The Effect of Age on the Systemic Absorption and Systemic Disposition of Ropivacaine after Epidural Administration

Mischa J. G. Simon, MD, Bernadette T. Veering, MD, PhD, Arie A. Vletter, BSc, Rudolf Stienstra, MD, PhD, Jack W. van Kleef, MD, PhD, and Anton G. L. Burm, MSc, PhD

Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands

Knowledge about the systemic absorption and disposition of ropivacaine after epidural administration is important in regard to its clinical profile and the risk of systemic toxicity. We investigated the influence of age on the pharmacokinetics of ropivacaine 1.0% after epidural administration, using a stable-isotope method. Twenty-four patients were enrolled in 1 of 3 groups according to age (group 1: 18–40 yr; group 2: 41–60 yr; group 3: ≥61 yr). Patients received 150 mg ropivacaine hydrochloride epidurally. After 25 min, patients received 50 mL 0.44 mg/mL deuterium-labeled ropivacaine (D3-ropivacaine) IV. Arterial blood samples were collected up to 24 h after epidural administration. Total plasma concentrations of ropivacaine and D3-ropivacaine were determined using liquid chromatography mass spectrometry. In the oldest patients, elimination half-life was significantly longer (ratio of the geometric means 0.60; 95% confidence interval, 0.37–0.99) and clearance was significantly decreased (mean difference, 194 mL/min; 95% confidence interval, 18-370 mL/min) compared with the youngest patients. The systemic absorption was biphasic. Absorption kinetics for ropivacaine (fractions absorbed: (F_1, F_2) and half-lives: ($t_{½,a1}$, $t_{½,a2}$) during the fast and slow absorption process: 0.27 ± 0.08 and 0.77 ± 0.12, respectively; 10.7 ± 5.2 min and 248 ± 64 min, respectively) were in the same range as for other long-acting local anesthetics. F_1 was on average 0.11 (95% confidence interval, 0.002-0.22) higher in the youngest compared with the middle age group. Observed age-dependent pharmacokinetic differences do not likely influence the risk of systemic toxicity in the elderly after a single epidural dose of ropivacaine.

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With an increasing number of elderly people (individuals 65 years of age and older) the demand for surgery will continue to increase (1). Regional anesthetic techniques are frequently used in elderly patients undergoing surgery. Aging influences the pharmacokinetics and pharmacodynamics of local anesthetics after perineural administration (2–6). The influence of age on the pharmacokinetics and the clinical profile have been studied for epidurally administered bupivacaine and levobupivacaine (2,4,6). With ropivacaine, only the influence of age on the neural blockade and hemodynamic changes after epidural administration have been investigated (5). Data on the influence of age on the pharmacokinetics of epidurally administered ropivacaine are lacking.

Ropivacaine (S(–)-1-propyl-2′,6′;-pipecoloxylidide hydrochloride monohydrate) is a long-acting, enantiomeric pure local anesthetic with a wider safety margin for systemic toxicity than bupivacaine (7,8). Both the systemic absorption and systemic disposition of ropivacaine after perineural administration are important in regard to the clinical profile and the risk of systemic toxicity. Disposition kinetics of ropivacaine have been obtained after IV administration in volunteers (9,10) and after epidural administration in surgical patients (11–13). However, absorption kinetics of ropivacaine after epidural anesthesia have been obtained only in young healthy male volunteers (14). Except for peak plasma concentration measurements to quantify the early systemic absorption, detailed data on the systemic absorption of ropivacaine in a surgical population are not available (15). In this study, the systemic absorption and disposition in a surgical population were determined and the influence of age on the pharmacokinetics of ropivacaine after epidural administration was investigated.

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Address correspondence to Mischa J.G. Simon, MD, Department of Anesthesiology(P-5), Leiden University Medical Center, Albinusdreef 2, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Address e-mail to M.J.G.Simon@lumc.nl.

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Methods

The study protocol was reviewed and approved by the Committee on Medical Ethics of the Leiden University Medical Center. Twenty-four ASA physical status I or II patients, who had given informed consent, were enrolled in 1 of 3 groups, according to age (group 1: 18–40 yr; group 2: 41–60 yr; group 3: ≥61 yr). These patients were part of a group of 54 patients, in which the effects of age on the neural blockade and hemodynamic changes were evaluated. The findings have been published previously (5).

