

Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers†

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Summary

We have compared the incidence of CNS symptoms and changes in echocardiography and electrophysiology during i.v. infusions of ropivacaine, bupivacaine and placebo. Acute tolerance of i.v. infusion of 10 mg min⁻¹ was studied in a crossover, randomized, double-blind study in 12 volunteers previously acquainted with the CNS effects of lignocaine. The maximum tolerated dose for CNS symptoms was higher after ropivacaine in nine of 12 subjects and higher after bupivacaine in three subjects. The 95% confidence limits for the difference in mean dose between ropivacaine and bupivacaine were -30 and 7 mg. The maximum tolerated unbound arterial plasma concentration was twice as high after ropivacaine ($P < 0.001$). Muscular twitching occurred more frequently after bupivacaine ($P < 0.05$). The time to disappearance of all symptoms was shorter after ropivacaine ($P < 0.05$). A threshold for CNS toxicity was apparent at a mean free plasma concentration of approximately 0.6 mg litre⁻¹ for ropivacaine and 0.3 mg litre⁻¹ for bupivacaine. Bupivacaine increased QRS width during sinus rhythm compared with placebo ($P < 0.001$) and ropivacaine ($P < 0.01$). Bupivacaine reduced both left ventricular systolic and diastolic function compared with placebo ($P < 0.05$ and $P < 0.01$, respectively), while ropivacaine reduced only systolic function ($P < 0.01$). (*Br. J. Anaesth.* 1997; 78: 507–514).

Key words

Anaesthetics local, ropivacaine. Anaesthetics local, bupivacaine. Cardiovascular system, effects. Central nervous system, effects. Pharmacodynamics.

The acute and most serious adverse effects of local anaesthetics involve the cardiovascular and central nervous (CNS) systems. They are usually because of accidental intravascular or intrathecal injections, or a pronounced overdose. CNS symptoms of local anaesthetic toxicity occur before cardiovascular symptoms and signs, and include numbness of the tongue, light-headedness, visual disturbances and muscular twitching; more serious signs include convulsions, coma, respiratory arrest and cardiovascular depression. Death, probably after intravascular administration of bupivacaine and etidocaine,¹

prompted studies on the mechanism of the cardio-toxic effects of local anaesthetics and search for drugs with less cardiotoxicity.²

Ropivacaine is a new, long-acting local anaesthetic, related structurally to bupivacaine and mepivacaine, used as the hydrochloride of the S-enantiomer, whereas bupivacaine and mepivacaine are racemic mixtures. It is less lipid soluble than bupivacaine,³ but its pharmacokinetic disposition is similar.⁴ In preclinical studies, ropivacaine showed less CNS and cardiac toxicity than bupivacaine.⁵ Studies in volunteers and patients suggest that ropivacaine is similar to bupivacaine in onset, duration and extent of sensory block, although motor block is less intense and of shorter duration.^{6–9}

The objective of this study was to determine if ropivacaine is tolerated better than bupivacaine when given as an i.v. infusion to volunteers, and also to evaluate the pharmacodynamic effects in relation to arterial and venous plasma concentrations.

Subjects and methods

We studied 12 healthy male subjects (table 1) who were assessed by physical examination, echocardiography, chest radiography and routine blood tests. No subject was receiving any medication or had a history of allergic reaction to local anaesthetics of the amide type.

The study was approved by the Ethics Committee of the Sahlgrenska University Hospital and written informed consent was obtained.

DRUG ADMINISTRATION

Drugs were administered according to a randomized (Latin squares), double-blind, crossover design to compare ropivacaine and bupivacaine with placebo; four subjects were allocated randomly to each of the

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†Presented in part at the XIV Annual European Society of Regional Anaesthesia Congress, Prague, Czech Republic, September 3–16, 1995.

three treatments. Before the study, all subjects were familiarized with the initial CNS effects of i.v. lignocaine (Xylocard 100 mg 5 ml⁻¹, Astra Hässle AB, Mölndal, Sweden, batch RB531) at a rate of 100 mg min⁻¹. Ten subjects received the full 200-mg dose and two subjects 180 mg. CNS symptoms appeared in all subjects and disappeared within 5–20 min. Lignocaine infusion was given between 3 and 111 (mean 34) days before the first blind infusion.

