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Epidural anaesthesia with levobupivacaine and ropivacaine : effects of age on the pharmacokinetics, neural blockade and haemodynamics

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Citation

Simon, M. J. G. (2006, May 11). *Epidural anaesthesia with levobupivacaine and ropivacaine : effects of age on the pharmacokinetics, neural blockade and haemodynamics*. Retrieved from <https://hdl.handle.net/1887/4384>

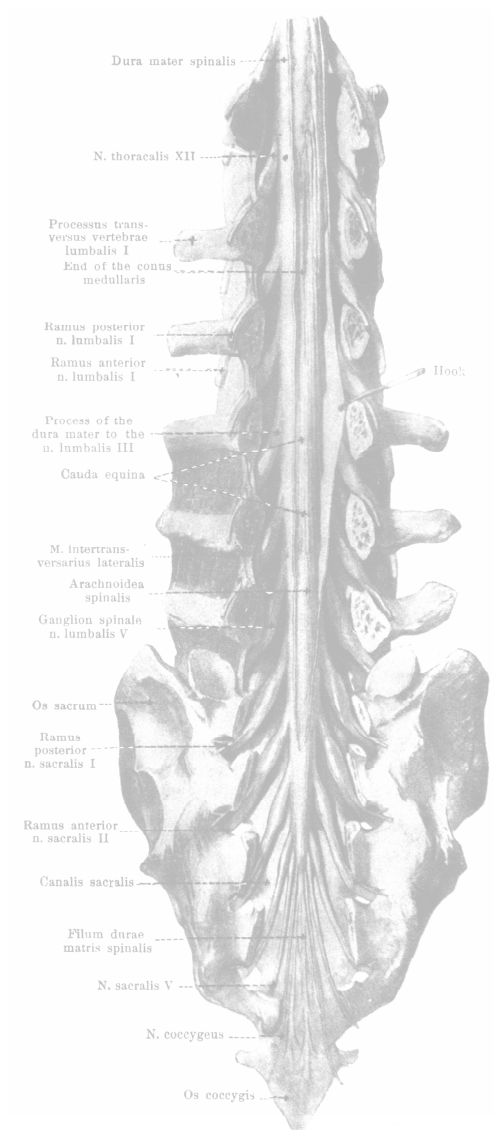
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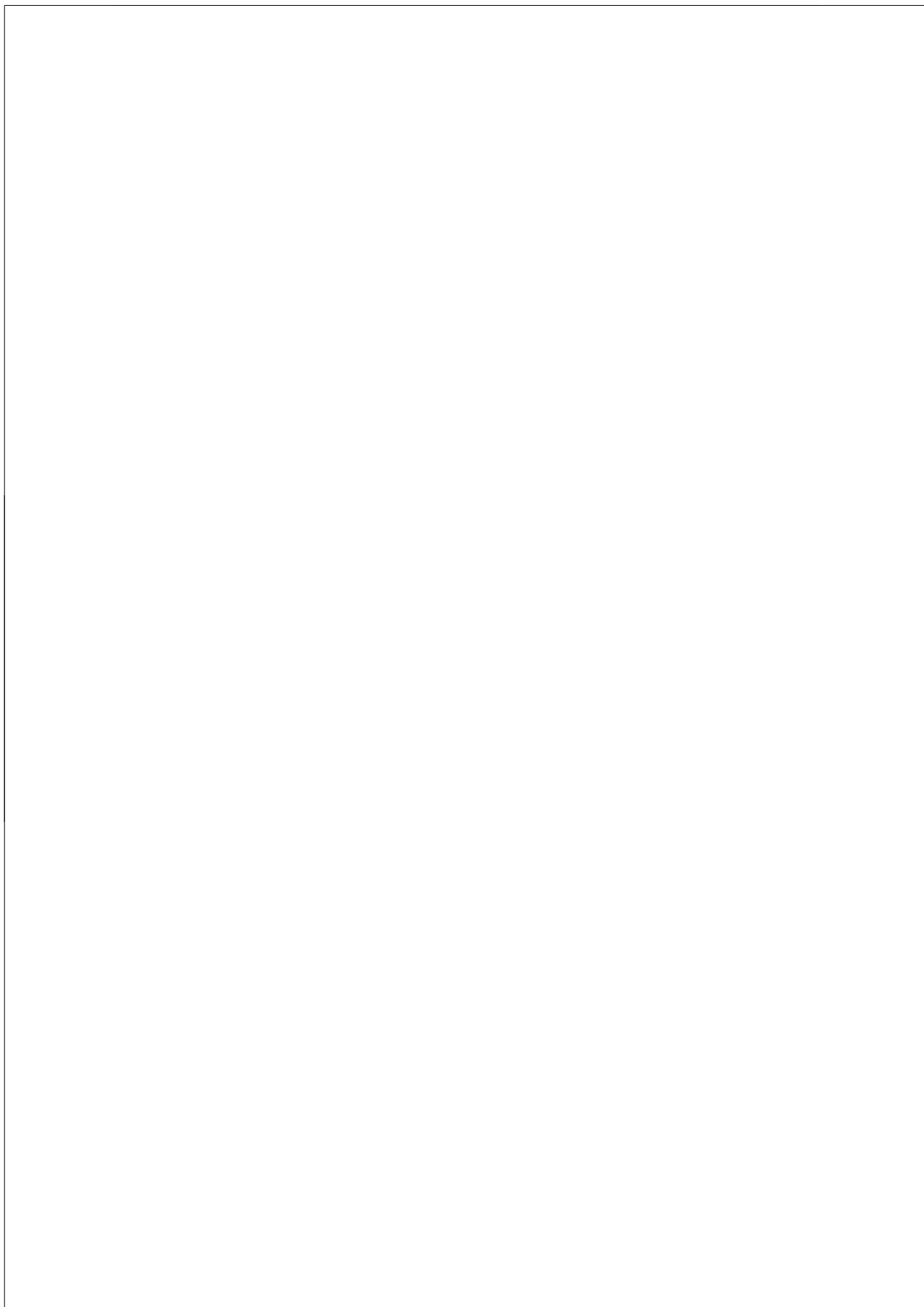
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Section II



Clinical Effects & Pharmacokinetics



**COMPARISON OF THE PHARMACOKINETICS OF
LEVOBUPIVACAINE AND A STABLE-ISOTOPE-LABELLED
ANALOGUE IN HEALTHY MALE VOLUNTEERS**

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published in an adapted form in the European Journal of Anaesthesiology 2004; 21: 460-70

Levobupivacaine (S(-)-1-butyl-2-piperidylformo-2', 6'-xylidide hydrochloride) is a recently introduced local anaesthetic. In contrast to bupivacaine, which is available as racemate, containing equal amounts of the R(+)- and S(-)-enantiomers, levobupivacaine only contains the pure S(-)-enantiomer. Studies have shown that the R(+)- and the S(-)-enantiomer of bupivacaine have different pharmacokinetic, pharmacodynamic and toxicological characteristics.¹⁻⁹

It is important to know the pharmacokinetics of local anaesthetics with regard to their clinical profile, particularly the duration of their action, and to the risk of systemic side-effects and toxicity.^{10,11} In this respect, both systemic absorption, *i.e.*, the uptake from the perineural site of administration into the blood, and systemic disposition (distribution and elimination) must be considered. Unfortunately, systemic absorption rates of local anaesthetics generally cannot be derived directly from the concentration-time profiles of a perineurally administered local anaesthetic, because slow absorption limits the rate of elimination of the drug from the body, which complicates the discrimination between absorption and disposition kinetics.¹² However, absorption and disposition kinetics of local anaesthetics can be determined in a single experiment using a stable-isotope method.¹² This method has been used in our institution to determine the systemic absorption kinetics of lidocaine and bupivacaine after epidural and subarachnoid administration.¹²⁻¹⁵ With this approach a stable-isotope-labelled analogue of the drug to be investigated is administered intravenously (*i.v.*) shortly after the unlabelled drug has been administered via the perineural route. A prerequisite for the use of this method is that the unlabelled drug and the stable-isotope-labelled analogue have similar distribution and elimination characteristics, *i.e.*, it presumes that labelling of the drug does not influence its pharmacokinetic profile.^{12,16}

To validate the use of deuterium-labelled levobupivacaine (D₃-levobupivacaine) in a stable-isotope method, we compared the disposition kinetics of levobupivacaine and D₃-levobupivacaine after rapid simultaneous *i.v.* administration in healthy male volunteers.

Methods

Volunteers

After approval of the study protocol by the Committee on Medical Ethics of the Leiden University Medical Center and after obtaining written informed consent, 8 healthy male volunteers, aged 18-32 years were included in the study. The health of the volunteers was substantiated by medical history and physical examination, haematology, clinical

chemistry and 12-lead electrocardiography (ECG). Volunteers with a history of clinically relevant allergy, known hypersensitivity to amide local anaesthetics, adverse events to any drug, or with a history of drug, alcohol or nicotine abuse were excluded. Volunteers who donated blood or lost more than 400 ml or who had been given an investigational drug or vaccine during the 12 weeks preceding the experiment or who had taken any medication during a period of 5 days before the experiment were also excluded.

Procedures

All experiments were performed in an operating room. The volunteers, positioned supine on an operating table, were attached to a device for ECG-recording and non-invasive blood pressure measurements (Cardiicap II[®], Datex-Ohmeda B.V., Hoevelaken, The Netherlands). ECG rhythm strips were produced pre-infusion, at 5-min intervals during the first 30 min following the start of the infusion, at 45 and 60 min, and thereafter hourly until 3 h post-infusion. Supine diastolic and systolic blood pressure, as well as supine heart rate, were measured at screening, pre-infusion, at 5-min intervals during the infusion, at 5, 10, 15 min post-infusion, and thereafter every 15 min until 3 h post-infusion.

Flexible i.v. cannulae (Biovalve[®], 18-gauge; Laboratories Vygon S.A., Ecouen, France) were inserted bilaterally in suitable veins in the forearm or on the hand, and were used for i.v. infusion of the study drug and for blood sampling, respectively. For each volunteer, a solution was prepared by the pharmacy of our hospital by adding 10 ml levobupivacaine 2.48 mg.ml⁻¹ and 10 ml D₃-levobupivacaine 2.41 mg.ml⁻¹ to 30 ml sodium chloride 0.9% (exact concentrations were derived from high performance liquid chromatography (HPLC) analysis certificates). D₃-levobupivacaine differs from levobupivacaine in that one of the methyl groups on the xylylidine ring is triple labelled with deuterium (-C²H₃). After a short stabilization period (about 15 min), approximately 50 ml of this solution was administered i.v., using a manually controlled pump (Becton Dickinson, Brézins, France). Total doses administered were determined by multiplying the infusion rate (5.0 ml.min⁻¹) and exact infusion times. All doses and concentrations are expressed as free base equivalents.

Blood samples and assays

Venous blood samples were collected before dosing and at the following target times after start of the infusion: 2, 5, 10, 15, 20, 30, 45, 60 min and 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7 and 8 h. Blood samples were temporarily stored on ice. Within 4 h after collection, the samples were centrifuged at 1500 g for 10 min at 4°C. The plasma was then transferred to clear pre-labelled tubes and these were immediately stored at about -20°C.

Plasma concentrations of levobupivacaine and D₃-levobupivacaine were determined by Inveresk Research (Tranent, Scotland, UK) using liquid chromatography-mass spectrometry (LC-MS) with positive ion atmospheric pressure chemical ionisation. One millilitre aliquots of the plasma samples, calibration samples (containing 10-500 ng levobupivacaine and D₃-levobupivacaine per ml plasma) or quality control samples (containing 30-400 ng levobupivacaine and D₃-levobupivacaine per ml plasma) were transferred to a test tube and 10 µL of the internal standard solution, containing 200 ng prilocaine, were added. Subsequently 1 ml of a saturated sodium bicarbonate solution was added and the contents of the test tubes were mixed on a vortex mixer. Then 6 ml methyl-tertiary-butyl-ether was added and the test tube was capped and shaken on a rotating action shaker for 10 min. After centrifugation for 10 min at 3000 r.p.m. the upper organic phase was transferred to a clean test tube and evaporated to dryness under a stream of nitrogen at 35°C. Finally the sample was reconstituted in 150 µl of the mobile phase and 40 µl were injected into the liquid chromatograph.

The analytical apparatus consisted of a Fisons Instruments VG Platform[®] mass spectrometer (Micromass (formerly Fisons Instruments), Manchester, UK), a Waters 510[®] HPLC pump (Waters Corporation, Milford, USA), and a Gilson 231[®] autosampler (Gilson Medical Electronics (France) S.A., Villiers-le-Bel, France) and was equipped with a 250 mm long 4.6 mm inner diameter analytical column, filled with Hichrom Chiral L-PGC, CHI-L-PGC(B)-250Å and a 10 mm long 4.6 mm inner diameter guard column, filled with Hichrom Chiral L-PGC, CHI-L-PGC(B)-10C5. The mobile phase consisted of hexane and ethanol (85:15 v/v) and the flow rate was 1 ml.min⁻¹. The column temperature was 40°C. Chemical ionization occurred in the positive ion mode. The corona and cone voltages were 3.5 kV and 15 V, respectively; source and probe temperatures were 150°C and 400°C, respectively. The following ions were monitored: m/z = 292 (D₃-levobupivacaine), m/z = 289 (levobupivacaine and R(+)-bupivacaine) and m/z = 221 (prilocaine). Data were quantified following peak integration using peak area internal standardisation with weighted (1/x) linear regression analysis for the calibration lines.

Retention times of D₃-levobupivacaine, levobupivacaine, R(+)-bupivacaine, and prilocaine were approximately 9.6, 9.6, 8.3 and 7.0 min, respectively. The interday accuracies of the quality control samples at concentrations of 30, 200 and 400 ng.ml⁻¹ were 101.5%, 104.4% and 99.7%, respectively, for levobupivacaine and 103.5%, 107.1%, and 101.3%, respectively, for D₃-levobupivacaine. The interday precisions for these samples were 8.5%, 4.3%, and 5.8% for levobupivacaine, and 6.3%, 4.5%, and 4.5% for D₃-levobupivacaine. Although the quality control samples also contained R-bupivacaine, the interday accuracy and precision for this compound were not formally assessed. The

limits of quantification were 10 ng.ml⁻¹ for D₃-levobupivacaine, levobupivacaine, and R(+)-bupivacaine.

