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Continuous Interscalene Analgesia with Ropivacaine 2 mg/ml after Major Shoulder Surgery

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Background: **In this open, randomized study, the pharmacokinetics, clinical efficacy, and safety of a 48-h continuous interscalene infusion of 2 mg/ml ropivacaine for postoperative pain relief were investigated in patients undergoing open major shoulder surgery.**

Methods: **An initial interscalene block with 30 ml ropivacaine, 7.5 mg/ml (225 mg), was performed. After completion of interscalene block, all patients (n = 24) received general anesthesia, and 6 h after interscalene block, a 48-h continuous interscalene infusion of 12 or 18 mg/h using 2 mg/ml ropivacaine was started. Total and unbound plasma concentrations of ropivacaine and 2.6-pipecoloxylidide (PPX; a major active metabolite) were determined during and up to 6 h after the interscalene infusion. Postoperative pain at rest was assessed by a visual analog scale. Supplementary analgesics and adverse events were recorded.**

Results: **Plasma concentrations of total and unbound ropivacaine were proportional to the total dose. At the end of the interscalene infusion of 9 ml/h, the mean ± SD plasma concentrations of total and unbound ropivacaine were 1.40 ± 0.54 and 0.03 ± 0.01 mg/l, respectively, and of total and unbound PPX were 0.70 ± 0.38 and 0.30 ± 0.20 mg/l, respectively. Plasma concentrations of unbound ropivacaine and unbound PPX, added together, remained well below threshold levels for systemic central nervous system toxicity. There were no significant differences between the groups for postoperative pain (median maximum of about 20 mm on the visual analog scale in both groups), analgesic consumption, or quality of pain relief assessed by the patient. No signs or symptoms of systemic local anesthetic toxicity were observed.**

Conclusion: **A 48-h continuous interscalene infusion of 6 or 9 ml/h ropivacaine, 2 mg/ml, started 6 h after an initial interscalene block of 30 ml ropivacaine, 7.5 mg/ml, provided satisfactory postoperative pain relief after major shoulder surgery and was well tolerated. Unbound plasma concentrations of ropivacaine and PPX remained well below threshold levels for systemic central nervous toxicity.**

MAJOR shoulder surgery is frequently associated with severe postoperative pain, especially within the first 48 h.[1] Postoperative interscalene analgesia by either continuous or patient-controlled infusion of local anesthetics is currently considered the gold standard after this type of surgery because it provides better pain relief and produces fewer side effects than intravenous patient-controlled analgesia with opioids.[2] Ropivacaine has been shown to be suitable in this clinical context[3] and possesses a greater margin of safety than bupivacaine.[4,5,6] The rational application of local anesthetics for 48 h necessitates a thorough understanding of their pharmacokinetics. However, to date, information about the pharmacokinetics of ropivacaine during continuous interscalene infusion is unavailable. The primary aim of this study was to assess the pharmacokinetics of ropivacaine and an active metabolite, 2,6-pipecoloxylidide (PPX), during a 48-h continuous interscalene infusion of 2 mg/ml ropivacaine at a rate of either 6 or 9 ml/h.

Materials and Methods

Patients

After obtaining institutional ethics committee approval (University Clinic Zurich/Balgrist, Zurich, Switzerland) and written informed consent from patients, we prospectively enrolled 27 adults (American Society of Anesthesiologists physical status I or II, age 18–75 yr, weight 50–100 kg, height 155–195 cm) scheduled for elective open shoulder surgery (rotator cuff repair, Bankart repair, arthroplasty).

Exclusion criteria were any contraindications to interscalene block; known allergy to ropivacaine, propacetamol, and morphine; administration of local anesthetics within 7 days prior to administration of ropivacaine; pregnant women and women not practicing adequate contraception; concomitant medication with potent cytochrome P-450 1A2 inhibitors (such as fluvoxamine and ciprofloxacin); neuropsychiatric disorders; and severe liver or renal disease (values two times above normal range).

According to a computer-generated randomization, patients were allocated to receive a continuous interscalene infusion of 2 mg/ml ropivacaine at a rate of either 6 or 9 ml/h (12 or 18 mg/h).

Patients were premedicated with 0.1 mg/kg midazolam given orally 1 h before arrival in the induction room. Interscalene brachial plexus block was performed through an interscalene catheter. The interscalene brachial plexus was identified using a nerve stimulator (Stimuplex® HNS 11; B. Braun Melsungen AG, Melsungen, Germany) connected to the proximal end of the metal inner needle (Stimuplex® A; 21-gauge stimulation needle; G. Braun Melsungen AG). Placement of the needle was considered successful when a contraction of the

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triceps muscle was obtained with a current output of less than 0.5 mA with an impulse duration of 0.1 ms.

