Effect of age on the clinical profile and systemic absorption and disposition of levobupivacaine after epidural administration


Department of Anaesthesiology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands

*Corresponding author. E-mail: m.j.g.simon@lumc.nl

Background. Pharmacokinetic and/or pharmacodynamic changes, which may occur with increasing age, could alter the clinical profile of the new local anaesthetic levobupivacaine. We investigated the effect of age on the absorption and disposition kinetics and the neural block characteristics after epidural administration of levobupivacaine 0.75%.

Methods. Thirty-one patients were enrolled in one of three age groups (Group 1, 18–44 yr; Group 2, 45–70 yr; Group 3, >70 yr). Twenty-five minutes after epidural administration of levobupivacaine (127.5 mg), they received ~25 mg deuterium-labelled levobupivacaine (D3-levobupivacaine) intravenously. Arterial blood samples were collected until 24 h after the epidural administration. Plasma concentrations were determined using liquid chromatography mass spectrometry. Plasma concentration–time data were analyzed by compartmental and non-compartmental analysis. Assessments of analgesia and motor block were made at set intervals until complete regression of the block.

Results. The upper levels of analgesia in the two oldest groups of patients were 3 dermatomes (95% confidence interval (95% CI): 0.5–5.0 dermatomes) higher than in the youngest group. The fraction absorbed (F1) was 0.07 (95% CI: 0.02–0.13) smaller and the absorption half-life (t1/2,a1), characterizing the initial fast absorption phase, 3.6 min (95% CI: 0.8–6.4) shorter in the oldest group compared with the youngest group.

Conclusions. Age influences the pharmacokinetics, in particular the early absorption kinetics, and the neural block characteristics after epidural administration of levobupivacaine. Changes in the upper level of analgesia are best explained by anatomical considerations and possibly pharmacodynamic changes in the elderly.

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

Levobupivacaine ((S)-1-butyl-2-piperidylformoyl-2', 6'-xylidide hydrochloride), the pure S-(-)-enantiomer of racemic bupivacaine, retains similar local anaesthetic properties and efficacy to racemic bupivacaine, but has been shown to have less cardiotoxic potential than the R-enantiomer or racemic bupivacaine. In addition, the enantiomers of bupivacaine have been shown to differ in their pharmacokinetics both in animal and human studies. 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. 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, that is the (secondary) absorption rate of a local anaesthetic after epidural administration is slower than the...
elimination rate after i.v. 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 of levobupivacaine after epidural administration has not been investigated, nor has the effect of age on the sensory and motor block of levobupivacaine. 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%.

Materials and methods

Subjects

The protocol of this study was reviewed and approved by the Committee on Medical Ethics of the Leiden University Medical Centre. 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 yr; Group 2, 45–70 yr; Group 3, >70 yr). 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 weighed 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 (≤60 yr) or 10 mg (≥60 yr) orally 45 min before induction of epidural anaesthesia. An 18-gauge 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 dominant arm for administration of fluids and medication. A 20-gauge catheter was inserted in the insert in the radial artery of the dominant arm for administration of fluids and medication. A 20-gauge cannula was inserted into a foot vein. Twenty-five minutes after the epidural injection, the patient received ~50 ml of a solution, containing 0.48 mg ml−1 deuterium-labelled levobupivacaine (D3-levobupivacaine; Celltech Chiroscience Ltd, Cambridge, UK) by constant-rate infusion into the foot vein, using a manually controlled pump (Becton Dickinson, Brézins, France). D3-levobupivacaine differs from levobupivacaine by the substitution of a deuterium-labelled methyl group (C2H5) for one of the methyl groups (CH3) to the xylidine 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, D3-levobupivacaine was not administered. Surgery commenced soon after completion of the i.v. infusion of D3-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 block 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 block). The results obtained in both extremities were added, giving a maximum score of 12 (complete motor block).

Systemic arterial pressure, measured invasively, and heart rate (from the ECG) 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 arterial pressure >30% of the pre-anaesthetic value or a systolic arterial pressure <90 mm Hg) was treated by administering ephedrine 5 mg i.v. and crystalloid fluids. Bradycardia (<55 beats min−1) was treated by administering atropine 0.5 mg intravenously.

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. 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 D\(_3\)-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 D\(_3\)-levobupivacaine. The limit of quantification was 10 ng ml\(^{-1}\) for D\(_3\)-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 D\(_3\)-levobupivacaine refer to the start of the i.v. infusion of D\(_3\)-levobupivacaine.

Disposition kinetics were derived by fitting bi- and tri-exponential functions to the plasma concentration–time data of D\(_3\)-levobupivacaine, using weighted (1/predicted concentration squared) least-squares non-linear regression analysis\(^4\) 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 (\(F_1, F_2\)) and the absorption half-lives (\(t_{1/2,a1}, t_{1/2,a2}\)) were derived by fitting a bi-exponential function to the 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.\(^4\)\(^\text{18}\) 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 epidurally, were eligible to be included into the pharmacokinetic analysis. Four patients were not included because of insufficient block (two 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.