Data analysis

Non-compartmental analysis was done in a spreadsheet program (Quattro Pro[®] version 8.0, Corel Corporation, Ottawa, Canada). The slope of the terminal log-linear part of the curve (k_z) was determined from the last 5 to 8 data points (mostly from $t = 150$ min onwards) using linear regression. Areas under the curve (AUC) and under the first moment curve (AUMC) from $t = 0$ to the last sampling time included (t_z) were derived using the linear trapezoidal rule when concentrations were increasing and the logarithmic trapezoidal rule when concentrations were decreasing. Subsequently, extrapolated AUCs and AUMCs from t_z to ∞ were calculated and added to obtain $AUC_{0 \rightarrow \infty}$ and $AUMC_{0 \rightarrow \infty}$. $AUC_{0 \rightarrow \infty}$, $AUMC_{0 \rightarrow \infty}$ and k_z were used to derive the disposition parameters terminal half-life ($t_{1/2,z}$), mean residence time (MRT), total plasma clearance (Cl), volume of distribution at steady state (V_{ss}) and volume of distribution during the terminal phase ($V_{d,\beta}$).^{12,17-19}

Compartmental analysis was performed using WinNonlin[®] version 1.1 (Scientific Consulting Inc, Apex, USA). Mono- and bi-exponential functions were fitted to the plasma concentration-time data of levobupivacaine and D₃-levobupivacaine using weighted (1/predicted concentration squared) least-squares non-linear regression analysis. A lag-time (restricted to ≤ 2 min) was included in the model, because the concentration in the first sample was usually very low, due to the venous sampling. Including a lag-time resulted in better fits in most subjects. The most appropriate model (1- or 2-compartment) was determined by inspection of the scatter of the data points around the fitted curves and comparison of the residual weighted sum of squares, using the F-test.

Statistical analysis

Derived pharmacokinetic data were analysed using the software-package SPSS[®] (v8.2.1, SPSS Inc, Chicago, IL, USA). Parametric general linear models and, when appropriate, non-parametric tests were performed. In all tests, $P < 0.05$ was considered the minimum level of statistical significance. Values for the $AUC_{0 \rightarrow \infty}$, determined by compartmental and non-compartmental analysis, and peak concentration (C_{max}) were normalized to a dose of 25.0 mg of levobupivacaine and D₃-levobupivacaine before statistical analysis. These values were then log-transformed and subjected to analysis of variance (ANOVA). Point estimates and the 90% confidence intervals (90% CIs) for the difference of the levobupivacaine to the D₃-labelled analogue were constructed using the error variance

obtained from the ANOVA. The point and interval estimates were back transformed to give estimates of the ratio of levobupivacaine relative to the D₃-analogue. The two preparations were considered equivalent when the 90% CI of the ratio of $AUC_{0 \rightarrow \infty}$, which is the measure of equivalence, lay within the acceptance range of 0.90 to 1.125.²⁰

The pharmacokinetic parameters distribution half-life ($t_{1/2,\lambda 1}$), elimination half-life ($t_{1/2,el}$), volume of central compartment (V_1), volume of peripheral compartment (V_2), volume of distribution at steady state (V_{ss}), volume of distribution during the terminal phase ($V_{d,\beta}$), mean residence time (MRT) and total plasma clearance (Cl), as determined by compartmental analysis and, where applicable, by non-compartmental analysis, were subject to ANOVA-techniques without log-transformation. Time to maximum plasma concentration (T_{max}) was evaluated by calculating the confidence intervals for differences by a non-parametric analysis, because of the discrete nature of the times of blood sampling, as was distribution clearance (Cl_d), because data were skewed.²¹

Results

Volunteers

The volunteers enrolled in this study were 18–32 years of age, had a body weight of 72.6 ± 4.9 kg (mean $\pm$ standard deviation) and height of 180 ± 6 cm. Total dose administered to the volunteers ranged from 23.32–23.72 mg for levobupivacaine and 22.61–23.01 mg for D₃-levobupivacaine. No clinically significant changes in vital signs and ECG were noted and no serious adverse events occurred during the study.

Pharmacokinetic parameters

Normalized (to a 25 mg dose) plasma concentrations of levobupivacaine and D₃-levobupivacaine (Figure 1) virtually coincided in all subjects. With few exceptions, the concentration ratios were between 0.9 and 1.1 and showed no significant changes over time (Figure 2).

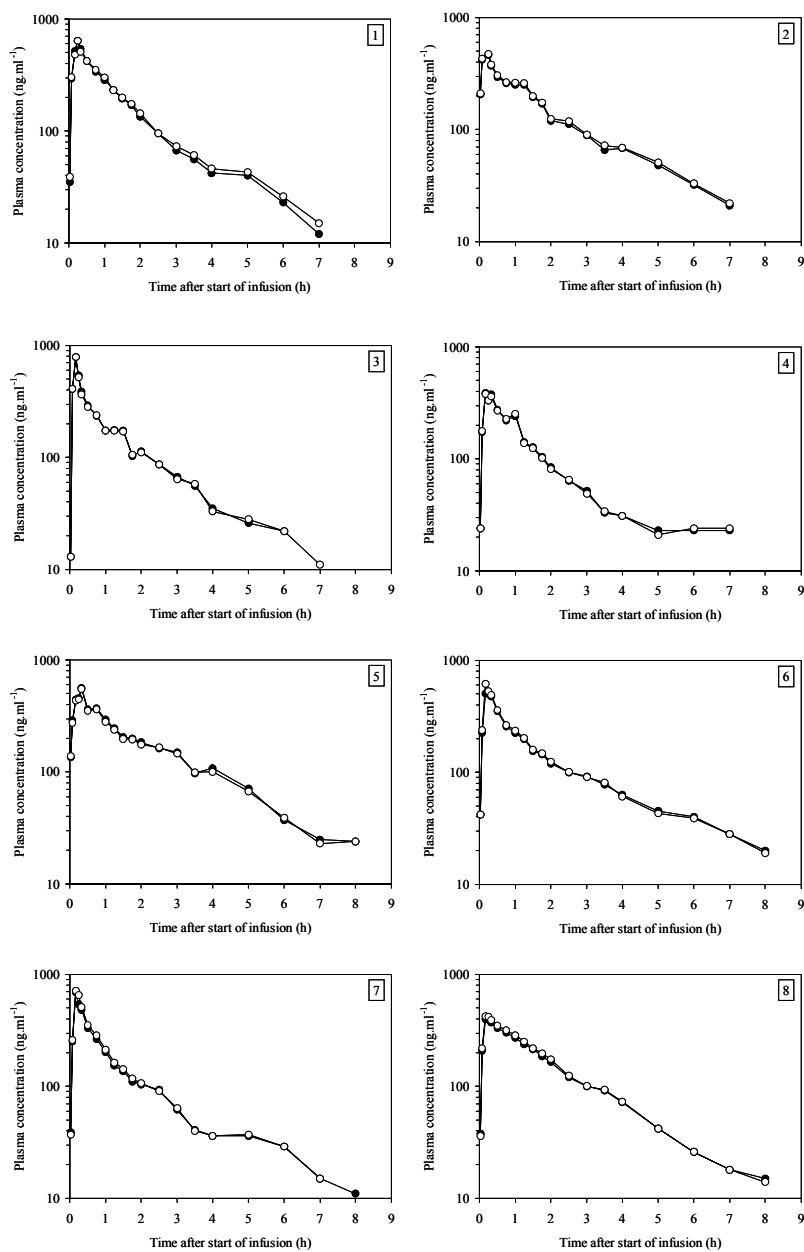


Figure 1. Plasma concentrations of levobupivacaine (circles) and deuterium-labelled levobupivacaine (dots) in individual subjects. All curves are normalized to a dose of 25.0 mg of both compounds.

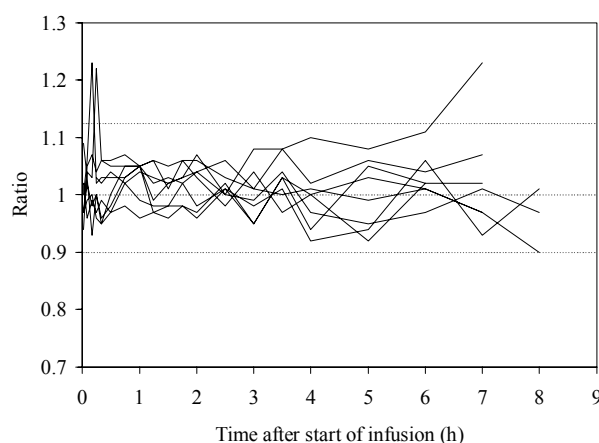


Figure 2. Plasma concentration ratios of levobupivacaine to deuterium-labelled levobupivacaine in individual subjects. Ratios were calculated after normalizing concentrations to a dose of 25.0 mg of both compounds. Limits of the acceptance range (0.90, 1.125) are shown.

Concentration-time data were best described by a bi-exponential function with a lag-time in 6 volunteers and a mono-exponential function with a lag-time in 1 volunteer. Because of little improvement in the bi-exponential versus the mono-exponential fits and the high correlation between several parameters of the bi-exponential function, a one-compartment model with a lag-time was assigned to the data of the latter volunteer (volunteer 8). Volunteer 4 was excluded from compartmental analysis, because both 1- and 2-compartment fits of the concentration-time data were considered inadequate.

The geometric means of the $AUC_{0 \rightarrow \infty}$ for levobupivacaine and the D_3 -analogue, determined by compartmental analysis, were 54.2 and 53.0 $\mu\text{g} \cdot \text{min} \cdot \text{ml}^{-1}$, respectively. The corresponding values, determined by non-compartmental analysis were 50.6 and 49.8 $\mu\text{g} \cdot \text{min} \cdot \text{ml}^{-1}$, respectively. The ratio estimate of the geometric means of $AUC_{0 \rightarrow \infty}$ of levobupivacaine and D_3 -levobupivacaine, determined by both compartmental and non-compartmental analysis, was 1.02. The corresponding 90% CIs were 1.00-1.04 and 1.00-1.03, respectively. These intervals were well within the acceptance range of 0.90 to 1.125, and therefore, the formulations were considered equivalent.

Pharmacokinetic data, derived by compartmental and non-compartmental analysis are shown in Table 1. Median values for the time to reach maximum concentration (T_{max}) were 11.5 min and 15.0 min for levobupivacaine and D_3 -levobupivacaine, respectively. There was no difference in maximum concentration (C_{max}) between levobupivacaine and D_3 -levobupivacaine.

Table 1. Pharmacokinetic data of levobupivacaine and D₃-levobupivacaine in healthy volunteers.

	Compartmental analysis (<i>n</i> = 7) [*]		Non-compartmental analysis (<i>n</i> = 8)	
	Levobupivacaine	D ₃ -levobupivacaine	Levobupivacaine	D ₃ -levobupivacaine
Area under the curve: AUC _{0-∞} (μg.min.ml ⁻¹)	54.7 ± 7.5	53.5 ± 8.1	51.4 ± 9.6	50.6 ± 9.6
Maximum concentration: C _{max} (ng.ml ⁻¹)			574 ± 143	557 ± 143
Distribution half-life: t _{1/2α} (min)	21 ± 10	20 ± 10		
Elimination/terminal half-life: t _{1/2β} /t _{1/2z} (min)	115 ± 19	113 ± 19	112 ± 14	113 ± 15
Mean residence time: MRT (min)	136 ± 20	136 ± 23	134 ± 19	134 ± 20
Total plasma clearance: Cl (ml.min ⁻¹)	465 ± 65 [†]	475 ± 68 [†]	504 ± 109	511 ± 104
Volume of the central compartment: V _c (l)	39 ± 13	40 ± 14		
Volume of distribution at steady state: V _{ss} (l)	62 ± 6	64 ± 8	66 ± 8	67 ± 10

Data are mean ± standard deviation; ^{*} one patient was excluded from the compartmental analysis (see text); [†] the difference in Cl between levobupivacaine and D₃-levobupivacaine, derived by compartmental analysis, but not by non-compartmental analysis is significant (*P* < 0.05).

The total plasma clearance (Cl), as determined by compartmental analysis, differed for levobupivacaine and D₃-levobupivacaine. However, this difference was small (2.3%) and not significant, when determined by non-compartmental analysis. Terminal half-lives ($t_{1/2,z}$), mean residence times (MRT), total plasma clearances (Cl), volumes of distribution at steady state (V_{ss}) and volumes of distribution during the terminal phase ($V_{d,\beta}$), derived by compartmental analysis, corresponded closely with those calculated by non-compartmental analysis. No differences for these parameters were observed between levobupivacaine and the D₃-labelled analogue.

Distribution half-lives ($t_{1/2,\alpha}$), volumes of the central compartment (V_1) and the volumes of the peripheral compartment (V_2) did not differ between levobupivacaine and D₃-levobupivacaine. Distribution clearances (Cl_d) showed wide standard deviations, due to the outlying data of volunteer 3. Median values were 393 ml.min⁻¹ for levobupivacaine and 418 ml.min⁻¹ for D₃-levobupivacaine. Nonparametric testing did not reveal a difference between the two formulations for this parameter.

Concentrations of R(+)-bupivacaine and its D₃-labelled analogue (the optical antipodes of levobupivacaine and D₃-levobupivacaine) were below the limit of quantification (< 10 ng.ml⁻¹) in all collected samples.

Discussion

Stable isotopes are powerful research tools to study the pharmacokinetics of extravascularly administered drugs.¹²⁻¹⁶ To be useful in this respect, the disposition kinetics of the stable-isotope-labelled analogue should be representative of those of the unlabelled regularly used drug. As demonstrated in this study in volunteers, D₃-levobupivacaine meets this requirement, since the ratios of the $AUC_{0 \rightarrow \infty}$ of levobupivacaine and D₃-levobupivacaine, as determined by compartmental and non-compartmental analysis, and the corresponding 90% CIs were well within the predefined acceptance range. Even though compartmental analysis showed a significant difference in the total plasma clearance, this difference was very small (2.3%), and not confirmed by non-compartmental analysis.

The use of confidence intervals to compare the bioequivalence of drugs is generally accepted.²⁰ To consider two preparations equivalent, the 90% CI of the chosen measure of equivalence, *i.e.*, in this study the ratio of the $AUC_{0 \rightarrow \infty}$ of levobupivacaine to D₃-levobupivacaine, has to be fully contained within given limits of acceptance. The limits of the acceptance range were set at 0.90 and 1.125, which means that the formulations could differ $\pm 10\%$. The acceptance range was asymmetrical due to the logarithmic

transformation of the $AUC_{0 \rightarrow \infty}$. This procedure is equal to the rejection of two one-sided hypotheses concerning bioequivalence, the primary concern of which is to limit the risk of erroneously accepting equivalence.²² In this study the ratio of the $AUC_{0 \rightarrow \infty}$ of levobupivacaine to D₃-levobupivacaine, estimated by compartmental analysis was 1.02. The limits of the corresponding 90% CI were 1.00-1.04 and 1.00-1.03 for compartmental and non-compartmental analysis, respectively. The 90% CI of the $AUC_{0 \rightarrow \infty}$ ratio was within the acceptance range and, therefore, the two preparations were judged equivalent.

