Effects of CNS Site-directed Carotid Arterial Infusions of Bupivacaine, Levobupivacaine, and Ropivacaine in Sheep

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Background: Previous preclinical safety studies in ewes have found intravenous levobupivacaine and ropivacaine to be less potent toward causing central nervous system (CNS) and cardiac toxicity than bupivacaine. Analogous cardiotoxicity has been demonstrated directly in various cardiac preparations ex vivo. Moreover, drug-related arrhythmogenicity has been demonstrated from direct CNS injection of local anesthetic agents in vivo, suggesting CNS-related cardiotoxicity. This study investigated whether CNS site-directed blood-borne drug administration (with minimal systemic recirculation) would demonstrate drug-related cardiotoxicity.

Methods: Direct CNS effects and indirect cardiotoxic sequelae were determined after bilateral carotid arterial infusions of levobupivacaine, bupivacaine, or ropivacaine in ewes. After pilot studies to validate the procedures, equimolar doses (24–96 μmol, ~7.5–30 mg) were infused over 3 min using a crossover design. Behavioral CNS signs, quantitative electroencephalographic (EEG), cardiovascular, and electrocardiographic effects were recorded. Drug blood concentrations in superior sagittal sinus and aorta were measured serially.

Results: Blood drug concentrations in the superior sagittal sinus were 5–10 times those concurrently in the aorta, confirming highly selective CNS delivery with minimal systemic recirculation. Dose-dependent CNS excitatory behavior and EEG changes, with increased mean arterial blood pressure, heart rate, cardiac output, and myocardial contractility, were found, consistent with sympathetic nervous system stimulation. The overall rank order of potency for these effects was ropivacaine < levobupivacaine < bupivacaine. Nonfatal cardiac arrhythmias were observed, but the type or frequency did not differ between drugs.

Conclusions: Although CNS site-selective drug delivery produced quantitative differences between bupivacaine, levobupivacaine, and ropivacaine in some CNS effects and cardiac sequelae, no differences were found in their arrhythmogenic potential.

PREVIOUS preclinical studies to evaluate safety have found the enantiopure long-acting local anesthetic agents levobupivacaine (S-bupivacaine) and ropivacaine to be less potent in causing central nervous system (CNS) and cardiac toxicity than (racemic) bupivacaine when administered intravenously to conscious adult female sheep.1–6 Such findings concur with various other laboratory experiments that have found dextrobupivacaine (the R-bupivacaine enantiomer component of bupivacaine) more toxic to the CNS and heart than levobupivacaine.7–12 Local anesthetic-induced cardiac toxicity affects myocardial contractility (quantitated by decreased left ventricular dP/dt max) and electrical activity (quantitated by QRS complex widening and arrhythmia frequency).13 Whereas the potency of the local anesthetic agents in depressing myocardial contractility is essentially proportional to their local anesthetic potency, that for disrupting electrical activity is disproportionately greater for bupivacaine than for levobupivacaine or ropivacaine. However, concurrent CNS toxicity complicates the presentation of cardiac toxicity because CNS excitatory behavior opposes the myocardial depressant activity and may itself generate cardiac conduction abnormalities.13 Local anesthetic agents injected directly into the CNS at or near brain stem regions of cardiac control can generate cardiac arrhythmias.14,15 Moreover, the effects of intravenous bupivacaine in decreasing the firing rate of relevant brain stem cells are enantioselective.16 Thus, local anesthetics apparently can cause indirect cardio toxicity by their direct actions on the brain and brain stem, with enantioselectivity as found with intravenous administration.

This study was conceived to gain insight into the role of CNS effects in cardiac toxicity from local anesthetic agents while the cardiovascular system was exposed to only subtoxic amounts of drug. It involved the CNS site-directed carotid arterial infusion of the drug and determined the direct CNS toxicity and the indirect cardiac sequelae, focusing on arrhythmogenesis. It was designed to complement a previous study of cardiac site-directed coronary arterial infusions of the same

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drugs in which the CNS was exposed to only subtoxic amounts of drug.\textsuperscript{17}

Materials and Methods

Subjects

The studies were approved by the local animal care and ethics committee. The subjects were nonpregnant Merino cross-bred ewes, aged approximately 18–24 months, and weighing between 44 and 57 kg (table 1).

