A.N. Sandler MBCHB MSC FRCPC,*
E. Arlander MSCPHARM,†
B.T. Finucane MBBCH BAO FRCPC,‡
A. Taddio PhD,§
V. Chan MD FRCPC,*
A. Milner MBBCH FFA(SA) FRCPC,‡
S.O. Callahan-Enright MBBCH BAO FFARCSI,‡
M. Friedlander MBCHB FRCPC,*
D. Muzyka MD FRCPC‡

Pharmacokinetics of three doses of epidural ropivacaine during hysterectomy and comparison with bupivacaine

Purpose: Ropivacaine is a new long-acting aminoamide local anaesthetic, structurally related to bupivacaine. The clinical efficacy of 125 mg, 187.5 mg and 250 mg ropivacaine have been reported and compared with 125 mg bupivacaine for epidural analgesia during hysterectomy. In the pharmacokinetic part of this study the objectives were to 1) determine the dose proportionality in the pharmacokinetics of epidural ropivacaine, and 2) compare the pharmacokinetics of 125 mg ropivacaine and 125 mg bupivacaine.

Methods: In a randomized, double-blind controlled study, patients received one of four treatment regimens with ropivacaine (125, 187.5 or 250 mg) or bupivacaine (125 mg) as a 25 ml epidural bolus administered over three minutes. Peripheral venous blood samples were collected over 24 hr for ropivacaine or bupivacaine quantification using gas chromatography with nitrogen sensitive detection. Pharmacokinetic variables were derived from plasma concentration-time curve data.

Results: Fifty two women entered the study. Demographic characteristics were similar among groups. Six patients were excluded due to inadequate sensory block or an insufficient number of plasma samples. The peak plasma concentration (C_{max}) of ropivacaine and the total area under the plasma concentration-time curve (AUC) increased proportionally with the dose. Apparent plasma clearance (CL) and the terminal half-life ($t_{1/2}$) were similar in the three ropivacaine groups. When compared with the 125 mg ropivacaine group, the bupivacaine group had a longer terminal half life ($P < 0.05$).

Conclusions: Epidural ropivacaine displays dose-proportional pharmacokinetic behaviour for doses of 125 mg to 250 mg. Ropivacaine has a shorter terminal half-life than bupivacaine.

Objectif : La ropivacaine est un nouvel anesthésique local aminoamide à action prolongée, de structure apparentée à la bupivacaine. L'efficacité clinique de 125 mg, de 187,5 mg et de 250 mg de ropivacaine a été décrite et comparée avec 125 mg de bupivacaine pour l'analgésie péridurale pendant l'hystérectomie. Les objectifs pharmacocinétiques de cette étude étaient de 1) déterminer la proportionnalité de la dose dans la pharmacocinétique de la ropivacaine péridurale, et de 2) comparer la pharmacocinétique de 125 mg de ropivacaine avec 125 mg de bupivacaine.

Méthode : Lors d'une étude contrôlée, randomisée et en double insu, des patientes ont reçu l'un des quatre régimes d'anesthésique avec la ropivacaine (125, 187,5 ou 250 mg) ou la bupivacaine (125 mg) sous forme d'un bolus péridural de 25 ml administré pendant trois minutes. Des échantillons de sang veineux périphérique ont été prélevés pendant 24 h pour le dosage de la ropivacaine ou de la bupivacaine en utilisant la chromatographie en phase gazeuse avec détection sensible à l'azote. Les variables pharmacocinétiques ont été dérivées des données de la courbe de la concentration plasmatique en fonction du temps.

Résultats : Cinquante-deux femmes ont participé à l'étude. Les caractéristiques démographiques étaient similaires dans les différents groupes. Six patientes ont été exclues à cause d'un blocage sensoriel insuffisant ou d'un nombre limité d'échantillons plasmatiques. La concentration plasmatique maximale (C_{max}) de ropivacaine et l'aire totale sous la courbe de la concentration plasmatique en fonction du temps (ASC) se sont accrues en proportion de la dose. La clairance plasmatique apparente (CL) et la demi-vie terminale ($t_{1/2}$) ont été semblables dans les trois groupes ayant reçu de la ropivacaine. Quand on l'a comparé au groupe de 125 mg de ropivacaine, le groupe de bupivacaine a présenté une demi-vie terminale plus longue ($P < 0,05$).

