

Epidural Infusion of Ropivacaine for Postoperative Analgesia after Major Orthopedic Surgery

Pharmacokinetic Evaluation

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Background: Changing plasma protein concentrations may affect the protein binding and pharmacokinetics of drugs in the postoperative phase. Therefore, the authors evaluated the pharmacokinetics of ropivacaine, administered by 72-h epidural infusion to provide postoperative analgesia.

Methods: Twenty-eight patients, scheduled for major orthopedic surgery during combined epidural and general anesthesia received a bolus dose of ropivacaine (50 or 75 mg), followed by constant-rate (10 ml/h) epidural infusion of ropivacaine 2 mg/ml (group 1) or 3 mg/ml (group 2). Total and unbound plasma concentrations of ropivacaine and pipecoloxylidide and plasma concentrations of α_1 -acid glycoprotein were determined. In addition, the urinary excretion of ropivacaine and major metabolites was measured.

Results: Total plasma concentrations of ropivacaine increased steadily during the infusion, reaching 2.7 ± 0.7 and 2.9 ± 0.5 mg/l in groups 1 and 2 after 72 h constant-rate infusion. Unbound ropivacaine concentrations reached average steady state levels of approximately 0.06 and 0.07 mg/l. Total and unbound concentrations of pipecoloxylidide increased to

1.0 ± 0.4 and 0.4 ± 0.2 mg/l (group 1) and 1.2 ± 0.4 and 0.5 ± 0.1 mg/l (group 2) after 72 h infusion. α_1 -Acid glycoprotein concentrations initially decreased, but thereafter increased steadily to approximately twice the baseline values.

Conclusions: Postoperative increases in plasma α_1 -acid glycoprotein concentrations enhance the protein binding of ropivacaine and pipecoloxylidide, causing divergence of total and unbound plasma concentrations. (Key words: Anesthetics; bio-transformation; metabolism; clearance.)

CLINICAL studies have shown that ropivacaine is a suitable local anesthetic for long-term epidural infusion for postoperative pain relief.¹⁻⁴ Compared with bupivacaine, ropivacaine may possess a greater margin of safety and be less arrhythmogenic after accidental intravenous injection.⁵

The rational application of long-term epidural infusions of local anesthetics necessitates a thorough understanding of their pharmacokinetics. However, currently there is limited information with respect to the pharmacokinetics of ropivacaine in postsurgical patients. A study in patients who received a 24-h constant-rate epidural infusion of ropivacaine for postoperative pain relief showed that total plasma concentrations of ropivacaine increase steadily, whereas unbound (free) concentrations of ropivacaine stabilize during the infusion.⁶ These observations reflect a decrease in the total plasma clearance, caused by an increase in the degree of protein binding, secondary to an increase in the plasma concentrations of α_1 -acid glycoprotein (AAG) over time. Because maximum plasma concentrations of AAG are not reached until several days after surgery,⁶⁻⁸ further changes in the pharmacokinetics may be anticipated when infusions are continued for several days. Therefore, we studied both the total and the unbound plasma concentration profiles of ropivacaine, pipecoloxylidide (a substantial metabolite of ropivacaine at long-term treatment, exhibiting pharmacologic activity, but considerably less than ropivacaine), and AAG during long-

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term (72 h) constant-rate infusions of ropivacaine for postoperative pain relief. In addition, we evaluated plasma concentrations of two other metabolites (3-OH-ropivacaine and 2-OH-methyl-ropivacaine), and the renal excretion of unchanged ropivacaine and these metabolites.

Materials and Methods

Patients

The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center (LUMC). After obtaining written informed consent, 29 patients (22–80 yr; 55–110 kg, American Society of Anesthesiologists physical status I–III), scheduled for total hip or total knee arthroplasty during combined epidural and general anesthesia, were enrolled in the study. Patients with a contraindication for epidural anesthesia, and patients with a history of allergy, sensitivity, or any other reaction to an amide-type local anesthetic, were excluded from the study. Also excluded were patients with a history of, or abnormal laboratory findings indicative of, renal or hepatic disease and patients with diseases that could interfere with postoperative pain experience or render clinical assessments difficult or unreliable, such as significant respiratory or neurologic disease or a psychiatric history. Further exclusion criteria included significant alcohol, drug, or medication abuse and participation in a clinical trial of a nonregistered drug within the 3-month period before admission to the study. Finally, pregnant women and women not practicing adequate contraception were also excluded.

Routine physical examinations were performed 2 or 3 days before inclusion in the study and at the time of discharge from the hospital, 2–4 weeks after surgery. Laboratory screenings (hematology and clinical chemistry) were performed 2 or 3 days before inclusion in the study, at discontinuation of the infusion of ropivacaine, and at the time of discharge.

Patients were randomly assigned to one of two groups to receive a continuous infusion of either 20 mg/h (group 1) or 30 mg/h (group 2) ropivacaine in a double-blind fashion. These dosing rates were anticipated to produce effective analgesia in both groups, with minimal or no motor block in patients from group 1 and possibly a more intensive motor blockade in patients from group

2. Patients for whom the study was discontinued were replaced by patients receiving the same treatment.

Anesthetic Procedures

The patients received either temazepam or midazolam as premedication. In the operating room, monitoring equipment was attached and intravenous cannulae for fluid and drug administration and blood sampling were introduced. A preload of a minimum of 500 ml crystalloid was administered before the start of the epidural puncture. Balanced electrolyte solutions were also administered during surgery and postoperatively, as necessary.

