiac Calcium Channels

There is evidence that bupivacaine can block cardiac calcium channels.[15-17] Functional consequences of such a block in the heart would include reduction in contractile function and delay in atrioventricular (AV) conduction. Recently it was shown that there was no difference in potency between bupivacaine enantiomers on L-type calcium channels in rat isolated ventricular myocytes.[17]

A comparison of the effects of levobupivacaine and bupivacaine on contractile function was made in three different *in vitro* preparations of cardiac muscle; left ventricular myocytes isolated from the

guinea-pig heart, right ventricular papillary muscles also isolated from the guinea-pig heart and pectinate muscles isolated from the human right atrium.[18] In guinea-pig left ventricular myocytes, the threshold concentration for bupivacaine in producing a significant negative inotropic effect (assessed using an isotonic video capture electronic edge detection system) was 5 μmol/L. Levobupivacaine was without effect on contractile function at this concentration. In the guinea-pig ventricular myocardium, approximately 10 μmol/L of each local anaesthetic was required to produce a 50% decrease in contractile force, as assessed using an isometric tension recording technique. Recovery of contractile force, following washout of local anaesthetic from guinea-pig cardiac myocytes, was 24% greater with levobupivacaine than bupivacaine, indicating that depression of mechanical function associated with levobupivacaine could be more easily reversed than with bupivacaine. Human atrial myocardium showed a similar sensitivity to guinea-pig ventricular myocardium for the negative inotropic effect (assessed using an isometric tension recording system) produced by levobupivacaine and bupivacaine with no difference in potency between the enantiomers.[18]

2.3 Effect on Cardiac Potassium Channels

The effects of levobupivacaine and dexbupivacaine on human cloned cardiac delayed rectifier potassium channels (hKv1.5), expressed in a mouse fibroblast cell line, were studied using the patch clamp technique.[19] At a concentration of 20 μmol/L, steady state block was 31% with levobupivacaine and 80% with dexbupivacaine. Apparent K_d values were 27.3 and 4.1 μmol/L, respectively, indicating a 7-fold advantage for levobupivacaine (theoretical 3.5-fold relative to bupivacaine). Myocardial potassium channel block can lengthen cardiac action potential, which may give rise to serious arrhythmias, e.g. torsade de pointes.[19] In this respect it would be interesting to confirm a potential advantage for levobupivacaine by studying the effects of the anaesthetics on human ether-a-go-go–related gene (HERG) potassium channels thought to be important for adverse drug effects related to the QT interval in humans.[20]

2.4 Other Cardiac Actions

It has been reported that the separate enantiomers of bupivacaine have similar inhibitory effects on radioligand binding to human myocardial β_2-adrenergic receptors. [21] There was also an absence of stereospecific effects of bupivacaine enantiomers on mitochondrial bioenergetics in the rat heart.[22]

2.4.1 Whole Heart Studies In Vitro

Levobupivacaine has been shown to have much less effect on increasing QRS duration in rabbit isolated hearts than either dexbupivacaine or bupivacaine,[23] which is consistent with evidence of a lesser inhibitory effect of levobupivacaine on myocardial sodium channels. A more recent study[24] compared levobupivacaine with bupivacaine, as well as ropivacaine in isolated rabbit hearts. The maximum observed increase in QRS width was significantly greater with bupivacaine than with levobupivacaine at the end of two infusion phases of 20 μmol/L from 0 to 5 minutes and 5 μmol/L from 5 to 20 minutes. The observed absolute increase in QRS duration at the end of the first 5 minute infusion was 86 ± 14ms for bupivacaine compared with 41 ± 15ms for levobupivacaine. A comparison of the number of arrhythmias recorded in the bupivacaine and levobupivacaine treated hearts is shown in table II.

In guinea-pig isolated perfused whole hearts, there appeared to be little difference between levobupivacaine and dexbupivacaine on contractility.[25] Dexbupivacaine, however, produced a significantly greater (30%) prolongation of AV conduction time than levobupivacaine.

