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Cardiotoxicity with Modern Local Anaesthetics

Is There a Safer Choice?

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Abstract

The recognition that long-acting local anaesthetics, particularly bupivacaine the *de facto* standard long-acting local anaesthetic, were disproportionately more cardiotoxic than their shorter-acting counterparts stimulated the development of the bupivacaine congeners, ropivacaine and levobupivacaine. These agents, like all local anaesthetics, can produce cardiotoxic sequelae by direct and indirect mechanisms that derive from their mode of local anaesthetic actions, i.e. inhibition of voltage-gated ion channels. While all local anaesthetics can cause direct negative inotropic effects, ropivacaine and levobupivacaine are less cardiotoxic than bupivacaine judging by the larger doses tolerated in laboratory animal preparations before the onset of serious cardiotoxicity (particularly electro-mechanical dissociation or malignant ventricular arrhythmias). Additionally, they are less toxic to the CNS than bupivacaine judging by the larger doses tolerated before the onset of seizures. This may be clinically important because CNS effects may be involved in the production of serious cardiotoxicity. Preclinical studies in humans are a 'blunt instrument' in their ability to distinguish significant differences between these drugs because of the relatively small doses that can be used. Nevertheless, available evidence from human studies corroborates the preclinical laboratory animal studies. Because clinically significant differences between these drugs are more quantitative than qualitative, i.e. toleration of a larger dose before manifestation of toxicity, we have concluded that these newer agents have a lower risk of causing serious cardiotoxicity than bupivacaine. Thus, compared with bupivacaine, the newer agents may be seen as 'safer', but they must not be regarded as 'safe'.

Local anaesthetics are drugs that, when applied in the region of a neural structure, produce reversible loss of conduction and thereby loss of sensation in the innervated region. They should be capable of producing a differential neural blockade, i.e. sensory without significant motor neural blockade, and have an acceptable difference between beneficial and toxic doses. Although many drugs have local anaesthetic properties, only a few satisfy these requirements and are used clinically for that purpose.

All local anaesthetics are capable of producing allergic, local and systemic toxicity, but these effects are rare with modern local anaesthetics. However, potentially serious toxicity of the central nervous system (CNS) and cardiovascular system (CVS) has been a problem from their earliest use. Reducing the risk of serious CVS toxicity is pres-

ently the main reason for new local anaesthetics being developed.

Cocaine, the prototype local anaesthetic introduced into clinical use during the 1880s, dramatically changed the history of anaesthesia. However, it was soon recognised that less toxic substances of this class of drug were desirable, especially if they also had a longer duration of action. In the early 20th century, a multitude of local anaesthetics were evaluated: most were derived from the well-proven procaine molecule, itself derived from the anaesthesiophore of cocaine. Long duration of local anaesthesia was produced either by making an 'oily' pharmaceutical formulation, or by producing enhanced lipophilicity of the molecule. The former approach was generally unsuccessful because of local neural toxicity. The latter approach produced numerous local anaesthetics of which tetracaine (amethocaine) and dibucaine (cinchocaine) became the principal clinically useful long-acting local anaesthetics from the 1930s until the 1970s. These agents had the reputation for causing CNS and CVS toxicity if absorbed rapidly or accidentally injected intravenously. They also had a reputation for unreliability; this was attributed to the chemical instability of their linkage groups (tetracaine, ester; dibucaine, carbamoyl), a problem that disappeared with the introduction of the amide linked agent, lidocaine (lignocaine), in the 1940s. However, lidocaine is not a particularly long-acting agent. There have been many attempts to increase its duration of action pharmaceutically. Of these, the method of adding a vasoconstrictor, introduced in the early 1900s with procaine, has proven the most enduring. Experimental methods also include the use of cyclodextrin complexes or encapsulation in biodegradable polymers. Contemporary approaches also include the use of repeated or continuous administration through catheters, themselves the product of newer developments in medical plastics.