For ethical reasons venous rather than arterial blood samples were collected in the volunteers. When compared to the data that would have been obtained with arterial sampling, the volume of the central compartment and the distribution half-life are probably overestimated and the distribution clearance underestimated. However, the sampling site probably has minimal effect on the elimination half-life, total plasma clearance, MRT and steady-state volume of distribution. In any case, the main objective of this study was to compare the pharmacokinetics of levobupivacaine and D₃-levobupivacaine and in this respect the sampling site is of minor importance.

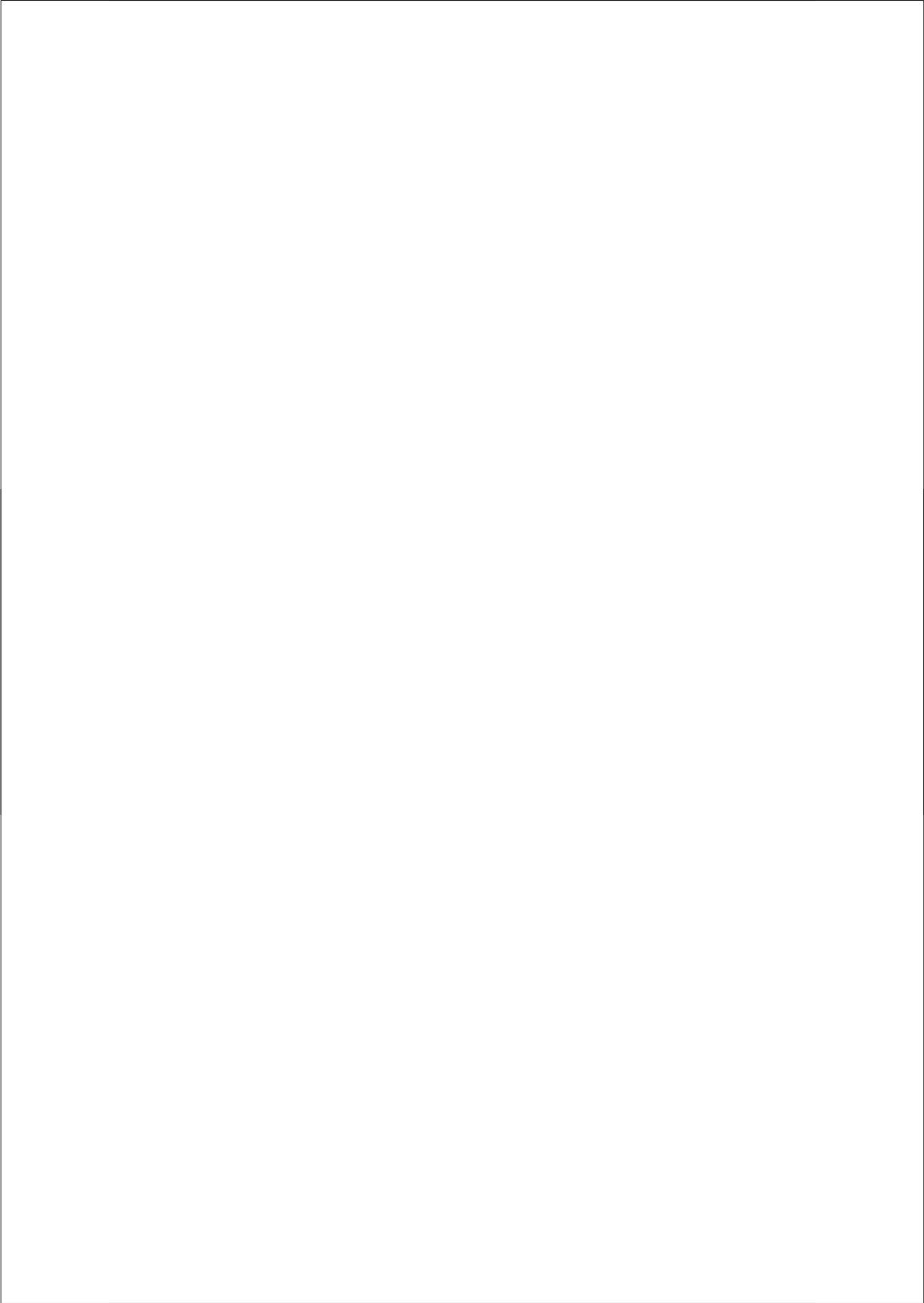
The pharmacokinetics of levobupivacaine in volunteers, as observed in the present study differ somewhat from the pharmacokinetics of S(-)-bupivacaine after i.v. administration of racemic bupivacaine.³ In that study, the total plasma clearance of S(-)-bupivacaine ($317 \pm 67 \text{ ml.min}^{-1}$) was lower and the elimination half-life ($157 \pm 77 \text{ min}$) and MRT ($172 \pm 55 \text{ min}$) were longer than found in the present study. On the other hand, a review on levobupivacaine reports a higher total plasma clearance (651 ml.min^{-1}) and a shorter MRT (85 min).²³ The discrepancies between these studies emphasize the large inter-individual variability and the relatively small sample sizes of the studies in volunteers. Eight volunteers participated in this study, but it must be emphasized that the main objective of this study was to compare the pharmacokinetics of D₃-levobupivacaine and levobupivacaine. From this perspective, the number of subjects included was more than sufficient, as is illustrated by the detection of a small and irrelevant difference in the clearance of the two compounds. Also, it cannot be excluded that the pharmacokinetics of S(-)-bupivacaine after i.v. administration of racemic bupivacaine are influenced by the presence of the R(+)-enantiomer. The absence of both R(+)-bupivacaine and its D₃-labelled analogue in this study indicates that no racemization of levobupivacaine occurs in human beings.²⁴

In conclusion, this study demonstrated that the disposition kinetics of levobupivacaine and D₃-levobupivacaine are similar and that, therefore, D₃-levobupivacaine can be used in a stable-isotope method to study the absorption and disposition of levobupivacaine in a single experiment.

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**THE SYSTEMIC ABSORPTION AND DISPOSITION OF
LEVOPUPIVACAINE 0.5% AFTER EPIDURAL ADMINISTRATION
IN SURGICAL PATIENTS**

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published in an adapted form in the European Journal of Anaesthesiology 2004; 21: 460-70

Levobupivacaine (S(-)-1-butyl-2-piperidylformo-2', 6'-xylidide hydrochloride) is a recently introduced local anaesthetic. In contrast to bupivacaine, which is available as racemate, containing equal amounts of the R(+)- and S(-)-enantiomers, levobupivacaine only contains the pure S(-)-enantiomer. Studies have shown that the R(+)- and the S(-)-enantiomer of bupivacaine have different pharmacokinetic, pharmacodynamic and toxicological characteristics.¹⁻⁹

It is important to know the pharmacokinetics of local anaesthetics with regard to their clinical profile, particularly the duration of their action, and to the risk of systemic side-effects and toxicity.^{10,11} In this respect, both systemic absorption, *i.e.* the uptake from the perineural site of administration into the blood, and systemic disposition (distribution and elimination) must be considered. At present, limited data are available on the pharmacokinetics of levobupivacaine^{12,13} and detailed data on the absorption kinetics following the epidural, or other routes of administration are lacking. Therefore, we determined, in this study the absorption and disposition kinetics of 0.5% levobupivacaine after epidural administration in surgical patients, using a stable-isotope method.¹⁴

This included the intravenous (i.v.) administration of a deuterium-labelled analogue (D₃-levobupivacaine) shortly after the epidural administration of the regularly used unlabelled levobupivacaine. However, a prerequisite for the use of this method is that the unlabelled drug and the stable-isotope-labelled analogue have similar distribution and elimination characteristics, *i.e.* it presumes that labelling of the drug does not influence its pharmacokinetic profile.^{14,15} The required pharmacokinetic equivalence of both drugs (levobupivacaine and D₃-levobupivacaine) has been demonstrated in a concomitant study (see also Chapter 7).

Methods

Patients

After approval of the study protocol by the Committee on Medical Ethics of the Leiden University Medical Center and after obtaining written informed consent, 15 patients, aged 23-85 years, ASA Grade I-II, were included in the study. They underwent minor orthopaedic ($n = 3$), urological ($n = 8$), or lower abdominal ($n = 4$) surgery. These procedures were chosen because the duration of surgery is relatively short (this study: < 135 min) and associated with a blood loss of less than 250 ml. Patients with a history of known hypersensitivity to amide local anaesthetics, severe respiratory, renal, hepatic or cardiac disease, in particular A-V or intraventricular conduction abnormalities, diabetes

mellitus, severe arteriosclerosis, or neurological, psychiatric or seizure disorders were excluded. Patients, whose height was under 150 cm or who weighed over 110 kg were also excluded; pregnant women were also excluded.

Procedures

Patients were premedicated with temazepam 20 mg (< 60 years) or 10 mg ($\geq$ 60 years) 45 min before induction of epidural anaesthesia. Dextrose/saline (500 ml) was rapidly infused before the epidural injection and the infusion rate was then maintained at $2 \text{ ml.kg}^{-1}.\text{h}^{-1}$. A 20-gauge catheter was inserted in the radial artery of the contralateral arm after local infiltration of the skin with lidocaine 0.5%. The epidural puncture was performed at the L3-L4 interspace with the patient in the sitting position using a midline or paramedian approach. After local infiltration of the skin with lidocaine 0.5%, the epidural space was identified by the loss of resistance to saline technique. With the bevel of a 16-gauge Hustead needle pointing cephalad, a test dose of 3 ml levobupivacaine 0.5% (Celltech Chiroscience Ltd, Cambridge, UK) was injected at a rate of 1 ml.s^{-1} . Three minutes later, if there were no signs of subarachnoid injection, incremental doses of 5, 5 and 6 ml levobupivacaine 0.5% were administered at a rate of 1 ml.s^{-1} with a 1-min interval between doses. The patient was then placed in the horizontal supine position. When satisfactory anaesthetic conditions had been achieved (usually 15-20 min after the epidural injection) an 18-gauge flexible cannula was introduced into a foot vein. Twenty-five minutes after completion of the epidural administration approximately 50 ml of a solution prepared by the pharmacy of our hospital, containing D_3 -levobupivacaine 0.48 mg.ml^{-1} (Celltech Chiroscience Ltd, Cambridge, UK), was administered at a constant rate of 5 ml.min^{-1} into the foot vein, using a manually controlled pump (Becton Dickinson, Brézins, France). Precise concentrations were derived from high performance liquid chromatography (HPLC) analysis certificates. If anaesthetic conditions were unsatisfactory after 20 min, D_3 -levobupivacaine was not administered. Surgery commenced soon after completion of the i.v. infusion of D_3 -levobupivacaine.

Blood samples and assays

Arterial blood samples were collected before dosing and 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60 min and 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h after the end of the epidural administration. Blood samples were temporarily stored on ice. Within 4 h after collection the samples were centrifuged at 1500 g for 10 min at 4°C . The plasma was then transferred to clear pre-labelled tubes and these were immediately stored at about -20°C .

Plasma concentrations of levobupivacaine and D₃-levobupivacaine were determined by Inveresk Research (Tranent, Scotland, UK), using liquid chromatography-mass spectrometry (LC-MS) with positive ion atmospheric pressure chemical ionization. Detail of the procedure have been described elsewhere (see also chapter 7). The interday accuracies of the quality control samples at concentrations of 30, 200 and 400 ng.ml⁻¹ were 103.3%, 103.5% and 103.9%, respectively, for levobupivacaine and 101.1%, 100.6%, and 99.8%, respectively, for D₃-levobupivacaine. The interday precisions for these samples were 4.3%, 5.9%, and 3.4% for levobupivacaine, and 3.6%, 3.3%, and 3.3% for D₃-levobupivacaine. The limits of quantification were 10 ng.ml⁻¹ for D₃-levobupivacaine, levobupivacaine, and R(+)-bupivacaine.

Data analysis

Pharmacokinetic data were derived using both compartmental and non-compartmental analysis. Sampling points for determining unlabelled levobupivacaine refer to the actual times after completion of the epidural test dose, which was deemed 0 min. Sampling points for determining D₃-levobupivacaine refer to the start of the i.v. infusion. All doses and concentrations are expressed as free base equivalents.

Non-compartmental analysis

Non-compartmental analysis was performed in a spreadsheet program (Quattro Pro[®] version 8.0, Corel Corporation, Ottawa, Canada). The slope of the terminal log-linear part of the curve (k_z) was determined from the last 3-7 data points using linear regression. Areas under the curve (AUC) and under the first moment curve (AUMC) from $t = 0$ to the last sampling time included (t_z) were derived using the linear trapezoidal rule when concentrations were increasing and the logarithmic trapezoidal rule when concentrations were decreasing. Subsequently, extrapolated AUCs and AUMCs from t_z to ∞ were calculated and added to obtain $AUC_{0 \rightarrow \infty}$, $AUMC_{0 \rightarrow \infty}$.¹⁶ $AUC_{0 \rightarrow \infty}$, $AUMC_{0 \rightarrow \infty}$ and k_z were used to derive the disposition parameters terminal half-life ($t_{1/2,z}$), mean residence time (MRT), total plasma clearance (Cl), volume of distribution at steady state (V_{ss}).¹⁶⁻¹⁸ The fraction of the dose absorbed into the general circulation was calculated by comparison of the AUC after epidural and i.v. administration, corrected for the difference in dose:¹⁴

$$F = \frac{AUC_{0 \rightarrow \infty \text{ levo}}}{AUC_{0 \rightarrow \infty \text{ D}_3\text{-levo}}} \times \frac{Dose_{\text{D}_3\text{-levo}}}{Dose_{\text{levo}}}$$

The mean absorption time (MAT) was calculated using the equation: $MAT = MRT_{\text{epidural}} - MRT_{\text{i.v.}}$, as described before,¹⁶ where MRT_{epidural} and $MRT_{\text{i.v.}}$ are the MRT of epidurally administered unlabelled levobupivacaine and i.v. administered D₃-levobupivacaine, respectively.