Conclusion : La ropivacaine péridurale a affiché un comportement pharmacocinétique proportionnel à la dose dans le cas des régimes de 125 mg à 250 mg. La ropivacaine a une demi-vie terminale plus courte que la bupivacaine.

From the Department of Anaesthesia, The Toronto Hospital and Mt Sinai Hospital and the Department of Anaesthesia, University of Toronto,* Astra Pain Control AB, Södertälje, Sweden,† Department of Anesthesia, University of Alberta, Edmonton, Alberta,‡ Department of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, and Faculty of Pharmacy, University of Toronto, Toronto, Ontario.§

Address correspondence to: Dr. A.N. Sandler, Department of Anesthesia, Bell Wing 4-644, The Toronto Hospital, 585 University Avenue, Toronto, Ontario, Canada M5G 2C4. Phone: 416-340-4800; Fax: 416-340-3698

Presented at the CAS annual meeting, Ottawa, 1995. Supported by a grant from Astra Pain Control AB, Södertälje, Sweden.

Accepted for publication June 16, 1998.

ROPIVACAINE (the S-enantiomer of 1-propyl-2', 6'-pipercoloxylidine hydrochloride monohydrate) is a new long acting local anaesthetic (Naropin®). Ropivacaine is structurally related to bupivacaine but is less lipid-soluble,¹ and, after intravenous administration, ropivacaine has a higher plasma clearance and a smaller volume of distribution.² The onset of action, duration of action and extent of sensory block of ropivacaine are similar to that of bupivacaine. The motor block, however, is less intense and of shorter duration.³⁻⁶ In preclinical studies, ropivacaine appeared to have less CNS and cardiac toxicity than bupivacaine.⁷⁻⁸

This pharmacokinetic evaluation was part of a double-blind randomized controlled clinical trial comparing the efficacy of 125 mg, 187.5 mg, and 250 mg of epidural ropivacaine and 125 mg of epidural bupivacaine during abdominal hysterectomy.⁹ The clinical results from the study revealed a dose-response effect with increasing doses of ropivacaine. We now report the results of the pharmacokinetic analysis. The objectives were to evaluate the dose-proportionality and pharmacokinetic behaviour of the three doses of epidural ropivacaine and compare the pharmacokinetics of epidural ropivacaine and bupivacaine.

Methods

The study protocol was approved by the Institutional Review Boards of two participating university-affiliated medical centres. Written informed consent was obtained from all participants. The study included 52 female patients scheduled for routine abdominal hysterectomy that participated in the clinical trial. Patients were eligible if they were: ASA physical status 1 or 2, age 18 - 60 yr, weight 50 - 90 kg, and height 150 cm. Patients with an allergy to local anaesthetics or other clinical contra-indications to epidural anaesthesia, cardiac arrhythmias, history of drug or alcohol dependence, severe psychiatric disturbances and language barriers were excluded.

Patients were randomized within each centre in blocks of eight to receive 25 ml of three different concentrations (doses) of ropivacaine or bupivacaine epidurally. The groups received either 125 mg (5 mg·mL⁻¹), 187.5 mg (7.5 mg·mL⁻¹), or 250 mg (10 mg·mL⁻¹) ropivacaine or bupivacaine 125 mg (5 mg·mL⁻¹). The study drugs were supplied by the manufacturer, Astra. Double-blinding was maintained by the identical appearance of the ropivacaine and bupivacaine solutions and ampoules.