In the 1950s, the quest for new local anaesthetics produced a family of N-alkyl piperidine 2,6-xylidides. It was found that increasing their N-*n*-alkyl carbon chain gave increased lipophilicity, as expected, along with increased tissue toxicity, and a bell-shaped relationship with both duration of neural blockade and systemic toxicity. In both latter cases, the relevant maxima occurred at C4 or C5 alkyl chain length (fig. 1). From this family, the N-methyl homologue, mepivacaine, was selected for clinical development on the basis of its favourable local anaesthetic activity combined with relatively low tissue and systemic toxicity in animals. The others were deemed unsuitable because of local tissue or systemic toxicity. However, it was soon realised that when the doses of these agents were scaled to equitoxicity in animal tests, a relatively longer duration neural blockade could be obtained with the more toxic agents. Subsequently, the N-*n*-butyl derivative, bupivacaine, was trialed in the 1960s and soon found acceptance in clinical anaesthesiology. Since then, despite a variety of new conventional local anaesthetics (e.g. etidocaine) or new molecular forms (e.g. biotoxins and cyclising lidocaine analogues) being trialed and/or introduced for producing long duration of action, bupivacaine has become the *de facto* standard long-acting local anaesthetic.

Nonetheless, bupivacaine remains a relatively toxic agent. It was recognised some 20 years ago that the risk of potentially fatal CVS toxicity from bupivacaine (and etidocaine) was disproportionately greater than from the currently available shorter-acting agents.[2,3] Bupivacaine-induced serious cardiotoxicity is characterised by malignant ventricular arrhythmias. Mechanisms involved with its cardiotoxicity include direct cardiac conduction and cardiac muscle effects as well as CNS-mediated effects (fig. 2). Although intuitive, it is now accepted that the potential for toxicity is exacerbated if an excessive dose is used, if the drug is absorbed or otherwise released into the circulation too rapidly, such as with sudden cuff deflation in Bier's block, or if the injection is made accidentally into a blood vessel. Awareness of the potential for toxicity has led to improved clinical techniques with bupivacaine, such as dose fractionation, to the restricted use of the most concentrated (0.75%) solution, and to the proscription for its use in Bier's

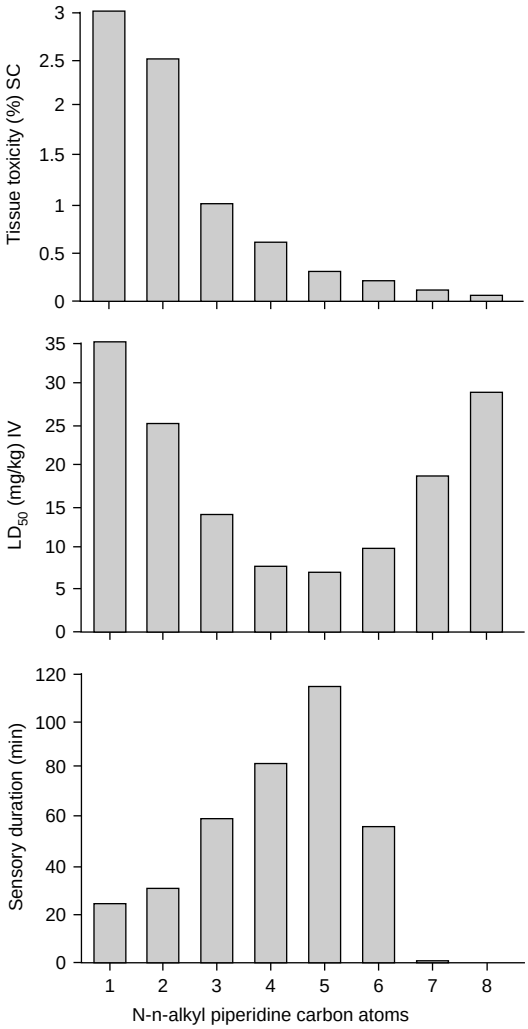

Fig. 1. Preclinical pharmacology of local anaesthetics of the N-n-alkyl piperidine 2,6-xylidide (bupivacaine) family. The panels show the relationship between the size of the N-n-alkyl substituent and local or tissue toxicity (% concentration producing tissue membrane damage) administered subcutaneously (SC) in rabbits, median lethal dose (LD_{50} in mg/kg) administered intravenously (IV) in rabbits, and duration of sensory peripheral nerve block (minutes) with a 0.25% solution in rat sciatic nerve.[1]