With the patient in either the sitting or the lateral decubitus position and after local infiltration of the skin with lidocaine 5 mg/ml, a 16- to 18-gauge epidural needle was inserted *via* the L2–L3 or the L3–L4 interspace with use of the paramedian approach. After identification of the epidural space with use of the loss-of-resistance-to-saline technique, and provided that neither cerebrospinal fluid nor blood was obtained during careful aspiration, an epidural catheter was introduced and advanced 5 cm cephalad. Subsequently, a test dose of 3 ml lidocaine, 10 mg/ml, with epinephrine (5 µg/ml) was injected, and, 5 min later, in the absence of signs of an intravascular or subarachnoid injection, a bolus dose of ropivacaine 5 mg/ml (Astra, Södertälje, Sweden, batch 471-36-1) was injected slowly. The bolus dose was 15 mg (75 mg#) in the first five patients. However, because hypotension developed in these patients, the dose in the remaining 23 patients was reduced to 10 ml (50 mg). Immediately after the end of the bolus injection, an epidural infusion of 10 ml/h ropivacaine, 2 mg/ml, (dose rate, 20 mg/h; group 1) or 3 mg/ml (dose rate, 30 mg/h; group 2) (Astra, Södertälje, batches 1202-4-1 and 1202-4-2, respectively) was started. This infusion was maintained during 72 h. However, when the degree of motor block was considered to be too intense or the level of sensory block too high, or both, the infusion rate was allowed to be decreased in 2-ml/h steps.

Twenty minutes after the start of the epidural infusion of ropivacaine and after verifying the presence of bilateral sensory blockade, general anesthesia was induced with use of thiopentone, pancuronium, or suxamethonium, as necessary, and 100–250 µg fentanyl. Anesthesia was maintained with nitrous oxide–oxygen, isoflurane, and pancuronium, as necessary. One patient received 10 mg etomidate intravenously. If the patient exhibited signs of inadequate anesthesia during surgery, fentanyl, 50 µg, was administered. Anesthesia was considered to be inadequate according to the criteria described by

Doses and concentrations in the solutions refer to ropivacaine-hydrochloride; in the pharmacokinetic evaluation, free base equivalents were used.

Ausems *et al.*⁹ After discontinuation of anesthesia, residual muscle relaxation was reversed with use of atropine and neostigmine.

Postoperative Treatment

When the patient was fully awake, a patient-controlled analgesia device (Graseby Model 3300; SIMS Graseby, Watford, UK) was connected and set to deliver 1 mg morphine bolus doses with a lock-out time of 5 min. No background infusion was administered. Flucloxacillin and gentamycin were used for antibiotic prophylaxis according to the hospital routines. Alizapride, 100 mg intravenously, was used as an antiemetic when severe nausea or vomiting occurred. Bradycardia was treated with atropine, 0.3–0.6 mg intravenously, and hypotension with ephedrine, 5–10 mg intravenously. Indomethacin could be administered orally, when indicated. Intravenous fluids were administered as necessary.

Blood and Urine Samples and Assays

Peripheral venous blood samples (4 or 8 ml) were collected from the arm contralateral to that used for drug administration before and 1, 2, 4, and 8 h after the start of the epidural infusion of ropivacaine. Further samples were collected at 8:00 PM on the day of surgery, and from then on at 4-h intervals, except at 4:00 AM, and finally at the time of discontinuation of the infusion (72 h after the start) and 1, 3, and 6 h after discontinuation of the infusion. In case of a decrease of the infusion rate, additional samples were collected just before and 2 h after the decrease. If the infusion was discontinued prematurely, a blood sample was obtained at the end of the infusion. The total volume of blood sampled from each patient did not exceed 150 ml. Blood samples were transferred to test tubes containing heparin (Venoject, Terumo Europe N.V., Leuven, Belgium) and centrifuged at room temperature within 60 min. Plasma was transferred into polypropylene tubes (Cryotube, A/S Nunc, Roskilde, Denmark) and stored at -20°C .

A blank urine sample was obtained before transportation of the patient to the operating room. Subsequently, urine was collected over 12-h intervals during ropivacaine infusion and over a 6-h interval after discontinuation of the infusion. Collected samples were weighed and then two 5-ml samples were transferred into polypropylene tubes (Cryotube, A/S Nunc) and stored at -20°C .

Total plasma concentrations of ropivacaine in all samples were determined with use of gas chromatography.¹⁰ The limit of quantification was set at $14\ \mu\text{g/l}$ ($0.05\ \mu\text{M}$), and the interassay coefficient of variation was 2% at