Inclusion and exclusion criteria, as well as the premedication, preparation before epidural puncture and the epidural procedure itself were the same for both studies, except that in this study a 20-gauge arterial cannula was inserted in a radial artery for purposes of blood sampling. Patients underwent minor lower limb, urological, gynecological (excluding obstetrics), or lower abdominal surgery. Patients who had a history of diabetes, neuromuscular disease, bleeding diathesis, clinically significant peripheral arteriosclerosis or previous lumbar surgery, radiculopathy, or chronic back pain were excluded. Patients who were hypersensitive to amide local anesthetics, weighed more than 110 kg, or were shorter than 150 cm, as well as pregnant female patients were also excluded. Patients were premedicated with temazepam 20 mg (<60 yr) or 10 mg (≥60 yr) orally. The epidural puncture was performed with the patient in the sitting position, at the L3-4 interspace, using a midline or paramedian approach. After identifying the epidural space with the loss-of-resistance to saline technique, a test dose of 3 mL prilocaine 1.0% with epinephrine 5 μg/mL was administered. Three min later, after exclusion of inadvertent intravascular or subarachnoid injection, a single dose of 15 mL ropivacaine 1.0% (AstraZeneca, Södertälje, Sweden) was administered at a rate of 1 mL/s. Patients did not receive additional sedation or general anesthesia during surgery.

When satisfactory anesthetic conditions (i.e., the presence of a bilateral sensory blockade, assessed by pinprick) were obtained (usually 15–20 min after the epidural injection) a flexible 18-gauge cannula was introduced into a foot vein. Twenty-five min after the epidural injection the patient received approximately 50 mL of a solution, containing 0.44 mg/mL deuterium-labeled ropivacaine (D3-ropivacaine; AstraZeneca) by constant-rate (5 mL/min) IV infusion into the foot vein, using a manually controlled pump (Becton Dickinson, Brézins, France). Deuterium-labeled ropivacaine differs from unlabeled ropivacaine by the substitution of 3 hydrogen atoms with deuterium at a methyl-group (-CH_3) on the xylidine ring, resulting in a C^2H_3-group (14). Total amounts of the infused solution were read from the infusion pump. Exact doses infused were determined by multiplying the total amount infused and the exact concentrations of the solution, determined by high-performance liquid chromatography certificates of analysis. If anesthetic conditions were not satisfactory after 20 min, D3-ropivacaine was not administered.

Arterial blood samples were collected up to 24 h after epidural administration with intervals gradually increasing from 5 min to 4 h (16). Samples were stored on ice and centrifuged for 10 min at 1500*g* and 4°C within 4 h. The plasma was transferred into prelabeled tubes and stored at −20°C.

Determination of total plasma concentrations of ropivacaine and D3-ropivacaine was performed at AstraZeneca R&D using ultrafiltration of the acidified plasma sample, followed by gradient reversed-phase liquid chromatography and tandem mass spectrometry detection with positive electrospray ionization (Micromass Quattro Ultima, Waters Corporation, Milford, MA). The plasma sample and the internal standard (at low pH) were pipetted into a 96-well ultrafiltration plate (Multiscreen® Ultracel-PPB, Millipore, Bedford, MA). The plate was covered and shaken for approximately 5 min. Thereafter the plate was centrifuged for 45 min at 2000*g* and 25°C. An injection volume of 5-10 μL of the ultrafiltrate was injected into the chromatographic system. A linear gradient was used and the mobile phases consisted of Acetonitrile and 0.1% formic acid. The column used was an *Ace*III C18, 100 × 2.1 mm (ACT, Aberdeen, Scotland, UK). The scan mode was multiple reaction monitoring using the precursor ion at m/z (M + 1) (m/z: 275, 278, 282), and after collisional dissociation the product ions 126, 129, and 133 were used for quantification of ropivacaine, D3-ropivacaine, and the internal standard D7-ropivacaine, respectively. For a range of duplicate quality-control samples, the interday accuracies were 0.4%–6.6% and −0.1%–4.3%, respectively, and the interday precisions were 4.5%–6.5% and 4.9%–7.2%, respectively, for ropivacaine and D3-ropivacaine. The limit of quantification was 2.74 and 2.77 ng/mL for ropivacaine and D3-ropivacaine, respectively.