blocks – all with definite impact. Although the number of fatalities involved was small, and it might be argued that improved practice alone was all that was necessary to preclude toxicity, the search for an improved local anaesthetic agent to replace bupivacaine has proceeded relentlessly over the past two decades.

Except for lidocaine, the current amide-type local anaesthetic agents are racemates, consisting of a 50:50 mixture of stereochemical isomers (termed R- and S-enantiomers). Although stereochemistry in cocaine was found to be potentially important in the 1920s, it was overlooked in modern local anaesthetics until Åberg (1972)[4] and Åkerman (1973),[5] then working at two rival Swedish pharmaceutical companies, described its pharmacological and toxicological relevance. In laboratory experiments, Åberg found lower toxicity of S-bupivacaine than of R- or *rac*-bupivacaine, judging by the greater doses required to cause convulsions and lethality;[1,6] this difference did not apply to mepivacaine (table I). In later laboratory experiments, Åkerman et al.[7] found that the N-*n*-propyl homologue of S-bupivacaine (ropivacaine) gave similar duration of neural blockade *in vivo* but less gross toxicity than bupivacaine; as well, it was longer acting than the R-ropivacaine enantiomer and this was ascribed to a greater vasoconstriction. Subsequent investigations have found significant quantitative differences between ropivacaine and bupivacaine as well as between the enantiomers of bupivacaine related to their actions of blocking voltage-gated ion channels in nerves, the heart and CNS, as well as in their pharmacokinetics.

As a consequence of preclinical pharmacological studies, the single enantiomer local anaesthetics, ropivacaine and the enantiopure S-bupivacaine (now registered as levobupivacaine),[1] are being promoted as being less cardiotoxic than bupivacaine. Some of the evidence from various studies used to arrive at this position is reviewed briefly in this article.

1 In the text, the term S-bupivacaine has been used to emphasise enantiomeric differences, whereas levobupivacaine has been used to designate use of the enantiopure drug. Also in the text, doses are taken to mean the salt preparations as used clinically. On this basis, levobupivacaine is based upon base concentrations whereas bupivacaine and ropivacaine are based upon hydrochloride salt concentrations.