$1.1\ \text{mg/l}$. Free (unbound) plasma concentrations of ropivacaine were determined in samples collected at 8:00 AM and 8:00 PM, and in the samples collected 4 h after starting and 6 h after stopping the infusion, with use of high-performance liquid chromatography after ultrafiltration.¹¹ The limit of quantification was set at $3\ \mu\text{g/l}$, with a coefficient of variation of 6.9% at $0.06\ \text{mg/l}$. AAG concentrations were estimated in all plasma samples with use of radioimmunoassay kits (NOR-Partigen α_1 -acid glycoprotein, Behring, Marburg, Germany).¹¹ The limit of determination was set at $4.7\ \mu\text{mol/L}$ with a coefficient of variation of 4.5% at $13\ \mu\text{M}$. Total and unbound plasma concentrations of pipercoloxylidide (PPX) were determined in samples collected after 8 h of infusion at 8 AM on the first and second postoperative day, and after 72 h infusion with use of high performance liquid chromatography with limits of quantification set at $0.05\ \mu\text{M}$.¹³ Unconjugated plasma concentrations of the metabolites 3-OH-ropivacaine and 2-OH-methyl-ropivacaine in samples collected at the end of the infusion were determined with use of high-performance liquid chromatography, with limits of quantification set at 0.5 and $0.5\text{--}0.5\ \mu\text{M}$, respectively.¹³ Concentrations of ropivacaine and these metabolites in urine were also determined with use of high-performance liquid chromatography, with limits of quantification set at $1.0\ \mu\text{M}$ for ropivacaine, $5.0\ \mu\text{M}$ for 3-OH-ropivacaine, $2.5\ \mu\text{M}$ for pipercoloxylidide and $2.5\text{--}5.0\ \mu\text{M}$ for 2-OH-methyl-ropivacaine.¹³

Clinical Assessments

Postoperatively, the requested (including unrewarded demands, *i.e.* within the lock-out time) and administered amounts of morphine (the number of rewarded demands times the bolus dose) were documented. Visual analog scale scores at rest were obtained frequently. Sensory block to thermal stimuli was assessed bilaterally with use of ice cubes. Motor block was assessed with use of a modified Bromage scale (scale 0–3). Heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressures (measured on the arm contralateral to the one used for blood sampling) were monitored with use of automatic equipment at 5-min intervals during surgery and frequently after surgery.

Data Analysis and Graphic Presentations

For each patient the highest total and unbound ropivacaine concentration measured at any time, the total concentration at the end of the infusion, and the unbound concentration at the last assessment time, *i.e.* on the morning of the third postoperative day, were tabu-

lated. Terminal half-lives were determined from the terminal slopes of the logarithm of the total concentration-*versus*-time curves with use of linear regression analysis. Areas under the total plasma concentration-time curves (AUC) and the unbound plasma concentration-time curves (AUC_u) were determined by use of the linear trapezoidal rule, with addition of the area, extrapolated to infinity. The unbound clearance (Cl_u) was calculated as: Cl_u = Dose/AUC_u. Mean unbound steady state plasma concentrations were estimated from the mean unbound plasma concentration-time curves. Total and unbound plasma concentrations of pipecoloxylidide at the end of the infusion were tabulated. Unbound fractions of ropivacaine and pipecoloxylidide were calculated as f_u = C_u/C, where C_u is the unbound and C the total plasma concentration in the same sample. Cumulative fractions excreted in the urine were calculated as f_e = A_e/Dose, where A_e is the amount (μmol) of ropivacaine or metabolite excreted during the infusion of ropivacaine and within 6 h after discontinuation of the infusion and Dose is the total dose of ropivacaine base (μmol) administered. The pharmacokinetic calculations were performed with use of the software package WinNonlin Professional version 2.0 (Pharsight Co., Mountain View, CA).

For graphic presentation of mean total and unbound plasma ropivacaine and pipecoloxylidide concentrations and plasma AAG concentrations, values measured at fixed times of the day were assigned to the relative (nominal) times (from the start of the infusion), if the fixed times were within a specified window (0.01 + 0.163 × nominal time up to 3 h, else 0.5 h) with respect to the nominal times. If this was not the case, values at the nominal times were derived by linear inter- or extrapolation of the nearest surrounding values.

Statistical Analysis

The sample size (12 valid patients/group) was chosen to provide sufficient information about the expected steady state plasma concentration in terms of confidence intervals. The calculations were made for an expected confidence interval length corresponding to 1- and two-sample, two-sided *t* tests (on the assumption of normally distributed data), an SD = 0.8 (based on previous observations⁶), significance levels of 5 and 10%, and a power of 80%. In these circumstances and assuming a steady state concentration ratio of 1.5, the 95% confidence interval for this ratio is 1.0–2.3, and steady state concentration levels in each treatment group can be estimated with a precision (half the width of the confidence interval) of 0.7 mg/l.

Data are summarized as mean ± SD or median and range. Clinical observations (sensory block levels, motor block scores, visual analog scale scores, among others) were not evaluated statistically. Pharmacokinetic data were compared between the groups by use of the two-tailed Student *t* test. Urinary excretion data were compared with use of the Mann-Whitney U test. AUC and AUC_u were evaluated for a possible dose effect with use of linear regression analysis. For each group, plasma AAG concentration and f_u-*versus*-time relations were evaluated, and the relation between f_u, subject, plasma AAG concentration, and time was evaluated with use of multiple linear regression analysis. *P* < 0.05 was considered to be significant.

Results

A total of 29 patients were enrolled in the study. In one patient from group 1, a dural puncture occurred. In two other patients from group 1, the epidural infusion of ropivacaine was discontinued after 33 and 27 min because the spread of analgesia was insufficient for surgery. These patients were excluded from the pharmacokinetic evaluation. In another two patients from group 1 the epidural infusion of ropivacaine was discontinued postoperatively after approximately 8.5 and 42.5 h because of an unstable blood pressure and occlusion of the epidural catheter. These patients were included in the pharmacokinetic evaluation, as appropriate. Demographic data of the patients that were included in the pharmacokinetic evaluation are presented in table 1. None of the women patients used oral contraceptives. Surgery was started between 8:47 AM and 1:23 PM. The type (hip or knee) and duration of surgery are also presented in table 1.

