

Pharmacokinetics of Ropivacaine in Uremic and Nonuremic Patients After Axillary Brachial Plexus Block

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Reports on the efficacy and pharmacokinetics of local anesthetics in uremic patients have been controversial. Our study involved 29 uremic and 28 nonuremic patients. We performed axillary block with ropivacaine 300 mg (50 mL). Venous blood samples were drawn for 24 h for assay of total and unbound plasma ropivacaine, 3-hydroxyropivacaine, pipercoloxylidide (PPX), and serum α_1 -acid glycoprotein (AAG). Block quality was similar in both groups. No toxicity occurred. Plasma clearance of ropivacaine was smaller and the area under the concentration-time curve of ropivacaine, 3-hydroxyropivacaine, and PPX larger in the uremic patients. The plasma concentration of PPX increased

until 24 h in uremic patients whose AAG concentrations were also larger throughout the study. The free fraction of ropivacaine in plasma was smaller in the uremic group when measured 60 min and 12 h after the block, but the unbound concentration of ropivacaine was larger in the uremic group at 12 h. Enhanced absorption of ropivacaine into circulation, increased binding to AAG, and probably reduced urinary excretion of the metabolites lead to larger total plasma concentrations of ropivacaine and its main metabolites in uremic patients.

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Large doses of local anesthetics are needed in brachial plexus blocks. Because of the risk of systemic toxicity of bupivacaine, the less toxic alternative, ropivacaine (1,2), may be used for blocks of similar intensity and duration (3,4). The central nervous system toxicity of any local anesthetic is directly related to its potency, but ropivacaine has been found to be only about half as arrhythmogenic as racemic bupivacaine. In humans, ropivacaine is metabolized to 2,6-pipercoloxylidide (PPX) by cytochrome P450 (CYP) 3A4 and to 3-hydroxyropivacaine (3-OH-ropivacaine) by CYP 1A2 (5). Both metabolites have significantly less anesthetic potency than ropivacaine (6). In uremic patients, the duration of brachial plexus block with lidocaine, mepivacaine, and bupivacaine has been reported to be shorter than in nonuremic patients (7,8), possibly because of fast absorption of the local anesthetic from the region of the brachial plexus into the

circulation. However, some other studies did not show any difference in patient-reported duration of brachial plexus block with lidocaine (9) or bupivacaine (10). The plasma concentrations of bupivacaine after brachial plexus block were larger (8) than, or similar (10) to, those in nonuremic patients.

Because only a very small fraction of ropivacaine is excreted unchanged into urine (approximately 1%) when the liver is functioning normally (11), dosage adjustment based on renal function has not been considered necessary. However, a significant fraction (approximately 50%) of PPX is normally excreted into urine, which might lead to accumulation of this potentially toxic metabolite (12) in uremic patients. The other main metabolite of ropivacaine found in humans, 3-OH-ropivacaine, is also excreted into urine, but its toxicity is probably negligible (6). Ropivacaine is highly bound to α_1 -acid glycoprotein (AAG), which entails that the concentration of AAG in plasma may markedly affect the pharmacokinetics of ropivacaine. It is not known to what extent the metabolites of ropivacaine accumulate in the uremic patient and, possibly, enhance the risk of toxicity. This study was designed to compare the efficacy and pharmacokinetics of ropivacaine between uremic and nonuremic patients after axillary brachial plexus block.

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Table 1. Patient Characteristics (mean \pm SD)

Variable	Uremic	Nonuremic	P value
No. Patients	29	28	
Male/female	20/9	12/16	<0.05
Age (yr)	57 \pm 16	47 \pm 13	<0.05
Height (cm)	172 \pm 10	169 \pm 8	NS
Weight (kg)	74 \pm 14	70 \pm 11	NS
Serum creatinine (μ mol/L)	491 \pm 156	79 \pm 9	<0.001

NS = not significant.