All patients received 10 mg diazepam *po* and 1000 ml intravenous fluids (Ringer's Lactate) over 30 min prior to surgery, and 11 patients were also given mida-

zolam prior to surgery. While in the lateral decubitus position, a #16 or 17 gauge Tuohy needle was advanced into the epidural space (L₂₋₃ or L₃₋₄), using the loss of resistance technique. A three ml test dose of lidocaine 1.5% with 5 µg·mL⁻¹ epinephrine was administered through the needle. If there were no signs of either intravascular or intraspinal injection, 25 ml study drug were administered in intermittent doses over three minutes. The needle was removed and the patient placed in the supine position. Surgery was initiated when the upper level of analgesia reached T₆ and adequate surgical analgesia at the site of the incision was achieved. The patient received general anaesthesia if the study drug did not result in adequate analgesia at the T₆ level and at the site of incision within one hour following epidural injection. Patients were monitored for the duration of their hospital stay. Blood pressure and heart rate were also recorded before and 5, 10, 15, 20, 25 and 30 min after start of injection of the study drug.

Blood sampling and drug assay

Peripheral blood samples of 5 ml were collected from a cubital vein in the arm contralateral to that used for administration of medications and intravenous fluid prior to epidural drug administration and at 5, 10, 15, 20, 25, 30, 45, 60 min and at 1.5, 2, 3, 4, 6, 9, 12, 20 and 24 hr after the start of injection of the epidural dose. Blood samples were taken in heparinized tubes and immediately centrifuged. Plasma samples were frozen at -20°C and stored until assay. Ropivacaine base and bupivacaine base assays were performed by Astra Pain Control using gas chromatography with a nitrogen sensitive detector with liquid-liquid extraction.¹⁰ The limit of quantification (LOQ) of the method was set to 0.01 mg·L⁻¹ for both ropivacaine and bupivacaine. The interassay precision during this study (CV) was 3 to 8% in the concentration range 0.03 - 3.0 mg·L⁻¹ for ropivacaine. The interassay precision (CV) was below 3% for bupivacaine in the concentration range 0.2 - 1.0 mg·L⁻¹. The recovery of bupivacaine and ropivacaine was close to 100%.

Pharmacokinetic evaluation

The pharmacokinetics of ropivacaine were determined using non-compartmental analysis and the computer program PHA 176, written in the RS/1 command language (release 5.0.1, Bolt Beranek and Newman Software Products Corp. Cambridge, MA). The maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were estimated directly from the individual plasma concentration-time curves. The total area under the plasma concentration *vs* time curve

FIGURE Individual plasma concentrations (lin-log) after epidural administration of ropivacaine and bupivacaine to patients scheduled for abdominal hysterectomy (a = ropivacaine 125, b = ropivacaine 187.5, c = ropivacaine 250, d = bupivacaine 125 mg).

TABLE I Demographic characteristics of the 46 patients included in the pharmacokinetic study after epidural administration of ropivacaine (125, 187.5, 250 mg) and bupivacaine 125 mg, respectively, to patients scheduled for abdominal hysterectomy. Times for start of epidural administration to start of surgery as well as duration of surgery are presented. Figures are median (range).

	<i>Ropivacaine</i> (125 mg) (n = 11)	<i>Ropivacaine</i> (187.5 mg) (n = 12)	<i>Ropivacaine</i> (250 mg) (n = 11)	<i>Bupivacaine</i> (125 mg) (n = 12)
Age (yr)	42 (37-58)	40 (28-49)	41 (24-49)	46 (35-57)
Height (cm)	168 (151-174)	164 (157-174)	161 (155-170)	164 (158-167)
Weight (kg)	69 (51-89)	67 (59-87)	65 (58-85)	66 (51-89)
Dose to start of surgery (min)	67 (52-133)	84 (36-113)	68 (48-123)	80 (48-158)
Duration of surgery (min)	70 (51-155)	75 (35-106)	55 (35-90)	70 (40-103)

TABLE II Pharmacokinetic parameters after epidural administration of ropivacaine (125, 187.5, 250 mg) and bupivacaine 125 mg, respectively, to patients scheduled for abdominal hysterectomy. Figures are median (range).