Before each blind infusion, subjects fasted for at least 6 h. Two i.v. cannulae were inserted into antecubital veins, one in each arm, and an arterial cannula in the left radial artery. Allen's test was performed before arterial cannulation to ensure normal collateral circulation through the ulnar artery. On six occasions, subcutaneous injection of 1% lignocaine 1 ml was given 30 min to 2 h before administration of the study drug to anaesthetize the skin before insertion of the arterial cannula. Subcutaneous injection of 1% mepivacaine 1 ml was given once because of painful insertion of the catheter. A transoesophageal atrial stimulation (TAS) electrode (Medtronic 6992) was introduced, after which the subjects rested for 30 min.

Each subject received ropivacaine 5 mg ml⁻¹ (Astra Pain Control, Sweden, batch 471-24-1), bupivacaine 5 mg ml⁻¹ (Astra Pain Control, Sweden, batch 417-46-1) and placebo (sodium chloride 9 mg ml⁻¹; Astra Pain Control, Sweden, batch 400-62-1) by i.v. infusion (Imed 960 volumetric infusion pump, Imed Scandinavia, Sweden). Different arms were used for drug infusion and blood sampling. The infusion rate was 2 ml min⁻¹, corresponding to 10 mg min⁻¹ of active drug.

Subjects were observed continuously by the attendant anaesthetist and were asked frequently open questions to describe any symptoms during and after infusion until complete disappearance of all symptoms. The infusion was discontinued at definite signs and symptoms of CNS effects or at the request of the subject. Otherwise, a maximum dose of 250 mg was given. In practice, no infusion was discontinued at the request of the subject. The subjects were recumbent during and for up to 2 h after infusion. The mean number of days between blind infusions was 50 (range 3–179).

ASSESSMENT OF CARDIOVASCULAR EFFECTS

A 12-lead ECG was recorded every 2–3 min from 5 min before and until 5 min after the infusion was stopped, and then 10 min after the end and 2 h after the start of the infusion. PQ interval, QRS width and QT intervals from the Q wave to the end of the T wave, QT_e, and to the top of the T wave, QT_t, were recorded and QT_c calculated. The electrocardiographic variables were measured as the mean of five consecutive values. The same variables were recorded during TAS, 5 min before and immediately after the infusion had been stopped and the echocardiogram had been recorded. Stimulation was applied at 100 or 120 beat min⁻¹, or both, in order to achieve comparable heart rates.

Doppler echocardiography was performed using an Acuson 128 XP computed sonograph equipped

with a 2.5-MHz transducer. All subjects were investigated in a slightly left lateral supine position. Echocardiograms were obtained 5 min before starting the infusion and then repeatedly every 3 min until the end of infusion. Echocardiograms after infusion were recorded 5 and 10 min after the end of infusion and 2 h after the start. Standard parasternal and apical views were stored on videotape. Cross-sectional M-mode recordings were made on chart paper at a speed of 50 mm s⁻¹ for off-line measurements of left ventricular (LV) end-diastolic and end-systolic dimensions. Ejection fraction (EF), stroke volume and cardiac output were calculated according to the formulae of Teichholz and colleagues.¹⁰ Colour Doppler was used for detection of valvular regurgitation at the mitral, aortic and tricuspid valves before and after infusion. Any regurgitation was denoted on a scale from 1 to 4, where 1 was small haemodynamically insignificant flow and 4, large acute regurgitation. Evaluation of regurgitant flows was made off-line by the echocardiographer blinded to the subjects. Pulsed-wave Doppler was used to record transmitral flow velocities from the apical four-chamber view, with the sample volume placed at the tips of the mitral leaflets. Doppler recordings were made on chart paper at a speed of 100 mm s⁻¹. The ratio of maximal flow velocities at atrial contraction (A) and early filling wave (E) was calculated as a variable of LV diastolic function. Transmitral flow deceleration time (MV dec), reflecting early diastolic properties of the left ventricle, was also measured. All echocardiographic and Doppler values represent the average of three consecutive cardiac cycles.

Intra-arterial systolic and diastolic arterial pressures were recorded before starting the infusion and every 1 min until the end, and also every 5 min until 30 min after the end of infusion.

Subjects were monitored for 4 h after infusion. A follow-up comprising physical examination and clinical laboratory tests was performed 2–3 weeks later.

BLOOD SAMPLING AND DRUG ASSAY

Samples of 5 ml of arterial and venous blood were obtained (Venoject) immediately before drug administration, and 2, 5, 10, 15, 20, 25, 30, 35 and 45 min, and 1 and 2 h after starting the infusions.