Methods

This study was approved by the institutional ethics committee and the Finnish National Agency for Medicines. Written, informed consent was obtained from the patients before the study. We studied 33 uremic patients scheduled for creation of an arteriovenous fistula in the antibrachial region for hemodialysis and 33 nonuremic patients undergoing hand surgery. However, four uremic and five nonuremic patients were excluded because additional doses of ropivacaine were needed before surgery. Patient characteristics are given in Table 1. Nine of the 29 uremic patients but none of the nonuremic patients had diabetes.

The patients were given their regular medication on the morning of surgery. In addition they received diazepam 0.2 mg/kg orally 60 min before the block. Monitoring consisted of a three-lead electrocardiogram, noninvasive oscillotometric arterial blood pressure, and pulse oximetry. An IV infusion of acetated Ringer's solution 250 mL/h was started before anesthesia. Potassium-free acetated Ringer's solution was used in the uremic patients. A perivascular axillary brachial plexus block was performed. The plexus was identified with a short-beveled electric stimulation needle (Stimuplex, B. Braun Melsungen AG, Melsungen, Germany) connected to a nerve stimulator by using a low current (<1.0 mA). After obtaining a peripheral motor response with a current near or below 0.5 mA, 50 mL of ropivacaine hydrochloride (Naropin; AstraZeneca, Södertälje, Sweden) diluted to 6 mg/mL (300 mg) was injected in 2 min, with intermittent aspiration. Verbal contact with the patients was maintained throughout the injection, and the patients had been informed about the signs of local anesthetic toxicity, such as numbness of the lips and tongue and lightheadedness, before the injections were made. Firm digital pressure was maintained during the injection and 3 min thereafter immediately distal to the injection site to prevent distal flow of the ropivacaine solution. The arm was then brought to rest at the patient's side. Sensory function of the ulnar, radial, median, and musculocutaneous nerves was tested with pinprick before the block and 5, 10, 15, 30, and 45 min after injection. The patients assessed the pinprick sensation as sharp (normal sensory function),

blunt (analgesia), or no sensation of touch (anesthesia). The degree of motor block in the muscles of the hand and the flexion and extension of the forearm were tested at the same time points and rated on a three-point scale (normal motor function, reduced motor function, and complete motor block). During surgery, IV diazepam for anxiety and fentanyl for surgical pain were given if needed. Postoperative pain was treated with tramadol or with ibuprofen and oxycodone, as required by the uremic and nonuremic patients, respectively.

Peripheral blood samples were drawn from a large vein in the nonoperated arm before the induction of the block; after 5, 30, and 60 min; and 3, 6, 12, and 24 h after the injection of ropivacaine. The concentrations of serum creatinine and AAG were assayed by using standard validated methods from the blood samples taken before the block in the clinical laboratory of the hospital, and AAG was also assayed 12 and 24 h after the induction of the block. The blood samples for the assay of ropivacaine and its metabolites were collected in 10-mL EDTA tubes (Venoject; Terumo Europe NV, Leuven, Belgium), which were then centrifuged within 60 min. The plasma samples were stored at -70°C until the assays were performed.

The total plasma concentrations of ropivacaine, PPX, and 3-OH-ropivacaine were determined by using liquid chromatography, with lidocaine as the internal standard (13). The quantification limits were 1 $\mu\text{g/L}$ for ropivacaine and 2 $\mu\text{g/L}$ for PPX and 3-OH-ropivacaine. The interday coefficient of variation (CV) for ropivacaine was 10.2% at 16.7 $\mu\text{g/L}$ ($n = 19$), 5.9% at 44.1 $\mu\text{g/L}$ ($n = 20$), 5.1% at 489 $\mu\text{g/L}$ ($n = 20$), and 2.9% at 1.54 mg/L ($n = 20$). The CV for PPX was 13.7% at 4.2 $\mu\text{g/L}$ ($n = 19$), 6.3% at 19.6 $\mu\text{g/L}$ ($n = 19$), 6.6% at 47.9 $\mu\text{g/L}$ ($n = 20$), and 2.3% at 532 $\mu\text{g/L}$ ($n = 20$). The CV for 3-OH-ropivacaine was 10.7% at 4.0 $\mu\text{g/L}$ ($n = 19$), 5.5% at 18.8 $\mu\text{g/L}$ ($n = 19$), 4.5% at 47.9 $\mu\text{g/L}$ ($n = 20$), and 4.4% at 507 $\mu\text{g/L}$ ($n = 20$). For the separation of the free (unbound) plasma concentrations of ropivacaine, the ultrafiltration method was used. The temperature was adjusted to 37°C and the pH to 7.4 by bubbling the sample with 5% CO_2 before the ultrafiltration.

