Acute Toxicity of Ropivacaine Compared with That of Bupivacaine

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SCOTT DB, LEE A, FAGAN D, BOWLER GMR, BLOOMFIELD P, LUNDH R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989;69:563–9.

The acute central nervous and cardiovascular effects of the local anesthetics ropivacaine and bupivacaine were compared in 12 volunteers in a randomized double-blind manner with use of intravenous infusions at a rate of 10 mg/min up to a maximal dose of 150 mg. The volunteers were all healthy men. They were familiarized with the central nervous system (CNS) toxic effects of local anesthetics by receiving a preliminary intravenous injection of lidocaine. The infusions of ropivacaine and bupivacaine were given not <7 days apart.

CNS toxicity was identified by the CNS symptoms and the volunteers were told to request that the infusion be stopped when they felt definite but not severe symptoms of toxicity such as numbness of the mouth, lightheadedness, and tinnitus. In the absence of definite symptoms, the infusion was stopped after 150 mg had been given.

Cardiovascular system (CVS) changes in conductivity and myocardial contractility were monitored using an interpretive electrocardiograph (which measured PR interval, QRS duration, and QT interval corrected for heart rate) and echocardiography (which measured left ventricular dimensions from which stroke volume and ejection fraction were calculated).

Ropivacaine caused less CNS symptoms and was at least 25% less toxic than bupivacaine in regard to the dose tolerated. Both drugs increased heart rate and arterial pressure. Stroke volume and ejection fraction were reduced. There was no change in cardiac output. Although both drugs caused evidence of depression of conductivity and contractility, these appeared at lower dosage and lower plasma concentrations with bupivacaine than with ropivacaine.

Ropivacaine is a less toxic compound than bupivacaine, but their relative therapeutic ratios must await the results of clinical trials in humans to assess the potency of ropivacaine compared with that of bupivacaine.

Key Words: ANESTHETICS, LOCAL—ropivacaine, bupivacaine. TOXICITY, LOCAL ANESTHETICS.

Ropivacaine is the (S)-enantiomer of 1-propyl-2′,6′-pipecoloxylidide, an amide local anesthetic with a structure similar to that of mepivacaine and bupivacaine. Animal studies (1–3) have indicated that ropivacaine is less toxic than bupivacaine. Both drugs have a comparatively long duration of action, but their relative potency has still to be determined in humans.

As virtually all local anesthetics produce a similar profile of symptoms and signs related to that of the central nervous system (CNS), it is relatively easy to compare them in volunteers in a randomized double-blind manner (4).

Cardiovascular toxicity is less easy to study, as clinical signs are not usually seen until the CNS toxicity is marked and well beyond that which is tolerable to either a volunteer or a patient. However, the detection of asymptomatic changes in cardiac conduction and contractility has been made easier with modern noninvasive technology, and this can be used to determine whether objective signs of changes in conductivity and contractility can be detected when only mild CNS toxicity is present.

As ropivacaine is a long acting local anesthetic, it should have a clinical profile similar to that of bupivacaine and a knowledge of their respective systemic toxicity in humans is of importance. To compare the acute toxicity of ropivacaine and bupivacaine on both the CNS and the cardiovascular system (CVS), the following study was undertaken.

Methods

Ethical permission for the study was obtained from the Lothian Health Board ethical committee. Twelve

Received from the Department of Anesthetics, Royal Infirmary, Edinburgh, Scotland; *Department of Cardiology, Western General Hospital, Edinburgh, Scotland; and †Astra ALAB, Söderttalje, Sweden. Accepted for publication April 25, 1989.

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healthy male volunteers took part. After a full medical examination including routine electrocardiography (ECG), biochemistry, and hematology, they were acquainted with the mild toxic effects of local anesthetics by receiving IV lidocaine given at a rate of 100 mg/min until the volunteer was aware of the early symptoms of toxicity (lightheadedness, tinnitus, numbness of the tongue). As soon as the subject was aware of definite symptoms, the injection was stopped. The dose producing such symptoms was 80–200 mg.

At the preliminary medical examination, each subject also underwent echocardiography. As it is not possible to obtain high grade echorecordings from every person, we wished to identify those who would be suitable for this particular method. In the event, 8 of the 12 proved suitable and echocardiography (vide infra) was performed on them during their two drug infusions.