Plasma was separated within 1 h of collection, frozen immediately and stored at –20 °C. Total concentrations of ropivacaine and bupivacaine base were measured by gas chromatography.¹¹ The limit of quantification of the method was 0.008 mg litre⁻¹, interassay precision approximately 5% and recovery close to 100%. Free concentrations of ropivacaine and bupivacaine were assayed by coupled-column liquid chromatography after ultrafiltration of the plasma samples. Ropivacaine and bupivacaine were detected by UV at 210 nm and the limit of measurement was 0.003–0.008 mg litre⁻¹.¹² Intra-assay precision was 3–9% for the two drugs determined from spiked plasma samples.

STATISTICAL METHODS

A sample size of 12 subjects was determined to have a power of approximately 90% and a type I error of 5% based on a mean difference in tolerated i.v. dose of 26 mg and with an SD of 25 mg.¹³

The main analyses of treatment differences were based on a parametric model assuming Gaussian distributed errors. A general linear (ANOVA) model comprising effects for subject, period, direct treatment and (residual) error was used to describe the variation in dependent variables. Tests for equality between all three treatments were performed using *F* tests and pairwise treatment comparisons with the two-sided *t* test using $\alpha \leq 0.05$ in all tests. Data from all three treatment groups were used to estimate residual (error) variance. In addition to the tests, 95% confidence intervals for pairwise treatment differences were calculated.

Concentration data were collected only for bupivacaine and ropivacaine treatment periods.

The association between dose or drug concentration and physiological effects and tolerance was evaluated. Symptoms were grouped in different categories before breaking the code. Total and unbound drug plasma concentrations were estimated in arterial and venous blood. The probability of experiencing CNS symptoms with increasing concentrations was estimated in plots of arterial free plasma concentration at the start of symptoms compared with the cumulative number of subjects with symptoms. The actual plasma concentration at the onset of symptoms was interpolated linearly between two adjacent points if no value was available at the time of measurement. The analysis was based on symptoms grouped in the following categories: hearing and/or visual disturbances, perioral numbness, tingling, paraesthesia and/or paralysis, muscular twitching and/or muscular rigidity, and dysarthria. The accumulated frequencies of various symptoms were classified into categories.

Data are reported as mean (SD).

Results

MAXIMUM TOLERATED DOSES

Nine of 12 subjects tolerated a higher and three a lower dose of ropivacaine compared with bupivacaine. All subjects tolerated the full placebo dose (table 1). The mean dose of ropivacaine (115 mg) was higher than that of bupivacaine (103 mg) (ns). The estimated 95% confidence limits for the difference in means between ropivacaine and bupivacaine were -30 and 7 mg.

MAXIMUM TOLERATED PLASMA CONCENTRATIONS

Unbound arterial plasma concentrations at the end of infusion, that is at the maximum tolerated dose, were consistently higher in all subjects after ropivacaine (table 1), and individual concentration ratios of ropivacaine to bupivacaine ranged from 1.2 to 4.7. Mean arterial unbound plasma concentrations were approximately twice as high after ropivacaine than after bupivacaine ($P < 0.001$). Total and unbound venous and total arterial plasma concentrations were similar after both drugs (table 2). Total and unbound arterial plasma concentrations were consistently higher than corresponding venous concentrations with both drugs during and up to 20 min after the end of infusion.

CNS SYMPTOMS

Symptoms of CNS toxicity occurred in all subjects during administration of active drug. The first symptom appeared after 2-8 min of infusion of both drugs. The most common symptoms were visual and hearing disturbances, dysarthria, tingling, perioral numbness, dizziness, paraesthesia, light-headedness, muscular twitching and muscular rigidity (fig. 1). More subjects reported muscular twitching after bupivacaine ($P < 0.05$). After placebo, one subject

Table 1 Subject characteristics, maximum tolerated doses and free arterial plasma concentrations of ropivacaine (Rop.) and bupivacaine (Bup.) at the end of i.v. infusion of 10 mg min⁻¹. Crossover study in 12 volunteers.
*Sodium chloride 9 mg ml⁻¹

