Plasma concentrations of ropivacaine given with or without epinephrine for brachial plexus block

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The purpose of this study was to determine the pharmacokinetic properties of the local anaesthetic ropivacaine used with or without epinephrine for brachial plexus block. Seventeen ASA physical status I or II adult patients undergoing elective orthopaedic surgery received a single injection of 33 ml ropivacaine for subclavian perivascular block and 5 ml to block the intercostobrachial nerve in the axilla. One group (n = 8) received 0.5 per cent ropivacaine without epinephrine (190 mg) and the other (n = 9) received 0.5 per cent ropivacaine with epinephrine 1:200,000 (190 mg). Plasma ropivacaine concentrations were measured from peripheral venous blood samples taken for 12 hr after drug administration. Ropivacaine base was determined in plasma using gas chromatography and a nitrogen-sensitive detector. The mean peak plasma concentration (C_{max}) was 1.6 ± 0.6 mg · L^{-1} and 1.3 ± 0.4 mg · L^{-1} after administration of ropivacaine with and without epinephrine. The median time to peak plasma concentration (t_{max}) was 0.75 hr and 0.88 hr and the mean area under the plasma concentration curve $AUC_{0\text{-}12h}$ was 7.7 ± 3.6 and 7.0 ± 3.4 mg · l hr^{-1}. The differences were not statistically significant. The terminal phase of the individual plasma concentration-time curves showed a varying and sometimes slow decline possibly indicating a sustained systemic uptake of ropivacaine from the brachial plexus. No central nervous system or cardiovascular symptoms attributed to systemic plasma concentrations of the drug were observed, with the dose (1.90–3.28 mg · kg^{-1}) of ropivacaine used. It is concluded that the addition of epinephrine does not alter the pharmacokinetic properties of ropivacaine when used for subclavian perivascular brachial plexus block.

Le but de cet étude était de déterminer la pharmacocinétique de l'anesthésique local ropivacaine utilisé avec ou sans épinéphrine pour un bloc de plexus brachiale. Dix-sept patients adultes ASA 1 ou 2 devant subir des chirurgies orthopédiques électives ont reçu une injection unique de 33 ml de ropivacaine pour un bloc périvasculaire sous clavière 5 ml afin de bloquer le nerf intercostal brachial à l'aisselle. Un groupe (n = 8) a reçu 0.5 pour cent de ropivacaine sans épinéphrine (190 mg) et l'autre (n = 9) a reçu 0,5 pour cent de ropivacaine avec épinéphrine 1:200,000 (190 mg). Les concentrations plasmatiques de ropivacaine ont été mesurées à partir d'échantillons veineux périphériques 12 heures après l'administration de la drogue. La base de ropivacaine a été déterminée dans le plasma utilisant la chromotographie et un détecteur sensible à l'azote. Les concentrations plasmatiques moyennes les plus élevées (C_{max}) était de 1,6 ± 0,6 mg · L^{-1} et 1,3 ± 0,4 mg · L^{-1} après administration de ropivacaine avec ou sans épinéphrine. Le temps moyen pour atteindre la concentration plasmatique maximale (t_{max}) était de 0,75 heures et 0,88 heures vu la moyenne de la surface sous la courbe de concentration plasmatique $AUC_{0\text{-}12h}$ était de 7,7 ± 3,6 et 7,0 ± 3,4 mg · l hr^{-1-1}. Les différences n'étaient pas statistiquement significatives. La phase terminale des courbes des concentrations plasmatiques-temps ont démontré un déclin variable el des fois lent indiquant possiblement une rétention systémique soutenue ds ropivacaine à partir du plexus brachial. Aucun symptôme cardiovasculaire ou nerveux central attribué aux concentrations plasmatiques de la drogue furent observé avec des doses de (1,90–3,28 mg · kg^{-1}) de ropivacaine utilisée. On conclut que l'addition d'épinéphrine n'altère pas la pharmacocinétique de la ropivacaine lorsqu'utilisée pour un bloc de plexus brachial.

