The Effect of Age on Systemic Absorption and Systemic Disposition of Bupivacaine after Subarachnoid Administration

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In order to evaluate the role of the pharmacokinetics of the age-related changes in the clinical profile of spinal anesthesia with bupivacaine, we studied the influence of age on the systemic absorption and systemic disposition of bupivacaine after subarachnoid administration in 20 male patients (22–81 yr), ASA Physical Status 1 or 2, by a stable isotope method. After subarachnoid administration of 3 ml 0.5% bupivacaine in 8% glucose, a deuterium-labeled analog (13.4 mg) was administered intravenously. Blood samples were collected for 24 h. Plasma concentrations of unlabeled and deuterium-labeled bupivacaine were determined with a combination of gas chromatography and mass fragmentography. Biexponential functions were fitted to the plasma concentration-time data of the deuterium-labeled bupivacaine. The systemic absorption was evaluated by means of deconvolution. Mono- and biexponential functions were fitted to the data of fraction absorbed versus time. The maximal height of analgesia and the duration of analgesia at T12 increased with age (r = 0.715, P < 0.001; r = 0.640, P < 0.01, respectively). In 18 patients the systemic absorption of bupivacaine was best described by a biexponential equation. The half-life of the slow systemic absorption process (r = −0.478; P < 0.05) and the mean absorption time (r = −0.551; P < 0.02) decreased with age. The total plasma clearance decreased with age (r = −0.550, P < 0.002), whereas the mean residence time and terminal half-life increased with age (r = 0.597, P < 0.01; r = 0.503, P < 0.05). The observed changes in the clinical profile with age cannot be attributed to changes in the systemic absorption profile after subarachnoid administration, but may be related to changes in the pharmacodynamics of local anesthetics. (Key words: Age factors. Anesthetic techniques: spinal. Anesthetics, local: bupivacaine. Pharmacokinetics: bupivacaine; age.)

CLINICAL studies have shown that the profile of anesthesia after subarachnoid administration of hyperbaric solutions of bupivacaine changes with increasing age.1,2 For example, in older patients the spread of analgesia is higher and the recovery from analgesia at the T12 and L2 levels is prolonged compared with that in young patients. These alterations presumably are due in part to age-related changes in the central and peripheral nervous system. These alterations in the clinical profile may be attributed in part to changes that occur with increasing age in the pharmacokinetics of local anesthetics injected into the subarachnoid space.3 It has been demonstrated that age affects the plasma concentration profile after subarachnoid administration of hyperbaric bupivacaine.1 In older patients, the total plasma clearance of bupivacaine is markedly reduced. With hyperbaric bupivacaine solutions, increasing age does not affect the peak plasma concentration (Cmax) but does prolong the corresponding peak time (tmax) and terminal half-life. The prolonged tmax and terminal half-life in older patients may reflect an altered systemic absorption profile but also may reflect an altered systemic disposition. Details on the systemic absorption rate after subarachnoid administration cannot be derived from the plasma concentration curves without a detailed description of the systemic disposition.

Until now no studies on the effects of age on the systemic absorption and systemic disposition of local anesthetics after subarachnoid administration have been available. Therefore, the aim of the current study was to investigate the effects of age on systemic absorption after subarachnoid administration of a hyperbaric solution of bupivacaine. Systemic absorption and systemic disposition kinetics were studied with a stable isotope method, developed by Burn et al.,4,5 using deuterium-labeled bupivacaine (bupivacaine-D containing three deuterium atoms), which has systemic disposition kinetics similar to unlabeled bupivacaine.6 In addition, the correlation between the effects of age on the systemic absorption rates and the spread and duration of action were investigated.

Materials and Methods

PATIENTS

The protocol was reviewed and approved by the Committee on Medical Ethics of the Leiden University Hospital, and informed consent was obtained from each patient. Twenty male surgical patients (ASA Physical Status 1 or 2, age 20–81 yr, weight 63–90 kg) scheduled for minor orthopedic, urologic, or lower abdominal surgery participated in the study. Patients with diabetes, a history of neurologic diseases, bleeding diathesis, or peripheral arteriosclerosis were excluded from the study. After completion of the study, patients were numbered according to their ages.
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DRUGS AND SOLUTIONS

The local anesthetic solution used in this study was hyperbaric (glucose 80 mg/ml) 0.5% bupivacaine HCl (bupivacaine 4.44 mg/ml) without epinephrine. The doses and concentrations are expressed in terms of base equivalents, unless specified otherwise.