Subject No.	Age (yr)	Weight (kg)	Height (cm)	Dose			Unbound arterial concn	
				Rop. (mg)	Bup. (mg)	Placebo (ml)*	Rop. (mg litre ⁻¹)	Bup. (mg litre ⁻¹)
1	23	83	194	90	70	50	0.57	0.26
2	28	85	191	90	125	50	0.62	0.42
3	33	91	182	120	90	50	0.34	0.13
4	29	85	185	110	95	50	0.57	0.35
5	27	90	184	130	165	50	0.59	0.51
6	29	82	186	160	120	50	0.50	0.30
7	29	75	177	150	135	50	0.62	0.44
8	28	82	184	85	70	50	0.49	0.24
9	29	81	183	150	85	50	0.69	0.34
10	28	90	190	70	100	50	0.41	0.21
11	27	81	187	120	100	50	0.42	0.28
12	28	74	176	105	85	50	0.85	0.18
Mean	28	83	185	115	103	50	0.56	0.30
SD	2.2	5.4	5.3	29	30		0.14	0.11
Min.	23	74	176	85	70		0.34	0.13
Max.	33	91	194	160	165		0.85	0.51

Table 2 Maximum tolerated plasma concentrations of ropivacaine and bupivacaine at the end of i.v. infusion of 10 mg min⁻¹ (mean SD) (min.–max.) Crossover study in 12 volunteers. ****P* < 0.001 (ropivacaine vs bupivacaine)

Sampling/drug	Plasma concentration (mg litre ⁻¹)	
	Total	Unbound
Arterial		
Ropivacaine	4.3 (0.6) (3.4–5.3)	0.56 (0.14)*** (0.34–0.85)
Bupivacaine	4.0 (1.4) (1.1–6.2)	0.30 (0.11) (0.13–0.51)
Venous		
Ropivacaine	2.2 (0.8) (0.5–3.2)	0.15 (0.08) (0.01–0.24)
Bupivacaine	2.1 (1.2) (0.8–4.5)	0.11 (0.10) (0.01–0.38)

reported tremor in the chin and another paraesthesia in the arms and numbness in the thumb, but the infusion was not interrupted.

Objective signs, for example muscular rigidity, muscular twitching and dysarthria, were frequent end-points for stopping the infusion, and one or more of these signs or other symptoms were observed in 10 subjects after ropivacaine and in all subjects after bupivacaine. The time from the end of infusion to disappearance of all symptoms was shorter after ropivacaine (13 (11) min) than after bupivacaine (20 (16) min) (*P* < 0.05).

Ropivacaine dose–response and concentration–

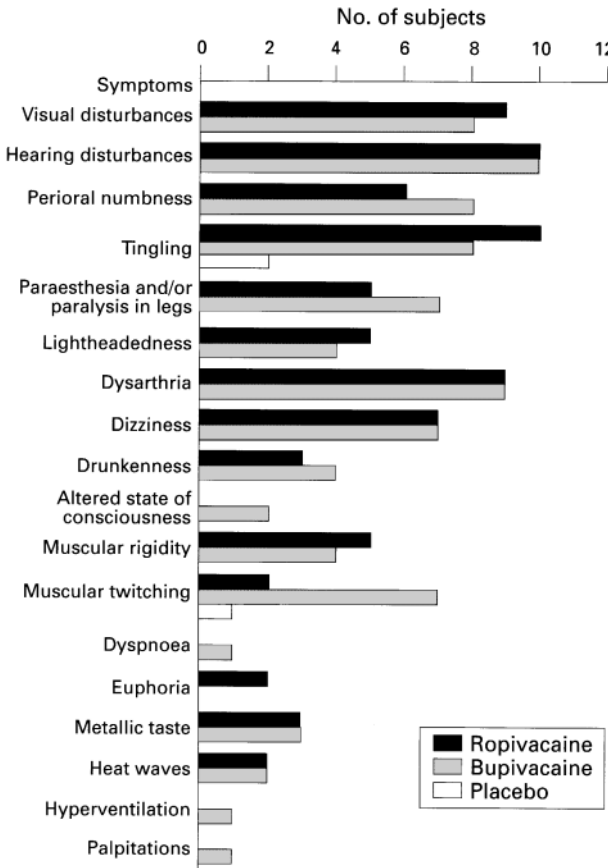


Figure 1 Number of subjects with symptoms, grouped in different categories, during and after i.v. infusion of ropivacaine and bupivacaine 10 mg min⁻¹ and placebo (saline). Crossover study in 12 volunteers.

