Anesthesiology
69:584–592, 1988

Pharmacokinetics of Lidocaine and Bupivacaine following Subarachnoid Administration in Surgical Patients: Simultaneous Investigation of Absorption and Disposition Kinetics Using Stable Isotopes

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The pharmacokinetics of lidocaine and bupivacaine following subarachnoid administration were studied in 12 surgical patients using a stable isotope method. After subarachnoid administration of the agent to be evaluated, a deuterium-labelled analogue was administered intravenously. Blood samples were collected for 24 h. Plasma concentrations of the unlabelled and the deuterium-labelled local anesthetics were determined using a combination of capillary gas chromatography and mass fragmentography. Bi-exponential functions were fitted to the plasma concentration-time data of the deuterium-labelled local anesthetics. The progression of the absorption was evaluated using deconvolution. Mono- and bi-exponential functions were then fitted to the fraction absorbed *versus* time data. The distribution and elimination half-lives of the deuterium-labelled analogues were 25 ± 13 min (mean ± SD) and 121 ± 31 min for lidocaine and 19 ± 10 min and 131 ± 33 min for bupivacaine. The volumes of the central compartment and steady-state volumes of distribution were: lidocaine 57 ± 10 l and 105 ± 25 l, bupivacaine 25 ± 6 l and 63 ± 22 l. Total plasma clearance values averaged 0.97 ± 0.21 l/min for lidocaine and 0.56 ± 0.14 l/min for bupivacaine. The absorption of lidocaine could be described by a single first order absorption process, characterized by a half-life of 71 ± 17 min in five out of six patients. The absorption of bupivacaine could be described adequately assuming two parallel first order absorption processes in all six patients. The half-lives, characterizing the fast and slow absorption processes of bupivacaine, were 50 ± 27 min and 408 ± 275 min, respectively. The fractions of the dose, absorbed in the fast and slow processes, were 0.35 ± 0.17 and 0.61 ± 0.16, respectively. The results indicate that both local anesthetics are completely absorbed intact from the subarachnoid space into the general circulation. (Key words: Anesthetics, local: bupivacaine; lidocaine. Anesthetic techniques: spinal. Pharmacokinetics: bupivacaine; lidocaine.)

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Received from the Department of Anesthesiology, University Hospital, and Center for Bio-Pharmaceutical Sciences, Division of Pharmacology, University of Leiden, The Netherlands. Accepted for publication May 16, 1988. Supported in part by Astra Läkemedel AB. Presented in part at the Fifth Congress of the European Society of Regional Anaesthesia, Malmö, September, 1986; and in part at the American Society of Anesthesiologists Meeting, Las Vegas, October, 1986.

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RECENTLY, THE PLASMA concentration profiles of lidocaine and bupivacaine after subarachnoid administration have been determined.[1–4] In the studies of Axelsson *et al.*[2,4] and Burm *et al.*,[3] the peak concentrations of lidocaine and bupivacaine were reached after approximately 1–1.5 h following administration of a hyperbaric solution and after 1.5–3.0 h following administration of an isobaric solution. These values are about two to four times longer than the peak times of lidocaine and bupivacaine after epidural administration.[5] The longer peak times after subarachnoid administration may reflect a relatively slow initial absorption rate from the subarachnoid space into the general circulation. However, definite conclusions on the absorption rate cannot be drawn from the values of the peak times, since these are also dependent on the drug's disposition kinetics. Therefore, determination of the absorption rates requires information on the disposition kinetics of the agents, which cannot be derived from the plasma concentration curves after subarachnoid administration,[3] but have to be obtained after intravenous administration.[6]

In this study, the absorption and disposition kinetics of lidocaine and bupivacaine after subarachnoid administration of hyperbaric solutions were investigated simultaneously in surgical patients using stable isotope labelled analogues having similar disposition kinetics as unlabelled lidocaine and bupivacaine.[7] The deuterium-labelled analogue of the local anesthetic to be investigated was administered intravenously after subarachnoid administration of the unlabelled local anesthetic. The disposition characteristics were then derived from the plasma concentration profile of the deuterium-labelled analogue. Subsequently these data were used to derive the absorption kinetics of the unlabelled local anesthetic.

Materials and Methods

PATIENTS

Seven male and five female patients (ASA Physical Status 1, age 22–50 yr, body weights 52–90 kg) scheduled

for minor orthopedic, urological, or general surgery participated in the study. The study was approved by the Committee on Medical Ethics of the University of Leiden and informed consent to participate was obtained from each patient.

Drugs and Solutions

Although all drugs were dissolved as HCl salts, the doses and concentrations are expressed in terms of base equivalents, unless specified otherwise.

Local anesthetic solutions for subarachnoid administration were hyperbaric (75 mg glucose/ml) 5% lidocaine · HCl (43.3 mg lidocaine/ml) and hyperbaric (80 mg glucose/ml) 0.5% bupivacaine · HCl (4.44 mg bupivacaine/ml), both without epinephrine.