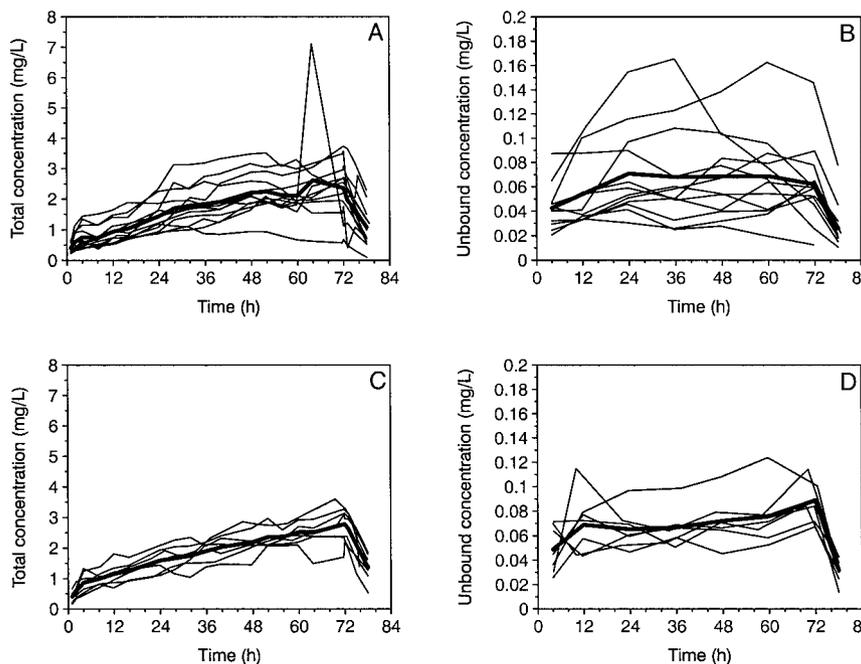
Table 1. Demographic Data of the Patients Included in the Pharmacokinetic Evaluation

	Group 1 (n = 14)	Group 2 (n = 12)
Sex (M/F)	2/12	5/7
Age (yr)	61 ± 16	66 ± 9
Weight (kg)	71 ± 11	82 ± 14
Height (cm)	169 ± 9	169 ± 8
ASA physical status (I/II/III)	4/8/2	6/6/0
Smokers/nonsmokers	3/11	5/7
Type of surgery (hip/knee)	10/4	10/2
Duration of surgery (h)	3.1 ± 1.1	3.0 ± 1.3

ASA = American Society of Anesthesiologists.

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Fig. 1. Individual total (A, C) and unbound (B, D) plasma concentrations of ropivacaine in patients receiving constant-rate infusions of 10 ml/h ropivacaine, 2 mg/ml (group 1, n = 12, A, B) or 3 mg/ml (group 2, n = 7, C, D), for 72 h. Thick lines represent mean values.



Pharmacokinetics

The epidural infusion of ropivacaine was maintained at a constant rate for 72 h in 12 patients from group 1 and in 7 patients from group 2. In four patients from group 2, the epidural infusion rate was decreased once ($n = 3$) or twice ($n = 1$) because the degree of motor block was considered to be too intense. In one patient from this group, the infusion was interrupted for 55 min after approximately 2 h because of a temporary catheter occlusion.

Individual and mean total and unbound plasma ropivacaine concentration–time curves in patients in whom infusion rate was constant for the full 72 h are presented in figure 1. Overall, total plasma concentrations increased steadily during drug infusion. The highest total plasma concentration measured in any patient at any time was 7.1 mg/l. This concentration was reached after 64 h of infusion of 2 mg/ml ropivacaine and markedly deviated from the curve of the patient, but no explanation was found for this observation. In contrast to total plasma concentrations, free plasma concentrations seemed to reach a plateau. Mean steady state concentrations in the patients with unchanged infusion rates were approximately 0.06 mg/l (group 1) and 0.07 mg/l (group 2). Pharmacokinetic data of the patients who received a constant-rate infusion for the full 72-h treatment period are presented in table 2. Data (not shown) of the patients in whom the infusion was discontinued prematurely or

interrupted or in whom the infusion rate was decreased were generally consistent with those in the patients receiving a 72-h constant-rate infusion. However, in one patient from group 2 in whom the infusion rate was decreased from 30 mg/h to 24 mg/h after 14 h, the total and unbound plasma concentrations increased to 5.0 mg/l and 0.198 mg/l, respectively, at the end of the infusion. These values were higher than those in any of the patients receiving 30 mg/h for the entire 72-h treatment period. Pharmacokinetic data (including patients with changed infusion rates, as appropriate) showed no significant relations with the dose or infusion rate.

Free fractions (f_u) of ropivacaine decreased with time (fig. 2), reflecting a steady increase in the degree of plasma protein binding. Plasma concentration of AAG increased steadily, after an initial decrease after the start of the infusion (fig. 2). Multiple linear regression analysis showed that approximately 80% of the variation in f_u was explained by subject, time, and plasma AAG concentrations ($R^2 = 0.81$). Similarly, approximately 65% of the variation in the unbound concentrations is explained by total ropivacaine plasma concentration, time, and plasma AAG concentration ($R^2 = 0.66$).