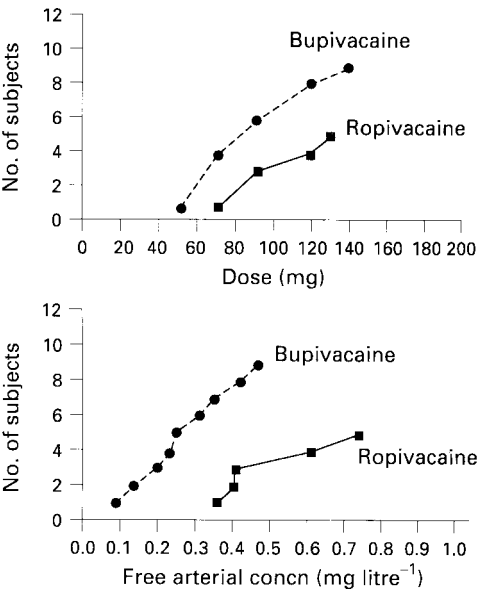


Figure 2 Cumulative number of subjects with muscular twitching or rigidity, or both, against dose (top) or unbound arterial plasma concentration (bottom) at onset of i.v. infusion of ropivacaine and bupivacaine 10 mg min⁻¹. Crossover study in 12 volunteers.

response curves for CNS symptoms were shifted consistently to the right compared with those of bupivacaine. This shift meant that symptoms of CNS toxicity appeared earlier and in more subjects at a certain dose or plasma concentration when bupivacaine was given. This difference between drugs was more pronounced for muscular twitching and muscular rigidity (fig. 2) than for dysarthria.

ARTERIAL PRESSURE AND HEART RATE

Both drugs increased systolic arterial pressure compared with placebo (table 3) (*P* < 0.001). The mean increase in systolic pressure was 7% after ropivacaine and 9% after bupivacaine.

Bupivacaine was associated with an increase in diastolic arterial pressure in all subjects (*P* < 0.001 vs placebo), whereas diastolic pressure increased in 10 of 12 subjects given ropivacaine. The mean increase was larger (26%) after bupivacaine than that after ropivacaine (13%) (*P* < 0.05 vs placebo). There was a 12% increase in heart rate after both ropivacaine and bupivacaine (*P* < 0.01 and *P* < 0.001 vs placebo).

ELECTROCARDIOGRAPHY

Bupivacaine increased QRS width in nine of 12 subjects at the end of infusion (fig. 3). The increase (6%) was significant relative to that for ropivacaine (three of 9 subjects (2.4%)) (*P* < 0.05) and placebo (–0.4%) (*P* < 0.05). During TAS at 120 beat min⁻¹, both ropivacaine (8.5%) and bupivacaine (9%) showed a significant increase in QRS width compared with placebo (*P* < 0.05). PQ interval and QTc did not change.

QTt decreased in eight of nine subjects given ropivacaine and in 10 of 12 subjects given bupivacaine, with mean decreases of –5.7% and –5.3%. QTc decreased in all nine subjects given ropivacaine and

Table 3 Haemodynamic, echocardiographic and electrocardiographic changes (mean (SD)) at maximum tolerated doses after i.v. infusion of ropivacaine and bupivacaine 10 mg min⁻¹ and placebo (saline). Crossover study in 12 volunteers. *Heart rate was measured from the ECG on the M-mode recordings. Statistically significant differences are given in the text

Variable	Ropivacaine		Bupivacaine		Placebo	
	Baseline	End of infusion	Baseline	End of infusion	Baseline	End of infusion
HR (beat min ⁻¹)	(n=12) 60 (9)	(n=12) 68 (7)	(n=12) 60 (10)	(n=12) 68 (10)	(n=12) 62 (15)	(n=12) 58 (10)
SAP (mm Hg)	143 (13)	152 (16)	141 (14)	154 (17)	138 (14)	134 (11)
DAP (mm Hg)	72 (8)	81 (10)	69 (5)	87 (12)	66 (8)	68 (7)
Echocardiography)	(n=12)	(n=12)	(n=12)	(n=12)	(n=12)	(n=12)
LVID _d (cm)	5.4 (0.2)	5.5 (0.5)	5.4 (0.3)	5.4 (0.3)	5.4 (0.3)	5.4 (0.3)
LVID _s (cm)	3.7 (0.3)	4.0 (0.4)	3.6 (0.3)	4.0 (0.3)	3.8 (0.3)	3.7 (0.3)
EF (%)	59 (6)	52 (8)	60 (7)	52 (6)	56 (7)	59 (5)
MV dec (ms)	166 (13)	157 (20)	165 (34)	152 (27)	168 (21)	176 (27)
A/E	0.60 (0.12)	0.64 (0.13)	0.60 (0.14)	0.66 (0.13)	0.54 (0.13)	0.56 (0.13)
SV (ml)	85 (11)	78 (21)	84 (16)	74 (14)	77 (11)	83 (10)
CO (litre min ⁻¹)	5.4 (1.1)	5.3 (1.6)	5.2 (1.2)	5.4 (1.7)	4.8 (1.3)	4.8 (0.7)
HR (beat min ⁻¹)*	64 (8)	67 (9)	63 (12)	73 (16)	62 (13)	59 (9)
Electrocardiography)	(n=9)	(n=10)	(n=12)	(n=12)	(n=12)	(n=12)
QRS (ms)	94 (7)	98 (7)	94 (6)	99 (8)	94 (7)	93 (7)
PQ (ms)	169 (23)	180 (21)	171 (13)	179 (18)	173 (17)	175 (21)
QTc (ms)	397 (23)	408 (28)	394 (20)	406 (19)	397 (25)	397 (22)
QTc (ms)	404 (23)	392 (21)	400 (26)	390 (22)	401 (25)	403 (24)
QTt (ms)	303 (16)	287 (18)	299 (19)	283 (21)	298 (20)	305 (20)
QTc-QTt (ms)	101 (13)	105 (15)	101 (13)	107 (19)	103 (7)	99 (10)