The deuterium-labelled local anesthetics, 2-diethylamino-(2′,2′,2′-$^2H_3$),6′-acetoxylidide and 1-butyl-(2′,2′,2′-$^2H_3$),6′-pipecoloxylidide are similar to lidocaine and bupivacaine, respectively, except for the substitution of a tri-deuteromethyl group for a methyl group. In the following these substances are referred to as lidocaine-D_3 and bupivacaine-D_3. The isotopic enrichment of lidocaine-D_3 (composition: lidocaine-D_3, -D_2, -D_1 and -D_0, 90.9%, 5.6%, 3.5%, and 0%) and bupivacaine-D_3 (composition: bupivacaine-D_3, -D_2, -D_1, and -D_0: 93%, 4%, 2%, 1%) made it necessary to subtract the contributions of the -D_2, -D_1, and D_0 forms to the dry crystals that were weighed out to prepare solutions. In the following all specified doses and concentrations refer to the pure -D_3 substances only. The isotonic aqueous solutions that were administered intravenously contained 0.454 mg/ml lidocaine-D_3 and 0.279 mg/ml bupivacaine-D_3, respectively.

Procedures

The patients were premedicated with lorazepam (2 mg sublingually) 1.5 h before the subarachnoid procedure. A central venous catheter (Piggy Back) was inserted into the basilic or the cephalic vein in the arm contralateral to the operative site, after local infiltration with lidocaine or bupivacaine. The agent used for infiltration never was the same as the one to be studied in order to avoid a contribution of the infiltrated agent to the plasma concentrations. The catheter was advanced until the tip was located in the superior vena cava, but at least 6 cm proximal to the junction of the azygos vein and the superior vena cava. Correct location of the tip of the catheter was verified using roentgenograms of the thorax.

Lumbar puncture was performed with the patient sitting. Following intravenous administration of atropine (0.25 mg) and local infiltration of the skin with lidocaine or bupivacaine (not the agent to be studied), a 25-gauge spinal needle was introduced into the subarachnoid space *via* the third lumbar vertebral interspace. When a free flow of clear cerebrospinal fluid (CSF) was obtained and after aspiration of CSF, the local anesthetic was injected, without barbotage, at a rate of approximately 0.15 ml/s. The total volumes administered were 2 ml lidocaine solution (dose 86.6 mg) or 3 ml bupivacaine solution (dose 13.3 mg). Immediately after drug administration, the patient was asked to turn to the supine position.

When satisfactory anesthetic conditions were obtained (usually within 10 min after the subarachnoid injection), a flexible cannula (Venflon®) was introduced into a vein in the foot, contralateral to the operative site. Through this cannula, 50 ml of the deuterium-labelled local anesthetic solution was administered by infusion at a rate of 5 ml/min using an ASID Bonz® PP 50-300 infusion pump. A foot vein was used for infusion to prevent admixing of blood enriched with freshly infused deuterium-labelled local anesthetic to the blood samples collected during the infusion. The infusion was started between 10 and 15 min after the subarachnoid injection. The administered doses of lidocaine-D_3 and bupivacaine-D_3 were 22.7 mg and 14.0 mg, respectively.

During the operation, the patients remained in the horizontal supine position on the operating table. Sedative drugs were not administered. The systolic and diastolic blood pressures and the heart rate were recorded prior to the subarachnoid injection and at 5-min intervals during the operation. When indicated, postoperative pain was relieved with methadone or paracetamol.

Sensory loss was assessed on both sides of the trunk, on the legs, and on the perineum using pin pricks. Lack of a sharp sensation to pin prick was defined as analgesia. Motor block of the legs was assessed bilaterally, whenever possible, by asking the patient to raise the extended leg, flex the knee, and flex the ankle, and was rated per joint (0 = none, 1 = partial, and 2 = complete blockade; maximal degree of blockade = 6). Assessments of sensory loss and motor block were made at 5-min intervals during the first 30 min after the subarachnoid injection, then at 15-min intervals until 4 h after the injection, and finally at 30-min intervals until analgesia and motor block were completely reversed. During the operation, only the upper analgesia levels could be determined.

Blood Samples and Assays

Central venous blood samples were collected before the subarachnoid injection, at 5-min intervals during the first 40 min after injection, and from then on at intervals gradually increasing from 10 min to 4 h until 24 h after the injection. Blood samples were transferred into heparinized centrifuge tubes. After centrifugation, plasma was collected and stored at −20° C.