Compartmental analysis

Compartmental analysis was performed using WinNonlin® version 1.1 (Scientific Consulting Inc, Apex, USA). Disposition kinetics were derived by fitting bi- and tri-exponential functions to the plasma concentration-time data of D₃-levobupivacaine, using weighted (1/predicted concentration squared) least-squares non-linear regression analysis.¹⁹

Absorption rates and the cumulative fractions absorbed were then estimated using a deconvolution method with unequal sampling times, as described by Iga *et al.*²⁰ The absorption rate between two time points was constrained to be non-negative. Subsequently, assuming a first-order absorption, the fractions absorbed (F_1 , F_2) and the absorption half-lives ($t_{1/2,a1}$, $t_{1/2,a2}$) were derived by fitting a bi-exponential function to the obtained cumulative fraction absorbed-time data, using unweighted least-squares non-linear regression analysis. This assumes that the absorption occurs by two parallel processes.^{14,19} The values of the parameters, characterizing the disposition and absorption processes were used to generate (simulate) plasma concentration-time curves after epidural administration of levobupivacaine for all individual patients. These curves were obtained by substituting parameter values into the equation describing a model with 2 parallel first-order absorption compartments and 3 disposition compartments.^{14,19} The generated values were compared with the measured concentrations of levobupivacaine. The absorption kinetics were also determined by fitting the same aggregated model to the measured plasma concentration-time data of unlabelled levobupivacaine, using weighted (1/predicted concentration squared) least-squares non-linear regression. In this approach, the disposition parameters were entered as constants. To evaluate whether this last step in the compartmental analysis improved the description of the measured plasma concentrations, the performance error (PE) for each plasma concentration-time pair and the median performance error (MDPE) and median absolute performance error (MDAPE) for each individual were calculated.²¹

Statistical analysis

The statistical analysis was performed, using the software-package SPSS® (v8.2.1, SPSS Inc, Chicago, IL, USA). The most appropriate compartmental model (bi- or tri-exponential) to describe the plasma-concentration data of D₃-levobupivacaine in each

individual was selected by inspection of the scatter of the data points around the fitted curves and comparison of the residual weighted sum of squares, using the F-test. The MDPE and MDAPE were subjected to analysis of variance (ANOVA). $P < 0.05$ was considered the minimum level of statistical significance. Pharmacokinetic data in patients who did and those who did not receive general anaesthesia were compared using two-sample t -tests.

Results

Patients

Fifteen patients received both levobupivacaine and D₃-levobupivacaine and were included in the pharmacokinetic evaluation. Table 1 shows the patient characteristics. Anaesthetic conditions seemed to be satisfactory after 20 min, but 5 patients ultimately received general anaesthesia later on because they experienced pain during surgery. However, pharmacokinetic data did not differ between patients who did and who did not receive general anaesthesia. Furthermore, mean values and standard deviations of the pharmacokinetic parameters were similar, whether these patients were included or not. Therefore, pharmacokinetic data reported herein are based on all 15 recruited patients.

Table 1. Patient characteristics.

Age (years)	58 ± 22
Sex (M/F)	9/6
Height (cm)	174 ± 11
Weight (kg)	74 ± 12

Data are mean ± standard deviation or frequencies.

Disposition kinetics

Plasma D₃-levobupivacaine concentrations were measurable in individual patients over periods, ranging from 336 to 1409 min (Figure 1, upper panel). Tri-exponential functions fitted the concentration-time curves better than bi-exponential functions for all patients. The values of the disposition parameters of D₃-levobupivacaine are shown in Table 2. The

values, derived by compartmental analysis, were similar to the results obtained by non-compartmental analysis.

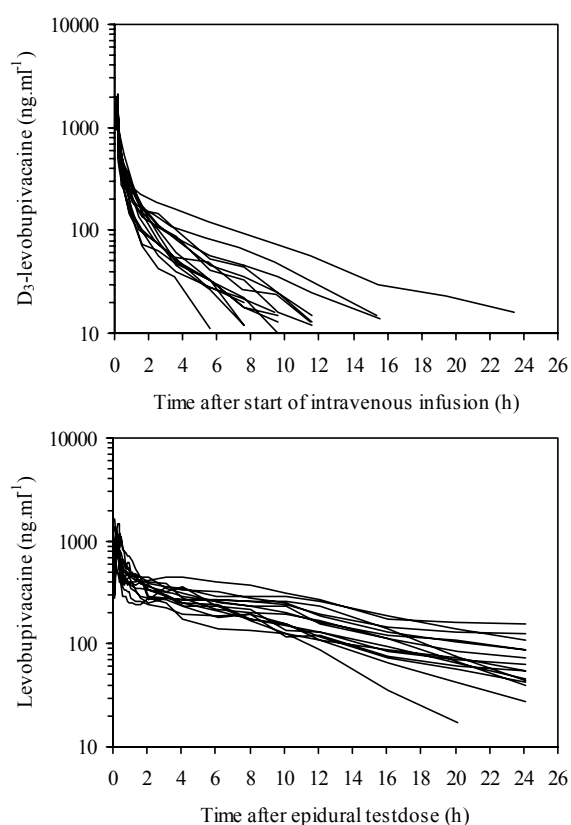


Figure 1. Plasma concentrations of D₃-levobupivacaine after rapid intravenous infusion (upper panel) and of levobupivacaine after epidural administration (lower panel) in individual surgical patients ($n = 15$). Although blood samples were collected for 24 h in all patients, plasma concentrations of D₃-levobupivacaine dropped below the detection limit (10 ng.ml⁻¹) at earlier points in time in most patients. In one patient, this was also the case for unlabelled levobupivacaine.

Absorption kinetics

Plasma levobupivacaine concentrations were measurable over the entire 24-h period, with one exception (Figure 1, lower panel). The maximum concentration of levobupivacaine (1086 ± 296 ng.ml⁻¹) was reached after 10.4 ± 4.4 min. In 3 patients it was reached at

5 min after completion of the test dose, *i.e.*, at the completion of the fractional administration of the epidural dose. Individual cumulative fraction absorbed-time curves are shown in Figure 2. These curves were adequately described by bi-exponential functions, reflecting 2 parallel absorption processes, in all patients. Results of these fits are presented in Table 3, along with the results of the fits of the aggregated model, including 2 parallel absorption compartments and 3 disposition compartments. In one patient F_1 and $t_{1/2,a1}$ were highly correlated and, therefore, the values of these parameters could not be estimated with confidence and were not included in the results and statistical evaluation. Concentrations, predicted by the aggregated models adequately fitted the measured levobupivacaine concentrations (Figure 3), but the fits, judged from the PE were slightly better when absorption kinetics were determined by fitting the aggregated model directly to the data (MDPE = -0.9%; MDAPE = 7.6%) rather than from the fraction absorbed-time data (MDPE = 2.5%, $P < 0.05$; MDAPE = 7.6%, $P > 0.05$). Systemic availabilities (F) and MAT, determined by non-compartmental analysis did not differ from those estimated by compartmental analysis (Table 3).

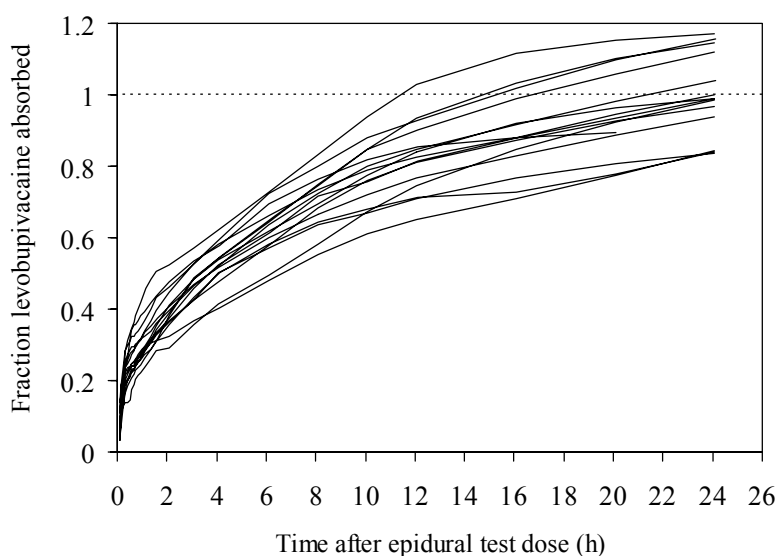


Figure 2. Cumulative fractions absorbed of levobupivacaine *versus* time in individual surgical patients ($n = 15$). Absorption-time data were obtained by deconvolution of the measured concentrations against the intravenous unit impulse response curve.

Table 2. Pharmacokinetic parameters characterizing the disposition of D₃-levobupivacaine after rapid intravenous infusion in patients under epidural anaesthesia.

	Compartmental analysis (n = 15)	Noncompartmental analysis (n = 15)
Fast distribution half-life: $t_{1/2\lambda 1}$ (min)	1.7 ± 0.6	
Slow distribution half-life: $t_{1/2\lambda 2}$ (min)	20 ± 8	
Elimination half-life: $t_{1/2\text{el}}$ (min)	196 ± 65	192 ± 67
Mean residence time: MRT (min)	179 ± 89	178 ± 87
Total plasma clearance: Cl (ml.min ⁻¹)	349 ± 114	356 ± 120
Volume of the central compartment: V _c (l)	4.8 ± 1.7	
Distribution volume at steady state: V _{ss} (l)	56 ± 14	56 ± 14

Data are mean ± standard deviation.

Table 3. Pharmacokinetic parameters, characterizing the absorption of levobupivacaine in patients under epidural anaesthesia.

	Compartmental analysis (<i>n</i> = 15)		Non-compartmental analysis (<i>n</i> = 15)
	Estimated from:		
	absorbed- time data [†]	concentration- time data [‡]	
Fast absorption process:			
Fraction absorbed: F ₁	0.22 ± 0.06*	0.23 ± 0.06*	
Half-life: t _{½,a1} (min)	5.2 ± 2.7*	4.9 ± 2.9*	
Slow absorption process:			
Fraction absorbed: F ₂	0.84 ± 0.14	0.91 ± 0.16	
Half-life: t _{½,a2} (min)	386 ± 91	414 ± 92	
Systemic availability: F	1.06 ± 0.14	1.15 ± 0.14	1.16 ± 0.14
Mean absorption time: MAT (min)	431 ± 118	479 ± 111	564 ± 168

Data are mean ± standard deviation; * n = 14 (see text); [†] parameters were derived by fitting a bi-exponential function to the fraction absorbed-time data; [‡] parameters were derived by fitting the aggregated model (assuming bi-phasic absorption and tri-exponential disposition with fixed disposition parameters) to the levobupivacaine concentration-time data.

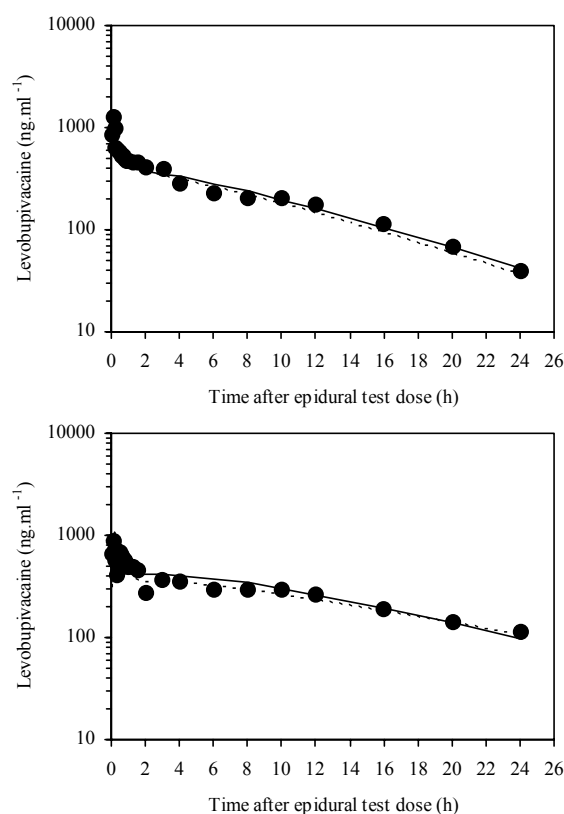


Figure 3. Graphs showing the patients in whom the measured concentration-time data were best (upper panel) and worst (lower panel) described by the aggregated pharmacokinetic models. Dotted line: concentrations predicted by the model, whereby absorption parameters were derived by fitting a bi-exponential function to the fraction absorbed-time data. Unbroken line: concentrations predicted by the model, whereby absorption data were derived by fitting the aggregated model, (assuming bi-phasic absorption) directly to the data. Disposition functions were tri-exponential and identical with both modelling procedures.

Discussion

Using a stable-isotope method, we determined the absorption and disposition kinetics of levobupivacaine in surgical patients. The study demonstrated that the systemic absorption of levobupivacaine after epidural administration is bi-phasic. This is in keeping with observations from previous studies examining the absorption kinetics of other local anaesthetics, including lidocaine, ropivacaine, and racemic bupivacaine.^{14,19,22,23}

The fraction of levobupivacaine absorbed during the fast absorption process ($F_1 = 0.22 \pm 0.06$) was somewhat less than that reported for bupivacaine ($F_1 = 0.29 \pm 0.09$).¹⁹ This may be attributed to a greater vasoconstrictive action of levobupivacaine,^{24,25} as vasoconstriction of the epidural vessels may decrease the absorption rate of the local anaesthetic from the epidural space into the systemic circulation. A recent study showed that the vasoactive effect of levobupivacaine is bi-phasic, *i.e.*, levobupivacaine is a vasoconstrictor at low concentrations and a vasodilator at high concentrations.²⁶ As exact concentrations of local anaesthetics at different sites within the epidural space are not known it is not possible to determine which mechanism (vasoconstriction or vasodilatation) prevails in clinical practice, but, in any case, the evidence suggests that levobupivacaine is likely to have a greater vasoconstrictive (or a less vasodilatory) action than bupivacaine.

As shown in both this and previous studies,^{14,19,22,23} the terminal half-life after epidural administration is considerably longer than the half-life after i.v. administration, due to the slow secondary absorption rate. When the absorption rate constant is smaller than the elimination rate constant observed after i.v. administration, the elimination rate constant after extravascular (*e.g.* epidural) administration will approximate the absorption rate constant (a drug cannot be removed from the blood before it has been absorbed into it). This complicates the discrimination between the absorption and disposition kinetics after epidural administration of a local anaesthetic agent. However, with the stable-isotope method, disposition kinetics can be readily derived from the concentration-time profiles of the labelled drug and subsequently used to derive the absorption characteristics of the unlabelled drug.^{14,19}

Although plasma concentrations of D₃-levobupivacaine dropped below the detection limit after 6-16 h in most patients, the concentrations were measurable over a time period of at least 2 to 3 times the elimination half-life, which is generally considered sufficient to characterize the pharmacokinetics accurately. Nevertheless, the fact that concentrations of D₃-levobupivacaine could not be determined over the entire 24-h period may have influenced the estimation of the systemic availability *F* slightly (see below).