Infusion. The study proper in each individual started several days after the IV lidocaine. No other drugs were taken in the week before the study and no alcohol or tobacco was consumed in the 24 h before the study. Each volunteer received two infusions, one of 0.5% bupivacaine HCl and one of 0.5% ropivacaine HCl (as aqueous solutions), at least 7 days apart and in a randomized order. The infusion rate was 10 mg/min (2 mL/min) with use of a Harvard infusion pump. The infusion was stopped at the request of the volunteer when he experienced definite CNS symptoms. If no symptoms occurred or were only of a minor degree, the infusion was stopped after 150 mg had been injected.

Monitoring. Symptoms of CNS toxicity were reported as and when they occurred, in response to frequent direct questioning, and were graded for severity on a 0–4 scale by the volunteer. Though the grades were recorded, they were used to assess the progress of toxicity in regard to time during the infusion and were not subjected to subsequent analysis.

The ECG was displayed continuously on a Roche 125 monitor and recorded continuously with a Medilog tape recorder. A 12-lead ECG was recorded before and every 5 min during the infusion. A recording was also taken at the end of the infusion, and every 5 min thereafter for 30 min. A Hewlett-Packard Pagewriter Interpretive Cardiograph was used for this purpose. This instrument calculates the PR interval, QRS duration, QT interval, QT interval corrected for heart rate, and QRS axis.

A Dynamap 845 was used to measure and record systolic and diastolic blood pressures, together with heart rate, at 2-min intervals throughout. Echocardiography was performed on 8 of the 12 subjects (vide supra) with use of an Ekoline 21 SKI M-mode machine. The eight subjects were placed on a specially made table on which they were horizontal with up to a 30° tilt to the left, the final position chosen being that which gave a clear echorecording. The echocardiograph machine was connected to an Ekoline 21 ultraviolet strip chart recorder on which the V5 ECG waveform was simultaneously recorded with the echocardiograph. A 2.25-MHz 13-mm-diameter piezoelectric ultrasound transducer was used. The chart speed was 50 mm/sec with tissue depth markers at 1-cm intervals and time markers at 0.5-sec intervals. Calibration was performed before the investigations by the hospital Department of Medical Physics and Medical Engineering. The transducer was placed either at the third or the fourth left parasternal intercostal space, whichever enabled the transducer to be closest to right angles to the body surface in all planes when recordings were made at the level of the anterior mitral valve leaflet (5). The positions of the subject and the transducer were the same for both infusions. After recording, the charts were marked out in preparation for digitization by one of us (GMRB) and checked by another (PB) before digitizing on a dedicated echocardiographic analysis system (Cardio-80, Kontron). Both observers were blinded to the identity of the drug infused.

The methodology used to determine the left ventricular dimensions followed the recommendations of the Committee on M-mode Standardization of the American Society of Echocardiography (6) and a standard textbook (7). The leading edge method (most anterior edge of endocardial lines) was always used and all measurements quoted were the mean of three cardiac cycles. End-diastolic diameter (EDD) was timed at the onset of the first deflection of the QRS complex on the simultaneously recorded ECG. End-systolic diameter (ESD) was timed from the peak of the motion of the posterior wall of the left ventricle. Heart rate (HR) was derived from the RR interval on the ECG over three cycles. The left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated by the program using the Teicholz formula (8): Stroke volume (SV) = EDV − ESV; Cardiac output (CO) = SV × HR. Shortening fraction (SF) was calculated from the formula SF = (EDD − ESD)/EDD × 100%. Ejection fraction (EF) was calculated from the formula EF = (EDV − ESV)/EDV × 100%.

Blood sampling. Five-milliliter samples of venous blood from the arm contralateral to that used for the

Table 1. Demographic Data of 12 Subjects Receiving Both Ropivacaine and Bupivacaine

Subject	Age (years)	Height (cm)	Weight (kg)
1	26	175	68
2	34	183	81
3*	20	183	66
4*	27	186	83
5*	30	173	69
6*	30	173	67
7*	31	172	58
8	26	186	69
9	21	167	75
10*	30	178	73
11*	32	175	77
12*	28	183	83
Mean	28	178	72
Range	20–34	167–186	58–83

*Indicates those subjects who underwent echocardiography.