Bupivacaine-D was dissolved in a slightly acid isotonic aqueous solution. Five-milliliter aliquots of these solutions were diluted with 45 ml normal saline prior to the administration. The final solution of bupivacaine-D contained 0.279 mg/ml bupivacaine-D.

PROCEDURES

The patients received lorazepam (1–2 mg sublingually) 1.5 h before induction and atropine (0.25 mg in patients over 55 yr and 0.5 mg in patients under 55 yr, intramuscularly) 45 min before induction of spinal anesthesia. A central venous catheter was introduced into the superior vena cava via the basilic or the cephalic vein after local infiltration with lidocaine 0.5%. The catheter was advanced until the tip was located in the central conduit but at least 6 cm proximal to the junction of the axygos vein and the superior vena cava. The correct location of the catheter was verified with x-rays of the thorax. A rapid intravenous infusion of 500 ml dextrose in saline was administered before the subarachnoid injection. Thereafter, the infusion rate was maintained at 2 ml · kg⁻¹ · h⁻¹.

After local infiltration of the skin with 0.5% lidocaine, the dural puncture was performed with a 25-G spinal needle through an 18-G introducer, in a midline approach at the L3–L4 space. During the procedure the patient was sitting. When a free flow of clear cerebrospinal fluid was obtained and after aspiration had been performed, the local anesthetic was injected without barbotage at a rate of approximately 0.15 ml/s. After injection of 0.5% bupivacaine (4.44 mg/ml), 3 ml in 8% glucose, the patient remained sitting for 2 min and then was placed in the supine horizontal position.

When satisfactory anesthetic conditions were obtained (usually 10–25 min after the subarachnoid injection) a flexible cannula was introduced into a vein in the foot. Through this cannula 48 ml of the bupivacaine-D solution was administered by infusion at a constant rate of 5 ml/min with a WT1® infusion pump (Adquip, Rotterdam, The Netherlands). The administered dose of bupivacaine-D was 13.4 mg. During the operation no sedatives were administered. Systemic arterial pressure, measured with an automatic cycling device (Accutorr 1, Datascope) and heart rate (from the ECG) were monitored during the anesthetic procedure and surgery and in the recovery room. If the systolic arterial pressure decreased more than 30% below the preanesthetic value or to less than 100 mmHg, ephedrine (5 mg, intravenously) was given.

Sensory loss was assessed on both sides of the trunk, on the legs, and on the perineum by pin pricks. Lack of a sharp sensation to pin prick was defined as analgesia. Bilateral motor block of the legs was assessed with a modified Bromage classification: the patient was asked to raise the extended leg, to flex the knee, and to flex the ankle, and was rated per joint (0 = no, 1 = partial, 2 = complete blockade; 12 = maximal degree of blockade). Assessments of sensory loss and motor block were made at 5-min intervals during the first 30 min after the subarachnoid injection and then at 15-min intervals until complete recovery.

BLOOD SAMPLES AND ASSAYS

Central venous blood samples were collected at gradually increasing intervals until 24 h after the injection. Plasma concentrations of bupivacaine and bupivacaine-D were determined by a combination of gas chromatography⁷ and mass fragmentography.⁸

DATA ANALYSIS

Plasma concentration–time data, obtained for bupivacaine-D, were analyzed by compartmental analysis. Biexponential equations were fitted to the data using weighted (1/²) least-squares nonlinear regression analysis with the software package Siphar (Simed, Créteil, France).

The Cmax values of unlabeled bupivacaine and the corresponding tmax values were derived directly from the plasma concentration–time data. The progression of the systemic absorption of the unlabeled bupivacaine was evaluated by point–area deconvolution.⁹ Then mono- and biexponential functions reflecting one first-order and two parallel first-order absorption processes, respectively, were fitted to the obtained data (fraction of the dose absorbed versus time) by unweighted least-squares nonlinear regression analysis.

Finally, the values of the pharmacokinetic parameters obtained for each individual were substituted into the equation describing the pharmacokinetic model in that individual, and the corresponding plasma concentration profile generated.⁵,¹⁰ This profile was compared to the measured concentrations.