Key words
ANAESTHETICS, LOCAL: ropivacaine;
ANAESTHETIC TECHNIQUES: regional, brachial plexus;
PHARMACOKINETICS: ropivacaine.

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Ropivacaine is an amide-type local anaesthetic primarily intended for peripheral nerve blockade and epidural anaesthesia. It is used as the hydrochloride monohydrate of the (S)-enantiomer and has a pKa of 8.1. The uptake of ropivacaine into human subcutaneous and epidural fat *in vitro* is intermediate to that of bupivacaine and lidocaine.[1]

Ropivacaine has been reported to be less toxic than bupivacaine but more toxic than lidocaine.[2,3] After IV infusion of ropivacaine to volunteers, it was shown to be less toxic than bupivacaine in producing mild central nervous system and cardiovascular toxicity.[4] Total plasma and blood clearances of 0.50 ± 0.12 L · min^{-1} and 0.72 ± 0.16 L · min^{-1}, an apparent volume of distribution (Vss) of 42 ± 15 and a terminal disposition half-life of 1.9 ± 1.0 hr has been reported after IV infusion of ropivacaine to volunteers. Plasma protein binding is high, 94 per cent, and most of the binding is accounted for by association with α_1-acid glycoprotein.[5]

The main objective of this study was to assess the anaesthetic characteristics and pharmacokinetic properties of 0.5 per cent ropivacaine with or without epinephrine when used for brachial plexus anaesthesia in patients undergoing orthopaedic surgery. The clinical results of the study were reported separately[6] and this report provides information on the plasma concentrations of ropivacaine that were produced.

Methods

This was an open label, nonrandomized trial which was part of a two-centre trial conducted at the University of Texas Health Science Center at San Antonio and the University of Illinois College of Medicine at Chicago. It was approved by the local Institutional Review Boards. The 17 patients included in the pharmacokinetic analysis were from the University of Texas Health Science Center at San Antonio.

The patients were ASA physical status I or II and scheduled to undergo upper extremity surgery under brachial plexus anaesthesia. Excluded from participating in the study were patients with a history of allergy to local anaesthetics of the amide type, significant neurological, cardiopulmonary or psychiatric disease, acute liver or renal disease, drug or alcohol abuse, and women of child-bearing age. Written informed consent was obtained from the patients and premedication was given with morphine (0.15 mg · kg^{-1} IM) and midazolam (dose range of 0–3 mg IV). Each patient then received a subclavian perivascular block according to the technique described by Winnie.[7] After elicitation of a paraesthesia, one group of patients ($n = 8$) received 0.5 per cent ropivacaine without epinephrine and the other group ($n = 9$) received 0.5 per cent ropivacaine with epinephrine 1:200,000. Thirty-three ml of anaesthetic solution were used for the subclavian perivascular block and 5 ml were used to block the intercostobrachial nerve in the axilla, which resulted in a total ropivacaine dose of 190 mg.

Concomitant medications given during anaesthesia included midazolam (ten patients), fentanyl (five patients) and diphenhydramine (one patient), which were all given for sedation. Other medications included cefazolin which was used prophylatically for surgery in four patients and metaclopramide which was given to one patient because of nausea.

Peripheral venous blood samples for analysis of ropivacaine plasma concentrations were drawn from a 16-gauge catheter placed in the contralateral arm. The samples (5 ml) were drawn into heparinized tubes at 0, 5, 10, 15, 20, 25, 30, 45, 60 and 90 min and at 2, 3, 4, 6, 9 and 12 hr after the end of the ropivacaine injection. The plasma was separated by centrifugation and stored at −20° C until assay.