The peak concentrations of ropivacaine, PPX, and 3-OH-ropivacaine and the corresponding peak ropivacaine concentration times (T_{max}) were observed directly from each plasma concentration-time profile. The area under the ropivacaine plasma concentration-time curve (AUC) was estimated by means of the logarithmic trapezoidal rule with extrapolation to infinity. For the metabolites, no extrapolation was performed, and the AUC was calculated up to 24 h. For each subject, the terminal log-linear phase of the plasma ropivacaine concentration-time curve was identified visually, and the elimination rate constant (k_{el}) was determined by using regression analysis.

Table 2. Analgesia by Pinprick of the Different Nerves of the Hand and Forearm and the Motor Block of the Hand Measured 45 Minutes After the Injection of Ropivacaine

Variable	Uremic (n = 29)	Nonuremic (n = 28)	P value
Ulnar nerve	29 (100%)	28 (100%)	NS
Median nerve	27 (93%)	28 (100%)	NS
Radial nerve	24 (83%)	27 (96%)	NS
Musculocutaneous nerve	26 (90%)	25 (89%)	NS
Flexion of forearm			
Normal function	0 (0%)	3 (11%)	
Reduced strength	8 (28%)	2 (7%)	
Complete motor block	21 (72%)	23 (82%)	<0.05
Extension of forearm			
Normal function	3 (10%)	1 (4%)	
Reduced strength	5 (18%)	7 (25%)	
Complete motor block	21 (72%)	20 (71%)	NS
Hand grip strength			
Normal function	0 (0%)	0 (0%)	
Reduced strength	6 (21%)	6 (20%)	
Complete motor block	23 (79%)	22 (80%)	NS

NS = not significant.

The elimination half-life of ropivacaine ($t_{1/2}$) was calculated from the equation $t_{1/2} = \ln_2/k_{el}$. The plasma clearance of ropivacaine (CL) was computed from $CL = \text{dose}/AUC$. The steady-state volume of distribution (V_{ss}) was calculated from $V_{ss} = \text{mean residual time (MRT)} \times CL$, and the volume of distribution during the elimination phase (V_z) was calculated from $V_z = CL/k_{el}$. The MRT was calculated from $MRT = AUMC/AUC$, where AUMC is the area under the first moment of the plasma concentration-time curve calculated by using the logarithmic trapezoidal rule with extrapolation to infinity.

For the calculations, all values below the limit of quantitation were set to zero. The pharmacokinetic variables were calculated with the use of the pharmacokinetic program MKMODEL (Version 5.0; Biosoft, Cambridge, UK).

The results are expressed as mean values \pm SD except in the figures, in which we, for clarity, used mean \pm SE. Unpaired Student's *t*-tests were used for comparison of the demographic variables, the serum concentrations of creatinine, and AAG. For the analysis of the quality of the block, a contingency table test was used. For the analysis of differences in the plasma concentrations of ropivacaine and its metabolites, as well as of the pharmacokinetic variables, two-way analysis of variance and unpaired Student's *t*-tests were used. Differences were regarded as statistically significant if $P < 0.05$. The statistical program was Systat for Windows (Version 7.0.1; SPSS Inc., Chicago, IL).