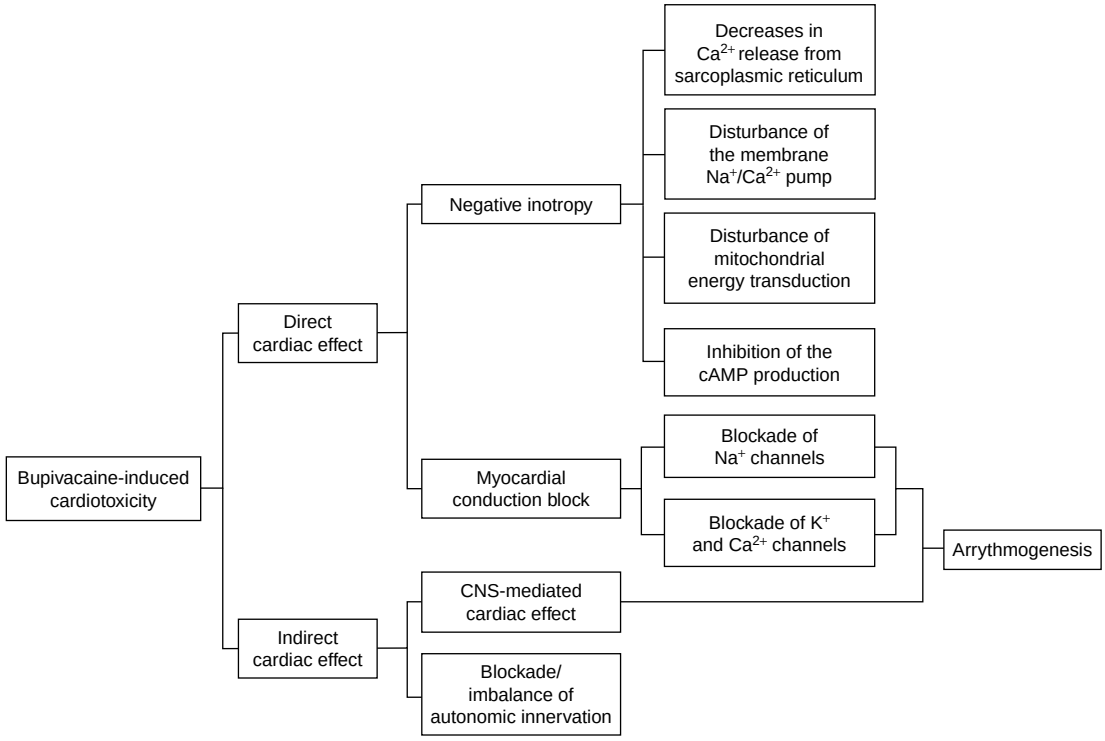

Fig. 2. Schema of mechanisms involved with local anaesthetic-induced cardiotoxicity. **cAMP** = cyclic adenosine monophosphate.

1. *In vitro* Studies at Cellular or Tissue Level

Local anaesthetics work by inhibition of voltage-gated Na^+ channels in neural membranes. As the drugs become distributed in the body after perineural administration, they can achieve sufficient concentrations to act at Na^+ channels in other excitable tissues. The cardiotoxicity of local anaesthetics is mainly attributed to Na^+ channel blockade[8] with the consequence that cardiac impulse conduction is slowed, leading to widening of QRS complexes, prolongation of PR interval, atrioventricular block, and development of fatal ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation due to unidirectional block and re-entry.[9]

Modest-to-equivocal enantioselectivity of inhibition of fast action potentials in isolated peripheral nerve attributable to Na^+ conductance has been found with the potency of R-bupivacaine being approximately 2-fold greater than S-bupivacaine, the potency of R-bupivacaine markedly exceeds that of S-bupivacaine by a factor of approximately 70-fold in the blockade of neuronal K^+ channels.[10,11] Local anaesthetics block Na^+ channels in a complex voltage- and frequency-dependent manner. In general, they have a higher affinity for the channels in open or inactivated form than for the resting form. To date, *in vitro* data suggest that both ropivacaine and S-bupivacaine are less potent at blocking the inward myocardial Na^+ current than *rac*-bupivacaine or R-bupivacaine. In dog ventricular myocytes, ropivacaine produced a lesser and briefer Na^+ current inhibition than *rac*-bupivacaine.[12] In a study of *rac*-bupivacaine and its enantiomers in guinea-pig ventricular myocytes, *rac*-bupivacaine was found to interact with both the activated and inactivated state of the Na^+ channels.[13] However, R-

bupivacaine produced a faster and more potent block of the inactivated channels than S-bupivacaine. Because the inactivated-state block plays a more important role during the plateau phase of the cardiac action potential, this may explain the higher cardiotoxicity of R-bupivacaine. In agreement with the above studies, *rac*-bupivacaine or R-bupivacaine has been shown to be more potent than S-bupivacaine and/or ropivacaine at decreasing the maximal rate of depolarisation (V_{max}), an indication of Na^+ current influx, and duration of action potential in guinea-pig papillary muscle[14-16] and in rabbit Purkinje fibre and ventricular muscle.[13] In the latter case, the duration of Purkinje fibre inexcitability and Purkinje fibre-ventricular muscle conduction block was shorter with ropivacaine than with *rac*-bupivacaine.[17] Faster recoveries of the V_{max} from block were also found with ropivacaine or S-bupivacaine than with *rac*-bupivacaine.[14-16]