Pharmacokinetic data were derived using both compartmental and noncompartmental analysis. Details of the pharmacokinetic analysis have been described earlier (6,16). Disposition kinetics were derived by fitting bi-exponential and tri-exponential functions to the plasma concentration-time data of D3-ropivacaine, using weighted (1/predicted concentration squared) least-squares nonlinear regression analysis with the software package WinNonlin version 4.1 (Pharsight Corp, Mountain View, CA).

The fractions absorbed (F_1, F_2) and the absorption half-lives ($t_{1/2,a1}$, $t_{1/2,a2}$) of the fast and slow absorption phase, respectively, were determined by fitting a bi-exponential function to the cumulative fraction absorbed-time data, using unweighted least-squares

Table 1. Group Characteristics and Demographic Data for All Patients

	Group 1 (18–40 yr) (n = 5)	Group 2 (41–60 yr) (n = 10)	Group 3 (≥61 yr) (n = 9)	Total (n = 24)
Age (yr)	30 (20–38)	51 (43–58)	74 (61–80)	54 (20–80)
Gender (M/F)	5/0	9/1	8/1	22/2
ASA (I/II)	4/1	10/0	3/6	17/7
Height (cm)	183 (170–191)	181 (158–183)	178 (166–185)	180 (158–191)
Weight (kg)	90 (67–100)	77 (65–92)	85 (61–100)	80 (61–100)

Values are median (range) or n.

nonlinear regression analysis. The absorption rates and the cumulative fractions absorbed were derived after deconvolution. Individual plasma concentration-time curves were generated from the derived absorption and disposition parameters and these were compared with the measured concentrations of ropivacaine after epidural administration. The absorption kinetics were also determined by fitting the summative model directly to the measured plasma concentration-time data of unlabeled ropivacaine, using weighted (1/predicted concentration squared) least-squares nonlinear regression. Both approaches used for estimating the absorption kinetics were compared by calculating the median performance error (MDPE) and median absolute performance error (MDAPE).

The most appropriate pharmacokinetic disposition model (2- or 3-compartment) was determined by inspection of the scatter of the data points around the fitted curves and comparison of the residual weighted sums of squares, using the F-test.

Sample sizes were calculated as described by Zar (17). On the basis of a previous study with ropivacaine (14), we assumed a within-groups variance of 10000 for total plasma clearance (Cl), the primary outcome variable. With a two-sided type 1 error of 0.05 and a power of at least 0.80, 8 patients per group (total 24 patients) were required to reveal a difference in Cl of 180 mL/min between any 2 groups.

Pharmacokinetic variables were analyzed using one-way analysis of variance with a term for age group, using the software-package SPSS 11.5.0 (SPSS Inc, Chicago, IL). All possible comparisons among the 3 age groups were made using Student's t-test. The sequentially rejective Bonferroni-Holm method was used to compensate for multiple comparisons. Normal distribution of the data was verified with the Kolmogorov-Smirnov test and homogeneity of variance was checked with Levene's test. If data were not distributed normally or in the presence of heterogeneity of variance, appropriate transformation of the data (i.e., log transformation) was performed. If the above assumptions were not met after transformation, the Kruskal-Wallis test was used.

Results

Group and patient characteristics are presented in Table 1. Only two female patients were included. No significant differences were observed among age groups.

Data derived by compartmental analysis resembled closely those derived by noncompartmental analysis, except for a small difference in the total fraction absorbed (F) (1.04 versus 1.10; $P = 0.008$, respectively). Therefore, only the results of the compartmental analysis are presented.

Plasma concentration-time data of ropivacaine and D3-ropivacaine are presented in Figure 1. A 2- or a 3-compartmental model was applied to the D3-ropivacaine concentration-time data in 3 and 20 patients, respectively. However, in one patient this could only be described with a one-compartment model.