Results

Twenty-nine uremic and 28 nonuremic patients completed the study. The patients in the uremic group

were older ($P < 0.05$) and included a larger proportion of men ($P < 0.05$) than the nonuremic group. However, with regard to height or weight, there was no difference between the groups. There was no significant difference in the quality of sensory block between the uremic and nonuremic patients (Table 2) when tested before the beginning of surgery, 45 min after the injection of ropivacaine. The quality of motor block was also similar except for flexion of the forearm (Table 2). No toxic symptoms occurred despite occasional large plasma concentrations soon after the injection of ropivacaine. In the uremic group, two patients received both IV fentanyl and diazepam, and one patient received diazepam during the operation. In the nonuremic patients in whom a tourniquet was used during the operations, these numbers were three and two, respectively.

The largest individual plasma concentration of ropivacaine was measured in the 5-min sample of a uremic patient. There was large interindividual variation in the plasma concentrations of ropivacaine (range at 5 min from 0.10 to 7.98 mg/L and from 0.11 to 1.49 mg/L in the uremic and nonuremic patients, respectively). The total mean plasma concentrations of ropivacaine (Fig. 1) and 3-OH-ropivacaine (Fig. 2A) were significantly larger ($P < 0.0001$) in the uremic group than in the nonuremic group. The AUC of ropivacaine ($P < 0.01$), 3-OH-ropivacaine ($P < 0.0001$), and PPX ($P < 0.05$) was greater in the uremic group. There was no difference in the T_{max} of either ropivacaine or 3-OH-ropivacaine between the two patient groups (Table 3).

The slowly increasing mean plasma concentrations of PPX were similar in the groups until 6 h (Fig. 2B). Thereafter, for the remaining 18 h, the concentration of PPX in the uremic patients, but not in the nonuremic

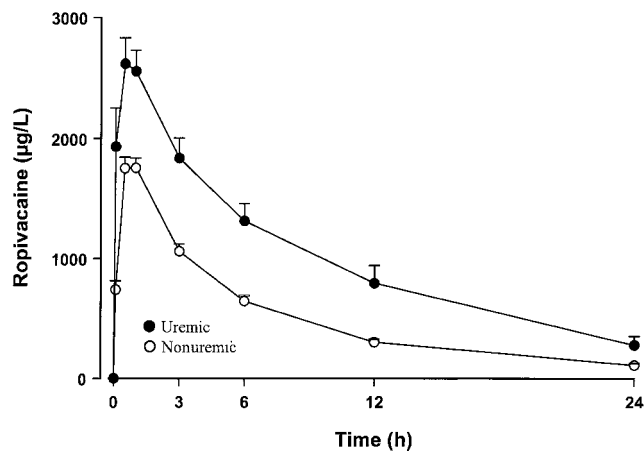


Figure 1. Plasma concentrations of ropivacaine (mean \pm SE) during and after axillary brachial plexus block in uremic and nonuremic patients.

patients, continued to increase. Some very large PPX concentrations (676 and 873 $\mu\text{g/L}$) were observed in the 24-h samples of the uremic patients. The T_{max} of PPX was longer ($P < 0.01$) in the uremic than in the nonuremic patients (Table 3). The pharmacokinetic variables of the uremic patients with diabetes and of those taking CYP 1A2-inhibiting (quinolone antibiotics, $n = 4$) or CYP 3A4-inducing (rifampicin, $n = 1$) drugs did not differ from the other patients' variables. None of the patients was taking theophylline, verapamil, cimetidine, ketoconazole, itraconazole, or fluvoxamine.

There was no postoperative increase in the serum AAG concentrations. However, the uremic group had larger concentrations of AAG ($P < 0.001$) before and 12 and 24 h after the block (Table 4).