2.4.2 Whole Animal Studies

The lethal dose of levobupivacaine, following intravenous administration in various animal species, has been shown to be consistently higher compared with bupivacaine and dexbupivacaine, as shown in table III. This indicates, without considering the modality of death, that levobupivacaine is intrinsically a safer drug than bupivacaine

Table II. Number of arrhythmias in rabbit isolated hearts (number of hearts with arrhythmias/total number of hearts) following a 5-minute infusion of bupivacaine or levobupivacaine[24]

Arrhythmias	Bupivacaine	Levobupivacaine
Intraventricular block[a]	5/7	2/7
PVC	1/7	0/7
VT	2/7	1/7
No arrhythmias	1/7	4/7

a Lack of ventricular electric activity during at least one cardiac cycle despite pacing.

PVC = premature ventricular contraction; **VT** = ventricular tachycardia lasting more than six consecutive beats.

at equal doses when given by peripheral intravenous injection (accidental or otherwise).

A comparison of the intravenous effects of levobupivacaine and dexbupivacaine 2 mg/kg on the cardiovascular system was carried out in anaesthetised rats.[28] Levobupivacaine produced mild bradycardia in only 4 of 12 animals, and 10 of 12 animals survived. In comparison, dexbupivacaine produced severe bradycardia, progressive hypotension, apnoea and death in all 12 animals treated with this agent. Malignant ventricular arrhythmias occurred in 4 of 12 of dexbupivacaine-treated and none of the levobupivacaine-treated rats. Wenckebach rhythm (second degree heart block) occurred in all dexbupivacaine-treated but in only 2 of 12 levobupivacaine-treated rats.

In anaesthetised pigs, levobupivacaine or bupivacaine was administered directly into the left anterior descending coronary artery (3mls over 10 seconds) in a blinded parallel manner to treatment groups of seven animals.[29] Drug doses were escalated, starting at 0.375mg and increasing to 0.75, 1.5 and 3mg then lmg increments until death. Key parameters measured included increase in QRS duration and the dose of anaesthetic causing death. The results showed that levobupivacaine had less effect on QRS duration than bupivacaine with a 25% difference in dose causing a 40ms increase and a 47% difference in dose causing a 90ms increase in the QRS duration. Injection of bupivacaine 4, 5 and 6mg resulted in the death of two, three and two pigs, respectively. The injection of levobupivacaine 7, 8 and 9mg caused the death of three, two and two animals, respectively. Thus, all pigs tolerated larger doses of levobupivacaine than bupivacaine. The mean lethal doses were levobupivacaine 7.9mg (range 7 to 9mg) and bupivacaine 5mg (range 4 to 6mg).

Studies with intravenous levobupivacaine and bupivacaine were conducted in two groups of seven awake sheep.[30] Doses were chosen either to avoid convulsions (6.25 to 37.3mg given over 1 minute), or to be convulsive (75 to 200mg given over 3 minutes). At subconvulsive doses, both drugs produced similar depression of left ventricular contractility. Convulsions occurred consistently with bupivacaine >75mg and at levobupivacaine >100mg. Subconvulsive doses of either anaesthetic produced minor effects on heart rate and blood pressure, whereas both of these effects were increased with convulsive doses. Cardiac output and myocardial blood flow were decreased

Table III. Lethal intravenous doses of bupivacaine, levobupivacaine and dexbupivacaine in various animal species

Species	Parameter	Bupivacaine	Levobupivacaine	Dexbupivacaine
Mice[26]	LD_{50} mg/kg ± SEM (n)	7.3 ± 1 (36)	9.6 ± 1.0 (36)[a]	7.9 ± 1.0 (36)
Mice[27]	Relative toxicity (95% confidence limits)	1.0	0.64 (0.59 to 0.69)[b]	1.1 (0.98 to 1.2)
Rats[26]	LD_{50} mg/kg ± SEM (n)	5.6 ± 0.2 (36)	7.2 ± 0.4 (36)[a]	3.8 ± 0.2 (36)
Rats[27]	Relative toxicity (95% confidence limits)	1.0	0.76 (0.68 to 0.86)[b]	1.2 (1.1 to 1.4)
Rabbits[26]	LD_{50} mg/kg ± SEM (n)	6.9 ± 0.7 (8)	9.7 ± 0.8 (8)[a]	5.5 ± 0.3 (8)
Rabbits[27]	Relative toxicity (95% confidence limits)	1.0	0.66 (0.58 to 0.75)[b]	1.03 (0.91 to 1.18)

a Value reported to be significantly higher than corresponding value for dexbupivacaine.

b Toxicity of levobupivacaine reported to be significantly lower than that for both bupivacaine and dexbupivacaine.