The final choice between the two exponential curves fitted to the fraction of the dose absorbed versus time data was done by inspection of the scatter of the data points with respect to the fitted curve and by comparison of the sum of squares by using the F test. The relationships between variables of the neural blockade and age and between pharmacokinetic parameters and age were evaluated by linear regression analysis and correlation analysis. A P value of less than 0.05 was considered statistically significant. Values were expressed as means ± SD.
Results

In all patients, anesthesia and surgery were uncompli
cated, and no supplementary analgesic or sedative medici
cation was necessary.

One older patient (patient 15, age 73 yr) received atrop
epine within 30 min after administration of the local an
esthetic because bradycardia (heart rate less than 60 beats
per min) had developed. Ephedrine 5 mg was given in
travenously to one younger (patient 10, age 54 yr) and
two older patients (patient 17, age 75 yr and patient 18,
age 79 yr) because systolic pressure decreased more than
30%; the lowest systolic blood pressure was never less
than 90 mmHg. In no patient did the mean decrease from
control mean arterial pressure during the 1st h exceed
10% or correlate with age. There was no statistical cor
relation between the height of the block and the decrease
in mean arterial pressure.

Characteristics of the neural blockade of each patient
are summarized in table 1. Bilateral levels of analgesia
were obtained in all patients. The upper level of analgesia
reached on average to T9 (range T5 to L1). The time to
maximal cephalad spread increased with age (r = 0.470,
P < 0.05). The maximal height of analgesia increased
with increasing age (r = 0.715, P < 0.001; fig. 1). Two-
segment regression and recovery from analgesia at the
T12 level took 65–130 min and 50–175 min, respectively.

The times to recovery from analgesia at T12 increased
with age (r = 0.64, P < 0.01; fig. 2). Time to maximal
degree and total recovery from motor blockade did not
change with age (table 1).

Total plasma concentrations of bupivacaine usually
could be determined accurately in all samples collected
up to 24 h after subarachnoid administration. However,
the determination of the concentration ratios in samples
collected more than 12 or 16 h after administration was
not possible. Concentration of bupivacaine-D in the sam-

![Table 1. Nerve Block Characteristics of Patients Receiving Spinal Anesthesia with Bupivacaine](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931344/)

*The times to two-segment regression, recovery at T-12, and total recovery from analgesia refer to the time at which maximum spread of analgesia was reached. The time to complete recovery from motor blockade refers to the moment of injection.*
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Fig. 2. Relationship between the duration of analgesia at T-12 and age.

samples collected beyond his time were estimated by extrapolation of the fitted concentration–time curve. Subsequently, corresponding concentrations of unlabeled bupivacaine in the samples collected beyond this time were determined by subtracting the extrapolated concentrations of bupivacaine-D from the total concentrations.

SYSTEMIC DISPOSITION

Representative examples of plasma concentration curves of bupivacaine-D and of the corresponding unlabeled drug for an older and a younger patient are shown in figure 3. The values of the pharmacokinetic data characterizing the systemic disposition of bupivacaine and the effect of age are shown in table 2. The total plasma clearance decreased with age ($r = -0.650, P < 0.002$; fig. 4). The terminal rate constant decreased with increasing age ($r = -0.570, P < 0.02$), whereas the corresponding terminal half-life ($r = 0.503, P < 0.05$) as well as the mean residence time ($r = 0.597, P < 0.01$) increased with age. Distribution characteristics did not change significantly with increasing age.

SYSTEMIC ABSORPTION

Detectable plasma concentrations of unlabeled bupivacaine were present in all samples collected beginning 5 min after subarachnoid administration. This indicates a fast onset of absorption into the general circulation. There was a positive correlation between the $t_{\text{max}}$ and age ($r = 0.474, P < 0.05$, table 3). However, the corresponding $C_{\text{max}}$ did not change with age.