Blockade of K^+ channels by the bupivacaine-like agents can prolong the action potential and further exacerbate Na^+ channel block. This has been suggested to be at least partly responsible for the bupivacaine-induced delay in cardiac conduction and arrhythmogenesis.[18,19] Using a patch-clamp technique, a study of the effect of the bupivacaine enantiomers on a cloned human cardiac K^+ channel (hKv1.5) showed that S-bupivacaine was 7-fold less potent than R-bupivacaine to block the channels.[20] More recently, it was demonstrated that the potency of ropivacaine at blocking the cardiac hKv1.5 was, respectively, 3 and 20 times less than with S- and R-bupivacaine.[21] These data suggest, at least partly, why ropivacaine and S-bupivacaine are less cardiotoxic in *in vivo* animal and human studies.

Although bupivacaine-related death is caused by the development of fatal ventricular arrhythmias,[22] local anaesthetic-induced negative inotropy may also contribute to the cardiotoxicity. A variety of studies have shown a parallelism between potencies for producing neural blockade and negative inotropy.[23] The latter can be the result of some or all of the following mechanisms:

- decreases in Ca^{2+} release from sarcoplasmic reticulum or in inward Ca^{2+} current,[24,25]
- disturbance of the membrane Na^+/Ca^{2+} pump,[26,27]
- inhibition of the basal and adrenaline-stimulated cyclic adenosine monophosphate production,[28] and
- disturbance of mitochondrial energy transduction.[29-33]

The last of these effects, although interesting biochemically, occurs at significantly greater concentrations than those found in the circulation after neural blockade.

In guinea-pig papillary muscle, ropivacaine was shown to produce a smaller reduction in the peak force of contraction than *rac*-bupivacaine.[14] However, similar decreases in contractile force by S-bupivacaine, *rac*-bupivacaine and/or ropivacaine were reported in rat left atrium[34] and guinea-pig papillary muscle,[15] although the tissues recovered from the effect faster with ropivacaine and S-bupivacaine than with *rac*-bupivacaine in the latter study.[16] In a study of the effects of bupivacaine

Table I. Comparative data (mean [SEM]) for central nervous system toxic and fatally toxic doses of local anaesthetics upon intravenous infusion in the rabbit (data from Åberg[6])

Agent	Infusion rate (mg/kg/min)	Convulsive dose (mg/kg)	Lethal dose (mg/kg)
RS-mepivacaine	5	22 [2]	53 [3]
R(–)-mepivacaine	5	18 [1]	38 [3]
S(+)-mepivacaine	5	20 [2]	48 [2]
RS-bupivacaine	1	3.3 [0.3]	6.9 [0.7]
R(+)-bupivacaine	1	2.7 [0.3]	5.5 [0.3]
S(–)-bupivacaine	1	4.7 [0.4]	9.7 [0.8]
For comparison			
Lidocaine (lignocaine)	5	14 [1]	41 [2]

and ropivacaine on heart cell mitochondrial bioenergetics, ropivacaine induced less inhibition of adenosine triphosphate synthesis than *rac*-bupivacaine in rat heart isolated mitochondria and sapping-skinned left ventricle fibres, suggesting less disturbance of mitochondrial energy metabolism by ropivacaine.[30] These data receive indirect support from a study of the isolated rat liver mitochondria, in which ropivacaine was also found to be less toxic than *rac*-bupivacaine.[31]