The total concentrations (lidocaine + lidocaine-D_3 and

bupivacaine + bupivacaine-D_3, respectively) of the local anesthetics in the plasma samples were determined using capillary gas chromatography.[8,9]†† The ratios of the concentrations of lidocaine-D_3 and lidocaine were determined using electron impact mass fragmentography,†† while the ratios of the concentrations of bupivacaine-D_3 and bupivacaine were determined using positive ion chemical ionization mass fragmentography.†† The concentrations of the individual substances were then calculated by combining the results of the gas chromatographic and the mass fragmentographic determinations. The coefficients of variation of the combined gas chromatographic and mass fragmentographic assays varied from 8 to 15% in the concentration ranges actually encountered in the plasma specimens collected from the patients and depended upon both the absolute concentrations and upon the concentration ratios. The absolute detection limits were 3 ng/ml for lidocaine and lidocaine-D_3 and 2 ng/ml for bupivacaine and bupivacaine-D_3.

Data Analysis

The plasma concentration-time data, obtained for lidocaine-D_3 and bupivacaine-D_3, were analyzed using compartmental analysis. Bi-exponential functions were fitted to the data using weighted ($1/y^2$) least-squares non-linear regression analysis. The following pharmacokinetic parameters, characterizing the disposition of bupivacaine-D_3, were then calculated: the distribution half-life ($t_{1/2,\lambda_1}$), the elimination half-life ($t_{1/2,\lambda_2}$), the volume of the central compartment (V_1), the total apparent volume of distribution at steady state (V_{ss}), and the total plasma clearance (CL). Noncompartmental analysis[10–12] was also performed to determine CL, V_{ss}, and the terminal half-life ($t_{1/2,z}$).

The peak concentrations (C_{max}) of unlabelled lidocaine and bupivacaine and the corresponding peak times (t_{max}) were derived directly from the plasma concentration-time data. The fraction (F) of the subarachnoid dose that ultimately reached the general circulation was determined from the administered doses and the areas under the curve of the unlabelled and labelled local anesthetics. The progression of the absorption of the unlabelled local anesthetic was evaluated using point-area deconvolution.[13] Then mono- and bi-exponential functions reflecting a single first order and two parallel first order absorption processes, respectively, were fitted to the obtained data (fraction absorbed *versus* time) using unweighted least-squares non-linear regression analysis. Subsequently, the pharmacokinetic parameters characterizing the absorption were calculated. A single first order absorption process was characterized by the fraction of the dose that reached the general circulation (F) and the corresponding absorption half-life. Two parallel absorption processes were characterized by two fractions (F_1 and F_2) and absorption half-lives ($t_{1/2,a_1}$, and $t_{1/2,a_2}$) corresponding with the fast and slow absorption processes, respectively.

Finally, the values of the pharmacokinetic parameters obtained for each individual were substituted into the equation describing the pharmacokinetic model in that individual, and then the corresponding plasma concentration profile was generated.[14] This profile was compared to the measured concentrations of the unlabelled drug to verify the validity of the derived model. Pharmacokinetic equations are presented in the Appendix.

The final choice between the two exponential curves fitted to the amount 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 using the F-test. A two-sample *t* test was used for intergroup comparisons. $P < 0.05$ was considered the minimum level of significance.

Results

There were no significant differences between the groups of patients receiving lidocaine or bupivacaine with respect to age, body weight, or male/female ratio.

In all patients, anesthesia and surgery were uneventful. The upper analgesia levels reached on average to T-6 (range T-2 to T-10) in patients who received lidocaine and to T-8 (T-5 to T-10) in patients who received bupivacaine. These levels were attained in 10–25 min. Four-segment regression took 72 (range 60–90) min with lidocaine and 93 (range 40–140) min with bupivacaine.

Total plasma concentrations of lidocaine and bupivacaine generally could be determined accurately in all samples collected up to 12 or 16 h after subarachnoid administration. However, the concentrations of lidocaine-D_3 in the samples collected more than 8 h after administration could not be determined, due to lack of sensitivity in the mass fragmentographic analysis. Similarly, the determination of bupivacaine-D_3 concentrations in samples collected more than on average 10 h after administration was not possible. Concentrations of unlabelled lidocaine and bupivacaine in the samples collected beyond these times were determined by subtracting the extrapolated concentrations of the deuterium-labelled local anesthetics from the total concentrations.

Disposition

Typical plasma concentration curves of lidocaine-D_3 and bupivacaine-D_3 and the corresponding unlabelled local anesthetics are shown in figure 1 and figure 2, re-

†† Burm AGL: Pharmacokinetics and clinical effects of lidocaine and bupivacaine following epidural and subarachnoid administration in man. Leiden, University of Leiden, 1985, pp 37–69.