The assay of ropivacaine in plasma was performed according to Osterlof *et al.* (Astra Pain Control AB, Sweden, technique to be published). Ropivacaine was extracted together with the internal standard, pentycaine (1-pentyl-2′,6′-pipecoloxylidide) from alkalinized plasma with n-hexane + methylene chloride (4 + 1). The extract was evaporated to dryness and the residue dissolved in a small volume of n-hexane + ethanol (9 + 1). The content of ropivacaine was determined by gas chromatography, splitless injection, on a fused silica capillary column with crosslinked methyl silicone as stationary phase. Helium was used as a carrier gas with a nitrogen-sensitive detector. All concentrations are expressed as mg ropivacaine base per litre plasma. The limit of determination was 0.01 mg · L^{-1} and the inter-assay precision obtained with 0.30 to 1.79 mg · L^{-1} plasma was 7.9 to 6.7 per cent (coefficient of variation).

The peak plasma concentration of ropivacaine (C_{max}) and time to peak (t_{max}) were estimated from the observed concentration time points. The area under the plasma concentrations time curve (AUC) was calculated by the linear trapezoidal rule. The apparent first-order elimination rate constant and the corresponding half-life were calculated by conventional methods.[8]

The two ropivacaine groups were compared by use of a Wilcoxon rank sum test with $P < 0.05$ considered statistically significant.

Results

Patient characteristics are listed in Table 1. Patient #1 was replaced by patient #17 because of a broken ampule. Ropivacaine provided satisfactory analgesia in all patients but one, indicating a technically correct administration of ropivacaine. The block of patient #16 was inadequate for surgery and he was given a supplemental radial nerve

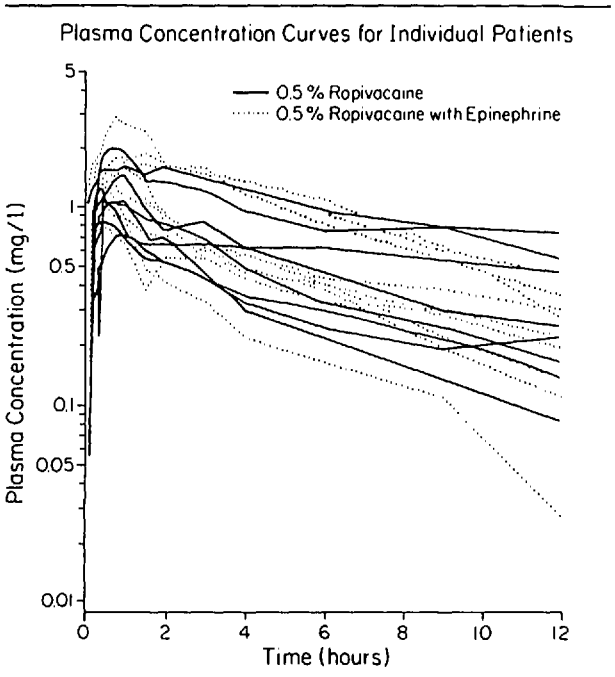

FIGURE 1 Plasma concentration of ropivacaine in individual patients after single administration of 33 ml 0.5 per cent ropivacaine (190 mg) without and with epinephrine (1:200,000) for brachial plexus block.

block with 1.0 per cent mepivacaine with epinephrine 1:200,000. The patient is included in the analysis of plasma concentrations.

The mean C_{max} was 1.6 mg·L^{-1} and 1.3 mg·L^{-1} following the block after 190 mg ropivacaine with and without epinephrine. The highest individual plasma concentration achieved was 2.9 mg·L^{-1} with and 2.0 mg·L^{-1} without epinephrine. Median t_{max} was 0.75 hr and 0.88 hr with similar ranges in both groups (Table II).

The individual plasma concentrations were within the same range regardless of whether ropivacaine was given with or without epinephrine (Figure 1). There was a tendency for higher plasma concentrations when ropivacaine was given with epinephrine (Table II, Figure 2) but the differences were not statistically significant (Table III).

In patient #6 the plasma concentration showed a very slow decline at 6 to 12 hr after injection. This precludes the estimation of a relevant terminal half-life during the observed time period in this patient. The slow decline of the plasma concentration (Figure 1) and, thus, long apparent half-lives of ropivacaine in patients #4, 5 and 12 (Table II) probably reflect a slow systemic absorption of ropivacaine in these patients.