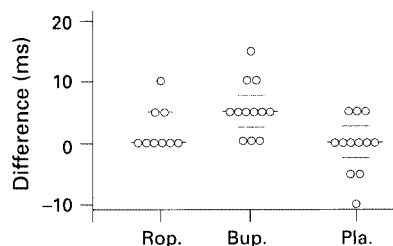


Figure 3 Individual (median, 25% and 75% quartiles) differences in QRS width during sinus rhythm between the value at the end of infusion and baseline and at the maximum tolerated dose after i.v. infusion of ropivacaine (Rop.) and bupivacaine (Bup.) 10 mg min⁻¹ and placebo (Pla.) (saline). Crossover study in 12 volunteers.

in nine of 12 subjects after bupivacaine. Mean decreases were -3.3% and -2.5%.

On assessing the last portion of the T-wave, the (QTc-QTt) was found to have increased in four of nine subjects after ropivacaine, four of 12 subjects after bupivacaine, and in one of 12 subjects after placebo, with mean increases of 3.8% and 5.8% and a mean decrease of -3.7%, respectively. Cardiac arrhythmias were not detected.

ECHOCARDIOGRAPHY

Diastolic function

There was a shorter transmitral flow deceleration time in six of 12 subjects when bupivacaine was administered (-8.1%, *P* < 0.05 *vs* placebo) compared with -5.5% after ropivacaine (fig. 4). The A/E ratio increased by a mean of 6.2% for ropivacaine and 9.3% for bupivacaine (ns).

Systolic function

Left ventricular ejection fraction decreased in nine of 12 subjects after ropivacaine and in 11 of 12 subjects

after bupivacaine. The mean changes in ejection fraction were -11.6% compared with -13.8% (*P* < 0.01 *vs* placebo for both drugs) (fig. 4). Stroke volume decreased an average of -8.1% after ropivacaine and -12.1% after bupivacaine (*P* < 0.05 *vs* placebo).

Cardiac output decreased in eight of 12 subjects given ropivacaine (-2.5%) and in five of 12 subjects given bupivacaine (-3.7%). One subject had a large

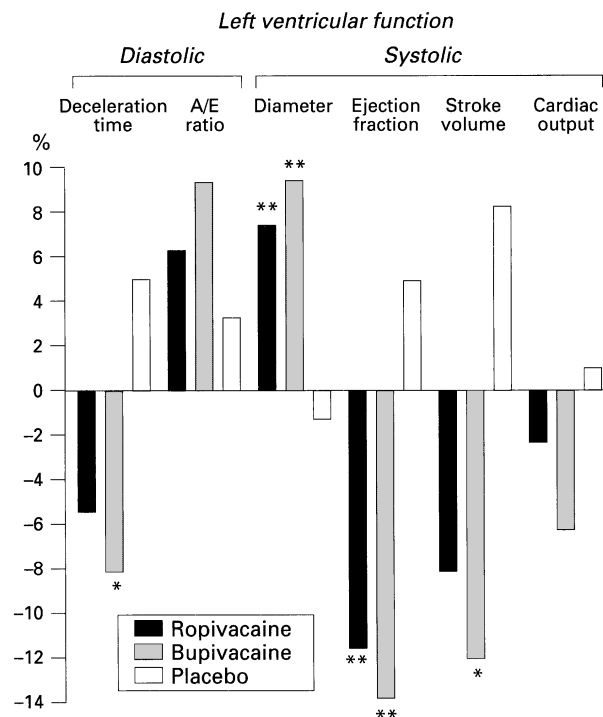


Figure 4 Mean percentage differences in echocardiographic variables between the value at the end of infusion and baseline and at the maximum tolerated dose after i.v. infusion of ropivacaine and bupivacaine 10 mg min⁻¹ and placebo (saline). Crossover study in 12 volunteers.

increase in cardiac output, however, when given bupivacaine (169%), in relation to a transient increase in heart rate from 51 to 110 beat min^{-1} . When this subject was excluded from analysis, the mean change in the bupivacaine group was -6.4% .