Values derived for the disposition kinetic variables after IV infusion of D3-ropivacaine or epidural administration of ropivacaine are presented for the 3 age groups in Table 2. All disposition parameters derived after IV infusion were analyzed parametrically, except for mean residence time (MRT). Before analysis, area under the curve (AUC), elimination half-life ($t_{1/2,el}$), and distribution clearance of the fast distribution compartment ($Cl_{d(r)}$) were log-transformed. There was a significant difference among groups for $t_{1/2,el}$ ($P = 0.033$) and Cl ($P = 0.023$). The difference between the youngest and the oldest age group for $t_{1/2,el}$ was significant ($P = 0.043$). The corresponding ratio of the geometric means of $t_{1/2,el}$ was 0.60 (95% confidence interval [CI], 0.37–0.99), meaning that $t_{1/2,el}$ was, on average, 40% longer in the oldest group compared with the youngest group. Also, there was a significant difference between these groups in Cl ($P = 0.028$), which was, on average, 194 mL/min (95% CI, 18-370 mL/min) less in the oldest group. The AUC and MRT derived after epidural administration were analyzed nonparametrically and parametrically after log-transformation, respectively. The parameters AUC and MRT did not reach statistical significance after correction for multiple comparisons.

Absorption kinetics of ropivacaine are presented in Table 3. Cumulative fraction absorbed-time curves of

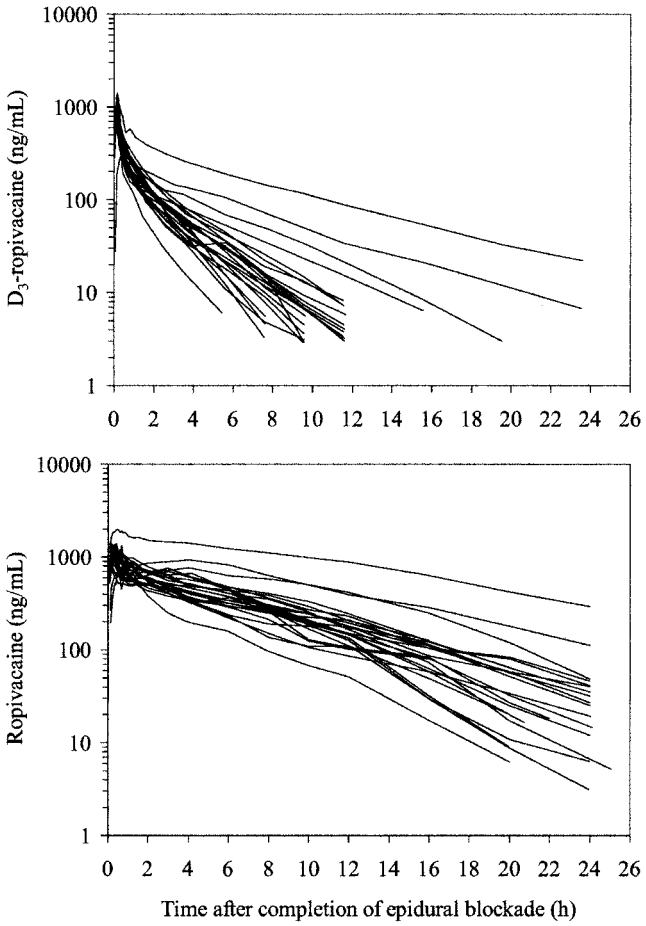

Figure 1. Individual plasma concentration-time curves of IV-infused D3-ropivacaine (upper panel) and epidurally administered ropivacaine (lower panel).

individual patients are shown in Figure 2. All curves were adequately described by a two-exponential function, representing two parallel absorption processes. Absorption parameters, such as F_1, $t_{½,a1}$, F_2 and total fraction absorbed (F), were analyzed parametrically without log transformation. Mean absorption time and $t_{½,a2}$ were tested nonparametrically. There was a statistically significant difference among groups for F_1 ($P = 0.032$). The youngest age group differed from the middle ($P = 0.045$; mean difference 0.11; 95% CI, 0.002–0.22) but not from the oldest age group ($P = 0.056$). No differences were observed for the other absorption parameters among age groups.

Values for absorption variables, estimated from the fraction absorbed-time data were in agreement with those derived after fitting the summative model with 2 absorption and one, two, or three distribution compartments directly to the unlabeled ropivacaine plasma concentration-time data. Differences in MDPE (1.74, −0.50 ($P = 0.001$), respectively) and MDAPE (6.0, 6.2 ($P = 0.80$), respectively) between the two methods were small, indicating that both described the plasma concentration-time data of epidurally administered ropivacaine well.