For the placement of the perineural catheter, the cannula-over-needle technique was used with a plastic cannula (Polymedic®, polyplex N50-T, 20-gauge external diameter; Te me na, Bondy, France). The catheter (Polymedic®, polyplex N50, 23 gauge with stylet) was introduced distally and advanced between the anterior and middle scalene muscle up to 2 to 3 cm. The catheter was subcutaneously tunneled over 4 to 5 cm through an 18-gauge intravenous cannula and fixed to the skin with adhesive tape. Interscalene block was performed with 30 ml ropivacaine, 7.5 mg/ml (225 mg), in all patients. An interscalene block was considered successful when a sensory block (inability to recognize cold temperature; pins-and-needles type of paresthesia at the tip of the first and third finger) and a motor block (inability to extend the arm involving the radial and median nerve) were present within 20 min after the administration of the local anesthetic. When the interscalene block was complete, general anesthesia was induced and maintained with propofol using the target-controlled infusion technique (target-controlled infusion pump, Graseby; SIMS Graseby Limited, Watford, Herts, United Kingdom). Tracheal intubation was facilitated using 0.8 mg/kg rocuronium and 0.1 mg fentanyl. At the end of surgery, patients were transferred to the recovery room. Time zero (t_0) was the administration of ropivacaine through the interscalene catheter for the initial block. Exactly 6 h after the initial block (t_{6h}), a continuous infusion of either 6 ml/h (12 mg/h) or 9 ml/h (18 mg/h) ropivacaine, 2 mg/ml, was started through the interscalene catheter. The infusion was maintained for 48 h and stopped 54 h after the initial interscalene block (t_{54h}).

Blood Sampling and Drug Assay

Peripheral blood was collected from the cubital vein in the arm contralateral to the arm undergoing surgery *via* an indwelling catheter not in use for drug and/or fluid injection/infusion. Blood samples of 8 ml were taken the day before surgery (baseline) and at $t_{3,4,5,6}$ (t_{6h} = start of infusion) $t_{8,12,18,30,54}$ (t_{54h} = end of infusion), $t_{56,58}$, and t_{60h}. The samples at t_3–t_6 were used to assess the contribution of concentrations remaining after the block on the plasma concentrations during the infusion. The samples were taken in heparinized tubes (Venoject®; Terumo, Leuven, Belgium), and plasma was separated by centrifugation at room temperature within 60 min of collection. The plasma was stored at −20°C until drug assay. Total plasma concentrations of ropivacaine and PPX were determined in all samples. Unbound plasma concentrations of ropivacaine and PPX as well as the plasma concentration of α_1-acid glycoprotein (AAG) were determined at the end of infusion (t_{54h}) and in the samples with the highest plasma concentrations of total ropivacaine and total PXX within the interval t_{3-6h} after the bolus dose and during the infusion (t_{6-54h}), respectively.

The total concentration of ropivacaine in plasma was determined by gas chromatography with a nitrogen-sensitive detector.[7] Liquid–liquid extraction was used for sample preparation. The limit of quantitation (LOQ) was 0.0027 mg/l and the interassay coefficient of variation (CV) was 4.8% at 0.0055 mg/l. The PPX was determined by coupled column liquid chromatography followed by mass spectrometric detection with electrospray ionization. The plasma samples were prepared by acidification followed by ultrafiltration. LOQ was 0.0023 mg/l and the interassay CV was 7.3% at 0.0046 mg/l. Unbound ropivacaine and PPX were determined by coupled column liquid chromatography with mass spectrometric detection using electrospray ionization, after ultrafiltration of the plasma samples. LOQ was 0.0027 mg/l for ropivacaine and 0.0023 mg/l for PPX. The interassay CV was 4.9% for ropivacaine and 8.0% for PPX at the total plasma concentrations of 0.55 and 0.23 mg/l, respectively. AAG was determined by an immunoturbidimetric method. LOQ was 3.0 μM and the CV was 2.1% at 20.7 μM.