Preparation

Surgical preparation was performed in two stages with the animal given general anesthesia. A left thoracotomy was performed for the placement of probes for hemodynamic and electrocardiographic (ECG) measurements. A second surgery was performed 7–10 days later for placement of infusion and sampling cannulae in the carotid arteries and superior sagittal sinus, a transit-time flow probe on the superior sagittal sinus, and electroencephalographic (EEG) electrodes.

During general anesthesia, a left thoracotomy was performed via the left 4/5 intercostal space. A flow probe (21 mm ART\textsuperscript{2}, Triton Technology Inc, San Diego, CA) was implanted around the pulmonary artery for cardiac output monitoring. A pressure transducer catheter (3.5-French Millar SPR-524, Millar Instruments Inc., Houston, TX) was placed into the left ventricle through the left ventricular free wall. The pericardium was closed, and two pairs of stainless steel internal ECG electrodes were sutured onto pericardium. All leads were exteriorized by tunneling subcutaneously to near midline of the dorsum. Bupivacaine intercostal nerve block was implemented just before thoracic closure. In addition, postoperative pain was managed by intravenous carprofen, 75 mg, and buprenorphine, 0.3 mg, injections after completion of surgery, followed by buprenorphine two or three times daily for 4 or 5 days at the discretion of the clinical investigators.

In the second surgery also performed with general anesthesia, each carotid artery was dissected free from surrounding tissue, and a polyurethane cannula (18 gauge, 70 cm, Cavafix, B Braun Melsengen AG, Melsengen, DE) was placed each side, to a depth of about 10 cm caudally, for the measurement of blood pressure and for arterial blood sampling; an epidural catheter (22 gauge, Spinocath, B Braun Melsengen AG, Melsengen, DE) was placed into each carotid artery 5 cm cranial to the sampling catheter to a depth of 3 or 4 cm for drug infusion in a retrograde manner. All catheters were introduced through half wall thickness purse-string sutures to guard against arterial leakage and were tunneled and exteriorized dorsally from the back of the neck. After midline trephination of the skull over bregma, a cannula (22 gauge, Spinocath, B Braun, Melsengen AG, Melsengen, DE) was placed in the superior sagittal sinus for sampling blood. Stainless steel EEG electrodes were introduced bilaterally through the trephination to reside between the skull and cerebral cortex. A transit-time flow probe (4ss, Transonic System Inc, Ithaca, NY) was placed on the sagittal sinus for measurement of blood flow.\textsuperscript{18} All cannulae, except for the two carotid arterial infusion lines, were then attached to a constant infusion of heparinized saline, 3 ml/h, via a minimum volume extension sets connected to high-pressure, low-flow restrictor devices. These were attached via a multiple port block from a pressurized 1-l saline bag, 0.9%, with heparin, 10,000 U, and fluocoxacillin, 1 g, added and kept pressurized by a cylinder of medical oxygen regulated to 300 mmHg. The carotid infusion lines were flushed at least three times a week with 50% glucose (heparinized, 240 U/ml). After the second surgery, the animals were allowed to recover in a metabolic crate for a minimum of 1 week before the first study was performed. Postoperative pain was managed as described previously. The animals were also given a clinical examination twice daily for several days after both surgical procedures.

Drugs and Doses

Equimolar doses of levobupivacaine HCl (Chirocaine, Chirosceince R&D Ltd, Cambridge, UK), bupivacaine HCl (Maracaine, Delta West, Perth, Australia), and ropiva-
caine HCl (Naropin, AstraZeneca Pty Ltd, Sydney, Australia) in 15 ml 0.9% saline were infused over 3 min. The relevant researchers were blinded to the drug identities, and the code was broken after completion of the data analysis.

**Experimental Details**

Because of the paucity of previously published information about the perfusion of the cortical and medullary areas of the sheep brain via the basilar and carotid arteries, preliminary studies of the cerebral vascular anatomy were performed using dissection and brachiocephalic arterial erosion cast techniques in dead animals. Our approach was based on various studies showing that carotid arteries supply all above brain stem in sheep\(^{19-21}\) and was validated by vascular anatomy erosion casts and by pilot studies.

Pilot studies were performed with bupivacaine in seven animals during general anesthesia to validate the drug infusion procedures, signal processing, dose ranging, and to gauge the effect on drug regional brain distribution from ligation of the vertebral arteries. The latter point arose from rationalization that the vein of pressure within the circle of Willis might be manipulated to deliver drug preferentially to cortex or brain stem. However, the pilot data did not provide evidence to support the theory that ligation of vertebral arteries would cause redistribution of blood to the brain stem so that the simpler preparation (without interference to the vertebral arteries) was used for the systematic studies. After evaluation of the pilot studies (see Results section), it was decided to use a crossover design so that each animal received the drugs in random order, in blocks of increasing dose. One threshold convulsant dose (24 \(\mu\)mol \(\approx\)7.5 mg) and up to three supracoalvulsant doses (48, 72, and 96 \(\mu\)mol) were used as described in table 1.