The free fraction of ropivacaine, measured at 60 min and 12 h after the injection, was smaller ($P < 0.001$) in the uremic group than in the nonuremic group (Table 4). The unbound plasma concentration of ropivacaine was similar between the groups 60 min after the block but was larger in the uremic group ($P < 0.05$) 12 h after the block. The largest individual concentration of free ropivacaine, 0.37 mg/L (in a uremic patient), was not associated with any toxic symptoms.

Discussion

Ropivacaine 300 mg, in a volume of 50 mL, for axillary brachial plexus block provided a similar sensory and motor block in uremic and nonuremic adult patients. Comparison between uremic and nonuremic patients of the duration of the brachial plexus block, based on the latency to the first appearance of pain or paresthesia in the operated arm, has shown the block to be of either shorter (7,8) or similar (9,10) duration in uremic patients. Because the type of surgery was different in

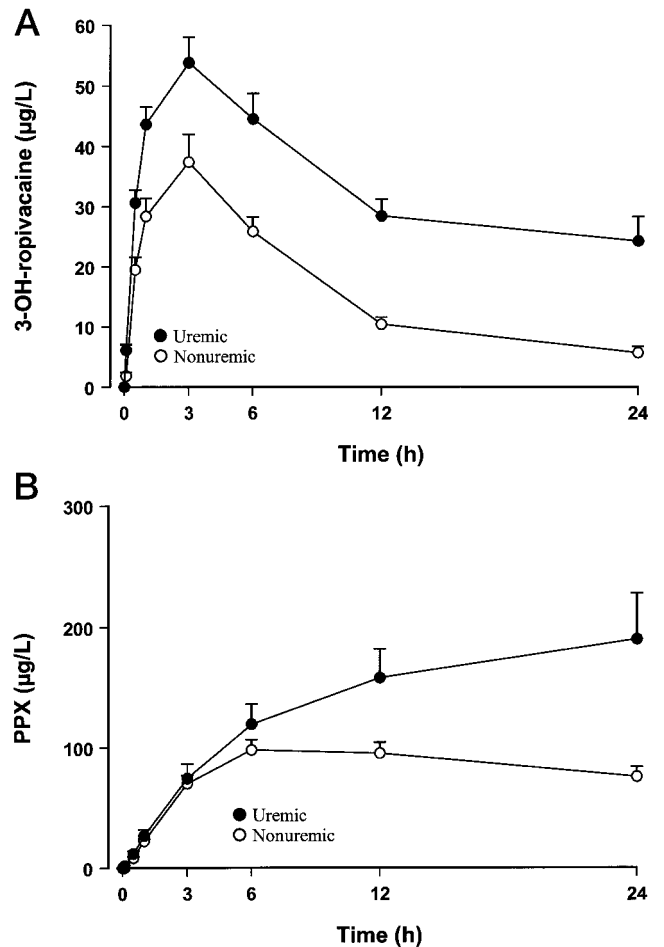


Figure 2. Plasma concentrations (mean \pm SE) of the ropivacaine metabolites 3-hydroxyropivacaine (3-OH-ropivacaine) (A) and pipercolonylidide (PPX) (B) during and after axillary brachial plexus block in uremic and nonuremic patients.

the uremic patients (arteriovenous fistula on the forearm) and the nonuremic patients (various operations of the forearm, wrist, and hand), the onset of pain cannot be considered a reliable measure of the duration of the block in our study. The power of many previous studies (7-10) might not have been sufficient to detect small differences in the duration of the block. In our study, despite significantly larger plasma concentrations of ropivacaine and its metabolites in the uremic patients, we could not demonstrate a poorer quality of block in the uremic patients, either. In any case, our pharmacokinetic data agree with the speculation of increased blood flow (hyperdynamic circulation) in uremic patients (14) rapidly flushing the deposits of local anesthetics (7). This concept is also supported by the rapidly increasing plasma concentrations of bupivacaine (8) and by shorter spinal blocks (pinprick analgesia) with bupivacaine in uremic patients (15). Despite the markedly improved treatment of uremia, by which, e.g., the severity of anemia has been greatly reduced, a high preanesthetic