Pharmacokinetic Calculations

The highest drug concentration after the start of the interscalene infusion (C_{high}), the time for C_{high} (t_{high}), and the plasma concentration at the end of the infusion (C_{end}) were derived directly from the data for total and unbound ropivacaine and PPX. The unbound fractions (f_u) of ropivacaine and PPX were calculated as unbound concentration (C_u) divided by total concentration in the same sample. Following the end of infusion, the terminal half-life (t1/2) was determined for total ropivacaine by linear regression of the four last data points on the plasma concentration-*versus*-time curve. Apparent unbound ropivacaine clearance ($CL_{u,app}$) was calculated assuming steady state at the end of infusion, *i.e.*, $CL_{u,app}$ = rate of infusion/$C_{u,end}$. As the toxic effects of ropivacaine and PPX are additive, the plasma concentrations of unbound ropivacaine and that of one twelfth of unbound PPX (C_u ropivacaine + C_u PPX/12) were added together at each sampling time at which both unbound ropivacaine and PPX were determined in each patient. The dose was expressed as ropivacaine base in all pharmacokinetic calculations. WinNonlin software version 1.5 (Pharsight Corporation, PaloAlto, CA) was used.

Clinical Assessments

Postoperative pain related to the surgery was assessed by the patient on a visual analog scale, from "no pain" (0 mm) to "worst pain imaginable" (100 mm), during rest at time points $t_{5,7,9,12,18,24,30,36,42,48,54h}$. If pain was not adequately controlled (visual analog scale score > 30 mm), patients received 2 g propacetamol (the prodrug of acetaminophen) intravenously, as first choice, to a maximum daily dose of 12 g, followed by 0.1 mg/kg morphine given

subcutaneously if pain remained over 30 mm on the visual analog scale after 20 min. The time to the first administration and the amount of supplementary analgesics were registered. The appearance of side effects (nausea, vomiting, pruritus) was collected from the start of insertion of the needle for the interscalene block until the patient's discharge. Side effects spontaneously reported by the patient or observed by the research team were recorded. We looked specifically for signs and/or symptoms of toxicity (such as lightheadedness, tinnitus, seizures).

Statistical Analysis

To describe the difference in magnitude (assuming shift in location) between two groups, the Hodges-Lehmann estimator has sometimes been used. The Hodges-Lehmann estimate in an unpaired situation is calculated as the median of all possible differences between an observation in one group and an observation in the other group. It is more robust when it comes to single gross outliers than the difference in means. The Hodges-Lehmann estimator and the corresponding confidence intervals were calculated for log-transformed data and then back-transformed to the original scale to get a nonparametric estimate and confidence interval for the ratio of the two group medians.

Dose proportionality for total and unbound plasma concentrations of ropivacaine and PPX was evaluated using C_{end}. After dose normalization, individual C_{end} values were log-transformed, and point estimates and 90% confidence intervals were calculated for the difference between the dose groups. Wilcoxon two-sample confidence intervals and associated Hodges-Lehmann point estimates were used. Point estimates and confidence interval limits are presented as antilogarithms. Estimates and confidence limits close to 1 indicate dose proportionality.

An explorative regression analysis was performed to study the relationship between f_u of ropivacaine and the predictors AAG, total plasma concentration of ropivacaine, total and free concentrations of PPX, time of measurement, and patient. Correspondingly, the relationships between f_u of PPX and AAG, total plasma concentration of PPX, total and free concentrations of ropivacaine, time of measurement, and patient were also studied. Regression models were compared using the Cp criteria of Mallows, with patient indicators forced into the models as fixed factors.

Pain scores were compared by the Wilcoxon two-sample confidence interval with Bonferroni correction for multiple comparisons (12 assessments). Differences between the two infusion groups concerning the time to first administration of supplementary analgesics were assessed using survival analysis. The total amount of morphine and propacetamol supplement was assessed by the Wilcoxon test. A *P* value less than 0.05 was considered to be statistically significant.

Table 1. Demographic Data

	Ropivacaine Dose Group	
	6 ml/h (n = 12)	9 ml/h (n = 12)
Sex (male/female)	9/3	4/8
Age (yr)	37 ± 18.5	47 ± 15.2
Weight (kg)	83 ± 10.9	75 ± 15.8
Height (cm)	179 ± 7.2	168 ± 7.8
ASA physical status (I/II)	9/3	5/7
Duration of surgery (min)	117 ± 23	132 ± 31

Values are mean ± SD.

Results

A total of 27 patients were enrolled in the study. One patient did not complete the study since the interscalene catheter was removed at t_{18h} because of the appearance of a painful swelling at the site of catheter insertion and a concomitant complete paralysis of the affected arm. One patient, who also received ropivacaine subcutaneously because of difficulties in inserting the catheter, and one who was transfused with large volumes of erythrocytes during the study were excluded from the pharmacokinetic evaluation. Demographic and surgical data of the 24 patients included in the pharmacokinetic evaluation were similar in the two groups and are summarized in table 1.