On the day of each study, the subject animal was brought into the laboratory with a companion animal, placed in a sling, and allowed to settle. Each study session consisted of three uninterrupted periods: 5 min, for baseline measurements; 30 min, beginning with a 3-min infusion of drug. The infusions were administered equally bilaterally via the intracarotid arterial infusion cannulae by a Harvard model 22 programmable syringe pump operating in constant rate delivery mode.

Measurements included ECG arrhythmia analyses, QRS width, PR interval, QT interval, RR interval from which heart rate was derived, cardiac output, stroke volume derived from the ratio of cardiac output to heart rate, mean arterial blood pressure, left ventricular pressure, and the maximum positive value of its differential (\(\frac{dp}{dt_{max}}\)) as an index of myocardial contractility. In addition, the quantitative EEG signal was recorded continuously, and the semiquantitative Central Effects Index (CEI) of behavioral effects was derived from a videotape record of the study.\(^{22}\) Briefly, the CEI consisted of the same investigator assigning the times of onset and, if clearly obvious, the offset along with serial scores on a scale of 0 (no apparent effect) to 100 (death) of sets of discrete behaviors ranked in severity and modeled according to a logistic population growth equation using the onset of convulsive behavior (CEI = 70) and death as point attractors. Its maximum value and area under the time–effect curve (respectively, peak CEI and AUC CEI) thus provide measures of intensity and duration of CNS behavioral effect for each dose of drug.\(^{23}\) The 5-min periods immediately preceding the saline and drug infusion periods were considered the relevant respective baseline periods for assessment of the effects of the saline control and drugs.

Verification of the selective site drug delivery was made through drug analysis of arterial and sagittal sinus serial blood samples,\(^{25}\) from which the maximum measured blood drug concentration (\(C_{max}\)) was noted. At the conclusion of the set of experiments, animals were anesthetized with pentobarbital, and food dye was immediately injected into the carotid artery cannulae followed 30 s later by an intracardiac injection of KCl. Tissue dye distribution and the probe placements were examined at post mortem. Subjects were to have been rejected if the dye distribution had failed to target the brain tissues as predicted.

**Data Acquisition and Processing**

Data from the various physiologic signals were gathered and stored digitally on a personal computer using AcqKnowledge 3.03 software (Biopac Systems Inc, Santa Barbara, CA) for postrun processing in a manner consistent with our previous and related study of site-directed coronary arterial infusion of the same drugs.\(^{17}\)

Cardiovascular and hemodynamic data were broken into 20-s epochs, and the means of values from each epoch were calculated and charted as continuous plots. ECG data were broken into 1-min baseline epochs; after the commencement of drug infusion, the data were broken into 30-s epochs to 8 min, 1-min epochs to 10 min, 2-min epochs to 20 min, 5-min epochs to 30 min, and 15-min epochs to 60 min. ECG measurements were determined as averages from five consecutive complexes toward the end of the epoch. QTc duration was determined from QT and RR according to the formula QTc = QT/√(RR). Arrhythmias were analyzed by recording the numbers of abnormal beats for each type of arrhythmia present\(^{17}\) to give the proportions of abnormal to the total number of beats within the time window; the same investigator analyzed all ECGs to maintain consistency of interpretation.

Quantitative EEG signals were analyzed for the 24- and 48- \(\mu\)mol doses in four frequency bands, 1–4 Hz, 4–8 Hz,
Data and Statistical Analyses

Data consisting of the differences between values in the saline control or drug periods and their respective baseline periods were, for convenience of comparison, expressed as percentages of the individual baseline values determined in the specific animal during the specific session. Data were analyzed for the magnitude and time of peak effects ($E_{\text{max}}$). In addition, the sum of the effect differences to 10 min (SED$_{10}$) for cardiovascular and hemodynamic data and to 5 min (SED$_5$) for ECG data were determined to capture differences between treatments (drugs and doses) in the magnitude and immediate time course. SED data are often used in studies of analgesic drug effects; they provide a useful univariate statistic for time series data and are analogous to AUC.$^{24}$