Discussion

This study provides a thorough description of the systemic absorption and disposition of ropivacaine after epidural administration, as well as an evaluation of the effect of age on the pharmacokinetic variables. We found that age influenced the disposition kinetics ($t_{1/2,el}$, Cl), as well as the absorption kinetics (F_1) of ropivacaine after epidural administration.

Disposition kinetics of ropivacaine have been obtained after IV infusion in healthy volunteers (9,10) or epidural administration in patients (11–13). Our results are generally in agreement with those found by these authors. However, the $t_{1/2,el}$ in our study was on average longer ($t_{1/2,el} = 139 \pm 63$ minutes) because we found an age-related increase in $t_{1/2,el}$. The values of the $t_{1/2,el}$ of the youngest age group of our study ($t_{1/2,el} = 101 \pm 24$ minutes) were similar to those obtained in the above-mentioned volunteer studies, conducted in young subjects ($t_{1/2,el} = 111 \pm 62$ minutes and 114 ± 36 minutes, respectively) (9,10).

Moreover, in our study the Cl was decreased in the oldest compared with the youngest group of patients. This is consistent with earlier observations from epidurally administered lidocaine and bupivacaine (2,18). In other studies with bupivacaine and levobupivacaine there was a trend towards small plasma Cl with increasing age (4,6). It is likely that age influences the plasma Cl of all above-mentioned local anesthetics.

Absorption kinetics of local anesthetics cannot be derived immediately from plasma concentration-time curves after perineural administration because they exhibit flip-flop kinetics. This means that slow absorption of local anesthetics from the epidural space into the systemic circulation rate-limits the elimination of the drug, thus directly affecting the elimination phase. A stable isotope method developed to determine the absorption kinetics of local anesthetics may be used when labeling of the local anesthetic under investigation with a stable isotope (in this study with deuterium) will not alter its pharmacokinetic profile (19). The pharmacokinetic equivalence of ropivacaine and its deuterium-labeled counterpart has been confirmed (10).

This study confirmed that, like other amide local anesthetics, the systemic absorption of ropivacaine after epidural administration occurs by two absorption processes, i.e., an initial rapid phase followed by a slower phase (4,6,14,16,19). In addition, the F_1 was larger in the youngest compared with the two oldest age groups, although the difference between the youngest and oldest patients was not significant. This

Table 2. Disposition Kinetics After Intravenous (D3-ropivacaine) or Epidural Administration (Ropivacaine)

	Group 1 (18–40 years) (n = 5)	Group 2 (41–60 years) (n = 10)	Group 3 (≥61 years) (n = 9)
Derived from D_3-ropivacaine concentration-time data			
Area under the curve: $AUC_{0\rightarrow\infty\ D3\text{-ropivacaine}}$ ($\mu g.mL^{-1}.min$)	42 (31–49)	53 (25–67)	63 (40–22)
Elimination half-life: $t_{½,el}$ (min)	110 (71–128)*	119 (87–162)	150 (76–346)*
Mean residence time: MRT_{iv} (min)	103 (87–132)	114 (65–151)	143 (82–419)
Total plasma clearance: Cl (mL/min)	492 ± 121†	415 ± 127	298 ± 115†
Fast distribution clearance: $CL_{d(r)}$ (mL/min)	972 (714–2203)	1274 (677–2533)	971 (567–2252)
Slow distribution clearance: $CL_{d(s)}$ (mL/min)	411 ± 287	281 ± 134	395 ± 220
Volume of the central compartment: V_c (L)	7.6 ± 4.7	7.8 ± 2.6	7.3 ± 2.5
Distribution volume at steady state: V_{ss} (L)	52 ± 11	44 ± 8	49 ± 13
Derived from ropivacaine concentration-time data			
Maximum concentration: C_{max} (ng/mL)	1080 ± 268	1074 ± 254	1226 ± 334
Time to maximum concentration: T_{max} (min)	20 (15–31)	13 (5–40)	16 (5–31)
Area under the curve: $AUC_{0\rightarrow\infty\ ropivacaine}$ ($\mu g.mL^{-1}.min$)	287 (230–318)	341 (169–460)	363 (284–1452)
Mean Residence Time: MRT_{niv} (min)	353 (312–375)	393 (248–600)	411 (303–693)

Data are mean ± SD or median (range), as appropriate.
* The difference between group 1 and 3 is significant (P = 0.043); † the difference between group 1 and 3 is significant (P = 0.028).