In this study, the i.v. infusions of D₃-levobupivacaine were started 25 min after the epidural injection of unlabelled levobupivacaine. The reason for this is that we wanted to start the infusion after a satisfactory epidural block had developed in order to avoid the administration of very expensive D₃-levobupivacaine to patients in whom a satisfactory block would not develop and that would *a priori* have been considered as drop-outs. Theoretically, the later administration of D₃-levobupivacaine might affect the estimation of absorption parameters. However, the feasibility of the administration of the labelled analogue after full development of the epidural block has been demonstrated in previous studies^{14,19} and is illustrated by the fact that the systemic availability (total fractions

absorbed) of lidocaine ($F = 0.97$),¹⁴ bupivacaine ($F = 0.94$ and $F = 0.97$),^{14,19} and levobupivacaine ($F = 1.06$) were close to unity.

The fraction of levobupivacaine absorbed during the slow absorption process ($F_2 = 0.84 \pm 0.14$) was higher than that reported for bupivacaine ($F_2 = 0.68 \pm 0.11$).¹⁹ This can in part be explained by the higher estimated total fraction absorbed (F) in this study, which exceeded 1 with both the compartmental and non-compartmental analysis. Theoretically, this means that the amount of levobupivacaine absorbed in the systemic circulation exceeded the amount that was administered epidurally, which is impossible. This finding might be related to the deconvolution method applied in this study. In this procedure, the absorption rates between two time-points in this study were constrained to be non-negative. On the other hand, it has been demonstrated that this deconvolution method slightly underestimates the cumulative fractions absorbed.^{20,23} This is also in keeping with our observation that the total fraction absorbed, estimated by fitting bi-exponential functions to the fraction absorbed-time data resulted in somewhat smaller estimates ($F = 1.06 \pm 0.14$) than those obtained by directly fitting a model with 2 parallel first-order absorption compartments and 3 disposition compartments to the measured plasma concentration-time data ($F = 1.15 \pm 0.14$) or by non-compartmental analysis ($F = 1.16 \pm 0.14$). However, a more likely explanation for the overestimation of F is that the AUCs of D₃-levobupivacaine were slightly underestimated. This was because plasma-concentrations of D₃-levobupivacaine could not be determined over the full 24-h study period, but dropped below the limit of quantification earlier. This probably resulted in an underestimation of the terminal half-life.

Values for the MAT differed between compartmental and non-compartmental analyses. These differences can be clarified, because MAT is calculated by subtracting $MRT_{i.v.}$ from $MRT_{epidural}$ and in either case the MRT is sensitive to small discrepancies in estimation of the AUC and AUMC.¹⁶

The disposition parameters $t_{1/2,el}$ and MRT derived in the patients were longer and clearance was lower than the corresponding values in volunteers (see Chapter 7). This might be related to differences in the populations (volunteers *versus* patients). Alternatively, changes in regional blood flows and possibly cardiac output, that are associated with epidural anaesthesia, may also contribute to the “slowing” of the pharmacokinetics in surgical patients compared to healthy volunteers.

Peak plasma concentrations of levobupivacaine after epidural administration have been found to be higher than those of bupivacaine, measured as mixed enantiomers,¹³ although others did not find a difference between levobupivacaine and racemic bupivacaine.¹² Peak plasma concentrations of S(-)-bupivacaine have also been shown to be higher than those of R(+)-bupivacaine after epidural administration of racemic bupivacaine.⁴ This reflects

mainly enantioselective disposition, secondary to differences in the protein binding of the S(–)-bupivacaine and R(+)-bupivacaine, rather than enantioselective absorption.⁴ This can be explained, because the absorption is largely dependent on the partitioning between epidural (fat) tissue and the blood draining the epidural space and because fat tissue can be considered an achiral environment.⁴ However, the absorption of levobupivacaine, given as a single agent, may very well differ from the absorption of S(–)-bupivacaine after administration of racemic bupivacaine, because the vasoactive properties of levobupivacaine and bupivacaine may differ. As explained above, the available evidence suggests that levobupivacaine is more vasoconstrictive/less vasodilatory than bupivacaine. Thereby, slower absorption of levobupivacaine into the blood may compensate the slower disposition from the blood of levobupivacaine compared to mixed bupivacaine enantiomers. This might explain why peak plasma concentrations of levobupivacaine and bupivacaine reported (as mixed enantiomers) in the study of Bader *et al.* did not differ.¹²

Fitting the model with 2 parallel first-order absorption compartments and 3 disposition compartments directly to the measured plasma concentration-time data, instead of first estimating the absorption characteristics and then construct an aggregated model to predict the plasma concentrations reduced (by definition) the weighted sum of squares and the bias, expressed as the MDPE for all blood samples. However, the inaccuracy, expressed as MDAPE value did not change.

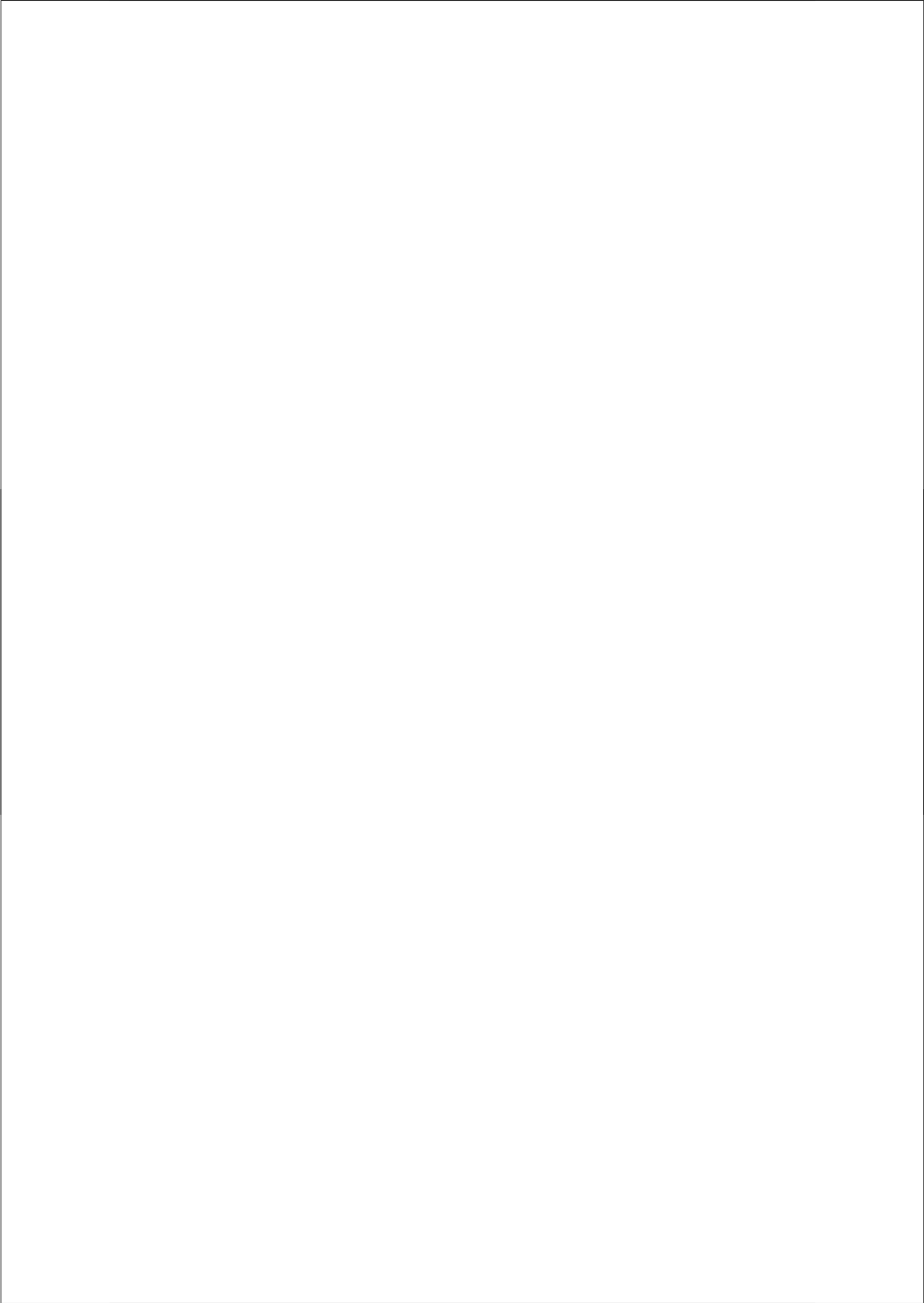
In this study, five of 15 patients were given general anaesthesia because they experienced pain during the operation. The rate of successful block (67%) in our patients undergoing various types of surgery, is comparable with the 62% in a study by Cox *et al.*,²⁷ in which patients underwent lower limb surgery after administration of 15 ml levobupivacaine 0.5%. To improve the success rate in patients undergoing lower limb surgery, the use of a more concentrated solution (0.75%) may be recommended.

In conclusion, using the stable-isotope method we were able to determine the disposition and absorption kinetics of levobupivacaine in surgical patients after epidural administration. In keeping with previous observations with other local anaesthetics, levobupivacaine showed a bi-phasic absorption pattern, whereby the smaller fraction of the dose was rapidly absorbed into the systemic circulation whereas the remainder was absorbed at a much slower rate. Comparison with earlier publications suggested that the fraction of levobupivacaine absorbed during the rapid primary absorption phase is smaller than the corresponding fraction of racemic bupivacaine.

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**THE EFFECT OF AGE ON THE CLINICAL PROFILE AND THE
SYSTEMIC ABSORPTION AND DISPOSITION OF
LEVOPUPIVACAINE 0.75% FOLLOWING
EPIDURAL ADMINISTRATION**

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British Journal of Anaesthesia 2004; 93: 512-20

The increased longevity of the world's population has resulted in a growing number of elderly people requiring medical care.^{1,2} Pharmacokinetic and/or pharmacodynamic changes may occur with increasing age, thereby possibly altering the clinical profile of drugs, including local anaesthetics.^{3,4} After epidural administration of bupivacaine and ropivacaine, the level of analgesia has been shown to increase with increasing age.³⁻⁵

Levobupivacaine (S(-)-1-butyl-2-piperidylformo-2', 6'-xylidide hydrochloride), the pure S(-)-enantiomer of racemic bupivacaine, retains similar local anaesthetic properties and efficacy to racemic bupivacaine,^{6,7} but has been shown to have less cardiotoxic potential than the R(+)-enantiomer or racemic bupivacaine.^{8,9} In addition, the enantiomers of bupivacaine have been shown to differ in their pharmacokinetics, both in animal and human studies.¹⁰⁻¹⁵

Plasma concentration profiles and the potential risk of systemic toxicity after perineural administration of a local anaesthetic depend on the administered dose and the interaction between the rate processes involved in drug absorption and systemic disposition.^{16,17} Unfortunately, absorption and disposition kinetics cannot be derived directly from the plasma concentration-time profile, because local anaesthetics exhibit flip-flop kinetics after epidural administration, *i.e.*, the (secondary) absorption rate of a local anaesthetic after epidural administration is slower than the elimination rate after intravenous administration of the agent. Thereby, slow absorption after epidural administration rate-limits the elimination of the agent from the body. Because of this systemic disposition kinetics and, consequently, also systemic absorption kinetics cannot be derived directly from the plasma concentration-time profiles after epidural administration of a local anaesthetic. However, with a stable-isotope method the absorption and disposition kinetics of a local anaesthetic can be derived simultaneously.¹⁸

Until now the effect of age on the systemic absorption and systemic disposition kinetics of levobupivacaine after epidural administration has not been investigated, nor has the effect of age on the sensory and motor blockade of levobupivacaine been studied. Therefore, the aim of this study was to investigate the effects of age on the clinical profile and systemic absorption and disposition after epidural administration of levobupivacaine 0.75%.

Methods

Patients

The protocol of this study was reviewed and approved by the Committee on Medical Ethics of the Leiden University Medical Center. The study was conducted in accordance with the provisions stated in the Declaration of Helsinki. Thirty-one patients, ASA I or II, who had given written informed consent were enrolled in one of three groups, according to their age (Group 1: 18-44 years; Group 2: 45-70 years; Group 3: 70 years and older). They underwent minor orthopaedic, urological, gynaecological (excluding obstetrics) or lower abdominal surgery. Patients who had a history of known hypersensitivity to amide local anaesthetics, severe respiratory, renal, hepatic or cardiac disease, in particular A-V or intraventricular conduction abnormalities, diabetes mellitus, severe arteriosclerosis, or neurological, psychiatric or seizure disorders were excluded. Patients, who weighted more than 110 kg or were shorter than 150 cm were also excluded. In addition, pregnant women were excluded.

Procedures

Patients were premedicated with temazepam 20 mg (< 60 years) or 10 mg ($\geq$ 60 years) orally 45 min before induction of epidural anaesthesia. An 18-gauge intravenous (i.v.) catheter was placed in the dominant arm for administration of fluids and medication. A 20-gauge catheter was inserted in the radial artery of the contra-lateral arm after local infiltration of the skin with lidocaine 0.5%. Before the epidural injection a rapid i.v. infusion of 500 ml saline 0.9% was administered. Subsequently, the infusion rate was maintained at $2 \text{ ml.kg}^{-1}.\text{h}^{-1}$.

The epidural puncture was performed with the patient in the sitting position, at the L3-L4 interspace, using a midline or paramedian approach. After local infiltration of the skin with lidocaine 0.5%, the epidural space was identified by the loss of resistance to saline technique. With the bevel of a 16-gauge Hustead needle pointing cephalad, a test dose of 3 ml levobupivacaine 5 mg.ml^{-1} (Celltech Chiroscience Ltd, Cambridge, UK) with epinephrine $5 \text{ }\mu\text{g.ml}^{-1}$ was injected at a rate of 1 ml.s^{-1} . Three minutes later, if there were no signs of subarachnoid or intravascular injection, 15 ml of levobupivacaine 7.5 mg.ml^{-1} was administered at a rate of 1 ml.s^{-1} . The patient was then placed in the horizontal supine position.