LD = lethal dose; **SEM** = standand error of the mean.

Table IV. Effect of local anaesthetic on spontaneous and PES-induced arrhythmias [33]

Local anaesthetic	Spontaneous		PES-induced		
	VF	asystole	VF	VT	extrasystole
Bupivacaine (n = 10)	1	0	1	0	5/9[a]
Levobupivacaine (n = 10)	0	0	1	0	5/10[a]
Lidocaine (lignocaine; n = 7)	0	0	1	0	0/7

a $p < 0.05$ significantly greater than the response from the lidocaine-treated dogs.

PES = programme electrical stimulation; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia.

with larger doses of both drugs. Doses of bupivacaine >75mg or levobupivacaine >100mg induced QRS widening and ventricular arrhythmias, but significantly fewer and less deleterious arrhythmias were induced by levobupivacaine than bupivacaine. Three animals died from the sudden onset of ventricular fibrillation after the administration of bupivacaine 150mg (n = 2) and bupivacaine 200mg (n = 1). None of the animals administered the same doses of levobupivacaine died. In a subsequent study, higher doses of levobupivacaine were administered and the estimated fatal intravenous dose for levobupivacaine in sheep was estimated to be 277 ± 50mg compared with 156 ± 31mg for bupivacaine.[31] In a third study, bupivacaine and levobupivacaine were given to sheep by intracoronary injection.[32] It was concluded that there were no significant differences between the anaesthetics in survival rates or fatal doses with this mode of administration, and that the intrinsic cardiotoxicities of levobupivacaine and bupivacaine in the sheep did not explain the lower lethality of levobupivacaine following intravenous administration in this species.

Groban et al.[33] compared the arrhythmogenic potential of bupivacaine, and levobupivacaine, as well as ropivacaine and lidocaine in anaesthetised, ventilated dogs using programmable electrical stimulation (PES) to induce ventricular arrhythmias. Animals were randomised to receive escalating incremental infusions of the local anaesthetic until cardiovascular collapse. There was no difference in the incidence of spontaneous or PES-induced ventricular tachycardia and ventricular fibrillations among animals exposed to levobupivacaine or bupivacaine (or indeed ropivacaine) [see table IV]. Compared with lidocaine, the incidence of PES-induced extrasystoles was significantly more frequent with bupivacaine- and levobupivacaine-treated dogs, but the difference between these two local anaesthetics were not significant.

3. Clinical Studies on Cardiotoxicity

In the clinical development of levobupivacaine two studies were carried out to evaluate the relative cardiotoxic potential of levobupivacaine and bupivacaine in humans following intravenous administration. In both of these studies, for ethical reasons, the maximum doses administered were much smaller than those administered to animals. In the first study [34,35] the cardiovascular effects of levobupivacaine were compared with those of bupivacaine, following administration to healthy male volunteers. Drugs were infused at 10 mg/min in a randomised, double-blind, crossover manner with a washout period of at least 1 week between treatments. The infusion of each drug was continued up to a maximum dose of 150mg or stopped following the first detection of CNS effects (including light-headedness, tinnitus, and numbness of the tongue). A range of cardiovascular parameters were measured including systolic and diastolic blood pressures, electrocardiogram (ECG) and an index of aortic blood flow, allowing assessments of cardiac index and stroke index to be made. An acceleration index, representing the initial maximum acceleration of blood flow during the onset of ejection, was also measured to estimate effects on myocardial contractility. Both drugs were well tolerated. The mean total doses of levobupivacaine and bupivacaine administered were 56.1 and