Pharmacokinetic Evaluation

The total plasma concentrations of ropivacaine increased slightly during the infusion, although the interscalene block of 225 mg ropivacaine produced plasma concentrations of total ropivacaine at 6 h that contributed to the steady state (fig. 1). There was less variation in the unbound ropivacaine concentration (fig. 2). During the infusion, the highest individual plasma concentration of total ropivacaine, 2.76 mg/l, was seen at t_{54h} in the 9-ml/h dose group, and the highest individual plasma level of unbound ropivacaine, 0.046 mg/l, was seen in the same patient. The terminal half-life after the end of the infusion varied between 1 and 12 h (table 2).

The unbound fraction of ropivacaine (f_u) decreased with time during the interscalene infusion reflecting an increase in the degree of plasma protein binding. Before the interscalene infusion, f_u ranged between 2 and 9% and at the end of infusion f_u varied between 1 and 3% (table 2). There was a postoperative increase in AAG over time with values between 10 and 30 μM before the start of the interscalene infusion and between 15 and 39 μM at the end of infusion. In the regression analysis of the relationship between f_u for ropivacaine and the predictors, Mallows' Cp indicates that a single predictor model should be used. In the model, 70% of the variability in f_u of ropivacaine could be explained by variation in AAG ($R^2 = 0.70$).

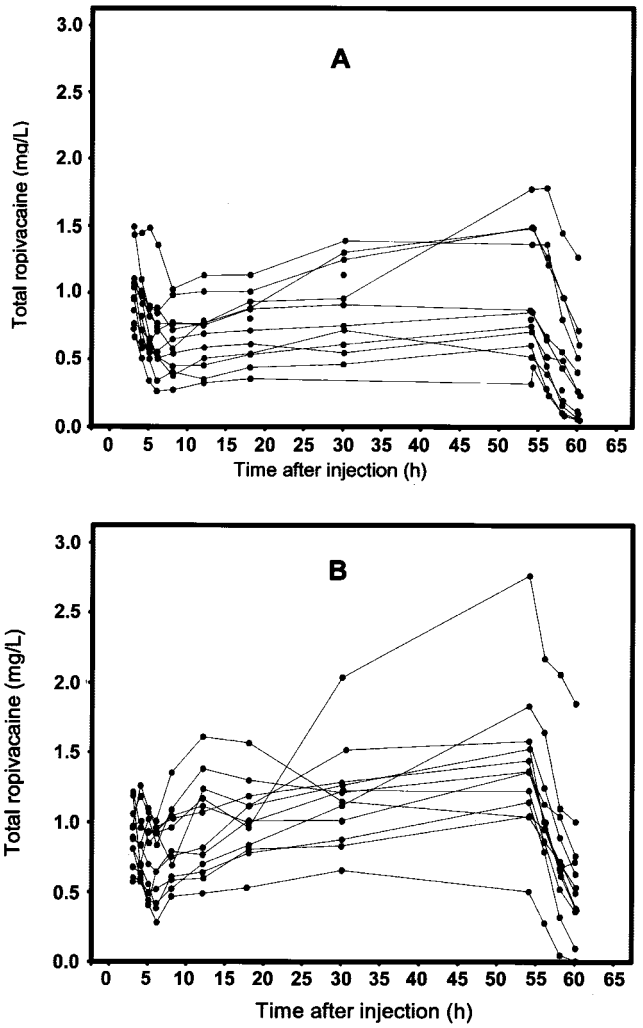

Fig. 1. Plasma concentrations of total ropivacaine 3 h before and during a 48-h interscalene infusion of 6 (*A*) and 9 ml/h (*B*) ropivacaine, 2 mg/ml (12 and 18 mg/h), started 6 h after an interscalene block with 30 ml ropivacaine, 7.5 mg/ml (225 mg).