Table 3. Absorption Kinetics of Ropivacaine in Patients After Epidural Administration

	Group 1 (18–40 yr) (n = 5)	Group 2 (41–60 yr) (n = 10)	Group 3 (≥61 yr) (n = 9)
Fast absorption process:			
- fraction absorbed: F_1	0.35 ± 0.08*	0.24 ± 0.07*	0.25 ± 0.08
- half-life: $t_{½,a1}$ (min)	13 ± 3	10 ± 6	10 ± 4
Slow absorption process:			
- fraction absorbed: F_2	0.71 ± 0.09	0.79 ± 0.09	0.79 ± 0.15
- half-life: $t_{½,a2}$ (min)	243 (219–267)	228 (180–431)	214 (181–280)
Systemic availability: F	1.06 ± 0.11	1.03 ± 0.04	1.03 ± 0.10
Mean absorption time: MAT (min)	242 (209–289)	256 (182–513)	270 (190–327)

Data are mean ± SD or median (range), as appropriate.
* The difference between group 1 and 2 is significant (P = 0.045)

is in agreement with the study using levobupivacaine, which showed a decrease of F_1 and $t_{½,a1}$ with age (6). A large F_1 may predispose to a high plasma concentration that, in turn, increases the risk of systemic toxicity. However, like bupivacaine and levobupivacaine, there were no differences in plasma concentration between age groups for ropivacaine (2,4,6). Therefore, from this point of view the risk of systemic toxicity in the elderly seems not to be increased.

The results of various epidural absorption studies are summarized in Table 4. Studies performed in our institution under quite similar conditions (4,6,16,19) showed nearly equal F_1 values for bupivacaine and ropivacaine. The F_1 of levobupivacaine seems to be somewhat less, which may be explained by the greater vasoconstrictive action of this drug (16,20). Vasoconstriction of the epidural vessels may decrease the uptake of local anesthetics from the epidural space into the systemic circulation. In contrast to bupivacaine, which has a more vasodilatory, less vasoconstrictive action, ropivacaine exhibits

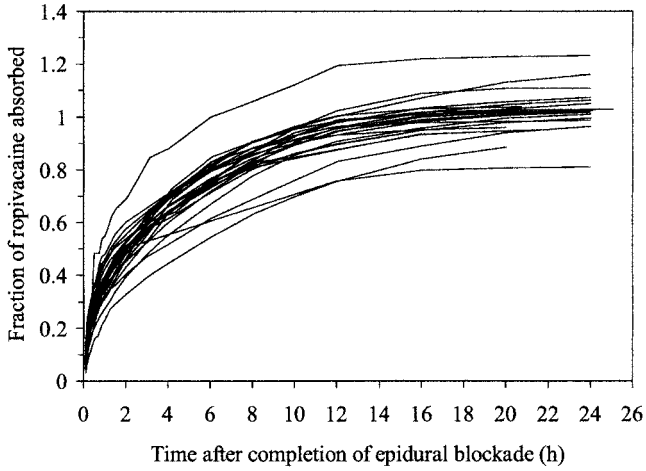

Figure 2. Cumulative fractions absorbed of ropivacaine versus time in individual surgical patients. Absorption-time data were obtained by deconvolution of the measured concentrations unlabeled ropivacaine concentration-time data against the IV unit impulse-response curve, derived from the D3-ropivacaine concentration-time data.