	<i>Ropivacaine</i> (125 mg) (n = 11)	<i>Ropivacaine</i> (187.5 mg) (n = 12)	<i>Ropivacaine</i> (250 mg) (n = 11)	<i>Bupivacaine</i> (125 mg) (n = 12)
C_{max} (mg·L ⁻¹)	0.69 (0.50-1.19)	1.11 (0.73-1.83)	1.77 (0.95-2.94)	0.60 (0.26-0.77)
t_{max} (hr ⁻¹)	0.5 (0.1-1.6)	1.0 (0.6-1.6)	0.6 (0.2-0.8)	0.55 (0.3-1.55)
AUC (mg·h·L ⁻¹)	4.70 (4.01-10.25)	12.52 (5.07-17.15)†	10.30 (7.15-20.41)‡	5.03 (2.47-7.55)§
CL (mL·min ⁻¹)	391 (179-430)	220 (161-544)†	357 (180-515)‡	367.6 (245-749)§
$t_{1/2}$ (hr)	4.8 (2.5-6.6)*	5.8 (2.8-13.5)†	3.6 (2.5-8.8)*‡	7.88 (5.57-10.05)*§

* $P < 0.05$ Rop 125 mg, 250 mg *vs* Bup 125 mg

† n = 9; ‡ n = 10; § n = 11

TABLE III Hodges-Lehmann estimates (95% CI) for dose-proportionality in ropivacaine C_{max} and AUC after epidural administration of ropivacaine (125, 187.5, 250 mg) to patients scheduled for abdominal hysterectomy.

<i>Ropivacaine dose ratio</i>	<i>187.5 mg/125 mg</i>	<i>250 mg/125 mg</i>	<i>250 mg/187.5 mg</i>
C_{max} (95% CI)	1.6 (1.3, 2.1)	2.5 (1.6, 3.4)	1.6 (1.0, 2.0)
AUC (95% CI)	2.0 (1.3, 2.9)	1.9 (1.5, 2.5)	0.9 (0.7, 1.5)

(AUC) was estimated by using the log-linear trapezoidal rule up to the last plasma concentration that was above the LOQ. The residual area up to infinity was calculated from the estimated plasma concentration at the last sampling time divided by the rate constant (λ), which was estimated by the methods of least squares from the terminal linear part of the log plasma *vs* time curve. The apparent elimination half-life, ($t_{1/2}$) was estimated as $\ln 2/\lambda$. The plasma clearance (CL/F) was calculated assuming 100% bioavailability and the formula $CL = \text{dose}/\text{AUC}$, where dose was of ropivacaine and bupivacaine base. The relative molecular mass (MW) of ropivacaine and bupivacaine HCl are 310.9 and 324.9, respectively. All pharmacokinetic parameters were based on time points measured from the start of the epidural injection. The complete pharmacokinetic analysis was restricted to patients with plasma samples up to 24 hr after dosing. For the

determination of C_{max} and t_{max} , all patients with a sufficient number of samples to identify a terminal fall of the concentration-time curve were included.

Statistical analysis

All data are presented as median (range). Demographic characteristics were compared among groups using the Kruskal-Wallis test. Dose-proportionality in AUC and C_{max} was evaluated using Wilcoxon rank sum tests and 95% confidence intervals (CI) with associated Hodges-Lehmann (HL) estimates (11). The HL-estimate is calculated as the median of all possible differences between observations in two groups. Dose-proportionality was expected to yield ratio estimates of 1.5, 2 and 1.3 respectively, when pairwise comparisons in AUC and C_{max} were made between ropivacaine doses of 187.5 mg *vs* 125 mg, 250 mg *vs* 125 mg, 250 mg *vs* 187.5 mg. In addition the relationships between dose and both

AUC and $C_{\max}$ were evaluated by linear regression with 95% CI calculated for the intercept (b) term ($Y = a \cdot \text{dose} + b$), where dose-proportionality is supported by a zero-intercept. Pharmacokinetic parameter estimates were compared among ropivacaine groups and between bupivacaine (125 mg) and ropivacaine (125 mg) using the Wilcoxon rank sum test and 95% CI. A P -value of < 0.05 was considered significant.