In 18 of 20 patients the systemic absorption of bupivacaine was best described by a biexponential equation, reflecting a biphasic absorption. In two older patients (patient 11, age 57 yr and patient 14, age 69 yr), the data was best fitted with a monoeponential function. Individual absorption data are shown in table 3. The rate constant, characterizing the late absorption phase, increased with age ($r = 0.547, P < 0.02$), whereas the corresponding slow absorption half-life decreased with age ($r = -0.478, P < 0.05$; fig. 5), as did the mean absorption time ($r = -0.551, P < 0.02$). The mean fraction, ultimately absorbed into the general circulation, was $0.97 \pm 0.08$. The predicted plasma concentrations generally were in good agreement with the measured concentrations (fig. 3). No systematic deviations were observed.

Discussion

The current study confirmed conclusions from a previous study$^1$ that the level of analgesia and the duration of analgesia at the T12 dermatome increase with increas-

Fig. 3. Plasma concentrations of unlabeled bupivacaine and bupivacaine-D$_3$, obtained after subarachnoid administration (15.3 mg) and upon intravenous infusions (15.4 mg), respectively. (Top) Data from an older patient (19); (bottom) data from a young patient (9). Open circles represent bupivacaine-D$_3$; filled circles represent unlabeled bupivacaine. The curves fitted to the bupivacaine-D$_3$ concentration–time data were obtained by nonlinear regression analysis. The curves through the unlabeled bupivacaine data points were generated with the pharmacokinetic data characterizing the systemic absorption (table 2) and systemic disposition (table 1) kinetics in these patients. These curves reflect the expected concentrations of unlabeled bupivacaine, based on the specified pharmacokinetic data.
TABLE 2. Disposition of Bupivacaine-D<sub>2</sub> after Rapid Intravenous Infusion in Patients under Spinal Anesthesia

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<th>C&lt;sub&gt;2&lt;/sub&gt; ng/ml</th>
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<th>t&lt;sub&gt;1/2,2&lt;/sub&gt; (min)</th>
<th>V&lt;sub&gt;C&lt;/sub&gt; (l)</th>
<th>V&lt;sub&gt;sa&lt;/sub&gt; (l)</th>
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C<sub>1</sub>, C<sub>2</sub> = hypothetical intercepts with the ordinate, which would be obtained after administration of the same dose (13.4 mg) as a bolus injection; t<sub>1/2,1</sub>, t<sub>1/2,2</sub> = distribution and elimination half-lives; V<sub>C</sub> = volume central department; V<sub>sa</sub> = steady-state volume of distribution; CL = clearance; r = Pearson’s correlation with age; MRT = mean residence time.

ing age, whereas the time until complete recovery from analgesia does not change with age. Factors that may contribute to the age-related changes are gradual degeneration of the central and peripheral nervous system,<sup>11,12</sup> changes in the anatomic configuration of the lumbar and thoracic spine,<sup>13</sup> and possibly a reduction of the volume of the cerebrospinal fluid.<sup>14</sup>

The effect of age on the plasma concentration time profile and the values of t<sub>max</sub> and C<sub>max</sub> also confirm the results of our previous study.<sup>1</sup> Furthermore, the current study demonstrated that the systemic absorption profile in most patients was biphasic. This is consistent with results reported by Burm et al.,<sup>5</sup> who studied the systemic absorption in patients aged 20–50 yr.

The current study demonstrated that the mean absorption time in older patients is shorter because of a higher late absorption rate. The explanation, however, for this faster late absorption in older patients is still unclear. The increase in the late absorption rate may reflect either a decrease in local binding or an increase in regional blood flow or both. Absorption of local anesthetics after subarachnoid administration is believed to occur predominantly after dural diffusion into the epidural space as well as by uptake into blood vessels—particularly those in the pia mater and the spinal cord itself—within the subarachnoid space.<sup>3,15</sup> After diffusion into the epidural space, local anesthetics may be sequestered into epidural fat, from which the drug is taken up into the systemic circulation.<sup>3,15</sup> In fact, the late absorption rate of bupivacaine after subarachnoid administration have been found to be similar to the late absorption rate after epidural administration; this suggests that late uptake occurs from the same site, probably epidural fat, with both routes of administration.<sup>4,5</sup>

A decrease in local binding might explain the higher rate of late absorption in older patients if it is assumed that the fat content in the epidural space of these patients

![Graph](image_url)
TABLE 3. Absorption of Bupivacaine after Subarachnoid Administration

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$C_{\text{max}}$ = peak concentration; $t_{\text{max}}$ = time to $C_{\text{max}}$; $F$ = fraction of dose reaching general circulation; $F_1$ = fraction of dose absorbed during the fast-absorption process; $F_2$ = fraction of the dose absorbed during the slow-absorption process; $T_{1/2A1}$ = fast-absorption half-life; $T_{1/2A2}$ = slow-absorption half-life; $r$ = Pearson's correlation with age; MAT = mean absorption time.

is decreased. However, this assumption probably is incorrect, in view of the overall increase in adipose tissue with increasing age. Studies on the effect of age on the epidural fat content are not available.