No subject showed signs of pathological valvular regurgitation according to colour Doppler findings before or after infusion.

ADVERSE EFFECTS

Transient pain and tenderness at the arterial cannulation site were reported by one subject during one blind infusion. No other adverse events occurred.

Discussion

Tolerance of local anaesthetics has been assessed in volunteers given continuous i.v. infusions.¹³⁻¹⁸ In general, the threshold decreases with increase in the infusion rate¹⁶ because the maximum plasma concentration is directly proportional to the dose and inversely proportional to cardiac output and infusion time.¹⁸ In our study, the infusion rate of 10 mg min^{-1} was a rational compromise between the maximum dose allowed and the time within which the short-lasting effects could be recorded.

In all subjects receiving an active drug, the infusion was stopped because of CNS symptoms before any arrhythmia or other clinically significant changes in haemodynamic state or electrocardiography occurred. However, the results showed statistically significant changes in both cardiac conduction and contractility. These data, supported by preclinical studies showing that ropivacaine is less CNS and cardiotoxic than bupivacaine,⁵ suggest that the potential of ropivacaine to produce CNS and cardiotoxicity is also less in humans. The general pattern of increasing CNS symptoms and signs and their order was similar to that reported previously with other local anaesthetics.¹⁸

Ropivacaine and bupivacaine produced a similar spectrum of symptoms involving the CNS, but the duration of symptoms was shorter after ropivacaine. Occasionally, early CNS symptoms made subjects temporarily unable to communicate their sensations reliably. Signs of excitatory CNS effects such as dysarthria, shivering, muscular twitching and muscular rigidity were frequent end-points for drug administration. Thus although the decision when to discontinue the infusion of necessity contains a subjective element, the decision to stop the infusion in this study could in all but two cases be based on objective criteria that were observed easily by the attending physician. This was probably made feasible by allowing higher maximum doses in this compared with the previous study¹³ where the infusion was stopped after 150 mg regardless of symptoms. In our study nine of the 12 subjects tolerated a higher dose of ropivacaine than bupivacaine, which is comparable with corresponding results in 10 of 12 subjects in the study of Scott and colleagues.¹³ The sequences of drug administration as a result of randomization in the three subjects who tolerated a higher dose of bupivacaine did not differ from

sequences in subjects who tolerated a higher dose of ropivacaine. Moreover, all subjects tolerated higher unbound plasma concentrations of ropivacaine than bupivacaine, which also renders unlikely any effect caused by the sequence of drug administration.

Differences between ropivacaine and bupivacaine were identified in terms of tolerated doses, maximum tolerated free plasma concentrations and time to disappearance of symptoms. The consistent shift to the right of the ropivacaine dose-response and concentration-response curves for CNS symptoms implied that higher doses and free plasma concentrations of ropivacaine were tolerated before symptoms were elicited.

Arterial blood carries local anaesthetic to various parts of the body after systemic administration, while peripheral venous blood returning from poorly perfused sampling tissues during rapid i.v. administration is not representative of the distribution to, and concentration at, the site of action for central effects of local anaesthetics.^{19,20} This is in agreement with the large arteriovenous concentration differences seen in our study. It is the free or unbound drug that is available for distribution, crossing biological membranes and binding to receptor sites where pharmacological effects are initiated. The toxic concentration, as estimated from peripheral venous free plasma concentrations after slower systemic drug input (without a marked arteriovenous concentration difference), would therefore be similar to free arterial plasma concentrations of ropivacaine and bupivacaine related to CNS symptoms in this study with a rapid drug input. A threshold for CNS toxicity was apparent at mean free arterial plasma concentrations of the order of 0.6 mg litre^{-1} for ropivacaine and 0.3 mg litre^{-1} for bupivacaine. A similar threshold for free venous plasma concentration has been reported to be 0.24 mg litre^{-1} after a slower continuous perineural infusion of bupivacaine.²¹ In a previous study,¹³ CNS and cardiovascular symptoms were associated with higher peripheral venous plasma concentrations of ropivacaine than bupivacaine although, as indicated by the authors, the use of arterial samples would have been more informative.