47.9mg, respectively and the corresponding maximum mean plasma concentrations were 2.62 and 2.25 μg/ml. Despite the mean total dose and plasma concentrations of levobupivacaine being higher than those of bupivacaine, levobupivacaine produced smaller mean changes in cardiac variables compared with bupivacaine. The mean values of the cardiac index, stroke index, acceleration index and ejection fraction were decreased at the end of infusion, but recovered rapidly. The change of the stroke index, acceleration index and ejection fraction from baseline to the end of the infusion was significantly greater with bupivacaine than levobupivacaine. Both levobupivacaine (nonsignificant) and bupivacaine (statistically significant) produced slight increases of the PR interval and corrected QT interval (QTc) at the end of infusion, and although the effects of bupivacaine on these cardiac parameters were greater compared with levobupivacaine, the difference between the drugs did not reach statistical significance.

In the second study the effects of levobupivacaine and bupivacaine were compared on QT dispersion, ECG and signal averaged ECG in 22 healthy volunteers.[4] Volunteers were given a lidocaine pre-test to define CNS effects, and were subsequently given bupivacaine until the same CNS adverse effects were produced. The dose of bupivacaine administered ranged from 30 to 120mg. Then, using double-blind parallel groups, levobupivacaine, or bupivacaine was administered up to the dose of bupivacaine previously administered. Volunteers were stratified, according to the initial dose of bupivacaine ≤75mg (group 1), or >75mg (group 2). The mean doses administered were levobupivacaine 67.7mg and bupivacaine 65.5mg. The mean ± SD maximum increases in the QTc interval up to 30 minutes were 11 ± 8ms and 6 ± 12ms for group 1 and 3 ± 11ms and 24 ± 17ms for group 2 treated with levobupivacaine and bupivacaine, respectively. The differences between levobupivacaine and bupivacaine was statistically significant in group 2, and it was concluded that with intravenous doses >75mg in healthy volunteers, levobupivacaine produced a significantly smaller increase in QTc than bupivacaine.

4. Clinical Studies on CNS Effects

The effects of levobupivacaine and bupivacaine on the electroencephalogram (EEG) were compared in a double-blind crossover study in 12 healthy volunteers.[36] The CNS depressant effects of intravenous levobupivacaine 40mg were less than that with the same dose of bupivacaine. Both local anaesthetics significantly reduced high alpha power of the EEG at all electrode positions, but the magnitude of effect was less with levobupivacaine than bupivacaine. Also, levobupivacaine did not cause an increase in theta power in the parietal, temporal and central regions of the brain as seen with bupivacaine. The depressant effect of levobupivacaine on the EEG was significantly less than that observed with bupivacaine, both in terms of the magnitude of the effect and the areas of the brain over which the effect was observed. However, the clinical significance of these effects is not fully understood.

5. Adverse Event Profile in Normal Clinical Use

In normal clinical use, bupivacaine and levobupivacaine are, in general, relatively safe.[37] Table V summarises reported incidences of CNS and cardiac related adverse events from the levobupivacaine phase II and III clinical programme where bupivacaine was used as the comparator. As can be seen from this table, the CNS and cardiac adverse event profiles for levobupivacaine and bupivacaine, during normal usage, appear to be very similar.

6. Safety in the Event of an Unintentional Overdose or Intravascular Injection

Three cases of investigator-suspected intravascular injection, were reported during the levobupivacaine development programme (phase II and III studies).[38] When the studies were unblinded, two of these patients had received racemic bupivacaine, and one patient had received levobupivacaine (table VI). In the two patients who received suspected intravascular injections of bupivacaine there were notable cardiovascular changes

Table V. Summary of cardiac and CNS adverse events reported during the levobupivacaine phase II/III clinical programme in bupivacaine-controlled studies [37]

Adverse event	Levobupivacaine (n = 509)		Bupivacaine (n = 453)	
	n	%	n	%
Cardiac				
Hypotension	100	19.6	93	20.5
ECG abnormal	16	3.1	17	3.8
Bradycardia	11	2.2	10	2.2
Tachycardia	9	1.8	7	1.5
Hypertension	5	1.0	8	1.8
CNS				
Nausea	59	11.6	66	14.6
Dizziness	26	5.1	22	4.9
Vomiting	42	8.3	30	6.6
Rigors	15	2.9	12	2.6
Headache	23	4.5	18	4.0
Somnolence	6	1.2	4	0.9
Anxiety	5	1.0	6	1.3

ECG = electrocardiogram.