Drug effect data were analyzed by fitting random effects linear models$^{25}$ using the cross-sectional time series regression facility (XTREG) of the statistical software Stata version 6 (Stata Corporation, College Station, TX). The random effects models allowed the fitting of dose-effect curves for all drug doses simultaneously while making allowance for random variation in level of effect among animals. Dose-effect relationships were tested for linearity by adding a quadratic term in dose and for parallelism by adding terms describing interactions between the linear dose trend and drug. Baseline values were included in the initial models as an explanatory covariate.$^{26}$ If a significant difference among dose-effect curves of the three drugs was found, curves of the drugs were compared pair-wise using Wald tests. The null hypothesis was that there was no difference in effects between the three drugs. A significance criterion of $P < 0.05$ was taken as weak evidence for rejection of the null hypothesis; a significance criterion of $P < 0.01$ was taken as strong evidence. All tests were two tailed.

Results

Cranial aortic erosion casts enabled the three-dimensional vascular anatomy to be visualized, and this assisted in placement of catheters (fig. 1). Because of the complexity and small size of most relevant afferent blood vessels, the carotid arterial infusion catheters could not be advanced to deliver blood-borne drug only to the brain; other craniofacial structures were also supplied concurrently. Hence, a conservative approach was adopted to place the catheter tip at a predefined point and thus to direct the drug dosage to the brain. The pilot studies verified the site-directed drug delivery approach by showing that brain tissue drug concentrations were similar to those found with fatal intravenous infusions of much larger doses.$^{1,27}$ The pilot studies also found that the brain stem regional average drug concentrations were approximately 50–70% of the higher CNS regions (fig. 2). A drug crossover, dose block paradigm thus was chosen to minimize the impact of individual anatomic variations; data from 11 animals were used in the final analysis (table 1; figs. 3–9).

Relevant Pharmacokinetics

As predicted from the vascular erosion casts and pilot experiments, drug blood concentrations in the superior sagittal sinus were approximately 5–10 times those concurrently in the aorta, indicating a highly selective site direction to the brain with minimal recirculation of drug...
in the arterial blood (fig. 3). $C_{\text{max}}$ was essentially linear with dose, and there were no systematic differences between drugs (fig. 4).

**Systemic Drug Effects**

No significant effects resulted from the infusion of saline as a control agent. With infusion of local anesthetic drugs, two animals died at 3.5 and 5.8 min as a sequel to severe hypoxemia and respiratory acidosis after infusion of 96 $\mu$mol of bupivacaine. In one of these sheep, respiratory arrest contributed to the development of hypoxia and acidosis. The deaths were not caused by an arrhythmia, but after effective cardiac output had ceased and before (terminal) electrical asystole, some electrical abnormalities were seen in both sheep, including ventricular asystole with complete AV block. Significant differences in drug effects were found in $E_{\text{max}}$ and SED data of the chosen measures (table 2, figs. 5–9) but not in the time at which $E_{\text{max}}$ occurred (data not shown). Dose–effect relationships, generated by the statistical analysis procedures, were parallel for the three drugs with the exception of PR interval, in which case the drug effects were compared at each dose. Differences between drugs are shown in table 2 as the 95% confidence intervals of the magnitude of the effect difference in the dose–effect curves for respective pairs of drugs; a summary of rank order of overall effect potency is also shown. It is reiterated that comparisons were made using drug-induced changes from baseline determined in each animal during the relevant experimental session. In this way, individual differences in sensitivity between animals, either inherent or by preparation, were accommodated by the random effects data analysis models.

**Central Nervous System Effects**

**Central Effects Index.** All doses of all drugs produced dose-related CNS excitatory effects in all animals. The 24-$\mu$mol doses produced hypertonia and sometimes convulsions. Convulsions occurred regularly with all larger doses, along with a maximal peak CEI. There were significant differences between drugs in peak CEI at the 24-$\mu$mol dose only, where ropivacaine was less than with bupivacaine ($P = 0.007$) and levobupivacaine ($P = 0.007$).
AUC CEI was greatest with bupivacaine and least with ropivacaine (ropivacaine < bupivacaine \(P < 0.001\) and levobupivacaine \(P = 0.016\); levobupivacaine < bupivacaine \(P = 0.033\)); the increase in AUC CEI with dose was essentially the result of increased duration of effect as peak effects were maximal (fig. 5).