When satisfactory anaesthetic conditions were achieved (usually 15-20 min after the epidural injection) an 18-gauge cannula was introduced into a foot vein. Twenty-five

minutes after the epidural injection, the patient received approximately 50 ml of a solution, containing 0.48 mg.ml^{-1} deuterium-labelled levobupivacaine (D_3 -levobupivacaine; Celltech Chiroscience Ltd, Cambridge, UK) by constant-rate (5 ml.min^{-1}) i.v. infusion into the foot vein, using a manually controlled pump (Becton Dickinson, Brézins, France). D_3 -levobupivacaine differs from levobupivacaine by the substitution of a deuterium-labelled methyl group (C^2H_3) for one of the methyl groups (CH_3) to the xylylidine ring. Total doses administered were determined by multiplying the infusion rate (5.0 ml.min^{-1}) and exact infusion times. If anaesthetic conditions were not satisfactory after 20 min, D_3 -levobupivacaine was not administered. Surgery commenced soon after completion of the i.v. infusion of D_3 -levobupivacaine.

Assessments

Analgesia, defined as inability to detect a sharp pinprick, was assessed bilaterally in the anterior axillary line using a short-bevelled 25-gauge needle. Results from both sides were averaged. Assessments were made every 5 min during the first 30 min after the epidural injection and subsequently every 15 min until complete regression of the sensory block. Motor blockade of the lower limb was evaluated at the same time by asking the patient to raise the extended leg (flexion of the hip) and to flex the knee and ankle, and was rated per joint (0 = no, 1 = partial, 2 = complete blockade). The results obtained in both extremities were added, giving a maximum score of 12 (complete motor blockade).

Systemic arterial pressure, measured invasively, and heart rate (from the electrocardiogram) were continuously displayed (Cardiocap, Datex-Ohmeda, Helsinki, Finland) and values recorded at the same times as analgesia assessments until at least 30 min after arrival at the recovery room. Hypotension (decrease in systolic blood pressure $> 30\%$ of the pre-anaesthetic value or a systolic blood pressure $< 90 \text{ mm Hg}$) was treated by administering 5 mg ephedrine i.v. and crystalloid fluids. Bradycardia ($< 55 \text{ beats.min}^{-1}$) was treated by administering 0.5 mg atropine i.v.

Blood samples and assays

Arterial blood samples were collected for 24 h at intervals gradually increasing from 5 min to 4 h. Samples were stored on ice and centrifuged for 10 min at 1500 g and 4°C within 4 h. The plasma was transferred into pre-labelled tubes and stored at about -20°C . Analysis of the concentrations was performed by Inveresk Research (Tranent, Scotland, UK), using liquid chromatography-mass spectrometry.¹⁹ The inter-day accuracies of the quality control samples at concentrations of 30, 200 and 400 ng.ml^{-1} were 102.6%, 102.1% and 99.5%, respectively, for levobupivacaine and 101.9%, 102.2%, and 99.2%,

respectively, for D₃-levobupivacaine. The inter-day precisions for these samples were 7.4%, 6.6%, and 7.3% for levobupivacaine, and 7.5%, 6.4%, and 7.4% for D₃-levobupivacaine. The limits of quantification were 10 ng.ml⁻¹ for D₃-levobupivacaine, levobupivacaine, and R(+)-bupivacaine.

Data analysis

Pharmacokinetic data were derived using both compartmental analysis and non-compartmental analysis. Data derived by compartmental analysis corresponded closely to those derived by non-compartmental analysis. Therefore, only the results of the compartmental analysis are presented. Times associated with plasma concentrations of levobupivacaine refer to the completion of epidural administration of levobupivacaine. Times associated with plasma concentrations of D₃-levobupivacaine refer to the start of the i.v. infusion of D₃-levobupivacaine.

Disposition kinetics were derived by fitting bi- and tri-exponential functions to the plasma concentration-time data of D₃-levobupivacaine, using weighted (1/predicted concentration squared) least-squares non-linear regression analysis⁴ with the software package WinNonlin version 1.1 (Scientific Consulting Inc, Apex, NC, USA).

Absorption rates and the cumulative fractions absorbed were estimated using a deconvolution method for unequal sampling times.²⁰ The absorption rate between two time-points was constrained to be non-negative. Subsequently, the fractions absorbed (F₁, F₂) and the absorption half-lives (t_{1/2,a1}, t_{1/2,a2}) were derived by fitting a bi-exponential function to the cumulative fraction absorbed-time data, using unweighted least-squares non-linear regression analysis. The values of the parameters, characterizing the disposition and absorption were used to generate (simulate) plasma concentration-time curves after epidural administration of levobupivacaine for all individual patients.^{4,18} The generated values were compared with the measured concentrations of levobupivacaine. To evaluate whether the aggregated model described the measured concentrations well, the performance error (PE) for each plasma concentration-time pair and the median performance error (MDPE) and median absolute performance error (MDAPE) for each individual were calculated.²¹ The mean absorption time (MAT) of levobupivacaine from the epidural space into the blood was calculated as $MAT = MRT_{n.i.v.} - MRT_{i.v.}$,²² where $MRT_{n.i.v.}$ and $MRT_{i.v.}$ are the mean residence time of epidurally administered unlabelled levobupivacaine and i.v. administered D₃-levobupivacaine, respectively, which were determined by dividing $AUMC_{0 \rightarrow \infty}$ (the area under the first moment of the plasma concentration-time curve) by $AUC_{0 \rightarrow \infty}$, (the area under the plasma concentration-time curve).

Statistical analysis

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. Neural block characteristics were analysed using one-way analysis of variance (ANOVA) with a term for age group, using the software-package SPSS (v8.2.1) and SAS (v6.07).

All possible comparisons between the 3 age groups were made using Student's *t*-test. The sequentially rejective Bonferroni-Holm method was used to compensate for multiple comparisons. This method implicates that to attain an overall 5% significance level, the greatest difference between age groups requires significance at 1.7%, the second greatest difference at 2.5%, and the smallest difference at 5%. The residuals from this analysis were graphically examined and, together with a Shapiro-Wilk test, normality was verified. Homogeneity of variance was checked graphically. If data were not distributed normally or in the presence of heterogeneity of variance, appropriate transformation of the data (*e.g.* log transformation) was performed. If the above assumptions were not met after transformation, then the non-parametric Kruskal-Wallis test with Dunn's test for the pair-wise comparisons were used.

Results

Subjects

Twenty-seven of the 31 patients, who received levobupivacaine epidurally, were eligible to be included into the pharmacokinetic analysis. Four patients were not included because of insufficient block (2 patients), failure of the arterial cannula and withdrawal of consent after dosing. Three more patients were not included in the efficacy analysis, because they received general anaesthesia during the operation.

Patients' characteristics are shown in Table 1. No differences between age groups were found for height and weight. Populations for the pharmacokinetic and efficacy analysis corresponded closely with the population included in the study.

Table 1. Demographic characteristics of all patients included.

	Group 1 (18-44 years) (n = 9)	Group 2 (45-70 years) (n = 14)	Group 3 (> 70 years) (n = 8)
Age (years)	32 (19-44)	57 (47-69)	78 (72-85)
Gender (M/F)	5/4	9/5	8/0
Height (cm)	174 ± 12	174 ± 12	174 ± 6
Weight (kg)	74 ± 15	82 ± 16	75 ± 16

Data are mean (range) for age, mean ± standard deviation or frequencies.

Analgesia and motor blockade

Neural block characteristics are presented in Table 2. The upper levels of analgesia in the two oldest groups of patients were 3 dermatomes (95% confidence interval (95% CI): 0.5-5.0) higher than those in the youngest age group (Figure 1). An intention to treat analysis including all patients enrolled in the study (group 1: $n = 9$; group 2: $n = 14$; group 3: $n = 8$) also showed similar significant differences between the youngest and the two oldest age groups. Although the mean values for the time until maximum caudal spread and the median values for the time until maximum cephalad spread showed a progressive decline with increasing age, the differences among age groups were not significant. Other analgesia parameters, such as the time from maximal cephalad spread of analgesia until the upper level of analgesia had regressed by two segments, the duration of analgesia at the L1-L2 dermatome level and the time until complete recovery from analgesia were not different between age groups. Parameters, characterizing the onset, intensity and duration of motor blockade were not different among the age groups.

Pharmacokinetic parameters

Plasma concentration-time data of levobupivacaine and D₃-levobupivacaine are presented in Figure 2. After inspection of the scatter around the D₃-levobupivacaine curves and using the F -test, a two-compartmental model described the plasma concentration-time curves of 5 patients well. A tri-exponential function was applied to the plasma concentrations-time data of the other patients. Fraction absorbed-time data are presented in Figure 3 and demonstrate a distinct bi-phasic absorption pattern.

Table 2. Neural block characteristics.

	Group 1 (18-44 years) (n = 6)	Group 2 (45-70 years) (n = 10)	Group 3 (>70 years) (n = 8)
Variables of analgesia			
Time to initial onset of analgesia at dermatome level L1-L2 (min)	8 (5-10)	5 (5-20)	5 (5-10)
Time until maximum caudad spread (min)	47 ± 49	19 ± 10	13 ± 4
Time until maximum cephalad spread (min)	35 (15-105)	30 (20-120)	18 (15-150)
Upper level of analgesia (dermatome)	Th9/Th8*	Th6/Th5*	Th6/Th5*
Time to regression over 2 segments (min)	166 ± 51	158 ± 59	174 ± 61
Duration of analgesia at dermatome level L1-L2 (min)	327 ± 69	327 ± 94	347 ± 82
Time until total recovery from analgesia (min)	465 ± 124	468 ± 119	502 ± 64
Variables of motor blockade			
Time to initial onset of motor blockade (min)	18 (15-30) [†]	23 (10-45) [†]	13 (10-30)
Maximum degree of motor blockade	10 (0-12)	8 (0-12)	7 (1-12)
Time until complete recovery from motor blockade (min)	265 ± 180	261 ± 142	292 ± 95

Data are mean ± standard deviation or median (range), as appropriate; * the differences between the Groups 1 and 2 ($P = 0.005$), 1 and 3 ($P = 0.007$) are significant (see also Figure 2); [†] one patient in both age groups did not attain a motor blockade; the data are censored.

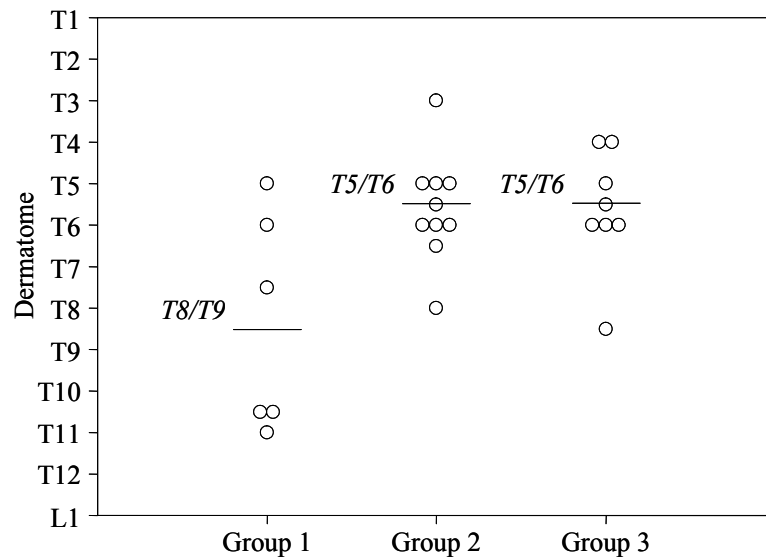


Figure 1. Mean (horizontal lines) and individual values (dots) for the upper level of anaesthesia during epidural anaesthesia with levobupivacaine 0.75% for the three age groups (Group 1: 18-44 years, Group 2: 45-70 years and Group 3: > 70 years). Data are averages of the levels measured on the right and left side of the trunk.

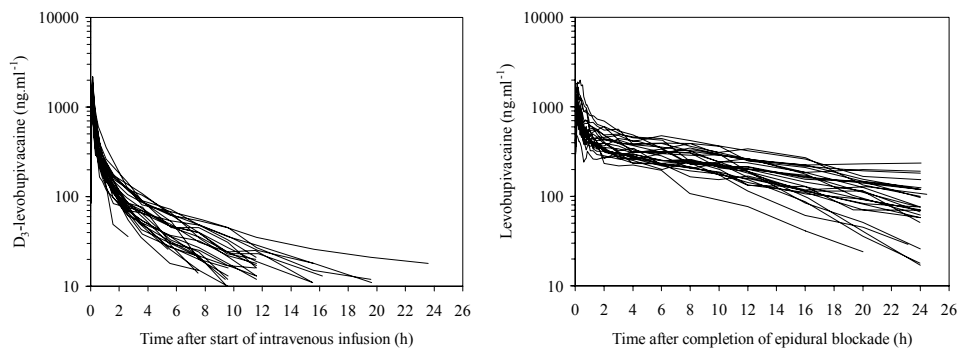


Figure 2. Plasma concentrations after intravenous infusion of D₃-levobupivacaine (left panel) and epidural administration of levobupivacaine (right panel) in individual subjects.

Table 3. Distribution and elimination kinetics of intravenously administered D₃-levobupivacaine and parameters derived from the epidurally administered levobupivacaine concentration-time data.

	Group 1 (18-44 years) (n = 9)	Group 2 (45-70 years) (n = 10)	Group 3 (> 70 years) (n = 8)
Derived from D ₃ -levobupivacaine concentration-time data			
Area under the curve: AUC _{0→∞} (μg ml ⁻¹ .min)	65 ± 21	66 ± 17	78 ± 21
Elimination half-life: t _{1/2el} (min)	180 ± 101	244 ± 78	296 ± 131
Mean residence time: MRTiv (min)	175 ± 101	209 ± 76	273 ± 140
Total plasma clearance: Cl (ml.min ⁻¹)	398 ± 144	365 ± 73	316 ± 83
Distribution clearance: CL _d (ml.min ⁻¹)	1567 ± 568	1615 ± 605	1215 ± 416
Volume of the central compartment: V _c (l)	8.6 ± 2.8	5.8 ± 3.1	8.6 ± 4.0
Distribution volume at steady state: V _{ss} (l)	61 ± 27	76 ± 30	79 ± 23
Derived from levobupivacaine concentration-time data			
Maximum concentration: C _{max} (ng ml ⁻¹)	1211 ± 412	1139 ± 350	1008 ± 249
Time to maximum concentration: T _{max} (min)	15 (7-27)*	6 (1-20)*	6 (2-7)*
Area under the curve: AUC _{0→∞} (μg ml ⁻¹ .min)	382 ± 130	354 ± 105	455 ± 125
Mean Residence Time: MRTniv (min)	643 ± 180†	669 ± 197†	929 ± 301†

Data are mean ± standard deviation or median (range), as appropriate; * the differences between Group 1 and 2 (*P* = 0.002), 1 and 3 (*P* = 0.0006) are significant; † the differences between Group 1 and 3 (*P* = 0.016), 2 and 3 (*P* = 0.024) are significant.