Cardiovascular effects were more pronounced after bupivacaine than after ropivacaine at maximum tolerated doses. Although there were statistically significant changes, they were generally small and unremarkable. A similar distinction between ropivacaine and bupivacaine in the dose-response in QRS width has been reported in anaesthetized pigs.²² The difference in systemic toxicity between ropivacaine and bupivacaine is likely to be clinically important.

In general, the cardiovascular system is more resistant to the effects of local anaesthetics than the CNS.²³ Extremely high concentrations depress spontaneous pacemaker activity in the sinus node and result in sinus bradycardia and sinus arrest. Similar depression at the AV node results in prolonged PQ/PR intervals and partial or complete AV dissociation. Local anaesthetics such as ropivacaine and bupivacaine inhibit rapid inward flow of sodium ions into cardiac cells during depolarization, thereby

slowing the rate of rise of the action potential during phase 0.^{24–26} Recovery from sodium channel block is faster after treatment with ropivacaine than after bupivacaine,²⁷ which is probably an important factor in the increased cardiotoxicity of bupivacaine. Impaired depolarization decreases cardiac contractility and increases QRS width. An increase in QRS width has been correlated with cardiotoxicity of local anaesthetics,²³ and also with quinidine and tricyclic antidepressant agents.

In this study, there was an increase in QRS width that was significantly smaller after ropivacaine than after bupivacaine; this is similar to previous findings.¹³ However, our study is unique by inclusion of a placebo group, and the effect on QRS was similar after ropivacaine and placebo. The development of CNS symptoms prompted discontinuation of the infusion, which prevented an unwanted further increase in QRS width. Both QT_t and the QT_e intervals decreased, but not to the same degree, so that the index (QT_e-QT_t) increased. This change, representing a shortening of the final portion of the depolarization time, is in accord with a class IB (lignocaine-like) antiarrhythmic mode of action.

When bupivacaine was administered, both systolic and diastolic LV functions were reduced significantly compared with placebo. When using ropivacaine, only significant changes in systolic variables were noted. Ropivacaine also tended to have a shorter restoration period, although this was not tested. The significant reduction in LV ejection fraction compared with placebo was caused by an increase in LV systolic diameter, which might imply reduced myocardial contractility. In young individuals with borderline hypertension, it has been shown that such a small increase in systolic arterial pressure is associated with supranormal LV systolic function.²⁸ The increase in afterload during infusion of both drugs would not be an explanation of the observed changes in LV systolic function in this group of young, healthy individuals.

In the placebo period after the total 25 min of the investigation, there was an increase in systolic function variables, ejection fraction and stroke volume, but a decrease in heart rate with maintained cardiac output. These findings represent the normal haemodynamic reaction to the resting situation, with fluid resorption into the circulation, which increases blood volume, and increased vagal tone causing a minor decrease in heart rate.

Using echocardiography, Scott and colleagues¹³ reported reduced LV systolic function after i.v. administration of ropivacaine and bupivacaine. Both drugs depressed cardiac contractility after intracoronary artery injection in anaesthetized pigs.²²

We also evaluated diastolic function. Changes in diastolic variables are influenced by several factors, such as heart rate, sympathetic tone and loading conditions. The techniques available for measuring diastolic function are limited in different ways. Using pulsed wave Doppler, we noted a difference between ropivacaine and bupivacaine in LV filling pattern compared with placebo. Our findings indicated changes towards a more restrictive filling pattern and reduced LV compliance with bupivacaine.

There were remarkably few placebo effects on the CNS and cardiovascular system.

Ropivacaine showed a higher tolerated dose and unbound plasma concentration based on the shift in dose–response and concentration–response curves for CNS symptoms. At doses producing CNS symptoms, cardiovascular changes, such as depression of conduction and diastolic function, were less pronounced with ropivacaine compared with bupivacaine.

Acknowledgements

We are grateful to Karin Bohlin, RN, Anita Ivarsson, RN and Carina Olausson, RN, for technical assistance, and to Torbjörn Arvidsson, PharmD and Jan Henriksson, PhD, Astra Pain Control AB, for their bioanalytical work and statistical analyses. This study was supported by a grant from Astra Pain Control AB, Södertälje, Sweden.

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