Results

A total of 52 patients participated in the study. Demographic characteristics were similar among the groups and no important differences in duration of surgery could be found (Table I). Forty six participants were eligible for complete or partial pharmacokinetic analysis. Four patients were identified as "technical failures" and excluded *a priori* because it could not be verified that the study drug was injected into the epidural space (rop 125 mg $n = 2$, rop 250 mg $n = 1$, bup 125 mg $n = 1$). Two patients were excluded due to an insufficient number of plasma samples (rop 187.5 mg and rop 250 mg). Five other patients were eligible for partial pharmacokinetic analysis only (i.e. estimation of $C_{\max}$ and $t_{\max}$) due to an insufficient number of plasma samples (rop 187.5 mg $n = 3$, rop 250 mg $n = 1$, bup $n = 1$).

In 35 (76%) patients, the study drug was injected in the L_{2-3} interspace; in the remainder, it was injected in the L_{3-4} interspace. Thirteen patients included in the complete pharmacokinetic evaluation received supplemental GA (rop 125 mg $n = 6$, rop 187.5 mg $n = 5$, bup 125 mg $n = 2$). Induction of GA was performed with thiopentone, propofol and maintained with nitrous oxide and isoflurane. Other medications administered concomitantly during surgery included midazolam ($n = 41$) and fentanyl ($n = 36$) with the frequency of drugs being equally distributed between the groups.

The individual plasma concentration-time profiles for the four study groups are shown in Figure a-d, including only patients from the complete pharmacokinetic evaluation, and the pharmacokinetic parameter estimates in Table II. The extrapolated areas of AUC were below 15% of the total AUC in all but seven patients when the extrapolated areas were between 15 and 25%. The ratios for $C_{\max}$ and AUC were consistent with the estimates predicted by dose-proportional pharmacokinetics (Table III). In addition, regression analysis revealed that both $C_{\max}$ and AUC had intercepts that did not differ from zero with 95% CI of -0.8 to $0.3 \text{ mg} \cdot \text{L}^{-1}$ ($C_{\max}$) and -3.4 to $6.2 \text{ mg} \cdot \text{h} \cdot \text{L}^{-1}$ (AUC). The CL was similar among the ropivacaine groups (P -NS) which further supports linear pharma-

cokinetics. The 95% CI for the differences in CL were -193 to $40 \text{ mL} \cdot \text{min}^{-1}$ (187.5 *vs* 125 mg), -79 to $102 \text{ mL} \cdot \text{min}^{-1}$ (250 *vs* 125 mg) and -30 to $193 \text{ mL} \cdot \text{min}^{-1}$ (250 *vs* 187.5 mg).

The $t_{1/2}$ as estimated from the last 3-6 data points on the terminal phase of the plasma concentration-time curve was essentially similar among the ropivacaine groups. The 95% CI for the differences between the groups were -1.0 to 3.6 hr (187.5 *vs* 125 mg) -2.0 to 0.0 hr (250 *vs* 125 mg) and -4.7 to 0.1 hr (250 *vs* 187.5 mg). The $t_{\max}$ in the 187.5 mg group was higher than both the 125 and 250 mg groups with 95% CI of 0.0 to 0.7 hr (rop 187.5 *vs* rop 125) and -0.2 to -0.7 hr (rop 250 *vs* rop 187.5).

One patient in the rop 125 mg group was excluded from the pharmacokinetic evaluation since no block was obtained and she had a $C_{\max}$ of $2.82 \text{ mg} \cdot \text{L}^{-1}$. As judged from the plasma-concentration time profile, and the fact that no block was achieved, she is assumed to have received an intravascular injection.