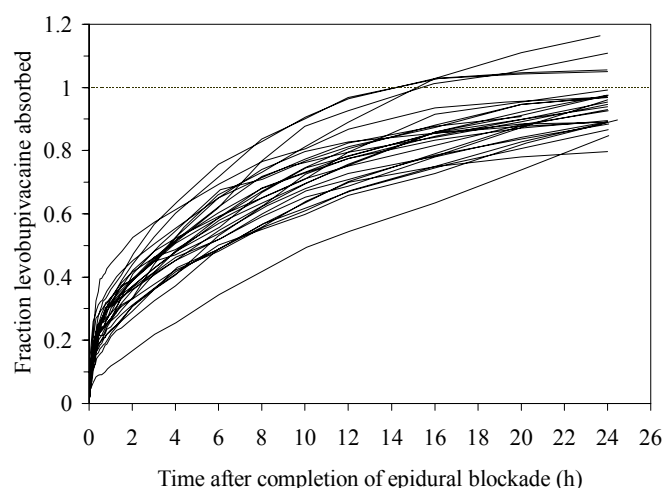


Figure 3. Cumulative fractions absorbed of levobupivacaine *versus* time in individual surgical patients. Absorption-time data were obtained by deconvolution of the measured concentrations unlabelled levobupivacaine concentration-time data against the intravenous unit impulse response curve, derived from the D₃-levobupivacaine concentration-time data.

Values of the parameters, characterizing the distribution and elimination in the 3 age groups are summarized in Table 3, those for the absorption parameters in Table 4. No differences were observed in the distribution and elimination kinetics of i.v. administered D₃-levobupivacaine, although there was a tendency of an increase in elimination half-life and mean residence time, and a decrease in total plasma clearance with increasing age. The mean residence time of epidurally administered levobupivacaine ($MRT_{n.i.v.}$) was 286 min (95% CI: 57-514) longer than in the youngest and 260 min (95% CI: 37-483) longer than in the middle age group.

The fraction absorbed (F_1) was 0.07 (95% CI: 0.02-0.13) smaller and the corresponding absorption half-life ($t_{1/2,a1}$) 3.6 min (95% CI: 0.8-6.4) shorter in the oldest compared to the youngest age group. Other absorption parameters, such as the fraction absorbed (F_2) and the absorption half-lives ($t_{1/2,a2}$) of the slow secondary absorption phase and the MAT were not different among the age groups.

The aggregated model with 2 parallel first-order absorption compartments and 2 or 3 disposition compartments described the measured plasma concentration-time data of unlabelled levobupivacaine well (MDPE: 2.1%; MDAPE: 7.5%).

Table 4. Absorption of levobupivacaine in patients under epidural anaesthesia.

	Group 1	Group 2	Group 3
	(18-44 years)	(45-70 years)	(> 70 years)
	(n = 9)	(n = 10)	(n = 8)
Fast absorption process:			
Fraction absorbed: F_1	$0.24 \pm 0.06^*$	0.21 ± 0.05	$0.17 \pm 0.05^*$
Half-life: $t_{1/2\alpha1}$ (min)	$8.9 \pm 2.6^\dagger$	7.5 ± 3.3	$5.3 \pm 2.2^\dagger$
Slow absorption process:			
Fraction absorbed: F_2	0.83 ± 0.14	0.76 ± 0.07	0.90 ± 0.15
Half-life: $t_{1/2\alpha2}$ (min)	418 ± 137	405 ± 131	534 ± 198
Systemic availability: F	1.08 ± 0.11	0.98 ± 0.08	1.08 ± 0.20
Mean absorption time: MAT (min)	468 ± 159	459 ± 148	658 ± 290

Data are mean $\pm$ standard deviation; * the difference between Group 1 and 3 is significant ($P = 0.014$);

† the difference between group 1 and 3 is significant ($P = 0.014$).

Discussion

Studies of the pharmacokinetics of local anaesthetics after epidural administration are complicated by the fact that these agents exhibit flip-flop kinetics.¹⁸ To overcome this, we have developed a stable-isotope method, which enables simultaneous determination of the absorption and disposition kinetics.¹⁸ The feasibility of this method has been demonstrated in various studies with different local anaesthetics.^{4,18,23} A prerequisite for the use of this method is that the systemic disposition kinetics of the stable-isotope-labelled local anaesthetic are similar to those of the unlabelled local anaesthetic. For levobupivacaine this has been verified in a previous study.¹⁹

In keeping with previous studies of the systemic absorption of bupivacaine after epidural administration,^{4,18,23} levobupivacaine showed a distinct bi-phasic absorption pattern. The absorption characteristics of levobupivacaine and other local anaesthetics after epidural administration, as determined with the stable-isotope method, are compared in Table 5. In so far as studies were performed in surgical patients under very similar conditions in our institution, initial absorption half-lives were very similar, irrespective of the agent and its physicochemical properties. During this phase the high concentration gradient would be

expected to promote rapid uptake from the epidural space into the blood draining the epidural space, whereby, in view of the lipophilicity of the local anaesthetics, local perfusion rather than diffusion is likely to be rate-limiting. In addition, it is conceivable that bulk uptake of local anaesthetic solution contributes to the rapid uptake into the circulation. At the same time local anaesthetic will also be taken up into tissues within the epidural space, in particular epidural fat, and distributed into the subarachnoid space. These local distribution processes are likely to be more rapid and more extensive with the agents that exhibit the greatest lipophilicity and tissue affinity. This may explain why the fraction of lidocaine (the least lipophilic agent), absorbed into the systemic circulation during the fast initial absorption phase is somewhat larger than the corresponding fractions of bupivacaine and levobupivacaine. During the slow secondary absorption phase local anaesthetic will be taken up from the local tissues into the blood and would be expected to become highly dependent upon tissue/blood partitioning. This could explain the much slower secondary absorption of bupivacaine and levobupivacaine as compared to lidocaine.

Table 5. Absorption kinetics of various local anaesthetics after epidural administration, as determined with a stable-isotope method.

Agent	Subjects	Age range (years)	F ₁	t _{½,a1} (min)	F ₂	t _{½,a2} (min)
Lidocaine ¹⁸	Patients (n = 6)	21 - 48	0.38 ± 0.12	9.3 ± 3.8	0.58 ± 0.07	82 ± 19
Ropivacaine ²³	Volunteers (n = 9)	24 - 43	0.52 ± 0.07	14.0 ± 7.0	0.48 ± 0.07	252 ± 54
Bupivacaine ¹⁸	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 ¹⁹	Patients (n = 15)	23 - 85	0.22 ± 0.06	5.2 ± 2.7	0.84 ± 0.14	386 ± 91
Levobupivacaine (this study)	Patients (n = 27)	19 - 85	0.21 ± 0.06	7.3 ± 3.0	0.83 ± 0.13	448 ± 160

Data are mean ± standard deviation; F₁: fraction absorbed during the first (rapid) absorption phase; t_{½,a1}: fast absorption half-life; F₂: fraction absorbed during the second (slow) absorption phase; t_{½,a2}: slow absorption half-life.

When compared with lidocaine, bupivacaine and levobupivacaine, the fraction of ropivacaine ($F = 0.52$) absorbed during the rapid initial absorption phase, as reported by Emanuelsson *et al.*²³ is larger. However, the systemic absorption kinetics of ropivacaine²³ were studied under quite different conditions, *i.e.*, in unpremedicated healthy volunteers rather than premedicated patients, and based on peripheral venous rather than central venous^{4,18} or arterial¹⁹ (this study) blood sampling.

Whereas a previous study on the systemic absorption and disposition kinetics of bupivacaine after epidural administration did not reveal an effect of age,⁴ the present study demonstrated a significant effect on the rapid initial absorption kinetics of levobupivacaine. In part this may be a result of the smaller number of patients ($n = 19$) that were included in the bupivacaine study, because the changes in F_1 and $t_{1/2,a1}$ in that study tended to change in the same direction as in the present study.

Changes in the initial absorption kinetics are best interpreted by considering changes in epidural blood flow and/or epidural fat content. In keeping with the overall increase in adipose tissue with increasing age, it can be argued that the epidural fat content may also be increased in older subjects. This would promote local tissue uptake, which could explain the decreased F_1 in older compared to younger patients. However, a study using epiduroscopy showed a decreased, rather than an increased epidural fat content with increasing age.²⁴ Therefore, changes in epidural fat content cannot explain the decrease F_1 in elderly. Possibly the uptake in other local tissue structures may become more important for local tissue uptake in the elderly, but this remains to be elucidated.

The shortening of $t_{1/2,a1}$ with increasing age is also difficult to explain. As discussed above, the initial absorption rate is likely to be highly dependent upon epidural blood flow. However, the effects of age on epidural blood flow have not been studied in detail. Moreover, in patients under epidural anaesthesia epidural blood flow may be modulated by effects of the epidural block, as well as direct effects of the local anaesthetic on local blood vessels within the epidural space.

In the entire study population a larger fraction absorbed during the initial absorption phase was associated with a higher peak concentration of levobupivacaine ($r = 0.54$; $P = 0.003$; Figure 4). As the F_1 was lower for the oldest group of patients, one may reason that this may attenuate the risk of systemic toxicity in older patients by lowering the peak plasma concentration after epidural administration of levobupivacaine. However, the peak plasma concentrations of the elderly group did not differ from those of the younger age groups. The explanation for this could be that the decrease in F_1 with increasing age is offset by the faster absorption of that fraction in the elderly. This is substantiated by the observation that the time to reach the maximum concentration (t_{max}) decreases with decreasing $t_{1/2,a1}$ ($r = 0.55$; $P = 0.003$; data not shown).

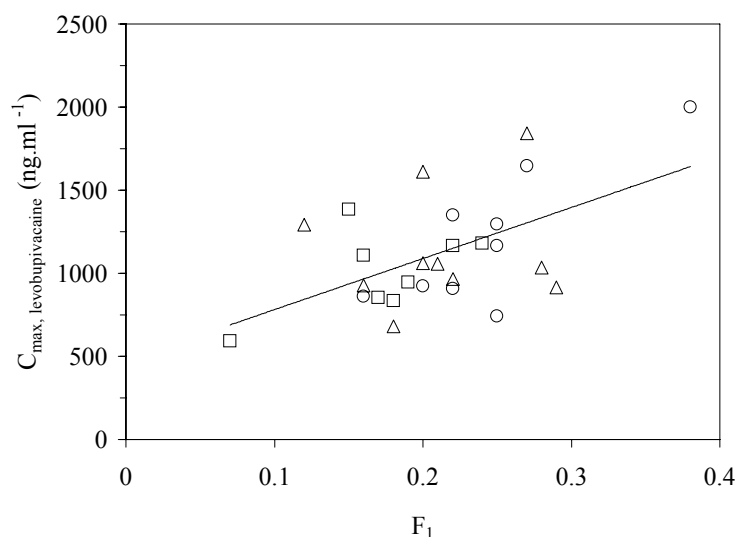


Figure 4. Graphical representation of the relationship between the peak plasma concentrations ($C_{\max}$) and the fractions absorbed during the initial absorption phase (F_1) for the youngest (circles), middle (triangles) and oldest age (squares) group of patients. In the entire study population, a larger F_1 was associated with a higher $C_{\max}$.

Peak levobupivacaine concentrations in this study (990 ng.ml^{-1} per 100 mg dose) were approximately 55% higher than peak bupivacaine concentrations (measured as mixed enantiomers) in a previous stable-isotope study of bupivacaine (640 ng.ml^{-1} per 100 mg dose).⁴ This can in part be explained by differences in the protein binding between levobupivacaine (S(-)-bupivacaine) and its enantiomer R(+)-bupivacaine.^{13,15} In another study, whereby racemic bupivacaine was administered epidurally and plasma concentrations of the individual enantiomers were measured, total peak S(-)-concentrations ($449 \pm 109 \text{ ng.ml}^{-1}$) were larger than peak R(+)-bupivacaine concentrations ($389 \pm 93 \text{ ng.ml}^{-1}$), but unbound peak S(-)-concentrations ($15 \pm 9 \text{ ng.ml}^{-1}$) were lower than unbound peak R(+)-bupivacaine concentrations ($20 \pm 11 \text{ ng.ml}^{-1}$).¹⁴ After i.v. administration total plasma S(-)-bupivacaine concentrations were higher, whereas unbound plasma S(-)-bupivacaine concentrations were lower than the corresponding R(+)-bupivacaine concentrations at all observation times.¹³ Taking into consideration that the intrinsic toxicity of levobupivacaine is less than that of R(+)-bupivacaine,^{8,9} these observations suggest that the margin of safety is wider with levobupivacaine than with racemic bupivacaine, both upon correct epidural administration and upon inadvertent intravascular injection. However, the effect of age on the toxicity of both local anaesthetics has not been established.

In this study the estimated systemic availability of levobupivacaine after epidural administration slightly exceeded the administered dose ($F > 1.0$). The overestimation of F is most likely related to postoperative changes in the protein binding of levobupivacaine and D₃-levobupivacaine, secondary to postoperative changes in the plasma concentrations of α_1 -acid glycoprotein (AAG). A recent study demonstrated that plasma AAG-concentrations and the protein binding of R(+)- and S(-)-bupivacaine in surgical patient decreased during the first 12 h after the infusion and from then on increased during the next days.¹⁵ In this study D₃-levobupivacaine concentrations were measurable only during the first 8-12 h after the i.v. administration in most patients, whereas levobupivacaine concentrations were measurable for all but 1 patient over the full 24-h study period. Had we been able to measure plasma D₃-levobupivacaine concentrations over the entire 24-h study period, the estimated terminal half-life of D₃-levobupivacaine (and thereby the area under the curve) might have been somewhat longer and, consequently, the estimated systemic availability of levobupivacaine somewhat smaller (*i.e.*, closer to 1).

In this study the systemic disposition kinetics were not different among the 3 age groups. These findings are in agreement with those reported in a previous epidural study with bupivacaine.⁴ However, total plasma clearance of bupivacaine has been found to decrease with increasing age after epidural and subarachnoid administration.^{3,25} A trend towards a lower total plasma clearance with increasing age was observed in both the previous study with bupivacaine⁴ and in this study with levobupivacaine. The consensus may be that the effect of age on the total plasma clearance is small and may be masked by factors such as the biological variation between subjects, individual phenotypes, environmental factors, undetected concomitant diseases and previous drug intake.