None of the patients in either group developed any adverse reactions suggesting cardiovascular or central

TABLE I Patient characteristics

Patient	*Age*	*Sex*	*Body weight (kg)*	*Height (cm)*
With epinephrine				
2	37	M	84	171
3	40	M	60	173
4	41	F	77	153
5	40	M	99	175
6	36	F	70	150
7	54	M	58	182
8	24	M	86	167
17	37	M	100	185
Mean	38		71	170
SD	11		10	9
Without epinephrine				
9	29	M	63	168
10	23	M	68	173
11	35	M	73	180
12	43	M	95	180
13	43	M	73	163
14	40	M	75	170
15	56	F	66	152
16	25	M	62	170
18	44	M	62	170
Mean	39		79	170
SD	8		16	13

TABLE II Pharmacokinetic variables derived from plasma concentrations after 190 mg ropivacaine without or with epinephrine for brachial plexus anaesthesia

Patient	*Epinephrine*	C_{max} *(mg·L^{-1})*	t_{max} *(hr)*	AUC_{0-12h} *(mg·L^{-1}·hr^{-1})*	$t_{\frac{1}{2}}$ *(hr)*
2	–	1.98	0.75	12.64	7.4
3	–	1.07	1.0	3.96	4.3
4	–	0.71	1.0	7.04	13.8
5	–	0.85	0.5	3.95	13.5
6	–	1.62	1.0	11.57	—†
7	–	1.13	0.42	5.46	6.0
8	–	1.48	1.0	6.57	5.4
17	–	1.23	0.42	4.39	5.9
Mean		1.26	0.88*	6.95	8.0
SD		0.42		3.39	3.9
9	+	1.26	0.5	3.11	2.8
10	+	1.87	1.5	11.40	5.0
11	+	1.65	1.5	12.16	3.0
12	+	1.02	0.5	6.07	11.1
13	+	1.40	0.42	6.02	6.1
14	+	2.91	0.75	13.26	6.0
15	+	0.82	0.5	4.64	10.3
16	+	2.11	0.75	6.36	3.8
18	+	1.26	0.75	5.92	3.9
Mean		1.59	0.75*	7.66	5.8
SD		0.64		3.63	3.0

*Median.
†Apparent steady-state conc 6–12 hr after dosing.

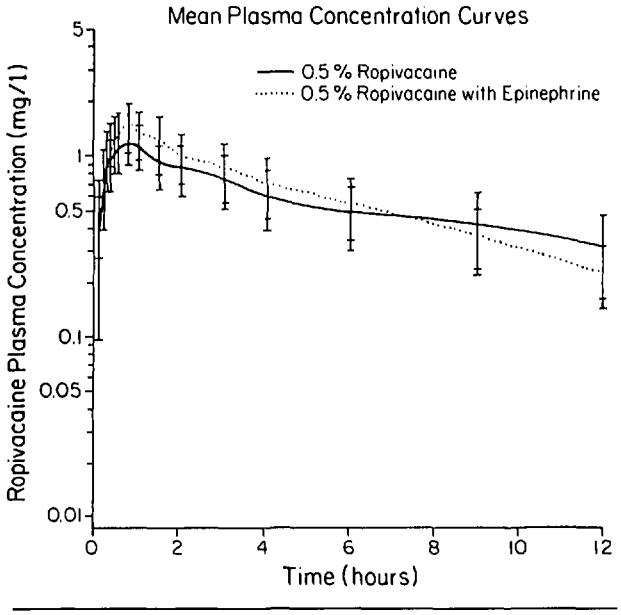

FIGURE 2 Mean (95 per cent confidence limits) plasma concentration of ropivacaine after single administration of 33 ml 0.5 per cent ropivacaine (190 mg) without or with epinephrine (1:200,000) for brachial plexus block.

nervous system (CNS) toxicity. The ropivacaine dose ranged from 1.90–3.28 $mg \cdot kg^{-1}$.