**Quantitative Electroencephalograms.** There was little change from baseline EEG with 24-\(\mu\)mol doses, but significantly increased power was clear from 48 \(\mu\)mol (fig. 6). Considering the \(E_{\text{max}}\) values (as % baseline), there were differences in amplitude between drugs in the whole 1- to 30-Hz spectrum and in the 1- to 4-Hz band, where bupivacaine was greater than ropivacaine (respectively, \(P = 0.003\) and \(P = 0.014\)), but not in the other separate frequency bands. There were significant differences between drugs across doses when considering \(\text{SED}_{10}\) for the entire 1- to 30-Hz spectrum (bupivacaine > ropivacaine \(P < 0.001\) and levobupivacaine > ropivacaine \(P = 0.038\)) and for the separate 1- to 4-Hz band (bupivacaine > ropivacaine \(P = 0.001\)). A periodic epileptiform pattern, consisting of discharges followed by quiescence that resembled burst suppression, precluded quantitative EEG analysis for 72- and 96-\(\mu\)mol doses. Overall, the duration of effect was greatest with bupivacaine and least with ropivacaine.

**Cardiovascular and Hemodynamic Effects**

Dose-dependent increases in mean arterial blood pressure, heart rate, cardiac output, and left ventricular dP/dt\(_{\text{max}}\), along with a decrease in stroke volume, were found. The time course of effects on heart rate after drug administration is shown in figure 7 as being representa-

![Fig. 5. The effects of bilateral carotid arterial infusion of 24-, 48-, 72-, and 96-\(\mu\)mol doses of bupivacaine, levobupivacaine, and ropivacaine infused over 3 min on the mean (with SEM error bars) of the peak (left) and area under the curve (right) of the Central Effects Index.](image)

![Fig. 6. The effects of bilateral carotid arterial infusion of bupivacaine (Bup), levobupivacaine (Lev), and ropivacaine (Rop) on the power in the electroencephalographic (EEG) signal separated into frequency bands as shown for the (bottom) 24- and (top) 48-\(\mu\)mol doses. Mean values (with 95% confidence intervals) are shown.](image)
of which were multiform, were observed from some doses of all of the local anesthetic agents. Their frequencies, corrected for the prevailing heart rate as stimulated by the doses of the drugs, averaged between 1–3 aberrant beats per 100, without differences between drugs. At the 24-μmol dose, premature ectopic beats were noted without significant ventricular tachycardia. At doses of 48 μmol or greater, a preponderance of ventricular tachycardia was noted with all three drugs and which tended to decrease with increased dose.

Discussion

This study demonstrated the feasibility of site-directed administration of blood-borne local anesthetic agents to the brain for determination of their direct CNS effects and indirect cardiac effects in chronic intact conscious animals. It found that local anesthetic drugs infused bilaterally into the carotid arteries of conscious sheep caused dose-related direct CNS and indirect cardiac effects with an overall rank order of potency bupivacaine > levobupivacaine > ropivacaine. Fatal arrhythmias were not found, and there were no differences between the drugs in producing nonfatal arrhythmias.

In the design of the studies, it was considered necessary to avoid general anesthesia and acute surgical stress. General anesthesia can alter the toxic response to local anesthetic agents and the disposition of drugs. These complications were precluded by using a conscious, previously instrumented, preparation. To ensure the appropriate distribution of the drug as would occur in the accidental intoxication of a clinical patient, it had to be administered to the brain as a blood-borne solute but without delivering potentially toxic drug blood concentrations to the heart. After preliminary investigation of the cerebrovascular anatomy in relation to the routes of regional drug delivery to brain, a discrete dose paradigm was designed with bilateral carotid arterial infusion (using small cannulae to not compromise the normal carotid blood flow). As judged by regional CNS tissue bupivacaine concentrations in pilot studies (fig. 2), drug delivery to the brain stem was abundant but was relatively less than to higher structures. Enantiomeric differences in CNS tissue uptake of bupivacaine, however, were not apparent.

In the systematic studies, it was found that drug blood concentrations in the superior sagittal sinus exceeded those concurrently in the aorta by a factor of approximately 5 (figs. 3 and 4). This verified that drug delivery to the CNS was much enriched compared with the rest of the body, whereas the magnitude of the aortic concentrations verified pharmacologically trivial drug delivery to the heart. Equivalent brain drug concentrations from intravenous infusions necessitate much larger doses to be applied to the whole body so that direct cardiovascular effects would also occur.