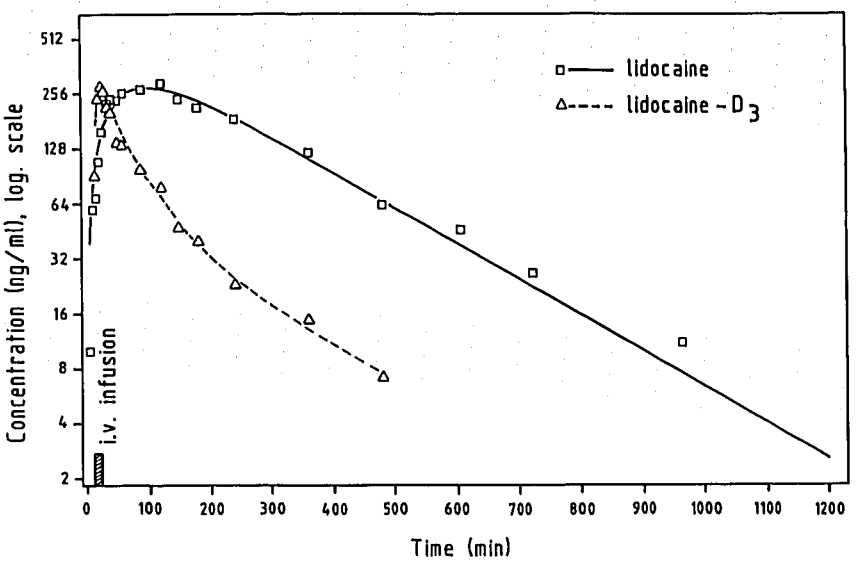

FIG. 1. Plasma concentrations of unlabelled lidocaine and lidocaine-D_3 obtained after subarachnoid administration (dose 86.6 mg) and upon intravenous infusion (dose 22.7 mg), respectively (data from patient 4). The squares and triangles represent the measured concentrations. The curve fitted to the lidocaine-D_3 concentrations was obtained by non-linear regression analysis. The curve through the lidocaine data points was generated using the pharmacokinetic data characterizing the absorption (table 3) and disposition (table 1) kinetics in this patient. This curve reflects the expected concentrations of unlabelled lidocaine based on the specified pharmacokinetic data.

spectively. The curves show a rapid increase in the plasma concentrations during the infusion, and after the infusion a rapid decrease, mainly due to drug distribution and a slower decrease reflecting drug elimination. The values of the derived pharmacokinetic parameters are presented in table 1 and table 2. In all patients, there was a good agreement between the values of the pharmacokinetic parameters determined by noncompartmental and by compartmental analysis.

ABSORPTION

Detectable plasma concentrations of both unlabelled lidocaine and unlabelled bupivacaine were present in all samples, collected 5 min after subarachnoid administration. This indicates a fast onset of absorption into the general circulation. The peak times were similar for lidocaine and bupivacaine (tables 3, 4). Dose for dose, the peak plasma concentrations also appear to be similar. The mean fractions of the dose, that ultimately reached the general circulation, determined by noncompartmental analysis, were close to 1.

Representative examples of the curves showing the fraction of the dose that reached the general circulation as a function of the time are shown in figure 3. The data obtained for lidocaine could be described adequately by a mono-exponential function in five out of six patients (table 3). In these patients the mean absorption half-life was 71 min. The data, obtained for the remaining patient who received lidocaine could be best fitted using a bi-

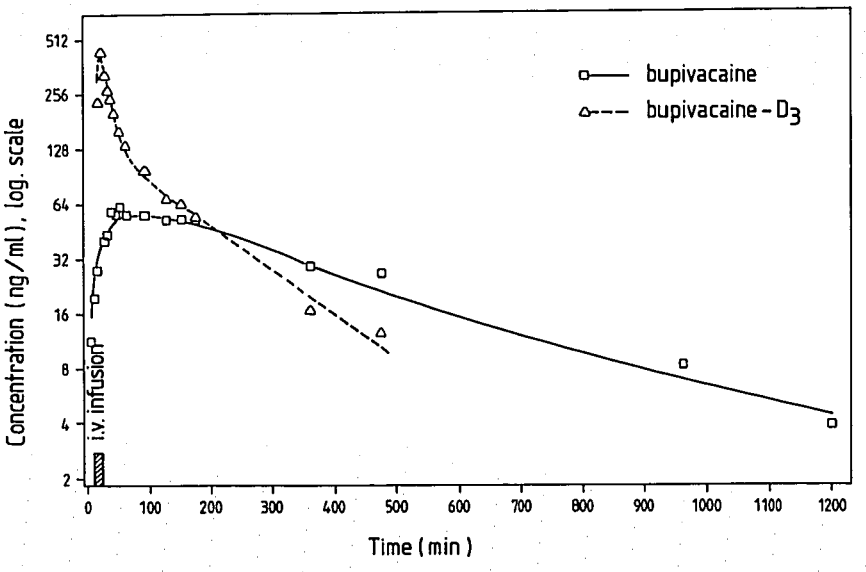

FIG. 2. Plasma concentrations of unlabelled bupivacaine and bupivacaine-D_3 obtained after subarachnoid administration (dose 13.3 mg) and upon intravenous infusion (dose 14.0 mg), respectively (data from patient 12). The squares and triangles represent the measured concentrations. The curve fitted to the bupivacaine-D_3 concentrations was obtained by non-linear regression analysis. The curve through the unlabelled bupivacaine data points was generated using the pharmacokinetic data characterizing the absorption (table 2) and disposition (table 4) kinetics in this patient. This curve reflects the expected concentrations of unlabelled bupivacaine based on the specified pharmacokinetic data.