Table 3. Pharmacokinetic Variables (mean ± SD) of Ropivacaine, Pipecoloxylidide, and 3-Hydroxyropivacaine After an Axillary Brachial Plexus Block with 300 mg (50 mL) of Ropivacaine

Variable	Uremic (n = 29)	Nonuremic (n = 28)	P value
Ropivacaine			
C _{max} (mg/L)	2.9 ± 1.4	1.8 ± 0.5	<0.001
T _{max} (h)	0.8 ± 0.7	0.8 ± 0.3	NS
AUC (mg/L · h)	29.2 ± 29.2	13.6 ± 8.4	<0.01
t _{1/2} (h)	8.6 ± 8.8	8.4 ± 10.5	NS
CL (mL/min)	254 ± 157	400 ± 162	<0.01
MRT (h)	11.3 ± 12.4	11.2 ± 14.9	NS
V _{ss} (L)	119 ± 57	211 ± 123	<0.001
V _z (L)	137 ± 87	236 ± 144	<0.01
Pipecoloxylidide			
C _{max} (mg/L)	198 ± 197	105 ± 50	<0.05
T _{max} (h)	15.6 ± 7.7	9.1 ± 5.1	<0.01
AUC (mg/L · h)	3102 ± 2899	1857 ± 1061	<0.05
t _{1/2} (h)	64.4 ± 93.1	41.4 ± 56.7	NS
3-Hydroxyropivacaine			
C _{max} (μg/L)	58 ± 23	39 ± 25	<0.01
T _{max} (h)	4.8 ± 5.6	2.8 ± 1.7	NS
AUC (mg/L · h)	714 ± 392	357 ± 200	<0.0001
t _{1/2} (h)	32.5 ± 52.9	9.1 ± 7.3	<0.05

C_{max} = peak plasma concentration; T_{max} = time to peak plasma concentration; AUC = area under the drug plasma concentration-time curve; t_{1/2} = elimination half-life; CL = plasma clearance; V_{ss} = steady-state volume of distribution; V_z = volume of distribution during the elimination phase; MRT = mean residual time; NS = not significant.

Table 4. The Concentration (mean ± SD) of Serum α₁-Acid Glycoprotein (AAG), Plasma Unbound Ropivacaine, and the Free Fraction (%) of Ropivacaine in 29 Uremic and 28 Nonuremic Patients

Variable	Uremic	Nonuremic	P value
Serum AAG (g/L)			
0 h	1.17 ± 0.39	0.63 ± 0.19	<0.001
12 h	1.13 ± 0.35	0.60 ± 0.27	<0.001
24 h	1.18 ± 0.46	0.63 ± 0.19	<0.001
Plasma unbound ropivacaine (mg/L)			
60 min	0.13 ± 0.05	0.14 ± 0.04	NS
12 h	0.03 ± 0.02	0.02 ± 0.01	<0.05
Plasma unbound ropivacaine (% of total concentration)			
60 min	5.2 ± 2.1	8.3 ± 2.2	<0.001
12 h	4.2 ± 1.7	6.0 ± 2.0	<0.001

NS = not significant.

cardiac index may still be found in uremic patients (16); this is probably maintained by large endogenous catecholamine levels.