(bradycardia and hypotension in one patient and tachycardia in the second patient) whereas the patient who received a similar dose of levobupivacaine intravascularly did not exhibit any cardiovascular changes. Further details of this accidental intravascular injection of levobupivacaine have been published.[39] The incident occurred in a 77-year-old woman presenting for elective total hip arthroplasty under epidural anaesthesia. Following the administration of 19ml of 0.75% levobupivacaine (a total of 142.5mg of levobupivacaine) accidental intravascular injection was suspected when the patient became disorientated and drowsy and her speech became slurred. The only intervention required to rescue this patient was the administration of two 40mg doses of intravenous thiopental for seizure prophylaxis; supplemental oxygen was increased (from 2 L/min via nasal cannula to 6 L/min via face mask). The serum levobupivacaine concentration in this patient determined 14 minutes after the cessation of the epidural injection (this will be well past the expected peak level) was reported to be 2.7 μg/ml which was equal to or greater than serum levels observed in previous cases of accidental intravascular bupivacaine injection where seizures or severe cardiac arrhythmias occurred. Serum levels as low as 1.8 μg/ml of bupivacaine have been detected within 5 minutes of injecting patients who experienced seizures.[39]

7. Reversibility of Cardiotoxicity

Until recently, there has been little available information comparing the ability to reverse the cardiotoxic effects associated with overdosage of local anaesthetics.

There is indirect evidence from binding kinetics, through *in vitro* preparations and whole animal studies, to suggest that reversibility of cardiotoxicity is faster with levobupivacaine than with bupivacaine. In the guinea-pig heart, levobupivacaine has a faster off-rate of binding to the sodium channel than dexbupivacaine and recovery of cardiac function is faster with levobupivacaine than

Table VI. Suspected intravascular injections during the levobupivacaine development programme (phase II and III studies)[38]

Procedure	Dose	Manifestation	Treatment
Epidural for caesarean section	120mg bupivacaine (0.5%)	Slurred speech, unresponsive, bradycardia, hypotension, transient uterine hypertonia	100% oxygen administered by mask, 10mg of ephedrine IV for blood pressure support
Brachial plexus block	150mg bupivacaine (0.5%)	Loss of consciousness, convulsions, and tachycardia	Propofol 40mg IV administered for the convulsions 100% oxygen
Epidural for orthopaedic surgery	142.5mg levobupivacaine (0.75%)	Drowsy, slurred speech, excitation. No cardiovascular changes	Two doses of 40mg IV thiopental for convulsant prophylaxis

IV = intravenous.

bupivacaine.[11] Moreover, following the intravenous infusion of levobupivacaine or bupivacaine in conscious sheep, arrhythmias due to levobupivacaine returned to sinus rhythm more readily than those due to bupivacaine.[30] However, this potential advantage of levobupivacaine over bupivacaine was not seen in a recent study in anaesthetised dogs.[40] Animals were randomised to receive incremental infusions of the local anaesthetics to the point of cardiovascular collapse. Hypotension and arrhythmias were treated with epinephrine (adrenaline), open-chest massage, and advanced cardiac life support protocols, respectively. Outcomes were defined as follows: successful [stable rhythm and mean arterial pressure (MAP) greater than or equal to 55mm Hg for 20 minutes]; successful with continued therapy (stable rhythm and MAP <55mm Hg after 20 minutes); and death. The cumulative doses (mean ± SEM) to collapse were 21.7 ± 2.6 mg/kg for bupivacaine and 27.3 ± 2.0 mg/kg for levobupivacaine. Figure 1 shows the resuscitative outcomes for the two local anaesthetics. Mortality rates with bupivacaine and levobupivacaine were 50 and 30%, respectively. Myocardial depression was primarily responsible for the profound hypotension, as the occurrence of lethal arrhythmias preceding resuscitation was not different between the two local anaesthetics. Epinephrine-induced ventricular fibrillation occurred more frequently in bupivacaine intoxicated dogs than levobupivacaine intoxicated dogs (4 of 9 dogs and 2 of 10 dogs, respectively), although the difference was not statistically significant. Although the mean unbound plasma concentrations at collapse were higher for levobupivacaine (mean 9.4 μg/ml; range 5 to 18 μg/ml) than for bupivacaine (mean 5.7 μg/ml; range 3 to 11 μg/ml) the difference was not statistically significant. The authors concluded that after bupivacaine or levobupivacaine, resuscitation is not always successful and the coadministration of epinephrine may lead to severe ventricular arrhythmias.