TABLE 1. Pharmacokinetic Data Characterizing the Disposition of Lidocaine-D_3 following Rapid Intravenous Infusion in Patients Under Spinal Anesthesia

	Noncompartmental Analysis			Compartmental Analysis				
Patient	$t_{1/2,z}$ (min)	V_{ss} (l)	CL (l/min)	$t_{1/2,\lambda_1}$ (min)	$t_{1/2,\lambda_2}$ (min)	V_1 (l)	V_{ss} (l)	CL (l/min)
1	118	132	1.33	12.1	111	48	133	1.34
2	70	87	1.08	13.0	67	57	88	1.08
3	121	119	0.91	16.3	132	52	124	0.93
4	125	123	0.91	35.7	154	76	125	0.89
5	103	80	0.78	42.0	146	61	85	0.79
6	79	70	0.80	29.1	116	50	77	0.78
Mean	103	102	0.97	24.7	121	57	105	0.97
SD	23	26	0.21	12.7	31	10	25	0.21

$t_{1/2,z}$ = terminal elimination half life; V_{ss} = volume of distribution at steady state; CL = clearance; $t_{1/2,\lambda_1}$, $t_{1/2,\lambda_2}$ = distribution and elimination half-lives; V_1 = volume central compartment.

exponential function, assuming two parallel absorption processes. For the bupivacaine data, a better fit was always obtained with a bi-exponential function. The mean half-lives characterizing the fast and slow absorption processes were 50 and 408 min, respectively (table 4). The fractions of the administered dose that ultimately reached the general circulation averaged 1.03 for lidocaine and 0.96 for bupivacaine, and were in good agreement with both the values obtained by noncompartmental analysis and the expected value (F = 1). This indirectly confirms the validity of the methods used.

The generated plasma concentrations of lidocaine and bupivacaine were in good agreement with the measured concentrations (figures 1 and 2). Systematic deviations were not observed.

Discussion

To determine the systemic absorption kinetics of local anesthetics following subarachnoid administration, it is essential to know the systemic disposition kinetics. If only the plasma concentration profiles following subarachnoid injection are determined and additional data on the disposition are lacking, difficulties are encountered in the interpretation of these profiles.[1–4,15] For example, it is difficult to estimate the absorption rate from the peak plasma concentration and the time at which this is reached, since these are also dependent upon the systemic disposition. Interindividual differences in the peak plasma concentrations and peak times may be due to either differences in the absorption rates or in the disposition. Also, a prolonged terminal half-life, as reported by Burm,[3,15] is suggestive of a slow absorption phase, but may as well reflect a slower elimination (*e.g.*, due to an increased volume of distribution) after surgery and spinal anesthesia.

The present stable isotope method enabled simultaneous investigation of both the absorption and disposition kinetics in surgical patients in the actual clinical situation. An inherent requirement of the method is that the disposition kinetics of the labelled analogue are representative for those of the unlabelled drug. This requirement is met, as has been demonstrated in a previous study in

TABLE 2. Pharmacokinetic Data Characterizing the Disposition of Bupivacaine-D_3 following Rapid Intravenous Infusion in Patients Under Spinal Anesthesia

	Model-independent Analysis			Compartmental Analysis				
Patient	$t_{1/2,z}$ (min)	V_{ss} (l)	CL (l/min)	$t_{1/2,\lambda_1}$ (min)	$t_{1/2,\lambda_2}$ (min)	V_1 (l)	V_{ss} (l)	CL (l/min)
7	120	59	0.57	11.5	116	20	60	0.58
8	86	41	0.45	30.0	92	32	43	0.46
9	174	68	0.65	26.3	151	34	64	0.65
10	193	103	0.77	8.9	185	18	103	0.78
11	105	43	0.42	26.5	115	25	41	0.41
12	133	68	0.45	9.4	124	23	66	0.46
Mean	135	64*	0.55‡	18.8	131	25‡	63†	0.56‡
SD	41	23	0.14	9.8	33	6	22	0.14

Differences with the values of lidocaine (see table 3): *$P < 0.05$; †$P < 0.02$; ‡$P < 0.005$. For definition of symbols, see table 1.

TABLE 3. Pharmacokinetic Data Characterizing the Absorption of Lidocaine following Subarachnoid Administration

	Noncompartmental Analysis			Deconvolution + Compartmental Analysis				
Patient	t_{max} (min)	C_{max} (ng/ml)	F	F_1	$t_{1/2,a_1}$ (min)	F_2	$t_{1/2,a_2}$ (min)	F
1	30	323	1.07	1.08	59	—	—	1.08
2	90	339	1.04	1.05	83	—	—	1.05
3	60	419	1.18	1.17	64	—	—	1.17
4	120	290	1.05	0.98	93	—	—	0.98
5	60	468	0.84	0.87	54	—	—	0.87
6	60	443	0.93	0.60	38	0.30	263	0.90
Mean	70	380	1.02	1.03*	71*	—	—	1.01
SD	31	72	0.12	0.11	17	—	—	0.11

t_{max} = time of peak concentration, C_{max} = peak concentration, F = fraction of dose reaching general circulation; $t_{1/2,a_1}$ = fast absorption half-life; $t_{1/2,a_2}$ = slow absorption half-life.
* Mean values and standard deviations for patients 1–5.