The plasma concentrations of both ropivacaine and its metabolites, PPX and 3-OH-ropivacaine, were larger in the uremic than in the nonuremic patients. The larger total plasma concentrations of ropivacaine are explained by the increased AAG concentrations in the uremic patients, in whom the free fraction of ropivacaine available for metabolism in the liver was thus reduced. In contrast to several other studies, there was

no postoperative increase in the plasma AAG concentrations in either patient group, probably because the operations were peripheral and caused little tissue damage. The impairment of renal function as such is not significant in the elimination of ropivacaine, whose excretion into the urine is minimal. However, because renal function is important to the elimination of PPX and 3-OH-ropivacaine, renal insufficiency may cause accumulation of these compounds. The peak concentrations of the three compounds were larger in the uremic patients. Despite the fact that clearance of ropivacaine was significantly reduced in uremic patients, this was not associated with an increase in t_{1/2}, because the distribution volume of ropivacaine was also markedly reduced in uremia, indicating enhanced plasma protein binding of ropivacaine in uremic patients. Similarly, increased concentrations of AAG (without uremia) reduce the volume of distribution and systemic clearance of saquinavir, which is also highly bound to AAG (17). None of our patients was taking fluvoxamine, which is a strong inhibitor of CYP 1A2 (a producer of 3-OH-ropivacaine).

An interesting finding was the retention of PPX in the plasma at the later stage (6–24 hours) of the observation period. Although some very large PPX concentrations were measured in the 24-hour samples of the uremic patients, the actual mean maximum plasma concentration could occur between the last two sampling times (12–24 hours). Because nearly half of an IV dose of PPX is excreted into urine (18), the delayed and larger increase in the PPX concentrations is caused by impaired urinary excretion of PPX. PPX

might also be retained in plasma by binding to AAG, whose concentration in plasma is large in uremia (19,20). However, this mechanism remains speculative because we did not assess the ratio of free and total PPX in this study. The degree of binding of PPX to the plasma proteins, mainly AAG, seems, however, to be much smaller than that of ropivacaine; only approximately 10%–20% of PPX has been shown to be bound to AAG in surgical patients (21).

Although the mean concentrations of PPX were small, large concentrations of PPX may unexpectedly develop, as seen in our study (PPX maximum, 873 $\mu\text{g/L}$). Thus, the free plasma concentrations of PPX (80%–90% of the total) may reach the toxic level although PPX is clearly less toxic than, e.g., bupivacaine (12,22).

The degree of protein binding of ropivacaine in plasma, when measured at 60 minutes (uremic group, 95%; versus nonuremic group, 92%) and at 12 hours (96% versus 94%, respectively) in our study, was in the same range as in earlier reports (23,24). Although the binding of ropivacaine to AAG was slightly increased in the uremic patients, there was considerable interindividual variation, and the largest individual concentration of free ropivacaine 60 minutes after the injection of ropivacaine was 0.37 mg/L. Toxicity was not seen in a uremic patient with a total ropivacaine concentration of 7.98 mg/L 5 minutes after injection. Although no blood was seen in repeated aspiration, in this patient some of the local anesthetic may have been injected inadvertently into a vein. Therefore, despite a smaller degree of toxicity than with, e.g., bupivacaine, ropivacaine should also always be used carefully and strictly monitored.

We conclude that the quality of axillary brachial plexus block with 300 mg of ropivacaine seems to be similar in uremic and nonuremic patients, although the pharmacokinetic data of our study show that faster absorption into the circulation and increased binding to AAG, reducing liver extraction, lead to significantly larger plasma concentrations of ropivacaine in uremic patients. The plasma concentration of the main metabolite, PPX, remains large in uremic patients 24 hours after the injection of ropivacaine, probably because of reduced renal excretion. No systemic toxicity was encountered, despite some large individual concentrations of ropivacaine and PPX in the uremic patients. Differences in the bioavailability of ropivacaine in our study probably partly accounted for these individual large concentrations. Urinary concentrations of ropivacaine or the metabolites were not measured in our study. However, our data on the plasma concentrations support the conclusions that urinary excretion of PPX is markedly delayed in uremic patients and that caution should be exercised when large doses of ropivacaine are administered to patients with impaired renal function, e.g., during

continuous blocks. However, the greater local anesthetic binding capacity to AAG in uremic patients might offer some protection against acute toxicity. This aspect, however, requires further study, including determination of the free unbound concentrations of PPX.

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