2. *Ex vivo* Whole Organ Studies

In a spontaneously beating rabbit heart preparation, the inotropic and chronotropic effects of *rac*-bupivacaine and ropivacaine were compared.[35] *rac*-Bupivacaine was more potent in causing dP/dt (rate of change of pressure) depression, decreased heart rate and reduced left ventricular systolic pressure. At higher doses, significantly fewer preparations with *rac*-bupivacaine survived the 30 minute drug exposure period than with ropivacaine. Moreover, ropivacaine produced less electrocardiographic disturbance, manifested by atrioventricular (AV) block and AV dissociation, and fewer ventricular arrhythmias compared with *rac*-bupivacaine. Studies on isolated rabbit perfused heart revealed that S-bupivacaine and/or ropivacaine caused less QRS widening and fewer episodes of ventricular tachycardia, fibrillation or asystole, than R-bupivacaine or *rac*-bupivacaine.[36,37] Ropivacaine washout from the heart was more rapid than S-bupivacaine and *rac*-bupivacaine.[37] Similarly, in an isolated guinea-pig heart study, R-bupivacaine and *rac*-bupivacaine were more potent at prolonging AV conduction time and producing AV dissociation than S-bupivacaine.[38]

3. Whole Body Studies

As indicated above, Na^+ channels in the brain and the heart, in particular, respond to local anaesthetics delivered via the systemic circulation. A resultant profile of CNS and cardiovascular symptoms and signs is remarkably consistent, differing quantitatively between the agents in their doses (and blood and relevant tissue concentrations). A wide range of intravenous doses in rats, sheep, dogs and pigs have been used to study cardiovascular responses; as these normally occur at greater doses than CNS effects, some of the studies have produced valuable data on comparative CNS toxicity, as well. A very limited dose range has been used in healthy volunteers.

3.1 Studies in Experimental Animals

Different paradigms have been used to emphasise particular issues. These include acute and chronic preparations, co-medicated and unmedicated animals, intravenous and regional (close arterial) doses, sub-toxic and toxic doses, single or multiple doses. There is not enough space to review the range of examples. However, the main aspects of design include the regional selectivity of administration (and whether this is achieved by site directed close arterial *vs* whole body intravenous administration), and whether a single versus multiple dose paradigm allows for pharmacokinetic considerations to be satisfied. Among large animal species, sheep are more sensitive to cardiotoxicity than dogs[39] and would thus seem a more 'fail-safe' species for possible extrapolation to humans.

Single-dose studies in conscious instrumented sheep, as used in the authors' laboratory, show clearly that lidocaine, bupivacaine, ropivacaine and levobupivacaine all produce negative inotropic effects, over similar time courses, of magnitudes in proportion to the local anaesthetic potencies, from intravenous doses that produce no overt symptoms and from intracoronary arterial infusions.[40-44] Although this is in agreement with the studies performed in isolated heart tissues,[45] the results of the paradigms diverge as the doses of all the agents are increased. Myocardial depression becomes reversed with the onset of significant overt CNS excitation and convulsions, but this cannot happen with isolated tissues. Hence, the intracoronary arterial infusion paradigm provides information about the effects, *in vivo*, without pharmacological 'noise' from the agents acting elsewhere.

Not surprisingly, the dose required to produce overt CNS symptoms differs significantly between agents, in accord with differences in local anaesthetic

potency. Enantiomeric differences occur with bupivacaine: in agreement with studies performed in laboratory rodents,[6] an intravenous bolus of R-bupivacaine 40mg always produced convulsions in sheep but the same dose of S-bupivacaine never produced convulsions.[41] Across several studies with a single 3 minute intravenous infusion in sheep, convulsant doses were found to decrease in the order: lidocaine [mean = 323 (95% confidence interval {CI} = 217-427) mg] > ropivacaine [156 (128-184) mg] > levobupivacaine [101 (87-116) mg] > bupivacaine [79 (72-87) mg].[40-43]