TABLE 4. Pharmacokinetic Data Characterizing the Absorption of Bupivacaine following Subarachnoid Administration

	Noncompartmental Analysis			Deconvolution + Compartmental Analysis				
Patient	t_{max} (min)	C_{max} (ng/ml)	F	F_1	$t_{1/2,a_1}$ (min)	F_2	$t_{1/2,a_2}$ (min)	F
7	60	54	0.95	0.43	62	0.59	396	1.02
8	120	57	0.90	0.35	65	0.84	902	1.19
9	90	59	0.88	0.54	80	0.37	449	0.91
10	10	78	0.98	0.24	12	0.71	185	0.95
11	40	71	0.78	0.08	20	0.61	119	0.70
12	50	62	1.01	0.48	61	0.51	396	0.99
Mean	62	64	0.92	0.35	50	0.61	408	0.96
SD	39	9	0.08	0.17	27	0.16	275	0.16

For definition of symbols, see table 3.

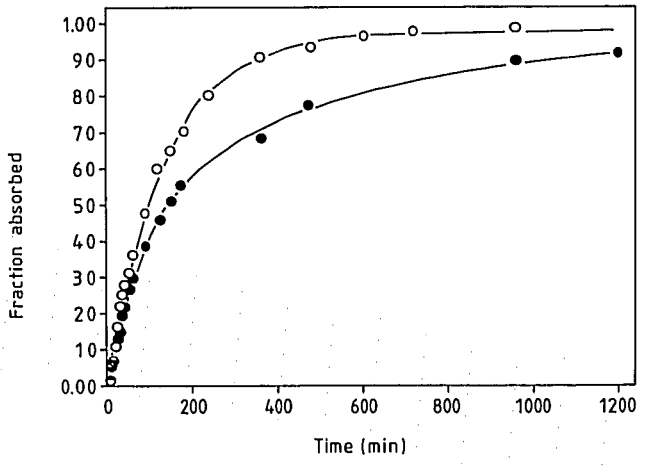

FIG. 3. Fraction of the lidocaine (patient 4) and bupivacaine (patient 12) doses absorbed into the general circulation as a function of the time after the subarachnoid injection. The data points reflect the values determined by deconvolution of the measured concentrations against the intravenous unit impulse response curve. Open circles represent lidocaine; filled circles represent bupivacaine. The curves fitted to the data points were obtained by non-linear regression analysis.

healthy volunteers which showed that substitution of a tri-deuteromethyl group does not alter the disposition of lidocaine or bupivacaine.[7] The feasibility of the stable isotope method has, furthermore, been demonstrated in an analogue study following epidural administration of lidocaine and bupivacaine and is confirmed by the present study.

A further requirement for the stable isotope method is that intravenous administration of stable isotopes does not interfere with the absorption of unlabelled drug. To verify this, the plasma concentrations obtained in the present study were compared to those obtained in a previous study in a comparable group of patients who were treated in a similar way, except for the intravenous administration of labelled analogues. This comparison showed that the peak plasma concentrations of lidocaine obtained in the present study (mean value 380 ng/ml) were lower than in the previous study (mean value 526 ng/ml, $P < 0.05$), whereas the corresponding peak times (70 and 71 min) were similar in both studies.[15] The peak plasma concentrations of bupivacaine (64 and 70 ng/ml),

as well as the corresponding peak times (62 min in both studies), were similar in both studies. The difference in the peak plasma concentrations of lidocaine could be explained by the difference in the total plasma clearances obtained in the present study (0.97 l/min) and in the previous study (0.80 l/min). Therefore, it can be concluded that it is unlikely that the intravenous administration of the deuterium-labelled analogues modified the absorption rates of the local anesthetics.

The mean values of the principal parameters characterizing the disposition of lidocaine-D_3 in this study were similar to those obtained in a previous study on the disposition of lidocaine-D_3 in volunteers (table 5).[7] However, the mean values of the volume of the central compartment and the distribution half-life were larger in this study. This might indicate an effect of the spinal block on the initial distribution of lidocaine, although other factors, such as differences in the populations, may also be responsible for the observed differences. The values of the parameters characterizing the disposition of bupivacaine-D_3 in this study appear to be similar to the values obtained in volunteers (table 5).