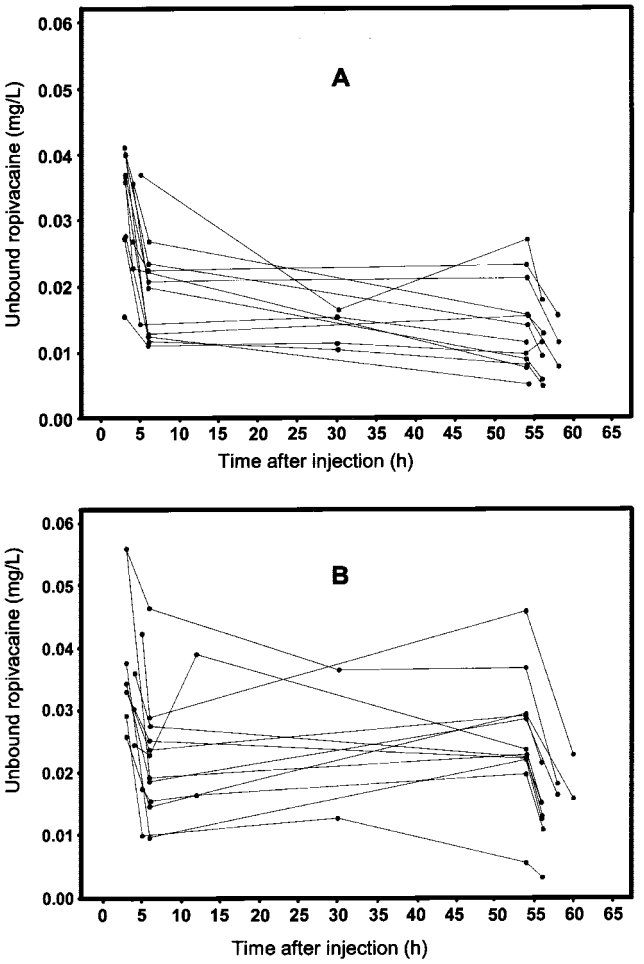

Fig. 2. Plasma concentrations of unbound ropivacaine 3 h before and during a 48-h interscalene infusion of 6 (*A*) and 9 ml/h (*B*) ropivacaine, 2 mg/ml (12 and 18 mg/h), started 6 h after an interscalene block with 30 ml ropivacaine, 7.5 mg/ml (225 mg).

The Hodges-Lehmann estimates of the ratio in dose-normalized C_{end} concentrations of total and unbound ropivacaine were close to 1, suggesting dose proportionality, which is not contradicted by the corresponding confidence intervals (table 3).

The plasma concentrations of PPX increased during the interscalene infusion and more so in the 9-ml/h dose group compared to the 6-ml/h dose group. In three of the patients in the 9-ml/h dose group, both total and unbound plasma concentrations of PPX at the end of infusion were somewhat higher than in the other patients in the same dose group (fig. 3). The larger increase in the highest dose group is mainly due to contribution from these three. The highest individual plasma concentrations of total PPX, 1.44 mg/l, and unbound PPX, 0.76 mg/l, were determined at the end of infusion in this group. f_u decreased during the infusion and varied between 37 and 98% before the start of the interscalene infusion and between 25 and 62% at the end of infusion. In the regression analysis of the relationship between f_u for PPX and the predictors, AAG was the best single predictor, explaining 77% of the variation in f_u of PPX ($R^2 = 0.77$). The Hodges-Lehmann estimates of the ratio of dose-normalized C_{end} concentrations of PPX (table 3) suggest that the mean plasma levels of total and unbound PPX are about 30% and 80% higher in the 9-ml/h ropivacaine dose group than expected from a proportional increase with dose.

The unbound plasma levels of PPX were, on a milligram-per-liter basis, up to 24 times higher than the unbound concentrations of ropivacaine (fig. 3). To evaluate the safety margin regarding systemic central nervous system toxicity, plasma concentrations of unbound ropivacaine were added to one twelfth of the concentrations of unbound PPX (fig. 4). The highest individual sum, 0.10 mg/l, was observed in the 9-ml/h dose group at the end of the interscalene infusion (table 2 and fig. 4).

Table 2. Pharmacokinetic Data

	12 mg/h*	18 mg/h*	Total†
Total ropivacaine			
C_{high} (mg/l)			
Mean ± SD	1.03 ± 0.42	1.46 ± 0.51	
Median (range)	0.88 (0.45–1.79)	1.41 (0.65–2.76)	
t_{high} (h)			
Mean ± SD	46 ± 12	43 ± 17	
Median (range)	54 (30–56)	54 (12–54)	
$t_{1/2}$ (h)			
Mean ± SD	3.9 ± 2.6	4.9 ± 3.0	4.4 ± 2.8
Median (range)	3.4 (1.5–11.1)	4.8 (0.9–11.8)	3.6 (0.9–11.8)
Unbound ropivacaine			
C_{high} (mg/l)			
Mean ± SD	0.018 ± 0.007	0.029 ± 0.010	
Median (range)	0.018 (0.008–0.027)	0.028 (0.013–0.046)	
t_{high} (h)			
Mean ± SD	32 ± 24	37 ± 23	
Median (range)	42 (6–56)	54 (6–54)	
fu before (%)			
Mean ± SD	3.5 ± 1.4	4.1 ± 1.9	
Median (range)	± 3.3 (2–6)	3.7 (2–9)	
fu end (%)			
Mean ± SD	1.4 ± 0.4	1.9 ± 0.5	
Median (range)	1.4 (1–2)	1.8 (1–3)	
CLu app (L/min)			
Mean ± SD	16 ± 8	13 ± 11	15 ± 10
Median (range)	14 (6.5–34.0)	11 (5.8–48.1)	12 (5.8–48.1)
Total PPX			
C_{high} (mg/l)			
Mean ± SD	0.38 ± 0.21	0.77 ± 0.44	
Median (range)	0.33 (0.11–0.68)	0.79 (0.13–1.44)	
t_{high} (h)			
Mean ± SD	56 ± 1	57 ± 2	
Median (range)	56 (54–58)	56 (54–60)	
Unbound PPX			
C_{high} (mg/L)			
Mean ± SD	0.12 ± 0.09	0.30 ± 0.20	
Median (range)	0.09 (0.027–0.317)	0.29 (0.033–0.763)	
t_{high} (h)			
Mean ± SD	49 ± 15	55 ± 2	
Median (range)	54 (6–58)	54 (54–60)	
fu before (%)			
Mean ± SD	59 ± 12	62 ± 19	
Median (range)	61 (37–77)	56 (43–98)	
fu end (%)			
Mean ± SD	32 ± 8	42 ± 11	
Median (range)	28 (25–51)	40 (27–62)	
Cu ropivacaine + Cu PPX/12			
C_{high} (mg/L)			
Mean ± SD	0.026 ± 0.011	0.052 ± 0.023	
Median (range)	0.023 (0.011–0.045)	0.049 (0.015–0.099)	