Electrocardiographic Effects

Mean PR interval, QRS width, and mean QTc interval decreased for the three largest doses of all three drugs, following the time course of changes in heart rate (fig. 9). Cardiac arrhythmias, predominantly premature ventricular and supraventricular ectopic beats, some in bigeminy or trigeminy, and ventricular tachycardias, some
The potential for relatively small doses of local anesthetic agents to cause CNS toxicity if directed to the brain is widely recognized clinically but is poorly documented pharmacologically. After clinical observation of unexpected CNS effects from local anesthetic agents injected around the head or neck, it was suggested that retrograde transport via arterial blood to the CNS may have been involved. Local anesthetic drugs have complex CNS effects. Tetraphasic EEG effects have been described in cats; the actions were found to be dose-dependent and progressed from depression to epileptiform stimulation with increasing rates of infusion, suggesting effects at a common receptor(s), probably a neuronal Na⁺ channel. In our study, the overall severity of CNS effects increased in the same rank order of potency as found by others with intravenous administra-

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tion in a variety of preparations, i.e., ropivacaine < levobupivacaine < bupivacaine. In this study, intracarotid doses of 48 μmol or greater (≈15 mg) almost always caused frank convulsive behavior. Overt CNS effects were always accompanied by cardiovascular changes, consistent with an abrupt onset of sympathetic nervous system discharge and were thus similar to the sequelae of bicuculline-induced seizures used as a model for epilepsy in sheep.

A quantitative EEG approach allows precision in describing drug CNS effects by apportioning their time course into changes in the frequency spectrum and amplitude components. In this study, drug-induced EEG changes were measurable across all EEG frequency bands, but quantitative differences between drugs were revealed mainly in the low frequency (1–4 Hz) region. Doses greater than 24 μmol produced significant EEG and behavioral effects. Overall, these results concur with qualitative EEG data from much greater doses of congeneric local anesthetic agents given intravenously in monkeys. Apart from Na\(^+\) channel blockade, local anesthetic drugs affect other neuronal receptor-mediated functions. At higher doses, they inhibit γ-aminobutyric acid receptor type A-mediated (GABA\(_A\)-ergic) transmission and stimulate N-methyl-D-aspartate (NMDA) receptors, the latter apparently without alteration of cardiac toxicity. It is not yet known whether such actions are enantioselective. Although neural and cardiac Na\(^+\) channel blockade is weakly enantioselective (dexbupivacaine-to-levobupivacaine potency ratio, ~1.5), some other potentially relevant actions, such as on β\(_2\) adrenoceptors and (rat) heart mitochondrial respiration, seem not to be demonstrably enantioselective.

It is clear that fatal arrhythmias did not result from direct CNS excitation or convulsions caused by CNS site-directed supraconvulsant doses of local anesthetic agents. At doses of 24 μmol, all three drugs caused mild overt CNS excitation, along with nonfatal cardiac arrhythmias, but without differences between drugs. At doses greater than 24 μmol, the three drugs caused marked convulsive behavior, but, again, fatal arrhythmias were not found. Nevertheless, because of the differences found previously between drugs in their potency for causing fatal arrhythmias with (supraconvulsant) intravenous doses, it is possible that bilateral carotid arterial infusion may not have delivered a sufficient

Fig. 9. Dose–effect relationships for electrocardiologic effects of bupivacaine, levobupivacaine, and ropivacaine infused bilaterally over 3 min into the carotid arteries of sheep. Panels from top: mean arterial blood pressure, heart rate, cardiac output, stroke volume, and left ventricular dP/dt\(_{max}\) as an index of myocardial contractility. (Left) Maximum measured values; (right) values for SED\(_{10}\). Mean values (with SEM error bars) are shown. Statistical inference is shown in table 2.
amount of drug to the brain stem to show differential arrhythmogenic potency or cause fatal arrhythmias. Despite their practical difficulty, we therefore suggest that further refinements in experimental design are worthy of consideration, for example, by enriching CNS site-directed drug delivery to the brain stem via the vertebral arterial supply or by preloading the heart with subtoxic amounts of drug before causing CNS excitatory effects. On the other hand, the possibility also remains that the small amounts of recirculated doses may have produced an antiarrhythmic effect.\(^{37}\)

In summary, this study presents a further step in new techniques to probe the cardiac toxicity of clinically important local anesthetic agents. Although it found that bupivacaine was, overall, more potent toward direct CNS toxicity and indirect cardiac toxicity than levobupivacaine and ropivacaine, it did not find differences between the agents in nonfatal arrhythmogenicity nor did it find fatal arrhythmias resulting from CNS site-directed carotid arterial infusion.

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