In most patients, absorption of lidocaine from the subarachnoid space could be described adequately by a single exponential function reflecting a single first order absorption process. In contrast, adequate description of the absorption of bupivacaine always required a bi-exponential function reflecting two parallel absorption processes. This difference is probably related to differences in the physicochemical properties of the agents. It is likely that the binding to tissues at and near the site of injection is more extensive for bupivacaine than for lidocaine, because bupivacaine is more lipid soluble and has a higher affinity for protein structures. The higher tissue/blood partition coefficients of bupivacaine may then explain the long absorption half-life.

The slow absorption of bupivacaine into the general circulation after subarachnoid administration affects (rate-limits) elimination from the body. This explains why the apparent elimination half-life measured after subarachnoid administration of bupivacaine is longer than the actual elimination half-lives obtained after intravenous administration.[3,15]

Comparison of the parameters that characterize the absorption of lidocaine and bupivacaine after subarachnoid and epidural administration[6] indicates remarkable differences as well as remarkable similarities. The fast initial absorption of lidocaine ($t_{1/2,a_1}$ = 9 min) and bupivacaine ($t_{1/2,a_1}$ = 7 min) after epidural administration was not observed after subarachnoid administration. For lidocaine, only one absorption phase was observed in most patients, while, for bupivacaine, the mean half-life of the faster absorption process was much longer after subarachnoid administration (50 min) than after epidural administration (7 min). The mean half-life that characterizes the absorption of lidocaine after subarachnoid administration (71 min) is similar to the half-life that characterizes the slower absorption process after epidural administration (82 min). The mean half-lives that characterize the slower absorption processes of bupivacaine after subarachnoid (408) and epidural (362 min) administration are also similar. The differences in the initial progression of the absorption after subarachnoid and epidural administration are probably related to differences in the vascularities of these spaces. The similarity of the rates of absorption of the slower processes indicates that after some time an equilibrium is reached in the concentrations of the local anesthetics in tissue structures within both spaces. This equilibrium may result after partial migration of the local anesthetics from the epidural into the subarachnoid space after epidural or vice versa after subarachnoid administration.[16] It is not unlikely that also after subarachnoid administration a portion of the administered dose is sequestered in epidural fat.

From the results of this study, it may be concluded that the absorption of local anesthetics after subarachnoid administration occurs relatively slowly. The slower initial absorption rates after subarachnoid administration explain why the peak in the plasma concentration curves is reached much later after subarachnoid administration than after epidural administration.

TABLE 5. Comparison of Pharmacokinetic Data Characterizing the Disposition of Lidocaine-D_3 and Bupivacaine-D_3 in Unpremedicated Healthy Volunteers (Without Spinal Block) and in Premedicated Surgical Patients (With Spinal Block)

	Lidocaine		Bupivacaine	
Parameter	Volunteers	Patients	Volunteers	Patients
$t_{1/2,\lambda_1}$ (min)	9.2 ± 7.0*	24.7 ± 12.7*	15.2 ± 10.9	18.8 ± 9.8
$t_{1/2,\lambda_2}$ (min)	98 ± 27	121 ± 31	109 ± 31	131 ± 33
V_1 (l)	39 ± 16*	57 ± 10*	28 ± 12	25 ± 6
V_{ss} (l)	98 ± 18	105 ± 25	65 ± 22	63 ± 22
CL (l/min)	0.87 ± 0.18	0.97 ± 0.21	0.62 ± 0.17	0.56 ± 0.14

Values are mean ± SD; *$P < 0.05$.

The authors thank Mrs. M. de Beer and Mr. P. Brocades-Zaalberg for their assistance with the clinical investigations, Mrs. M. P. R. R. Gladines for her assistance with the laboratory determinations, and Mrs. M. P. M. Toelen for typing the manuscript.

Appendix

Pharmacokinetic Data Analysis

Bi-exponential equations fitted to the plasma concentration-time data of the labelled local anesthetics:

$$C = \frac{C_1}{\lambda_1 \cdot T} \cdot (1 - e^{-\lambda_1 \cdot t}) + \frac{C_2}{\lambda_2 \cdot T} (1 - e^{-\lambda_2 \cdot t}) \text{ for } t \leq T \quad [1] \text{ and}$$

$$C = \frac{C_1}{\lambda_1 \cdot T} (1 - e^{-\lambda_1 \cdot T}) \cdot e^{-\lambda_1 \cdot (t-T)} + \frac{C_2}{\lambda_2 \cdot T} (1 - e^{-\lambda_2 \cdot T}) \cdot e^{-\lambda_2 \cdot (t-T)} \text{ for } t > T \quad [2]$$

where C is the plasma concentration, t is the time after the start of the infusion, and T is the duration of the infusion. λ_1 and λ_2 are rate constants characterizing the distribution and elimination phases. C_1 and C_2 are the hypothetical intercepts with the ordinate, which would be obtained after administration of the same doses as a bolus injection.