Total and unbound plasma concentrations of pipercoloxylidide both increased during the infusion (fig. 3). Total and unbound concentrations measured at the discontinuation of the infusion are shown in table 2. No plasma concentrations of 3-OH-ropivacaine and 2-OH-

Table 2. Pharmacokinetic Data in Patients Receiving a 72-h Epidural Ropivacaine Infusion

	Group 1 (n = 12)	Group 2 (n = 7)
Total plasma ropivacaine concentrations		
Highest (mg/l)	3.1 ± 1.5*	2.9 ± 0.5
End of infusion (mg/l)	2.4 ± 0.9	2.8 ± 0.5
t _{1/2} (h)	5.2 ± 2.5	5.5 ± 1.8
AUC (mg · h · l ⁻¹)†	142 ± 44	156 ± 24
Unbound plasma ropivacaine concentrations		
Highest (mg/l)	0.087 ± 0.040	0.091 ± 0.021
8:00 AM on last day (mg/l)	0.062 ± 0.033	0.088 ± 0.016
AUC _u (mg · h · l ⁻¹)†	4.8 ± 2.6	5.5 ± 1.1
Cl _u (l/min)	5.1 ± 1.8	5.5 ± 1.7
Total plasma PPX concentrations		
End of infusion (mg/l)	1.0 ± 0.4	1.2 ± 0.4
Unbound plasma PPX concentrations		
End of infusion (mg/l)	0.4 ± 0.2	0.5 ± 0.1

* Data include one outlying value (see text). Median values are 2.7 mg/l (group 1) and 3.0 mg/l (group 2).

† Because some patients received a bolus dose of 75 mg instead of 50 mg, data are normalized for dose (group 1, 1,490 mg; group 2, 2,210 mg).

AUC = area under the total plasma concentration–time curve; AUC_u = area under the unbound plasma–concentration time curve; Cl_u = unbound clearance; PPX = pipercoloxylidide.

methyl-ropivacaine were detected. Unbound fractions of pipercoloxylidide decreased from 82 ± 18 and 89 ± 23% after 8 h to 41 ± 8 and 44 ± 9% after 72 h in groups 1 and 2, respectively. The variation in f_u was mainly explained by variations in plasma AAG concentrations.

Urinary excretion data during the period from the start of the infusion until 6 h after discontinuation of the infusion in the patients who received a ropivacaine infusion lasting 72 h (n = 12 for each group) are presented in table 3 and did not differ between the groups. Excretion of unchanged ropivacaine represented only a small fraction of the dose in all subjects. Urinary excretion of 3-OH-ropivacaine and pipercoloxylidide accounted for

approximately 20 and 10% of the dose. 2-OH-methyl-ropivacaine was not detectable in urine. The excretion of pipercoloxylidide increased with time, whereas the excretion of 3-OH-ropivacaine decreased with time (fig. 4). Consequently the total excretion rate was almost constant in time.

Clinical Effectiveness

Postoperative morphine consumption during the 72-h study period was low (group 1: median, 16 mg; range, 0–126 mg; group 2: median, 23 mg; range, 0–46 mg). The number of unrewarded demands during the same period was small (group 1: median 3, range, 0–36; group 2: median 5, range 0–58). One patient from group 1 and two patients from group 2 received indometacin, 25–100 mg rectally or orally, at least once at the surgeon's request. Median visual analog scale scores were less than 30 at all observation times. Median upper levels of sensory blockade were highest after 4 h of infusion (T8 in group 1, T5 in group 2) and subsequently decreased to 0 or 1. Motor block scores were mostly 0 or 1. Motor block scores of 2 or more were observed at least once in 4 of 14 patients (29%) in group 1 and in 11 of 12 patients (92%) in group 2.

Discussion

The primary objective of the current study was to evaluate the pharmacokinetics of ropivacaine in patients receiving a long-term epidural infusion of ropivacaine for postoperative pain relief. Total plasma concentration and unbound plasma concentrations of ropivacaine and pipercoloxylidide both were evaluated because concentrations at the targets for systemic toxicity in the central nervous system and the heart are believed to be more closely related to unbound concentrations. Therefore unbound plasma concentrations of local anesthetics associated with regional anesthetic procedures may be

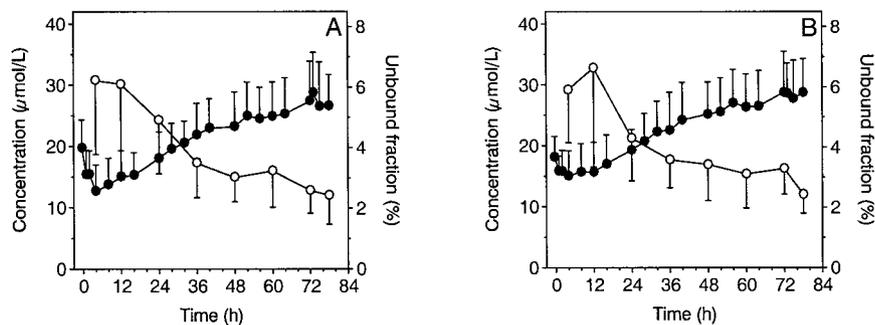
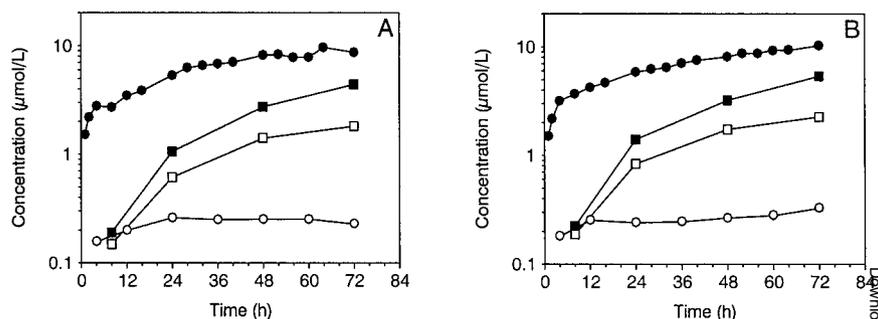