The $t_{1/2}$ was shorter in the ropivacaine 125 and 250 mg groups than in the bupivacaine group ($P < 0.05$). There was no difference in apparent CL between bupivacaine and any of the ropivacaine groups, 95% CI -68 to $156 \text{ mL} \cdot \text{min}^{-1}$ (bup *vs* rop 125), -21 to $207 \text{ mL} \cdot \text{min}^{-1}$ (bup *vs* rop 187.5) and -94 to $106 \text{ mL} \cdot \text{min}^{-1}$ (bup *vs* 250 mg). One patient in the bupivacaine group was excluded from the analysis due to an extended absorption/elimination phase which disqualified a calculation of AUC/ $t_{1/2}$.

No serious adverse events were reported in the study. The most frequently reported adverse events were nausea, hypotension, vomiting and urinary retention/dysuria.⁹ The proportion of patients with adverse events was similar among the four dose groups although hypotension was most frequently reported in the rop 250 mg group. The patient in the rop 125 mg group with an intravascular administration, as described above, experienced "numbness of the head with metallic taste" six minutes after start of injection, which was close to the $C_{\max}$ at eight minutes. With the exception of these symptoms, no events that may have been signs of effects from local anaesthetics on the Central Nervous System (CNS) were recorded.

Discussion

This is the first double-blind randomized controlled trial to evaluate the pharmacokinetic behaviour of different epidural doses of ropivacaine during major abdominal surgery. In addition, it is the first to investigate a 250 mg ($10 \text{ mg} \cdot \text{mL}^{-1}$) dose. A previous study of intravenous ropivacaine showed the drug to possess linear pharmacokinetics.¹² Our results also show that

epidural ropivacaine exhibits dose-proportional pharmacokinetics as based on the results of a dose proportional increase in $C_{\max}$ and AUC, and a similarity in CL over the dose-range administered.

The pharmacokinetic parameters obtained in this study are similar to previous studies investigating epidural ropivacaine. Emanuelsson *et al.* investigated the pharmacokinetics in healthy volunteers of continuous ropivacaine infusions (10, 20, and 30 mg·hr⁻¹) and reported CL rates of 427-452 mL·min⁻¹.¹³ Morrison *et al.* reported slightly lower values (282-314 mL·min⁻¹) in a study of the pharmacokinetics of 100 mg of epidural ropivacaine in patients.¹⁴ The median estimates for ropivacaine $t_{1/2}$ in our study (3.7 - 5.8 hr) are also comparable to the results by Morrison (5.3 - 5.5 hr).¹⁴

We observed shorter $t_{1/2}$ and a slightly greater $C_{\max}$ for ropivacaine than for bupivacaine. These results are similar to those from a previous study of 100 mg epidural bupivacaine and ropivacaine.¹⁴ A likely explanation to the lower $C_{\max}$ of bupivacaine is the greater volume of distribution for bupivacaine in comparison to ropivacaine. The longer $t_{1/2}$ after bupivacaine could be explained by the higher lipophilicity of bupivacaine in comparison to ropivacaine, which increases the uptake in epidural fat and thereby decreases the rate of absorption from the epidural space.¹⁵ The terminal phase after an epidural dose is absorption rate limited, since the terminal $t_{1/2}$ was similar to the absorption $t_{1/2}$ as shown by Emanuelsson *et al.*¹⁶ The duration of CNS symptoms have been reported to be shorter after ropivacaine than after bupivacaine,¹⁷ an expected consequence of their differences in half-life.

Although CL and $t_{1/2}$ did not differ among the ropivacaine groups, the 187.5 mg group had a lower median CL rate, longer $t_{1/2}$ and increased AUC (Table II). No obvious reason for this could be found since the patient characteristics, distribution of concomitant medications and duration of surgery were similar among the groups. The requirement of general anaesthesia differed among the groups, but patients with GA generally did not show any deviating pharmacokinetic results.

We conclude that ropivacaine shows dose-proportional pharmacokinetics after epidural bolus doses up to 250 mg. Epidural ropivacaine has a shorter terminal half-life than bupivacaine.