Pharmacokinetic parameters of ropivacaine and PPX during a 48-h interscalene infusion of 6 and 9 ml/h ropivacaine, 2 mg/ml (12 and 18 mg/h), started 6 h after an interscalene block with 30 ml ropivacaine, 7.5 mg/ml (225 mg).

* n = 12 patients; † n = 24 patients.

CLu app = apparent unbound ropivacaine clearance; C_{high} = highest drug concentration; t_{high} = time for C_{high}; fu = unbound fraction of ropivacaine; PPX = 2.6-pipecoloxylidide.

Clinical Evaluation

The pain scores at rest were similar in both groups. Time to first administration and dose of supplementary analgesics were comparable in the two groups. The proportion of patient rating pain relief as excellent was higher in the 9-ml/h ropivacaine group, 63%, as compared with 43% in the 6-ml/h ropivacaine group.

Blood pressure, pulse rate, respiratory, and oxygen saturation remained stable throughout the study. No seizures or other signs or symptoms of local anesthetic toxicity were observed in any patient. The incidences of nausea were 14% and 10% in the 6- and 9-ml/h groups, respectively (not significant). Neither vomiting nor pruritus was recorded in either group.

Table 3. Plasma Concentrations of Ropivacaine and PPX

C_{end} (mg/l)	12 mg/h	18 mg/h	H-L Estimate	90% CI
Total ropivacaine			1.33	0.70–1.05
Mean ± SD	0.98 ± 0.44	1.40 ± 0.54		
Range	0.45–1.78	0.50–2.76		
Unbound ropivacaine			1.32	0.94–1.85
Mean ± SD	0.014 ± 0.007	0.026 ± 0.010		
Range	0.005–0.027	0.005–0.046		
Total PPX			1.33	0.86–2.15
Mean ± SD	0.35 ± 0.18	0.70 ± 0.38		
Range	0.11–0.60	0.10–1.20		
Unbound PPX			1.80	0.93–3.28
Mean ± SD	0.12 ± 0.08	0.30 ± 0.20		
Range	0.03–0.27	0.03–0.74		

Plasma concentration at the end of a 48-h interscalene infusion (C_{end}) of 6 and 9 ml/h ropivacaine, 2 mg/ml (12 and 18 mg/h), given 6 h after an interscalene block with 30 ml ropivacaine, 7.5 mg/ml (225 mg).

H-L = Hodges–Lehman; PPX = 2.6-pipecoloxylidide.

Discussion

The main findings of this first study dealing with the pharmacokinetics of a 48-h continuous interscalene infusion of either 6 and 9 ml/h ropivacaine, 2 mg/ml, are (1) a dose-proportional increase in the plasma concentrations of total and unbound ropivacaine and (2) plasma concentrations of unbound ropivacaine and unbound PPX (an active metabolite) well below threshold levels for systemic central nervous system toxicity.