Fig. 2. Mean total plasma concentrations of α_1 -acid glycoprotein (closed symbols) and mean free fractions of ropivacaine (open symbols) in patients receiving constant-rate infusions of 10 ml/h ropivacaine, 2 mg/ml (group 1, n = 12, A) or 3 mg/ml (group 2, n = 7, B), for 72 h. Error bars represent standard deviations.

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Fig. 3. Mean total (closed symbols) and unbound (open symbols) plasma concentrations of ropivacaine (circles) and pipecoloxylidide (squares) in patients receiving constant-rate infusions of 10 ml/h ropivacaine, 2 mg/ml (group 1, n = 12, A) or 3 mg/ml (group 2, n = 7, B), for 72 h.



better indicators of the systemic safety than are total plasma concentrations. The study showed that although total plasma concentrations of ropivacaine increase with time during the infusion, unbound plasma concentrations reach a plateau after approximately 24 h. These observations reflect an increase in the degree of plasma protein binding of ropivacaine, which is related to an increase in the plasma concentrations of AAG. AAG, also known as orosomucoid, is a so-called acute phase protein that is sensitive to stressful situations, including surgical trauma, and may be altered by various disease states.¹⁴ Measurements of AAG concentrations after major surgical procedures have shown that these increase gradually and may not reach a maximum until the sixth to twelfth postoperative days.⁶⁻⁸ Consequently, the protein binding of local anesthetics that are mainly bound to AAG will increase continuously, as demonstrated in this and other studies.^{6,8,15} The consequences of the change in protein binding vary. With drugs such as ropivacaine and bupivacaine, which are eliminated almost entirely by biotransformation in the liver and have a relatively small hepatic extraction ratio, an increase in the degree of protein binding may be expected to result in a decrease in the total plasma clearance.¹⁶⁻¹⁹ This may explain why ropivacaine concentrations continued to increase during long-term postoperative infusion. In contrast, an increase in the degree of protein binding will have little or no effect on the unbound plasma clearance, which is mainly dependent on the hepatic enzyme capacity. This may explain why unbound plasma concentrations remained relatively stable after 12-24 h.

A factor that is frequently ignored in relation to the risk of adverse systemic reactions of local anesthetics is the role of metabolites. In this respect, pipecoloxylidide, a dealkylation product formed by biotransformation of ropivacaine and bupivacaine, deserves attention when these local anesthetics are administered for prolonged time periods. The current study showed that a 72-h epidural infusion of ropivacaine results in plasma con-

centrations of pipecoloxylidide that approach the plasma concentrations of ropivacaine. More importantly, unbound pipecoloxylidide concentrations at the end of the infusion were approximately eight- to ninefold higher than unbound ropivacaine concentrations. As with ropivacaine, the unbound fraction of pipecoloxylidide decreased during the infusion, but, unlike unbound ropivacaine concentrations, unbound pipecoloxylidide concentrations did not reach a plateau. In part, this may be caused by slower elimination of pipecoloxylidide (half-life = 8.8 h) compared with ropivacaine (half-life = 1.9 h).²⁰ With a constant production of pipecoloxylidide, one would predict a constant unbound plasma pipecoloxylidide concentration after approximately 24-36 h, *i.e.*, 48-60 h after the start of ropivacaine infusion. Because of the low sampling frequency for determination of unbound plasma concentrations of pipecoloxylidide, it is possible that we missed the steady state. Therefore, further studies will be necessary to determine the time at which the steady state is reached and the magnitude of the steady state concentrations that are ultimately achieved.

Signs or symptoms indicative of systemic toxicity did not occur in the current study. Comparison of the highest unbound ropivacaine concentrations in the individual patients (range, 0.04-0.2 mg/l) to the threshold concentration for mild central nervous system toxicity

Table 3. Urinary Excretion of Ropivacaine and Metabolites

	Group 1 (n = 12)	Group 2 (n = 12)
Ropivacaine (%)	1.1 (0.4-7.5)	1.4 (0.6-2.5)
3-OH-ropivacaine (%)*	18 (12-31)	18 (12-25)
PPX (%)	10 (5-16)	10 (5-20)
Total (%)	31 (26-39)	31 (25-36)

Data represent fractions of the total dose and are presented as median (range).

* Conjugated and unconjugated.

PPX = pipecoloxylidide.