Increasing doses of local anaesthetic agent are associated with a greater probability of serious cardiovascular toxicity and a fatal outcome, although the mechanisms may differ according to agent. In sheep, 3-minute intravenous infusions of bupivacaine (≥100mg) have been found to induce ventricular arrhythmias, including ventricular tachycardia and ventricular extrasystoles along with supraventricular episodes and conduction delay (bundle branch block, second degree heart block and supraventricular extrasystoles). Fatal ventricular fibrillation was found to occur with doses of 125 to 200mg in some animals.[22,42] Levobupivacaine at 100mg was found not to induce discernible arrhythmias and, although doses from 150mg could induce ventricular tachycardia, extrasystoles and bigeminy, fatalities were not found with doses less than 225mg.[41,43] Other electrocardiologic findings with both bupivacaine and levobupivacaine typically include PR interval prolongation, increased voltage of QRS complexes, widened QRS complexes, ventricular extrasystoles and bundle branch block. When higher doses were infused intravenously over 3 minutes in sheep, the mean fatal doses were found to be in the order lidocaine 1450 (95% CI = 1145-1745) mg > ropivacaine 325 (191-451) mg = levobupivacaine 277 (240-313) mg > bupivacaine 161 (135-187) mg.[22,40,42,43] In all cases observed with bupivacaine, a sudden onset of fatal ventricular tachycardia-fibrillation occurred without concurrent hypoxia or acidosis. In animals receiving lidocaine, respiratory depression with bradycardia and hypotension without arrhythmias ('pump failure') was the cause of death. However, some animals receiving ropivacaine and levobupivacaine had a bupivacaine-like ventricular fibrillation-related death and others died of electro-mechanical dissociation or a lidocaine-like pump failure death. Reasons for these differences are not yet known.

In other single dose studies in sheep, we have found that direct left coronary arterial infusions, to preclude CNS actions, revealed no difference in intrinsic cardiac toxicity between bupivacaine, ropivacaine and levobupivacaine as judged by the lack of significant differences in their fatal doses.[44] In contrast to the studies with intravenous administration, deaths occurred by ventricular fibrillation in all cases. Other investigators have used a repeated cumulative dose close left coronary arterial injection in pigs and found that, although fatal ventricular fibrillation was the common mode of death, both ropivacaine (7.8 SEM 2.0mg) and levobupivacaine (7.3 SEM 1.5mg) have greater margins of safety in their fatal dose than bupivacaine (5.0 SEM 0.8mg).[46]

Reasons for the differences in findings between the single dose studies in sheep and the repeated dose studies in anaesthetised pigs can only be speculative at present; similarly with the mode of death by ventricular fibrillation or by pump failure with ropivacaine and levobupivacaine. However, enantioselective cardiovascular depressant effects and arrhythmogenic effects via central mechanism effects at the *nucleus tractus solitarius* have also been described in rats.[47] It is quite possible that differences in potency for CNS toxicity could impact on the cardiovascular toxicity found between intravenous and intracoronary arterial infusion, as well as between single and repeated doses where significant systemic absorption would have been likely.

Studies in dogs indicate that the margin of safety from single supraconvulsant doses of ropivacaine is greater than that of bupivacaine, judging by the probability of survival.[48] At twice the convulsant doses of these agents, the incidence of untreated fatal arrhythmogenic death from ropivacaine (33%) was significantly less than that from bupivacaine

(83%).[48] In another series of studies, after aborting the convulsions from a supraconvulsant dose of ropivacaine or bupivacaine and aggressive antiarrhythmic treatment, survival from ropivacaine was 100% whereas that from bupivacaine was 67%.[49] It is still not possible to give a definitive clinical treatment plan for local anaesthetic-induced serious cardiotoxicity.

3.2 Studies in Humans

Clearly, studies in humans are conducted in the most relevant species; however, even preclinical studies imply conservative administration. Indeed, because such studies are performed over a limited portion of the dose-response relationship, principally revealing threshold CNS effects, they are a 'blunt instrument' in their ability to explore margins of safety and similar properties, compared with studies in experimental animals.