The influence of age on local perfusion within the subarachnoid and epidural space also is unknown. Subarachnoid administration of a local anesthetic may alter local perfusion by sympathetic blockade, by a direct effect on local blood vessels, or by an effect on the autoregulatory mechanism. Changes in spinal cord blood flow (SCBF) after subarachnoid administration of local anesthetics are best explained in terms of their direct vasoactive action on the local blood vessels. Subarachnoid administration of bupivacaine in dogs resulted in a decrease of the SCBF, which was best explained by a local vasoconstrictive effect of bupivacaine. If these observations are applicable to humans, one may speculate that older patients are less sensitive to the vasoconstrictive action of bupivacaine in the administered dose, so that SCBF and possibly epidural blood flow decrease less in older than in younger patients.

The clinical implications of the faster systemic absorption of bupivacaine in older patients are not clear. It has been postulated that the duration of spinal anesthesia depends upon the rate of vascular absorption. Based on the faster absorption in older patients, one then may expect a shorter duration of action. However, in the current study, the total duration of analgesia was independent of age, and the duration of analgesia at the T12 dermatome even increased with increasing age. This apparent contradiction can be explained only by altered pharmacodynamics in the elderly. Several studies in surgical patients indicated that after subarachnoid or epidural administration, the effect of local anesthetics is enhanced in older patients as compared to younger patients.

A recent study with in vitro nerve preparations indicated that nerves from old rabbits are more sensitive to conduction blockade induced by local anesthetics than are

![Graph](attachment:image.png)

**FIG. 5.** Relationship between the slow absorption half-life and age.
nerves from adolescent rabbits. These observations can be interpreted as a decrease in the minimum effective concentration with increasing age. Verification of this interpretation, however, requires knowledge of concentration–time profiles close to the nerves, e.g., in CSF. These profiles cannot be derived from the current study, since it is not known how CSF concentrations are related to the unabsorbed fraction. On the other hand, measurement of CSF concentrations also has serious limitations, because the distribution of local anesthetics within CSF is not homogeneous. Therefore, the CSF concentration–time profiles, determined at only one sampling site, are not representative to the concentration–time profiles at other sites.

It has been suggested that the systemic absorption of local anesthetics from the subarachnoid space depends on the absorption surface, i.e., on the longitudinal spread of local anesthetic. From this, one may reason that the faster absorption of bupivacaine in older patients results from a larger absorption surface area. However, this probably is incorrect, because a greater longitudinal spread results in a lower concentration gradient for diffusion, which offsets the effect of a larger surface area. In addition, it is doubtful that the higher level of blockade in older patients reflects a more extensive longitudinal spread of the solution. The higher level of analgesia in older patients may just as well be attributed to a greater sensitivity, such that with the same local anesthetic concentrations, at higher thoracic segments, blockade occurs in older but not in younger patients.

The marked reduction of the total plasma clearance is consistent with our results in three previous studies, in which the total plasma clearance decreased with age after both epidural and subarachnoid administration of bupivacaine. Since bupivacaine exhibits a relatively low extraction ratio, the observed age-related decline in total plasma clearance is more likely to have resulted from a change in the hepatic enzyme metabolic activity or in the protein binding of bupivacaine, rather than from any alteration in liver blood flow.

In conclusion, this study demonstrated that after subarachnoid administration of a hyperbaric bupivacaine solution, the late absorption rate of bupivacaine increases with increasing age. This greater rate is not accompanied by a shorter duration of action, possibly because the effect of the faster systemic absorption is offset by a change in this drug's pharmacodynamics.

The authors thank Mr. D. G. D. de Lange for his assistance with the clinical experiments; Ms. M. P. M. Toelen and Ms. E. A. Dullaart for typing the manuscript; and Mr. J. W. H. de Voogt for preparing the illustrations.

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