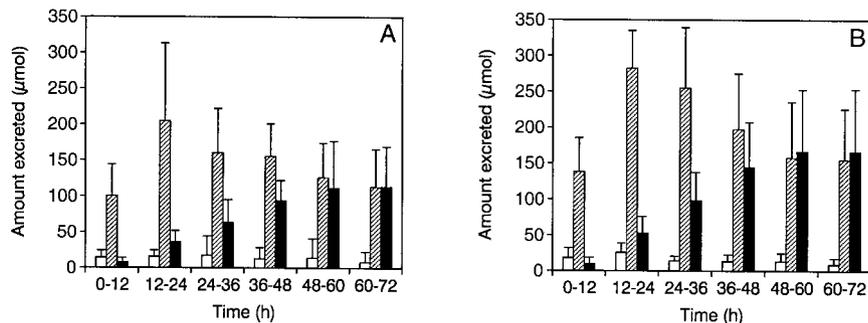


Fig. 4. Mean amounts of ropivacaine (white bars), 3-OH-ropivacaine (conjugated and unconjugated, hatched bars), and pipercoloxylidide (dark bars) excreted in the urine in subsequent 12-h intervals during the 72 h of continuous epidural infusion of ropivacaine, 2 mg/ml (group 1, $n = 13$, A) or 3 mg/ml (group 2, $n = 12$, B). Data from group 1 include one patient in whom the infusion was discontinued after 42.5 h. Data from group 2 include patients in whom the infusion rate was decreased. Standard deviations are shown on top of the bars.

derived after rapid intravenous infusion of ropivacaine in healthy subjects (0.34–0.85 mg/l), also suggests a sufficient margin of safety with use of the studied infusion regimens.²¹ A toxic threshold concentration for pipercoloxylidide has not been established in humans. However, in rats, pipercoloxylidide has been shown to be at least 20 times less toxic (in terms of dose equivalents) than ropivacaine,²² and plasma pipercoloxylidide levels associated with mild systemic side effects are approximately 10 times higher than those observed in the current study.**

Although a linear relation was expected between the plasma concentrations and the infusion rate, and between the AUCs and total doses, this could not be established in this study. In part, this may be explained on the basis of interindividual variability.

The study confirmed that pipercoloxylidide and 3-OH-ropivacaine are major metabolites of ropivacaine.²³ Urinary excretion of pipercoloxylidide and 3-OH-ropivacaine until 6 h after discontinuation of the infusion accounted for approximately 30% of the dose, whereas the excretion of unchanged ropivacaine was negligibly small. The urinary excretion was overall in good agreement with previous observations during variable-rate epidural infusion of ropivacaine.¹⁵ The relatively low urinary recovery may in part be explained by the fact that urine collection ended 6 h after discontinuation of the infusion. At this time, substantial amounts of ropivacaine and metabolites, in particular pipercoloxylidide, are still in the body. In addition, metabolites not evaluated in this study, such as 3-OH-pipercoloxylidide, and excretion *via* other routes may in part explain the low recovery rate. In volunteers administered a 15-min infusion of ropivacaine, 86% of the dose was recovered from urine and 9%

from feces after 96 h.²⁴ An interesting observation in this study was that the urinary excretion rate of 3-OH-ropivacaine decreased over time, whereas the excretion of pipercoloxylidide increased over time, reaching a plateau on the third postoperative day (fig. 4). This suggests progressive change in metabolic pattern during prolonged epidural infusion, which may explain why, despite the relatively short urine collection time, the fraction of the dose accounted for by urinary excretion of pipercoloxylidide (10%) in this study was considerably larger than the fraction accounted for in 96 h after short intravenous infusion in volunteers (2%).²⁴

Clinically, the infusion regimens appeared to be well tolerated, although blood pressures during surgery were frequently unstable. This may be a consequence of the epidural block *per se*, in addition to the effects of general anesthesia. Because of the incidence of hypotension, the initial bolus dose of ropivacaine was reduced from 75 mg to 50 mg after the first five patients. Postoperatively both infusion regimens of ropivacaine provided effective pain relief, as judged by the low morphine consumption, low frequency of unrewarded demands, and visual analog scale scores. These observations are in accordance with a previous study by Badner *et al.*³

Sensory block levels were relatively high in the immediate postsurgical phase, but decreased to low thoracic-high lumbar levels on the first postoperative day in most patients. Motor blockade was overall more intensive in the patients receiving the more concentrated ropivacaine solution and was the main reason to reduce the infusion rate in 4 of 12 patients receiving this regimen. A similar tendency toward a more intensive motor block, with shorter-duration (21 h) infusion of either a 3-mg/ml solution or higher infusion rates of a 2-mg/ml solution, has been reported by other investigators.^{1–3,25} Because the 2-mg/ml solution offered similar pain relief to the 3-mg/ml solution, but less intense motor block, the 2-mg/ml solution is preferable for postoperative pain relief.

** Halldin MM: Plasma protein binding of pipercoloxylidide in rats. Astra report 802-550-LF-0417-01, April 20, 1998. Astra Pain Control AB, Södertälje, Sweden.

In conclusion, plasma concentrations of ropivacaine and its metabolite pipecoloxylidide increase profoundly during the infusion, whereas unbound plasma concentrations of ropivacaine reach a plateau, and unbound concentrations of pipecoloxylidide increase less than total plasma concentrations of pipecoloxylidide. These observations can be explained on the basis of changes in the degree of plasma protein binding, which are related to changes in plasma AAG concentrations, which increase continuously as a result of the surgical intervention. Although plasma concentrations of ropivacaine and pipecoloxylidide both were relatively high, signs or symptoms indicative of systemic toxicity did not occur in any patient.