Discussion

Although previous studies have reported lower peak plasma concentrations of bupivacaine when epinephrine was added for brachial plexus block,[9–11] this was not seen in the present study of ropivacaine. Ropivacaine seems to increase vascular smooth muscle activity and decrease blood flow at the site of injection over a wider range of concentrations compared with bupivacaine.[2] Kopacz *et al.*[12] showed that ropivacaine reduced, whereas bupivacaine increased, cutaneous blood flow in pigs. When epinephrine was added to ropivacaine, no further reduction in blood flow was seen. However, when epinephrine was added to bupivacaine it reduced the blood flow. If the lowering of plasma concentrations by the addition of epinephrine to local anaesthetics is due to a decrease in vascular absorption then one might predict that epinephrine would reduce plasma levels of bupivacaine but would have little effect on plasma levels of ropivacaine. This may explain why epinephrine had no effect on the pharmacokinetic behaviour or on the blockade in the present study.

TABLE III The 95% confidence intervals (based on the Wilcoxon rank sum test) for the differences in pharmacokinetic variables derived from plasma concentrations after 190 mg ropivacaine with or without epinephrine for brachial plexus anaesthesia

	C_{max} $(mg \cdot L^{-1})$	t_{max} (hr)	AUC_{0-12h} $(mg \cdot L^{-1} \cdot hr^{-1})$	$t_{\frac{1}{2}}$ (hr)
Median	0.22	0.10	0.60	−2.05
95% CI	−0.22, 0.88	−0.50, 0.50	−2.35, 5.12	−7.5, 0.70

A terminal plasma half-life, of the order of 1.9 hr, has been reported after IV administration of ropivacaine.[5] This suggests that the higher apparent half-life seen in this study after brachial plexus block reflects slow drug absorption. Thus, it is not possible to make a reliable estimate of the extrapolated AUC beyond the 12 hr observation period, precluding an extended pharmacokinetic analysis of the results from the study.

The plasma concentrations following the block declined relatively slowly over the 12 hr sampling period, which is consistent with the long duration of action of ropivacaine.[6] The association between the apparent half-life in plasma and duration of block further suggests that the decline of plasma concentrations in these patients, at least to some extent, reflects the rate of systemic absorption of ropivacaine.

Scott *et al.* reported that when ropivacaine was given as a rapid IV infusion to volunteers, mild central nervous system symptoms were recorded in five of 12 subjects and appeared at venous plasma concentrations in the range of 1 to 2 $mg \cdot L^{-1}$. However, the association between plasma concentration and symptoms was weak and the concentrations were often higher after the symptoms had disappeared. The reason for this may be that arterial and venous plasma concentrations had not reached equilibrium at the time of appearance of symptoms.

Although peak plasma concentrations of ropivacaine up to 2–3 $mg \cdot L^{-1}$ were seen in some patients in this study, symptoms from the CNS were not observed. We cannot explain the difference in plasma concentrations and toxicity between our study and the data reported by Scott *et al.*[4] It should be noted, however, that the patients reported by Scott *et al.*[4] were unpremedicated volunteers that had been familiarized with the CNS toxic effects of local anaesthetics. The patients in our study had no previous knowledge of toxic symptoms and were given midazolam, which may have contributed by masking such symptoms. In addition, the rapidity at which the plasma concentrations were achieved may also account for some differences in toxicity. The plasma levels noted in the study by Scott *et al.*[4] were achieved rapidly following intravenous administration, whereas our plasma levels were achieved more slowly as the drug was released into the blood stream from the brachial plexus. It has been noted by Scott that peripheral venous plasma concentrations during rapid IV infusion are unreliable, particularly in relation to CNS changes, because of the large arteriovenous concentration differences that exist.[4,13] The slower

increase in plasma levels seen with brachial plexus block may allow more time for equilibration between arterial and venous concentrations. As central nervous system or cardiovascular symptoms attributed to the drug were not observed, brachial plexus block with 190 mg ropivacaine seems safe.

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