Table 4. Absorption Kinetics of Amide Local Anesthetics After Epidural Administration, as Determined with a Stable-Isotope Method

Agent	Subjects	Age range (yr)	F_1	$t_{½,a1}$ (min)	F_2	$t_{½,a2}$ (min)
Lidocaine (19)	Patients (n = 6)	21–48	0.38 ± 0.12	9.3 ± 3.8	0.58 ± 0.07	82 ± 19
Bupivacaine (19)	Patients (n = 6)	23–49	0.28 ± 0.04	7.0 ± 4.6	0.66 ± 0.12	362 ± 141
Bupivacaine (4)	Patients (n = 19)	20–82	0.29 ± 0.09	8.4 ± 3.7	0.67 ± 0.11	326 ± 83
Levobupivacaine (16)	Patients (n = 15)	23–85	0.22 ± 0.06	5.2 ± 2.7	0.84 ± 0.14	386 ± 91
Levobupivacaine (6)	Patients (n = 27)	19–85	0.21 ± 0.06	7.3 ± 3.0	0.83 ± 0.13	448 ± 160
Ropivacaine (this study)	Patients (n = 24)	20–80	0.27 ± 0.08	10.7 ± 5.2	0.77 ± 0.12	248 ± 64
Ropivacaine (14)	Volunteers (n = 9)	24–43	0.52 ± 0.07	14.0 ± 7.0	0.48 ± 0.07	252 ± 54

Data are mean ± SD.
F_1 = fraction absorbed during the first (rapid) absorption phase; $t_{½,a1}$ = fast absorption half-life; F_2 = fraction absorbed during the second (slow) absorption phase; $t_{½,a2}$ = slow absorption half-life.

vasoconstrictive properties (21,22). Furthermore, both the S(–) enantiomers of ropivacaine and bupivacaine showed vasoconstrictive properties in cerebral pial arterioles in an animal model (23). From the vasoactive action of these drugs it would be expected that the F_1 of ropivacaine would be somewhat less than that of bupivacaine. However, it is possible that this process is counteracted by a decreased local distribution, which is accounted for by the lower lipid solubility of ropivacaine. The $t_{½,a1}$ of ropivacaine was longer than those found for the other long-acting local anesthetics bupivacaine and levobupivacaine (4,6,16). The vasoconstrictive action of ropivacaine may delay the initial absorption of the local anesthetic.

The F_2, expressed as a percentage of the total fraction absorbed was larger and the $t_{½,a2}$ was shorter for lidocaine (60% and 80 min for F_2 and $t_{½,a2}$, respectively), compared to those derived for the long-acting local anesthetics bupivacaine (70%, 335 min), ropivacaine (75%, 248 min) and levobupivacaine (80%, 426 min). During the slow absorption phase the uptake into the systemic circulation from the local tissues of the epidural space is probably highly dependent on blood/tissue partitioning, especially uptake from the epidural fat. Therefore, the lower lipid solubility of lidocaine may explain the difference in the secondary absorption kinetics between this drug and the long-acting local anesthetics.

Using a stable-isotope method Emanuelsson et al. (14) determined the absorption kinetics of ropivacaine and found a larger F_1 and a smaller F_2, compared with the values obtained in this study. The differences can be explained by dissimilarities in study design, such as the inclusion of unpremedicated healthy volunteers instead of premedicated surgical patients in our study. In addition, the derived absorption variables in their study were based on peripheral venous sampling rather than on arterial blood sampling in our study.

Regarding the risk of systemic toxicity, unbound rather than total plasma concentrations are relevant. Studies during prolonged epidural infusion of ropivacaine showed that postoperative increases in plasma α_1-acid glycoprotein concentrations are associated with increases in the plasma protein binding and in the total plasma concentrations of ropivacaine (24,25). However, unbound plasma concentrations were shown to be relatively unaffected and leveled off after 24 hours. In the present study, total plasma ropivacaine concentrations decreased continuously after reaching a maximum at approximately 20 minutes. Therefore, we do not believe that in the context of the present study, unbound plasma concentrations are of importance.

A limitation of this study is the relative small number of patients included in the youngest age group. This was caused by difficulties of including young, relatively healthy patients from our hospital population. Besides, there is a trend to day-care surgery in young healthy patients, which exclude participation in this study that lasted for at least 24 hours. The small number of included young patients may have influenced the results of this study. Nevertheless, the differences in $t_{1/2,el}$, Cl and F_1 were significant, although they showed rather wide 95% CIs.

In conclusion, this study showed that the disposition, as well as the absorption, kinetics after epidural administration of ropivacaine are influenced by age. The Cl was smaller and $t_{1/2,el}$ was longer in the oldest age group, whereas F_1 was larger in the youngest age group. The consequence of these findings is that after a single epidural dose the risk of systemic toxicity in the elderly is not likely to be increased.

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