Table 2. Individual and Mean IV Doses of Ropivacaine and Bupivacaine Tolerated in 12 Subjects

Subject	Tolerated IV dose (mg)	
	Ropivacaine	Bupivacaine
1	150	150
2	150	120
3	67	65
4	65	75
5	150	95
6	62	60
7	150	85
8	150	133
9	150	105
10	137	82
11	150	138
12	110	75
Mean ± SD	124 ± 38	99 ± 30
	$P < 0.01$	

infusion were taken before the infusion was started, at the time of reporting the first symptoms, at the end of the infusion, and every 5 min thereafter until 10 min after the disappearance of all symptoms. The plasma was separated and frozen at −20°C before analysis. The concentration of ropivacaine in the plasma was determined by gas chromatography with use of nitrogen sensitive detection at the Astra Bio-analytical Laboratories, Södertalje, Sweden.

Data analysis. Wilcoxon signed rank tests were used to compare the between treatment data (bupivacaine versus ropivacaine) and also the within treatment data (control values versus data during and after infusion with each drug). As the measured variables differed in regard to sampling time due to the difference in time to first symptoms, the measurements have been identified as C = control data (preinfusion); F = data at first symptoms; E = end of infusion; E + X = end of infusion + x min. The null hypothesis was rejected at the $P < 0.05$ level.

Results

The demographic data of the 12 subjects are shown in Table 1.

Dose of drug. Seven subjects tolerated the full 150-mg dose of ropivacaine, but only one tolerated the same dose of bupivacaine. The individual doses are shown in Table 2. The mean dosage of ropivacaine was 124 mg and of bupivacaine 99 mg. This difference was statistically significant ($P < 0.01$).

Symptoms. The onset of symptoms from the start of the infusion was on average 4 min with bupivacaine and 6 min with ropivacaine ($P < 0.02$). The time to maximal effect was 10 min with bupivacaine and 12 min with ropivacaine ($P < 0.05$). The duration of symptoms (17 min with bupivacaine and 15 min with ropivacaine) did not differ significantly. The symptoms were those expected from local anesthetic drugs and similar to those during the preliminary lidocaine injection. The severity and frequency of symptoms were greater with bupivacaine, only one subject tolerating the maximal dose (150 mg) compared with 7 with ropivacaine.

Plasma concentrations. Although there were individual variations, the majority of the symptoms occurred at plasma concentrations of either drug between 1 and 2 μg/mL. The mean plasma concentrations of the two drugs at the appearance of symptoms (F), at the end of infusion (E), and 5 min (E + 5) and 30 min (E + 30) after the infusion are shown in Figure 1. The concentrations of ropivacaine were greater than those of bupivacaine at all sample times, these being significantly different ($P < 0.05$) at E and E + 5. By the end of the infusion, on average 25% more ropivacaine had been given than bupivacaine.

Cardiovascular changes. The mean data for arterial pressure and heart rate for all 12 subjects are shown in Figures 2a and 2b. Both drugs were associated with small increases in both pressure and heart rate, which were statistically significantly different from control values ($P < 0.01$) except for the change in heart rate with ropivacaine which was not statistically significant. There were no differences between the drugs.

The mean data for PR interval, QRS duration, and QT interval (corrected for heart rate) are shown in

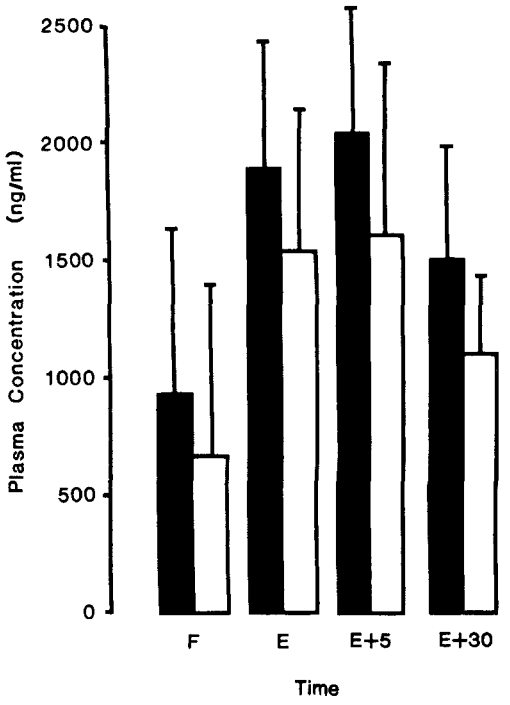

Figure 1. Mean plasma concentrations of ropivacaine (solid bar) and bupivacaine (open bar) at the following sample times: appearance of first CNS symptoms (F), end of infusion (E), and 5 min (E + 5) and 30 min (E + 30) after the infusion. There was a statistically significant difference ($P < 0.05$) between drugs at E and E + 5. Vertical lines represent 1 SD.