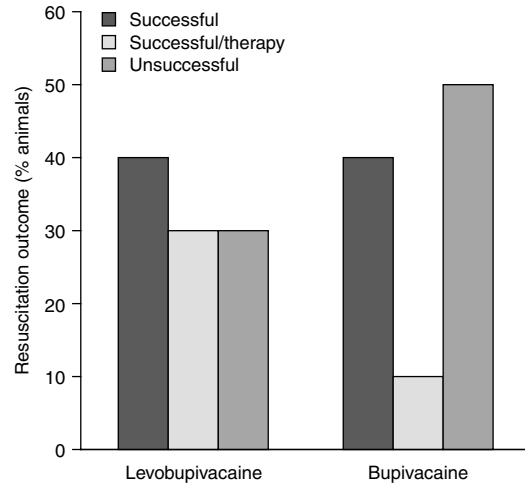

Fig. 1. Resuscitation outcomes after administration of levobupivacaine and bupivacaine until cardiovascular collapse in anaesthetised dogs.

8. Costs

According to the British National Formulary (March 2001) the cost of bupivacaine (5 mg/ml 10 ml ampoule) is listed as £1.21 (2001 values) and the equivalent for levobupivacaine is listed at £1.90, some 57% higher. These prices do not necessarily reflect the price charged to hospitals in the UK. In the US, the average wholesale price of 5 mg/ml 10ml ampules was $US5.48 and $US8.61 for bupivacaine and levobupivacaine, respectively, the latter again being 57% more expensive.[41]

9. Conclusions

Substantial data exist which indicate that levobupivacaine on an equivalent dose basis, is inherently safer than bupivacaine when administered by the peripheral intravenous route in conscious animals. 50% Lethal dose (LD_{50}) values obtained in mice, rats and rabbits indicate that the margin of safety regarding lethality is such that 32 to 57% more levobupivacaine is required to produce death.[26,27] LD_{50} data do not exist for humans, but there is reason to assume that the animal data (as is the case with most other pharmaceutical products) are valid for humans. Some, but not all studies, carried out in larger animal species also sup-

port the fact that levobupivacaine is a safer drug. In particular, in conscious sheep following peripheral intravenous administration, the mean lethal dose was estimated to be 78% higher with levobupivacaine than bupivacaine.[30,31] Furthermore, surrogate endpoints for both cardiac and CNS toxicity indicate that levobupivacaine is less toxic in humans following intravenous administration.[35,36] Assuming that the local anaesthetic potency of levobupivacaine is the same as that for bupivacaine, in the author's opinion, based on safety data alone, levobupivacaine should always be used in preference to bupivacaine in the clinic.

One reason why this is currently not the case may well be related to a sense that bupivacaine no longer has a safety issue, nevertheless, as outlined in the introduction, deaths are still occurring with the drug. A second reason may be related to the significantly higher cost of levobupivacaine, which invites a thorough evaluation of its cost versus safety benefit. This, by some, may not be perceived to be currently in favour of levobupivacaine, considering its higher price. If the price of levobupivacaine were closer to bupivacaine, then the argument to switch to levobupivacaine would undoubtedly be much stronger. Alternatively or additionally, with the continued clinical use of levobupivacaine the database available to make safety comparisons with bupivacaine will increase and this may allow cost benefit arguments to be made more forcefully in favour of levobupivacaine in the future.

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Correspondence and offprints: Dr *Robert W. Gristwood*, Arachnova Limited, St John's Innovation Centre, Cambridge, CB4 0WS, United Kingdom.
E-mail: robert.gristwood@arachnova.com