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References

1. Scott DA, Chamley DM, Mooney PH, Deam RK, Mark AH, Hägglöf B: Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery—A dose finding study. *Anesth Analg* 1995; 81:982-6
2. Turner G, Blake D, Buckland M, Chamley D, Dawson P, Goodchild C, Mezzatesta J, Scott D, Sultana A, Walker S, Hendrata M, Mooney P, Armstrong M: Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery. *Br J Anaesth* 1996; 76:606-10
3. Badner NH, Reid D, Sullivan P, Ganapathy S, Crosby ET, McKenna J, Lui A: Continuous epidural infusion of ropivacaine for the prevention of postoperative pain after major orthopaedic surgery: A dose-finding study. *Can J Anaesth* 1996; 43:17-22
4. Schug SA, Scott DA, Payne J, Mooney PH, Hägglöf B: Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. *Br J Anaesth* 1996; 76:487-91
5. Feldman HS, Arthur GR, Covino BG: Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog. *Anesth Analg* 1989; 69:794-801
6. Erichsen C-J, Sjövall J, Kehlet H, Hedlund C, Arvidsson T: Pharmacokinetics and analgesic effect of ropivacaine during continuous epidural infusion for postoperative pain relief. *ANESTHESIOLOGY* 1996; 84:834-42
7. Aronson K-F, Ekelund G, Kindmark C-O, Laurell C-B: Sequential changes of plasma proteins after surgical trauma. *Scand J Clin Lab Invest* 1972; 29(suppl) 124:127-36
8. Wulf H, Winckler K, Maier C, Heinzow B: Pharmacokinetics and protein binding of bupivacaine in postoperative epidural analgesia. *Acta Anaesthesiol Scand* 1988; 32:530-4
9. Ausems ME, Hug CC, Stanski DR, Burm AGL: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *ANESTHESIOLOGY* 1986; 65:362-73
10. Björk M, Pettersson K-J, Österlöf G: Capillary gas chromatographic method for the simultaneous determination of local anaesthetics in plasma samples. *J Chromatogr A* 1990; 533:229-34
11. Arvidsson T, Eklund E: Determination of free concentration of ropivacaine and bupivacaine in blood plasma by ultrafiltration and coupled-column liquid chromatography. *J Chromatogr B Biomed Sci Appl* 1995; 668:91-8
12. Mancini G, Cabbonara AO, Heremans JF: Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* 1965; 2:235-54
13. Arvidsson T, Askemark Y, Halldin MM: Liquid chromatographic bioanalytical determination of ropivacaine, bupivacaine and major metabolites. *Biomed Chromatogr* 1999; 13:286-92
14. Wood M: Plasma drug binding: Implications for anesthesiologists. *Anesth Analg* 1986; 65:786-804
15. Scott DA, Emanuelsson B-M, Mooney PH, Cook RJ, Junstrand C: Pharmacokinetics and efficacy of long-term epidural ropivacaine infusion for postoperative analgesia. *Anesth Analg* 1997; 85:1322-30
16. Lee A, Fagan D, Lamont M, Tucker GT, Halldin M, Scott DB: Disposition kinetics of ropivacaine in humans. *Anesth Analg* 1989; 69:736-8
17. Tucker GT, Mather LE: Clinical pharmacokinetics of local anaesthetics. *Clin Pharmacokinet* 1979; 4:241-78
18. Wilkinson GR: Clearance approaches in pharmacology. *Pharmacol Rev* 1987; 39:1-47
19. Smallwood RH, Mihaly GW, Smallwood RA, Morgan DJ: Effect of a protein binding change on unbound and total plasma concentrations for drugs of intermediate hepatic extraction. *J Pharmacokinet Biopharm* 1988; 16:529-42
20. Arlander E, Ekström G, Alm C, Carrillo JA, Bielenstein M, Böttger Y, Bertilsson L, Gustafsson LL: Metabolism of ropivacaine in humans is mediated by CYP1A2 and to a minor extent by CYP3A4: An interaction study with fluvoxamine and ketoconazole as in vivo inhibitors. *Clin Pharmacol Ther* 1998; 64:484-91
21. Knudsen K, Beckman Suurküla M, Blomberg S, Sjövall J, Edvardsson N: Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; 78:507-14
22. Danielsson BRG, Danielsson MK, Lindström Böö E, Arvidsson T, Halldin MM: Toxicity of bupivacaine and ropivacaine in relation to free plasma concentrations in pregnant rats: A comparative study. *Pharmacol Toxicol* 1997; 81:90-6
23. Ekström G, Gunnarsson U-B: Ropivacaine, a new amide-type local anesthetic agent, is metabolized by cytochromes P450 1A and 3A in human liver microsomes. *Drug Metab Dispos* 1996; 24:955-61
24. Halldin MM, Bredberg E, Angelin B, Arvidsson T, Askemark Y, Elofsson S, Widman M: Metabolism and excretion of ropivacaine in humans. *Drug Metab Dispos* 1996; 24:962-8
25. Zaric D, Nydahl P-A, Philipson L, Samuelsson L, Heierson A, Axelsson K: The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers: A double-blind study. *Reg Anesth* 1996; 21:14-25