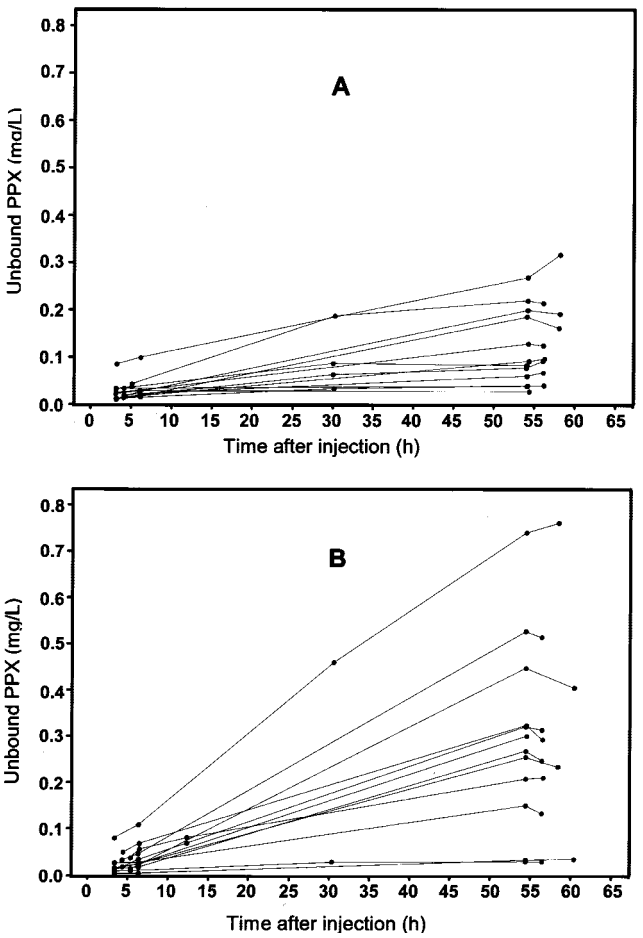

Fig. 3. Plasma concentrations of unbound 2.6-pipecoloxylidide (PPX) 3 h before and during a 48-h interscalene infusion of 6 (*A*) and 9 ml/h (*B*) ropivacaine, 2 mg/ml (12 and 18 mg/h), started 6 h after an interscalene block with 30 ml ropivacaine, 7.5 mg/ml (225 mg).

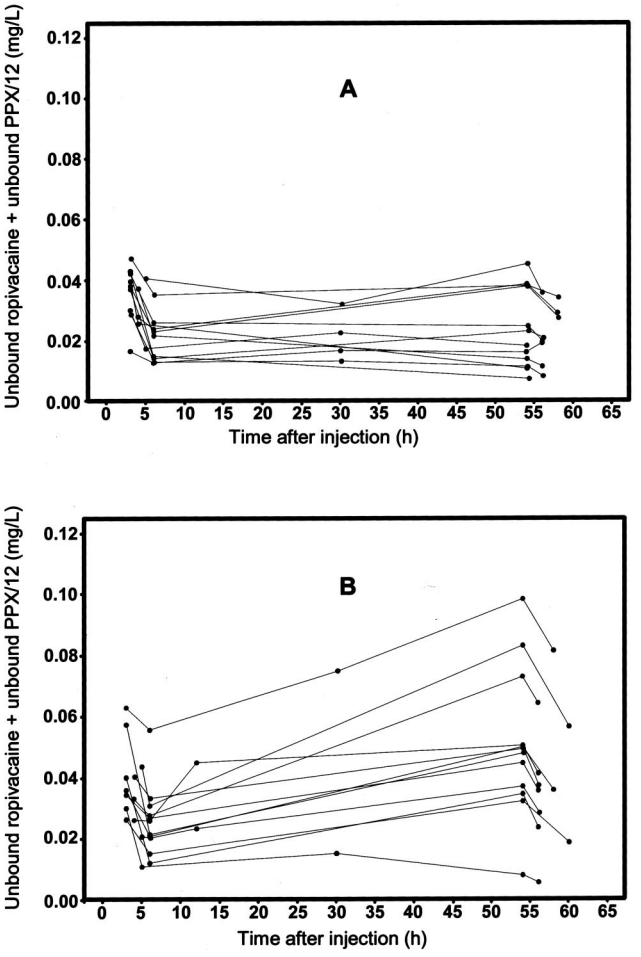

Fig. 4. Plasma concentrations of unbound ropivacaine and unbound 2.6-pipecoloxylidide (PPX)/12 3 h before and during a 48-h interscalene infusion of 6 (*A*) and 9 ml/h (*B*) ropivacaine, 2 mg/ml (12 and 18 mg/h), started 6 h after an interscalene block with 30 ml ropivacaine, 7.5 mg/ml (225 mg).