Figures 3a, 3b, and 3c. Bupivacaine significantly increased all three, both at the end of infusion (E) and 5 min later (E + 5). Ropivacaine significantly increased the PR interval only at E + 5. The only statistical difference between the drugs was in regard to the QRS duration at E + 5.

No cardiac arrhythmias were detected during the infusions or on replay of the Medilog tapes. The echocardiographic data obtained with ropivacaine and bupivacaine in the eight subjects in which this investigation was carried out are shown in Table 3. The mean control values, and those obtained at the end of infusion when CNS toxicity was maximal, are shown. Neither drug caused a significant change in EDD, but the ESD was increased with both drugs, though statistical significance was only reached with ropivacaine. Therefore, SV decreased significantly with both drugs as did SF and EF. Heart rate increased significantly with both drugs (as opposed to all 12 subjects). There was consequently no change in calculated cardiac output. Both systolic and diastolic blood pressures in these eight subjects increased significantly with both drugs. The mean plasma concentration of bupivacaine in the eight echocardiograph subjects was 1.22 μg/mL, which was 38% lower than that of ropivacaine, 1.70 μg/mL ($P < 0.05$). The respective mean doses in the eight subjects were 81 mg for bupivacaine and 108 mg for ropivacaine.

Discussion

There was a clear difference between the drugs in regard to their ability to produce mild symptoms of CNS toxicity. The 12 subjects tolerated 25% more ropivacaine than bupivacaine. This result almost certainly underestimates the difference between the drugs, because on seven occasions, the maximal dose allowed by the protocol (150 mg) was reached with ropivacaine compared with only one occasion with bupivacaine. The CNS symptoms were similar to those experienced in previous studies (9), and no unexpected side effects were noted.

The plasma concentrations measured were unremarkable and consistent with the pharmacokinetic data previously determined for the two drugs (10,11). The apparent paradox that the peripheral venous concentrations of both drugs were greater in most subjects 5 min after the infusion ended (E + 5) than when the infusions were stopped (E), is most probably because arterial and venous plasma concentrations had not reached equilibrium at E. The arterial concentrations would be highest at or very soon after the end of the infusion and greater than the venous concentration. Because drug was still being taken up by the tissues of the upper limb, it would take some minutes for the venous concentration to equalize with the arterial concentration. The use of peripheral venous plasma concentrations during rapid high dose IV infusions is fraught with problems, particularly when they are to be related to CNS changes (12). However, the use of arterial samples, which would be more informative, was not considered appropriate for the present volunteer study.

In spite of these reservations, it is reasonable to suggest that symptoms of CNS toxicity occur at lower plasma concentrations with bupivacaine than is the case with ropivacaine. There was a 40% difference between the mean plasma concentrations of the two drugs at the time symptoms first appeared (F). At the peak concentrations after stopping the infusions, ropivacaine concentrations were on average 27% higher than those of bupivacaine, in spite of the subjects having considerably less severe symptoms. The consistent increases in heart rates and arterial pressures during the infusions have been noted previously with local anesthetics (8). Although these increases might be explained by anxiety, it seems to be so reproducible that one must accept it as a