Acknowledgment

The authors are grateful to Torbjörn Arvidsson PhD for bioanalytical work and Sven Sandin BSc for statistical analysis.

References

- 1 Rosenberg PH, Kytä J, Alila A. Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into n-heptane, rat sciatic nerve, and human extradural and subcutaneous fat. *Br J Anaesth* 1986; 58: 310-4.
- 2 Lee A, Fagan D, Lamont M, Tucker GT, Halldin M, Scott DB. Disposition kinetics of ropivacaine in humans. *Anesth Analg* 1989; 69: 736-8.
- 3 Brown DL, Carpenter RL, Thompson GE. Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. *Anesthesiology* 1990; 72: 633-6.
- 4 Kerckamp HEM, Gielen MJM, Edström HH. Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia. *Reg Anesth* 1990; 15: 204-7.
- 5 Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *Br J Anaesth* 1991; 66: 31-7.
- 6 Zaric D. Quantitative methodological studies of motor and sensory blockade in epidural analgesia with special reference to early mobilization and a new local anaesthetic - ropivacaine. Doctoral thesis, ISBN 91-554-3487-8, Uppsala University, Uppsala, Sweden 1995.
- 7 Feldman HS. Toxicity of local anaesthetic agents. In: Rice SA, Fish KJ (Eds.). *Anaesthetic Toxicity*. New York: Raven Press 1994: 107-33.
- 8 Reiz S, Häggmark S, Johnsson G, Nath S. Cardiotoxicity of ropivacaine - a new amide local anaesthetic agent. *Acta Anaesthesiol Scand* 1989; 33: 93-8.
- 9 Finucane BT, Sandler AN, McKenna J, *et al.* A double-blind comparison of ropivacaine 0.5%, 0.75%, 1.0% and bupivacaine 0.5%, injected epidurally, in patients undergoing abdominal hysterectomy. *Can J Anaesth* 1996; 43: 442-9.
- 10 Björk M, Pettersson K-J, Österlöf G. Capillary gas chromatographic method for the simultaneous determination of local anaesthetics in plasma samples. *J Chromatogr* 1990; 533: 229-34.
- 11 Lehmann EL. *Nonparametrics. Statistical Methods Based on Ranks*. San Francisco: Holden-Day Inc., 1975: 182B5, 418-21.
- 12 Emanuelsson B-M, Persson J, Sandin S, Alm C, Gustafsson LL. Intraindividual and interindividual variability in the disposition of the local anesthetic ropivacaine in healthy subjects. *Ther Drug Monit* 1997; 19: 126-31.
- 13 Emanuelsson B-M K, Zaric D, Nydahl P-A, Axelsson KH. Pharmacokinetics of ropivacaine and bupivacaine during 21 hours of continuous epidural infusion in healthy male volunteers. *Anesth Analg* 1995; 81: 1163-8.
- 14 Morrison LMM, Emanuelsson BM, McClure JH, *et al.* Efficacy and kinetics of extradural ropivacaine: comparison with bupivacaine. *Br J Anaesth* 1994; 72: 164-9.

- 15 *Burm AGL, Vermeulen NPE, van Kleef JW, de Boer AG, Spierdijk J, Breimer DD.* Pharmacokinetics of lignocaine and bupivacaine in surgical patients following epidural administration. Simultaneous investigation of absorption and disposition kinetics using stable isotopes. *Clin Pharmacokin* 1987; 13: 191–203.
- 16 *Emanuelsson B-MK, Persson J, Alm C, Heller A, Gustafsson LL.* Systemic absorption and block after epidural injection of ropivacaine in healthy volunteers. *Anesthesiology* 1997; 87: 1309–17.
- 17 *Knudsen K, Beckman M, Suurküla Blomberg S, Sjövall J, Edvardsson N.* Central nervous and cardiovascular effects during i.v. infusions of ropivacaine, bupivacaine, and placebo in healthy volunteers. *Br J Anaesth* 1997; 78: 507–14.