Equations used for the noncompartmental analysis of the plasma concentration-time data of the labelled local anesthetics:[10-11]

$$t_{1/2,z} = \frac{0.693}{k_z} \quad [3]$$

$$CL = \frac{D}{AUC} \quad [4]$$

$$V_{ss} = \frac{D \cdot AUMC}{AUC^2} - \frac{D \cdot T}{2AUC} \quad [5]$$

where k_z is the slope of the log plasma concentration versus time curve, D the dose, AUC the area under the plasma concentration-time curve, and AUMC the area under the first moment of the plasma concentration curve. The AUC and the AUMC were determined using the linear and logarithmic trapezoidal rule, when appropriate, with addition of the extrapolated areas between the last sampling time and infinity.[12]

Equation used to determine the fraction of the subarachnoid dose that reached the general circulation:

$$F = \frac{AUC_{sa} \cdot D_{iv}}{AUC_{iv} \cdot D_{sa}} \quad [6]$$

where sa and iv refer to the subarachnoid and intravenous routes, respectively.

Unit impulse response curve for point area deconvolution:

$$C = C_1^* \cdot e^{-\lambda_1 \cdot t} + C_2^* \cdot e^{-\lambda_2 \cdot t} \quad [7]$$

The values C_1, C_2, λ_1, and λ_2 were derived from the plasma concentration-time curves of the deuterium-labelled local anesthetics (equations 1 and 2). The values of C_1 and C_2 were then adjusted for the difference in the intravenous and the subarachnoid doses to give C_1^* and C_2^*.

Mono- and bi-exponential equations, fitted to the data, obtained by point-area deconvolution (fraction absorbed *versus* time):

$$F_t = F \cdot (1 - e^{-k_a \cdot t}) \quad [8]$$

and

$$F_t = F_1 \cdot (1 - e^{-k_{a_1} \cdot t}) + F_2 \cdot (1 - e^{-k_{a_2} \cdot t}) \quad [9]$$

where F_t is the fraction absorbed at time t after subarachnoid administration, and F is the fraction that is ultimately absorbed into the general circulation. The second equation assumes that the absorption occurs by two parallel processes, characterized by the rate constants k_{a_1} and k_{a_2} and the corresponding fractions F_1 and F_2.

Equations, describing the plasma concentration profiles following subarachnoid administration:

a) in case of mono-exponential absorption (single first order absorption process):

$$C = \left(\frac{k_a \cdot F \cdot D \cdot (k_{21} - k_a)}{V_1 \cdot (\lambda_1 - k_a) \cdot (\lambda_2 - k_a)}\right) \cdot e^{-k_a \cdot t} + \left(\frac{k_a \cdot F \cdot D \cdot (k_{21} - \lambda_1)}{V_1 \cdot (k_a - \lambda_1) \cdot (\lambda_2 - \lambda_1)}\right) \cdot e^{-\lambda_1 \cdot t} + \left(\frac{k_a \cdot F \cdot D \cdot (k_{21} - \lambda_2)}{V_1 \cdot (k_a - \lambda_2) \cdot (\lambda_1 - \lambda_2)}\right) \cdot e^{-\lambda_2 \cdot t} \quad [10]$$

where k_{21} represents the rate constant, characterizing the transfer of local anesthetic from the peripheral to the central compartment.

b) in case of bi-exponential absorption (two parallel first order absorption processes):

$$C = \left(\frac{k_{a_1} \cdot F_1 \cdot D \cdot (k_{21} - k_{a_1})}{V_1 \cdot (\lambda_1 - k_{a_1}) \cdot (\lambda_2 - k_{a_1})}\right) \cdot e^{-k_{a_1} \cdot t} + \left(\frac{k_{a_2} \cdot F_2 \cdot D \cdot (k_{21} - k_{a_2})}{V_1 \cdot (\lambda_1 - k_{a_2}) \cdot (\lambda_2 - k_{a_2})}\right) \cdot e^{-k_{a_2} \cdot t} + \left(\frac{k_{a_1} \cdot F_1 \cdot D \cdot (k_{21} - \lambda_1)}{V_1 \cdot (k_{a_1} - \lambda_1) \cdot (\lambda_2 - \lambda_1)} + \frac{k_{a_2} \cdot F_2 \cdot D \cdot (k_{21} - \lambda_1)}{V_1 \cdot (k_{a_2} - \lambda_1) \cdot (\lambda_2 - \lambda_1)}\right) \times e^{-\lambda_1 \cdot t} + \left(\frac{k_{a_1} \cdot F_1 \cdot D \cdot (k_{21} - \lambda_2)}{V_1 \cdot (k_{a_1} - \lambda_2) \cdot (\lambda_1 - \lambda_2)} + \frac{k_{a_2} \cdot F_2 \cdot D \cdot (k_{21} - \lambda_2)}{V_1 \cdot (k_{a_2} - \lambda_2) \cdot (\lambda_1 - \lambda_2)}\right) \cdot e^{-\lambda_2 \cdot t} \quad [11]$$

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