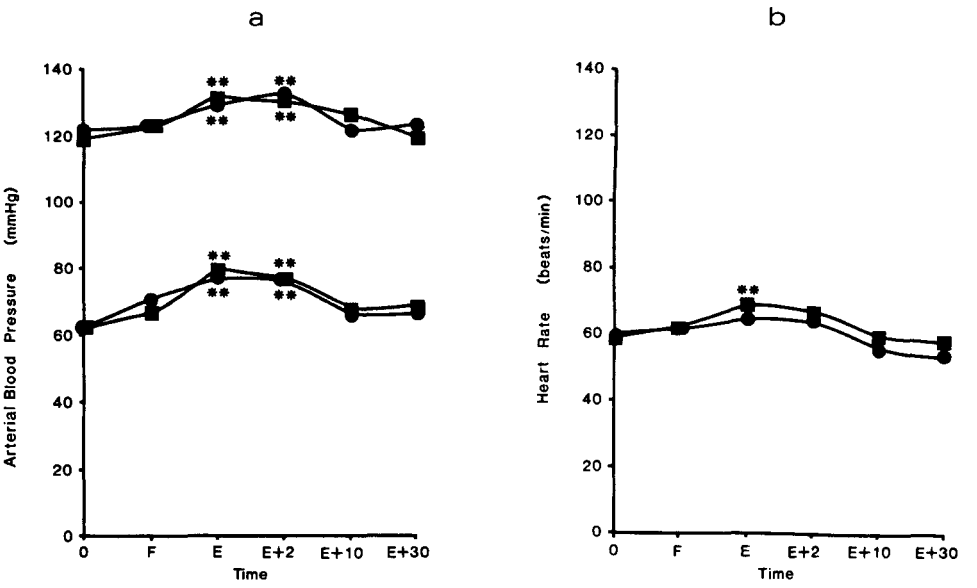

Figure 2. **a)** Mean systolic and diastolic arterial pressures, and **b)** mean heart rates before, during, and after the infusion of ropivacaine and bupivacaine. 0 = control values, F = first symptoms, E = end of infusion, E + 2, E + 10, and E + 30 = 2, 10, and 30 min after end of infusion. **Indicates statistically significant difference, $P < 0.01$, compared with control value. ● = ropivacaine, ■ = bupivacaine.

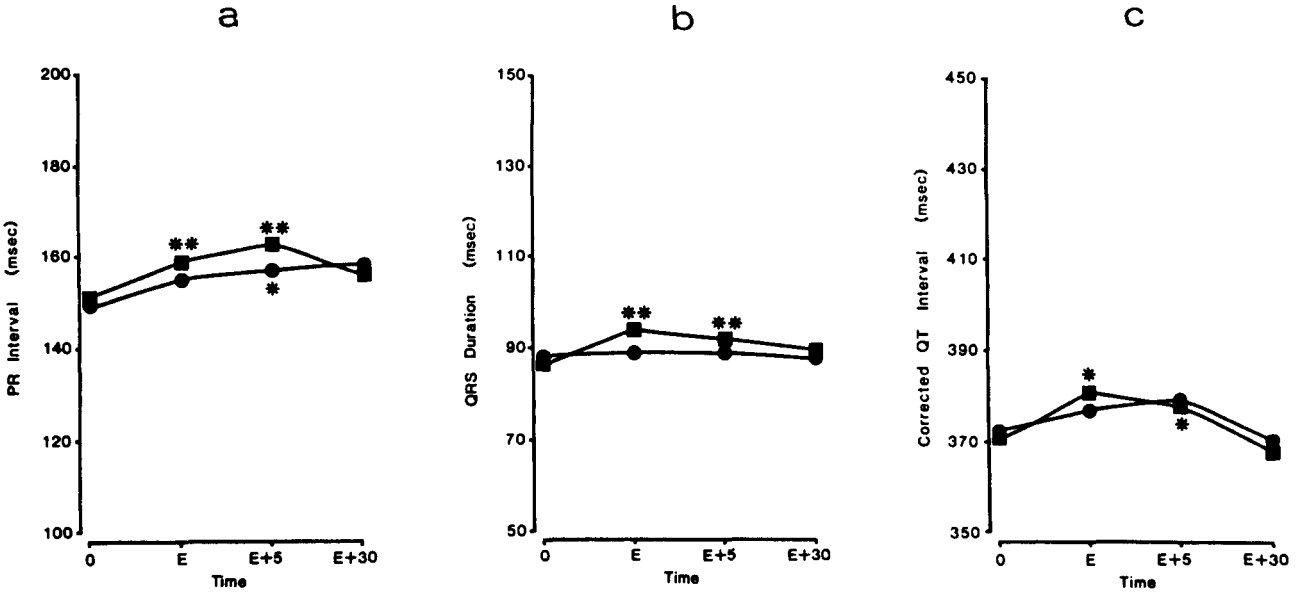

Figure 3. **a)** Mean PR intervals, **b)** mean QRS duration, and **c)** mean QT intervals (corrected for heart rate) before, during, and after infusion of ropivacaine or bupivacaine. 0 = control values, F = first symptoms, E = end of infusion, E + 2, E + 10, and E + 30 = 2, 10, and 30 min after end of infusion. **Indicates statistically significant ($P < 0.01$) change from control; *indicates $P < 0.05$. The drugs only differed significantly, $P < 0.05$, in regard to QRS duration at E + 5. ● = ropivacaine, ■ = bupivacaine.

pharmacodynamic effect of amide local anesthetic drugs.