As discussed before, in this study the older group of patients showed a smaller F_1 than the younger group of patients. Consequently, more molecules may be available for the neuron-blocking properties of the specific local anaesthetic. This could influence the intensity and the spread, as well as the duration of the block and may in part explain the differences in level of analgesia between younger and older patients. However, other factors are likely to be involved. These include gradual degeneration of the central and peripheral nervous system and reduced leakage of the solution from the epidural space into the paravertebral space as a result of sclerosis of the intervertebral foramina.²⁶⁻²⁸ Furthermore, changes in the connective tissue ground substances with increasing age may result in changes in local distribution, *i.e.*, in the distribution rate of the local anaesthetic from the site of injection (the epidural space) to the sites of action.

The observations on the effects of age on the clinical profile of levobupivacaine correspond closely with earlier similar studies with racemic bupivacaine, which also demonstrated a higher level of analgesia in older patients, but relatively little or no change in the onset or duration of sensory block and in motor block characteristics.^{3,4} This

similarity is not surprising in view of other recent studies which demonstrated a very similar efficacy of levobupivacaine and racemic bupivacaine after epidural administration.^{6,7}

In conclusion, this study showed that age influences the pharmacokinetics, in particular the early absorption, and the neural block characteristics after epidural anaesthesia with levobupivacaine. Changes in the upper level of analgesia are best explained by anatomical considerations and possibly pharmacodynamic changes, rather than by pharmacokinetic changes in the elderly.

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**EFFECTS OF AGE ON SYSTEMIC ABSORPTION AND SYSTEMIC
DISPOSITION OF ROPIVACAINE 1.0% AFTER
EPIDURAL ADMINISTRATION**

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Anesth Analg 2006; 102: 276-82

With a still growing number of elderly people (individuals being 65 years of age and older) the demand for surgery will continue to increase.¹ Regional anaesthetic techniques are frequently used in elderly patients undergoing surgery. Aging influences the pharmacokinetics and pharmacodynamics of local anaesthetics 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 haemodynamic 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 anaesthetic 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 with regard to the clinical profile and the risk of systemic toxicity. Disposition kinetics of ropivacaine have been obtained after intravenous administration in volunteers^{9,10} and after epidural administration in surgical patients.¹¹⁻¹³ However, absorption kinetics of ropivacaine after epidural anaesthesia 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.

Methods

Patients

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 years; group 2: 41-60 years; group 3: ≥ 61 years). These patients were part of a group of 54 patients, in which the effects of age on the neural blockade and haemodynamic changes were evaluated. The findings of that study 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, gynaecological (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 backpain, were excluded. Patients, who were hypersensitive to amide local anaesthetics, weighed more than 110 kg or were shorter than 150 cm, as well as pregnant female patients were also excluded.

Procedures

Patients were premedicated with temazepam 20 mg (< 60 years) or 10 mg ($\geq$ 60 years) orally. The epidural puncture was performed with the patient in the sitting position, at the L3-L4 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 $5 \mu\text{g} \cdot \text{ml}^{-1}$ 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 $1 \text{ ml} \cdot \text{s}^{-1}$. Patients did not receive additional sedation or general anaesthesia during surgery.

When satisfactory anaesthetic 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 $0.44 \text{ mg} \cdot \text{ml}^{-1}$ deuterium-labelled ropivacaine (D_3 -ropivacaine; AstraZeneca, Södertälje, Sweden) by constant-rate ($5 \text{ ml} \cdot \text{min}^{-1}$) intravenous infusion into the foot vein, using a manually controlled pump (Becton Dickinson, Brézins, France). Deuterium-labelled ropivacaine differs from unlabelled ropivacaine by the substitution of 3 hydrogen atoms with deuterium at a methyl-group ($-\text{CH}_3$) on the xylylidine 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 anaesthetic conditions were not satisfactory after 20 min, D_3 -ropivacaine was not administered.

Blood samples and assays

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 1500g and 4°C within 4 h. The plasma was transferred into prelabelled tubes and stored at -20°C.

Determination of total plasma concentrations of ropivacaine and D₃-ropivacaine was performed at AstraZeneca R&D (Södertälje, Sweden), using ultrafiltration of the acidified plasma sample, followed by gradient reversed-phase liquid chromatography and tandem mass spectrometry detection with positive electrospray ionisation (Micromass Quattro Ultima, Waters Corporation, Milford, USA). The plasma sample and the internal standard (at low pH) were pipetted into a 96-well ultrafiltration plate (Multiscreen® Ultracel-PPB, Millipore, Bedford, MA, USA). The plate was covered and shaken for about 5 min. Thereafter, the plate was centrifuged for 45 min at 2000g 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 3 C18, 100 x 2.1 mm (ACT, Aberdeen, Scotland, UK). The scan mode was multiple reaction monitoring (MRM) 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 limits of quantification were 2.74 and 2.77 ng.ml⁻¹ for ropivacaine and D₃-ropivacaine, respectively.

Data analysis

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- and tri-exponential functions to the plasma concentration-time data of D₃-ropivacaine, using weighted (1/predicted concentration squared) least-squares non-linear regression analysis with the software package WinNonlin version 4.1 (Pharsight Corp, Mountain View, USA).

The fractions absorbed (F₁, F₂) 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 non-linear 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 aggregated model directly to the measured

plasma concentration-time data of unlabelled ropivacaine, using weighted (1/predicted concentration squared) least-squares non-linear regression. Both approaches used for estimating the absorption kinetics were compared by calculating the median performance error (MDPE) and median absolute performance error (MDAPE).

Statistical analysis

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⁻¹ between any 2 groups.

Pharmacokinetic variables were analysed using one-way analysis of variance (ANOVA) with a term for age group, using the software-package SPSS 11.5.0 (SPSS Inc, Chicago, USA). All possible comparisons between 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 non-compartmental 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.

Table 1. Group characteristics and demographic data of all patients.

	Group 1 (18-40 years) (n = 5)	Group 2 (41-60 years) (n = 10)	Group 3 (≥ 61 years) (n = 9)	Total (n = 24)
Age (years)	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*

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 intravenous infusion of D₃-ropivacaine or epidural administration of ropivacaine are presented for the 3 age groups in Table 2. All disposition parameters derived after intravenous infusion were analysed 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 (95% CI): 0.37-0.99), meaning that $t_{1/2,el}$ was on average 40% longer in the oldest group, compared to the youngest group. Also, there was a significant difference between these groups in Cl ($P = 0.028$), which was on average 194 ml.min⁻¹ (95% CI: 18-370 ml.min⁻¹) less in the oldest group. The AUC and MRT derived after epidural administration were analysed non-parametrically and parametrically after log-transformation, respectively. The parameters AUC and MRT did not reach statistical significance after correction for multiple comparisons.

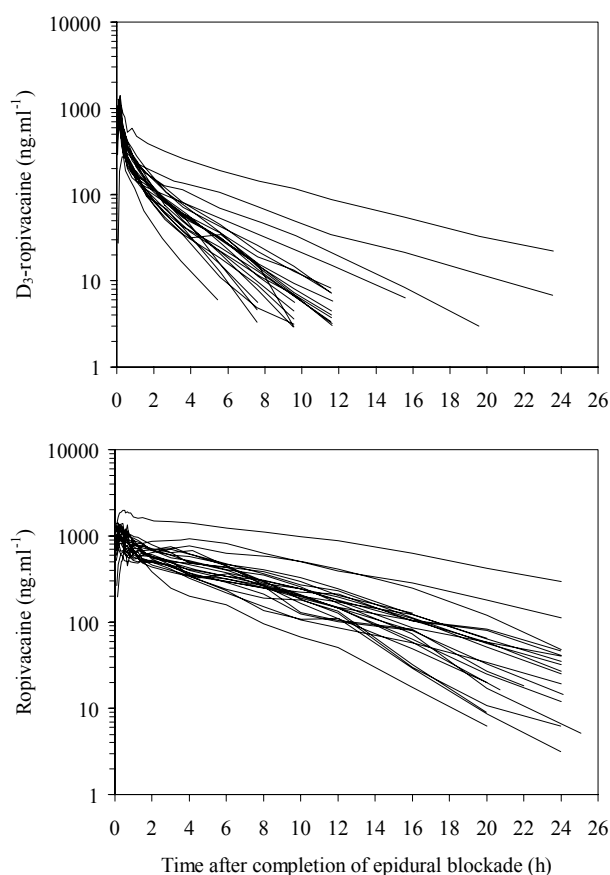


Figure 1. Individual plasma concentration-time curves of intravenously-infused D₃-ropivacaine (upper panel) and epidurally-administered ropivacaine (lower panel).

Absorption kinetics of ropivacaine are presented in Table 3. Cumulative fraction absorbed-time curves of 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 , $t_{1/2,a1}$, F_2 and total fraction absorbed (F), were analysed parametrically without log transformation. Mean absorption time (MAT) and $t_{1/2,a2}$ 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.

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→∞} D ₃ -ropivacaine (μg.ml ⁻¹ .min)	42 (31-49)	53 (25-67)	63 (40-22)
Elimination half-life: t _{1/2el} (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 ⁻¹)	492 ± 121 ‡	415 ± 127	298 ± 115 ‡
Fast distribution clearance: CL _{d(r)} (ml.min ⁻¹)	972 (714-2203)	1274 (677-2533)	971 (567-2252)
Slow distribution clearance: CL _{d(s)} (ml.min ⁻¹)	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 ⁻¹)	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→∞} ropivacaine (μg.ml ⁻¹ .min)	287 (230-318)	341 (169-460)	363 (284-1452)
Mean Residence Time: MRT _{iv} (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. Haemodynamic data.

	Group 1 (18-40 years) (n = 5)	Group 2 (41-60 years) (n = 10)	Group 3 (≥ 61 years) (n = 9)
Fast absorption process:			
- fraction absorbed: F1	0.35 ± 0.08 ^a	0.24 ± 0.07 ^a	0.25 ± 0.08
- half-life: t _{1/2,a1} (min)	13 ± 3	10 ± 6	10 ± 4
Slow absorption process:			
- fraction absorbed: F2	0.71 ± 0.09	0.79 ± 0.09	0.79 ± 0.15
- half-life: t _{1/2,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)

Median (range), as appropriate; MAP = mean arterial pressure; ^a difference is significant between Group 2 and 3 ($\chi^2 = 7.8$; $p = 0.005$); [†] difference is significant between Group 1 and 3 ($p = 0.002$); ^{*} difference is significant between Group 2 and 3 ($p = 0.0009$) and Group 1 and 3 ($p = 0.0001$); [§] difference is significant between Group 1 and 3 ($\chi^2 = 9.7$; $p = 0.002$).

Values for absorption variables, estimated from the fraction absorbed-time data were in agreement with those derived after fitting the aggregated model with 2 absorption compartments and one, two or three distribution compartments directly to the unlabelled 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.

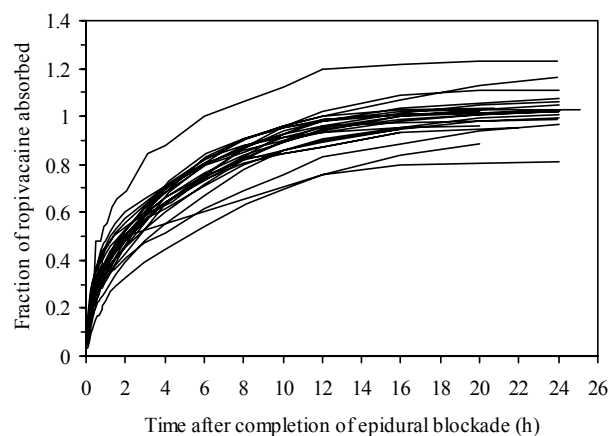


Figure 2. Cumulative fractions absorbed of ropivacaine *versus* time in individual surgical patients. Absorption-time data were obtained by deconvolution of the measured concentrations unlabelled ropivacaine concentration-time data against the i.v. unit impulse-response curve, derived from the D₃-ropivacaine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

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 parameters. 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 intravenous 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 ($t_{1/2,el} = 139 \pm 63$ min), 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 ($t_{1/2,el} = 101 \pm 24$ min) were similar to those obtained in the abovementioned volunteer studies, conducted in young subjects ($t_{1/2,el} = 111 \pm 62$ min and 114 ± 36 min, respectively).^{9,10}

Moreover, in our study the Cl was decreased in the oldest, compared to 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 lower plasma clearance with increasing age.^{4,6} It is likely that age influences the plasma clearance of all abovementioned local anaesthetics.

Absorption kinetics of local anaesthetics 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 anaesthetics 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 anaesthetics, may be used when labelling of the local anaesthetic 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-labelled counterpart has been confirmed.¹⁰

This study confirmed that, like other amide local anaesthetics, 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, F_1 was larger in the youngest, compared to the two oldest age groups, although the difference between the youngest and oldest patients was just not significant. This is in agreement with the study using levobupivacaine, which showed a decrease of F_1 and $t_{1/2,al}$ 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 with bupivacaine and levobupivacaine, there were no differences in the maximum plasma concentrations 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 's 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 agent.^{16,20}

Vasoconstriction of the epidural vessels may decrease the uptake of local anaesthetics from the epidural space into the systemic circulation. In contrast to bupivacaine, which has a more vasodilatory, less vasoconstrictive action, ropivacaine exhibits 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 agents 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 $t_{1/2,al}$ of ropivacaine was longer than those found for the other long-acting local anaesthetics bupivacaine and levobupivacaine.^{4,6,16} The vasoconstrictive action of ropivacaine may delay the initial absorption of the local anaesthetic.

Table 4. Absorption kinetics of amide local anaesthetics after epidural administration, as determined with a stable-isotope method.

Agent	Subjects	Age range (years)	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. F₁: fraction absorbed during the first (rapid) absorption phase; t_{½,a1}: fast absorption half-life; F₂: fraction absorbed during the second (slow) absorption phase; t_{½,a2}: slow absorption half-life.

The F₂, 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 F₂ and t_{½,a2}, respectively), compared to those derived for the long-acting local anaesthetics 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 agent and the long-acting local anaesthetics.

Using a stable-isotope method, Emanuelsson et al.¹⁴ determined the absorption kinetics of ropivacaine and found a larger F₁ and a smaller F₂, compared to 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 parameters 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 (AAG) 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 levelled off after 24 hours. In the present study, total plasma ropivacaine concentrations decreased continuously after reaching a maximum at approximately 20 min. 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 relatively 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 excludes participation in this study that lasted for 24 hours. The small number of included young patients may have influenced the results of this study. Nevertheless, the differences in $t_{1/2,el}$, CI and F_1 were significant, although they showed rather wide 95% CI's.

In conclusion, this study showed that the disposition, as well as the absorption kinetics after epidural administration of ropivacaine are influenced by age. The CI was lower 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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