The plasma concentrations of total and unbound ropivacaine at the end of infusion increased in proportion to dose for the 6- and 9-ml/h groups. This is in accordance with previous findings in which the pharmacokinetics of ropivacaine were linear up to the highest intravenous bolus infusion (80 mg) tested.[8] Furthermore, total plasma concentrations of ropivacaine were proportional to the total dose at the end of a 21-h epidural infusion in volunteers,[9] as were the areas under the curve of total and unbound plasma concentrations of ropivacaine after postoperative epidural infusion of 10 and 20 mg/h[10] and total and unbound maximum plasma concentrations after intraarticular injection of ropivacaine in the knee joint.[11]

In plasma, ropivacaine is mainly bound to AAG, *i.e.*, an acute phase protein that increases postoperatively.[10,12,13] A linear drug protein binding is expected in this study as the molar concentration of AAG was about three times higher than the molar concentration of ropivacaine. AAG levels increased during the interscalene infusion with a subsequent decrease in the unbound fraction of ropivacaine, which was expected due to the increase in binding capacity. Consequently, the variation in AAG plasma concentrations explained a large part of the variability in the unbound fraction of ropivacaine as previously reported.[10] As ropivacaine is eliminated by liver metabolism with an intermediate to low hepatic extraction ratio,[14,15] its rate of elimination should, according to theory, depend on the unbound plasma concentration.[10]

The plasma clearance is then expected to vary with changes in the unbound fraction, *i.e.*, a decrease in clearance results in an increase in total plasma concentrations during the infusion as seen in this study and previously reported.[10,16] The concentrations remaining from the initial interscalene block also contributed to the plasma concentrations of total ropivacaine during the interscalene infusion. Furthermore, in the patients with a short terminal half-life, a rapid steady state was expected, while in the patients with a long terminal half-life of up to 12 h, steady state was not to be expected until the end of infusion. On the other hand, the intrinsic (unbound) clearance of ropivacaine should remain unchanged as illustrated by the stable unbound concentrations during the infusion in this study and previous studies.[10,15]

PPX is an active metabolite of ropivacaine. It is a minor metabolite after a single dose[14,15] but a major metabolite during epidural infusion.[16] In the present study, the plasma concentrations of total and unbound PPX after the highest infusion rate, 18 mg/h, were higher than expected from a proportional increase in dose, partly because of a contribution from the three patients showing the highest plasma concentrations and increase during the interscalene infusion. One of these patients also showed the highest plasma concentration of total ropivacaine. The higher plasma concentrations of total and unbound PPX in these three patients could not be explained by differences in demographics, duration or type of surgery, or concomitant medication. Total and unbound plasma concentrations of PPX have been reported to increase during a 72-h postoperative epidural infusion of ropivacaine[16] and tended to reach a plateau after about 48 h, which is supported by the half-life of PPX, 9 h.[15] In the present study, the variation in AAG could explain 77% of the variation in f_u for PPX, which suggests that also PPX is mainly bound to AAG in plasma.

In the present study, the mean unbound plasma concentrations of ropivacaine and PPX at the end of the 9-ml/h interscalene infusion of 2 mg/ml ropivacaine were lower (0.026 and 0.12 mg/l) than after a 72-h postoperative epidural ropivacaine infusion of 20 mg/h (0.06 and 0.4 mg/l),[16] and the apparent unbound clearance of ropivacaine (14.6 l/min) was consequently higher than following the epidural infusion (5 l/min).[16] The apparent unbound clearance of ropivacaine (10 l/min) after 24-h continuous postoperative epidural infusions of 10 and 20 mg/h ropivacaine[10] and that reported after intravenous administration to volunteers, 8 l/min,[8] are closer to that in the present study.

The systemic toxicity of local anesthetics is related to the unbound rather than the total plasma concentration. During the infusion, the highest individual plasma concentration of unbound ropivacaine was 0.05 mg/l, and that of unbound PPX was 0.76 mg/l. The threshold level for central nervous system toxicity of unbound ropivacaine was 0.34–0.85 mg/l in healthy subjects after intravenous infusion of ropivacaine.[5] The threshold for the central nervous system toxicity of unbound plasma concentration of PPX in rats is about one twelfth of that of unbound ropivacaine.[17] Since the toxic effects of ropivacaine and PPX are additive, we calculated the sum of unbound ropivacaine and one twelfth of unbound PPX. The highest individual sum, 0.1 mg/l, was well below the threshold level for central nervous system toxicity.

The control of pain and the occurrence of side effects (nausea, vomiting) are also in accordance with the reported results of continuous infusion of local anesthetics through the interscalene catheter.[3,18,19]

In conclusion, the plasma concentrations of unbound ropivacaine and PPX added together remained well below threshold levels for systemic central nervous system toxicity, during a 48-h interscalene infusion of either 6 or 9 ml/h ropivacaine, 0.2%, after major shoulder surgery.

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