The interpretive ECG used in this study greatly assisted the analysis of changes in cardiac conduction and was able to detect small but real increases in PR interval, QRS duration, and QT interval corrected for heart rate. Local anesthetic drugs are known to cause changes in both conductivity and contractility of the myocardium (13), although clinical evidence of the latter is usually only apparent with very high plasma concentrations, considerably greater than those which cause convulsions. A major cause of death with bupivacaine appears to be ventricular fibrillation (14,15). The present study has shown that effects on both conductivity and contractility can be detected at much lower plasma concentrations when more sensitive methods are used. Echocardiography is especially useful as it is noninvasive. Although M-mode echocardiography has been largely replaced by two-dimensional machines in the diagnostic field, it is an

Table 3. Cardiovascular Variables (mean ± SD) and Mean Plasma Concentrations in Eight Subjects Undergoing Echocardiography Before and at the End of IV Infusion

	Ropivacaine			Bupivacaine			Ropivacaine vs. bupivacaine (*P*)
	Control	End of infusion	Control vs. end infusion (*P*)	Control	End of infusion	Control vs. end infusion (*P*)	
EDD (cm)	5.2 ± 0.4	5.1 ± 0.4	NS	5.1 ± 0.2	5.0 ± 0.4	NS	NS
ESD (cm)	3.4 ± 0.2	3.7 ± 0.4	0.05	3.2 ± 0.2	3.5 ± 0.5	NS	NS
SV (mL)	80.8 ± 19.5	68.9 ± 14.8	0.05	80.8 ± 13.6	67.4 ± 19.2	0.05	NS
SF (%)	34.4 ± 4.4	28.7 ± 5.8	0.05	36.5 ± 4.5	29.7 ± 8.3	0.05	NS
EF (%)	62.9 ± 6.0	54.6 ± 8.5	0.05	65.8 ± 5.9	55.7 ± 12.6	0.05	NS
HR (beats/min)	52.8 ± 7.2	63.1 ± 10.0	0.05	54.8 ± 10.3	60.4 ± 10.3	0.05	NS
CO (L/min)	4.3 ± 1.1	4.4 ± 1.1	NS	4.4 ± 0.7	4.0 ± 1.0	NS	NS
SAP (mm Hg)	121.9 ± 16.0	128.9 ± 14.0	0.05	118.0 ± 8.5	127.1 ± 8.5	0.05	NS
DAP (mm Hg)	65.1 ± 9.9	78.7 ± 8.7	0.05	60.6 ± 6.6	78.9 ± 10.1	0.05	NS
Plasma concentration (μg/mL)	—	1.70 ± 0.54	—	—	1.22 ± 0.42	—	0.05

CO = cardiac output; DAP = diastolic arterial pressure; EDD = end-diastolic diameter; EF = ejection fraction; ESD = end-systolic diameter; HR = heart rate; NS, not significant; SAP = systolic arterial pressure; SF = shortening fraction; SV = stroke volume.

accurate method for determining the dynamic changes in a normal heart (7,16,17). EF and SV were reduced though the increase in heart rate kept the cardiac output unchanged. All the variables that showed significant changes nevertheless remained within normal limits.

Such changes as did occur were associated with lower plasma concentrations of bupivacaine than was the case with ropivacaine. At the time of stopping the infusions, the venous plasma concentration of bupivacaine was 38% less than that of ropivacaine. Changes in the echocardiograph similar to those seen in the present study have been described with disopyramide, but not with lidocaine at a plasma concentration of 4 μg/mL (18). Obvious clinical signs of CVS changes due to local anesthetic drugs occur at plasma concentrations considerably greater than those which cause CNS symptoms and signs. However, it is now possible to detect CVS changes before clinical signs develop. We believe this work is the first study in humans to show changes in both conductivity and contractility of the myocardium at plasma concentrations of local anesthetic that only cause minor symptoms of CNS toxicity.

Ropivacaine is a less toxic drug than bupivacaine in regard to the production of mild CNS and CVS toxicity by intravenous infusion. Whether ropivacaine has a greater therapeutic ratio than that of bupivacaine can only be determined by clinical trials designed to elucidate the relative local anesthetic potency of the two drugs. Although there are published data (19) on relative potency in the rat and the dog, animal studies should only be accepted as rough guides to the situation in humans. For example, Feldman and Covino (19) found considerable species difference between the rat and the dog and were only able to assess motor blockade. The significance of the difference in systemic toxicity shown in the present study cannot be assessed until reliable clinical data are available.

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