The earliest study demonstrating the cardiological responses to the modern local anaesthetics compared intravenous bupivacaine with lidocaine and mepivacaine at equi-anaesthetic doses in healthy volunteers.[50] This study did not find bupivacaine to be more toxic than the other agents. Various other experimental[51,52] and clinical use studies[53] looked for, but did not find, unexpected disproportionate toxicity of bupivacaine. Nonetheless, the alarm was raised in 1979 in an editorial that claimed evidence of disproportionate CVS toxicity of bupivacaine and its newer counterpart etidocaine, especially in pregnant patients undergoing labour.[2] The decade that followed saw clinicians becoming much more conscious of the factors that might impact on local anaesthetic toxicity, especially the rate of administration of the agent, along with the demise of etidocaine, and the development of ropivacaine.

Ropivacaine is better tolerated than bupivacaine when infused intravenously based on subjective CNS effects. Mean doses, in healthy volunteers, of bupivacaine 99 (SD 30) mg and ropivacaine 124 (SD 38) mg were tolerated before the participants' CNS symptoms became troublesome.[54,55] During this time, cardiovascular changes were brief and generally small with both drugs; these included increases in heart rate and arterial blood pressure, decreases in stroke volume and ejection fraction. These changes did not differ between drugs. Brief cardiac conduction changes occurred, PR and QTc increased to some extent with both drugs, QRS widening occurred for bupivacaine but not ropivacaine.[54] In a similar paradigm, infusion of bupivacaine or levobupivacaine infused intravenously at 10 mg/min to tolerability found that the mean tolerated doses were 47.9 and 56.1mg, respectively. Despite these relatively small doses, small and brief cardiovascular changes were demonstrable. Slightly increased electrocardiographic PR and QTc intervals did not differ between drugs; however, the changes occurring in stroke index, acceleration index and ejection fraction index were greater for bupivacaine than levobupivacaine.[56]

Within a clinical dosage range, both ropivacaine and levobupivacaine can cause gross CNS adverse effects, given the circumstances of rapid systemic absorption or intravascular injection. Frank convulsions have been reported from both;[57-59] however, cardiotoxic sequelae do not necessarily follow. Nevertheless, the significance that cardiotoxicity can be induced by direct CNS administration of local anaesthetics in animals, that there is enantioselectivity of such an effect, and that the CNS and control of cardiac function are directly connected via the brain stem, all indicate that CNS toxicity is not to be underestimated with regard to its potential cardiotoxicity threat. This area remains important for further (pre-clinical) research.

4. Conclusions

Some questions naturally arise. 'Are there really clinically significant differences between ropivacaine and levobupivacaine and the drug that they might displace, bupivacaine, especially since clinical practice has improved over the last 2 decades?' A cynic might rephrase the question 'Is it pharmacology or commercial interests that drives the plan?'

A sanguine look shows that most nerve block procedures pass by without significant repercussions because of a combination of reliable drugs, good

technique and, occasionally, good luck. Thankfully rarely, bad technique and/or bad luck prevails. In this case, the use of a drug with a lower toxic potential may make the difference in avoiding problems.

It is sometimes stated that the newer local anaesthetics have 'lower cardiotoxicity than bupivacaine'. This is not strictly correct. All local anaesthetic agents can produce CNS toxicity, decreased myocardial contractility and potentially fatal cardiac arrhythmias from clinical doses. Because the doses of the newer agents required to induce CNS and cardiac toxicity are greater than of bupivacaine, there is less probability of a 'toxic dose' being used. Hence, we believe that the statement should be that the newer local anaesthetics have a 'lower risk of causing serious cardiotoxicity than bupivacaine'. Most anaesthesiologists would agree that ropivacaine is perhaps one-fourth less potent than bupivacaine,[60,61] whereas levobupivacaine is approximately equipotent.[62] It is possible that some of the gains in reduced toxicity for ropivacaine are offset by the larger doses required for neural blockade, but this should not be the case with levobupivacaine.

Despite optimism about the enhanced safety of these drugs, anaesthesiologists should remember that a syringe full of ropivacaine or levobupivacaine still contains a potentially lethal dose. Compared with bupivacaine, the newer agents may be seen as 'safer', but they must not be regarded as 'safe'.

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