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 (two 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.

Analgesia and motor block
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 dermatomes) higher than those in the youngest
age group (Fig. 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 between 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 block were not different between 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 five patients well. A tri-exponential function was applied to the plasma concentration–time data of the other patients. Fraction absorbed–time data are presented in Figure 3 and demonstrate a distinct bi-phasic absorption pattern.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics (all patients included). Data are mean (range) for age, mean (SD) or frequencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (18–44 yr)</td>
<td>Group 2 (45–70 yr)</td>
</tr>
<tr>
<td>(n=9)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32 (19–43)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>5/4</td>
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<tr>
<td>Height (cm)</td>
<td>174 (12)</td>
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<tr>
<td>Weight (kg)</td>
<td>74 (15)</td>
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</tbody>
</table>

**Table 2** Neural block characteristics. *Differences between Groups 1 and 2 (P=0.005), and Groups 1 and 3 (P=0.007) were significant (see also Fig. 2). One patient in both age groups did not attain a motor block; the data were censored. Data are mean (SD) or median (range), as appropriate

| Group 1 (18–44 yr) | Group 2 (45–70 yr) | Group 3 (>70 yr) |
| (n=6) | (n=10) | (n=8) |
| 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 caudal 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) |
| Motor block | | |
| Time to initial onset of motor block (min) | 18 (15–30) | 23 (10–45) | 13 (10–30) |
| Maximum degree of motor block | 10 (0–12) | 8 (0–12) | 7 (1–12) |
| Time until complete recovery from motor block (min) | 265 (180) | 261 (142) | 292 (95) |

Values of the parameters, characterizing the distribution and elimination in the three 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 (MRTₙiv) was 286 min (95% CI: 57–514 min) longer than in the youngest and 260 min (95% CI: 37–483 min) longer than in the middle age group.

The fraction absorbed ($F₁$) was 0.07 (95% CI: 0.02–0.13) smaller and the corresponding absorption half-life ($t¹/₂,a₁$) 3.6 min (95% CI: 0.8–6.4 min) shorter in the oldest compared with the youngest age group. Other absorption
parameters, such as the fraction absorbed ($F_2$) and the absorption half-life ($t_{1/2,a,2}$) of the slow secondary absorption phase and the MAT were not different between the age groups.

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

**Discussion**

Studies of the pharmacokinetics of local anaesthetics after epidural administration are complicated by the fact that these agents exhibit flip-flop kinetics. To overcome this, we have developed a stable-isotope method, which enables simultaneous determination of the absorption and disposition kinetics. The feasibility of this method has been demonstrated in various studies with different local anaesthetics. 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.

In keeping with previous studies of the systemic absorption of bupivacaine after epidural administration, 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 with lidocaine. When
compared with lidocaine, bupivacaine, and levobupivaca-


cine, the fraction of ropivacaine \((F=0.52)\) absorbed during the rapid initial absorption phase, as reported by Emanuelsson and colleagues\(^2\) is larger. However, the systemic absorption kinetics of ropivacaine\(^2\) were studied under quite different conditions, such as in unpremedicated healthy volunteers rather than premedicated patients and based on peripheral venous rather than central venous\(^4\,\,^18\) or arterial\(^19\) (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, the present study demonstrated a significant effect on the rapid initial absorption kinetics of levobupivacaine.\(^3\) 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 tissue with increasing age. 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 F₁ in older compared with younger patients. However, a study using epiduroscopy showed a decreased, rather than an increased epidural fat content with increasing age. Therefore, changes in epidural fat content cannot explain the decrease F₁ 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 t₁/₂,al 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; Fig. 4). As the F₁ 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 F₁ 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 t₁/₂,al (r=0.55; P=0.003; data not shown).

Peak levobupivacaine concentrations in this study (990 ng ml⁻¹ per 100 mg dose) were ~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). This can in part be explained by differences in the protein binding between levobupivacaine ((S)-bupivacaine) and its enantiomer R(+)-bupivacaine. In another study, whereby racemic bupivacaine was administered epidurally and plasma concentrations of the individual enantiomers were measured, total peak S(−)-concentrations (449 (109) ng ml⁻¹) were larger than peak R(+)bupivacaine concentrations (389 (93) ng ml⁻¹), but unbound peak S(−)-concentrations (15 (9) ng ml⁻¹) were lower than unbound peak R(+)bupivacaine concentrations (20 (11) ng/ml). 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. Taking into consideration that the intrinsic toxicity of levobupivacaine is less than that of R(+)bupivacaine, 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 α₁-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. 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 one 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 between the three age groups. These findings are in
agreement with those reported in a previous epidural study with bupivacaine. However, total plasma clearance of bupivacaine has been found to decrease with increasing age after epidural and subarachnoid administration. A trend towards a lower total plasma clearance with increasing age was observed in both the previous study with bupivacaine 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 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. Furthermore, changes in the connective tissue ground substances with increasing age may result in changes in local distribution, such as 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. 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.

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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