Epidural, Intrathecal Pharmacokinetics, and Intrathecal Bioavailability of Ropivacaine

François-Xavier Rose, PharmD*

Jean-Pierre Estebe, MD, PhD†

Maja Ratajczak, PharmD*

Eric Wodey, MD, PhD†

François Chevanne, BS*

Gilles Dollo, PharmD, PhD*

David Bec, BS*

Jean-Marc Malinovsky, MD, PhD*

Claude Ecoffey, MD†

Pascal Le Corre, PharmD, PhD*

BACKGROUND: Ropivacaine is used by the epidural route for postoperative pain management with various neuraxial techniques. Given the widespread use of these techniques and the relative paucity of data on spinal disposition of local anesthetics, we evaluated through an experimental animal model, the spinal disposition of ropivacaine, allowing further studies of factors influencing their intrathecal bioavailability.

METHODS: Sheep received an IV bolus dose of ropivacaine (50 mg), and 1 wk after, an intrathecal dose of ropivacaine (20 mg) followed 3 h later by epidural ropivacaine (100 mg). A simultaneous microdialysis technique was used to measure epidural and intrathecal drug concentrations after both epidural and intrathecal administrations.

RESULTS: Absorption-time plots showed a large variability in the systemic absorption after both intrathecal and epidural administration, with an apparent faster systemic absorption after intrathecal administration. In the intrathecal space, the elimination clearance was around three-times higher than the distribution clearance. In the epidural space, the relative contribution of elimination and distribution to ropivacaine disposition was different, indicating a more pronounced influence of the distribution process. The intrathecal bioavailability after epidural administration was 11.1% ± 7.6%.

CONCLUSIONS: Using an animal model, we showed that drug dispositions in the intrathecal and epidural compartments are different, and that the intrathecal bioavailability of ropivacaine after epidural administration is low, and highly variable.

(Anesth Analg 2007;105:859–67)

Local anesthetics are routinely administered by the epidural route for postoperative pain management (1,2). Among them, bupivacaine and ropivacaine are frequently used, and ropivacaine has been associated with less cardiovascular and central nervous system toxicity (3,4). Ropivacaine is used with various neuraxial techniques (e.g., single-shot bolus; bolus plus continuous infusion, bolus controlled by the patient with various doses and lockout periods).

By using microdialysis in a rabbit model, we previously showed that the intrathecal bioavailability of local anesthetics after epidural administration was rather low and increased with lipophilicity, ranging from 7% to 16% (5,6). These results were not in agreement with previous findings on the impact of

This article has supplementary material on the Web site: www.anesthesia-analgesia.org.

DOI: 10.1213/01.ane.0000278129.37099.fa

physicochemical properties on the intrathecal bioavailability of opioids (7,8). Furthermore, the spinal disposition of drugs is rather complex; an increase in intrathecal bioavailability after epidural administration has been correlated to a decrease in the absorption rate through meninges (6,9). These findings suggest competition between the clearance and distribution processes handling drugs within the epidural space.

Given the diversity of the techniques of epidural administration used clinically, as well as the increasing use of combined spinal-epidural analgesia, an experimental animal model evaluating the spinal disposition of epidurally administered drugs would be of interest. It should be stressed that the investigation of intrathecal bioavailability requires a specific study design, i.e., measurement of drug intrathecal concentrations after both epidural and intrathecal administration. Hence, we designed a study in Lacaune ewes, an animal reference model, to evaluate the intrathecal bioavailability of ropivacaine and its intrathecal, epidural, and systemic pharmacokinetics after intrathecal and epidural administration using a simultaneous microdialysis technique.

METHODS

Chemicals

Ropivacaine, bupivacaine, and etidocaine were used as substances of interest (SI), internal standard (IS) of microdialysis, and IS of high-performance

liquid chromatography, respectively. A Ringer's solution was used as the perfusion fluid for microdialysis. Commercially available ropivacaine (Naropein 10 mg/mL, Astra-Zeneca, France) was used and diluted with NaCl 0.9%.

Microdialysis

Microdialysis was performed using a CMA 102 microinjection pump coupled to a CMA/20 microdialysis probe (membrane length of 10 mm, shaft length 140 mm, 0.5-mm outer diameter, molecular weight cut-off 20 kDa). Dialysates were collected by dilution using a CMA 142 microfraction collector (CMA Microdialysis, Solna, Sweden).

In Vitro Experiment

The probe was placed in a solution of ropivacaine under magnetic stirring 50 rpm, and was perfused with a solution of bupivacaine. The influence of ropivacaine and bupivacaine concentration (0.1, 0.5, 1, 2.5, 5 mg/mL), of flow rate (0.5, 1, 2, 5 μL/min), and of temperature (room temperature and 37°C) on the relative recovery (RR) of ropivacaine and on the relative loss (RL) of bupivacaine was investigated.

Retrodialysis, using bupivacaine as the IS, was applied to calibrate the microdialysis probes. This calibration technique is based on the principle that the RL of an IS added to the perfusate is related to the RR of the SI (10). The K factor value, defined as the ratio RL_{IS}/RL_{SI}, was used to determine the extracellular concentration of the compounds of interest according to

$$C = C\text{-dialysate} \times (K/RL_{IS})(11)$$

The validation of the calibration was achieved by comparing retrodialysis with the zero-net flux method as described previously (5,12). Bupivacaine can be used as an IS to study the disposition of ropivacaine (RL of bupivacaine = 0.55 ± 0.03 and RR of ropivacaine estimated by the zero-net flux method RR = 0.56 ± 0.02).

In Vivo Experiment

Microdialysis probes were perfused at 1 μL/min with a solution of bupivacaine (1 mg/mL in a Ringer's solution). After probe insertion in the intrathecal and epidural spaces, an *in vivo* equilibration with determination of RL bupivacaine ($n = 10$ for each probe tested) was achieved over a period of 45 min. Because of the high sampling frequency in the *in vivo* experiments, an accurate collection of microvolume dialysates was achieved by immersion of a prolongator of the outlet tubing of microdialysis probe into 100 or 200 μL of a 1 μg/mL etidocaine solution for intrathecal or epidural probes, respectively. A collection interval of 1 min during the first 15 min of experiment, and of 5 min during the further experiment allowed the sampling of 1 and 5 μL of dialysate, respectively.

Throughout the experiments, the RL of bupivacaine was determined in each sample and used to correct the dialysate concentrations.

Before and after *in vivo* implantation, the probes were tested *in vitro* to verify the lack of significant deterioration by comparison of RL bupivacaine. The interbatch variability among microdialysis probes was low. The *in vitro* RL of bupivacaine checked before *in vivo* implantation was 0.49 ± 0.04 ($n = 10$).

In Vivo Study Design

Animals

The study was performed according to a protocol approved by the Local Committee of Laboratory Investigation and Animal Care of our institution and was in accordance with the rules and guidelines concerning the care and use of laboratory animals used for experiments. The experiment was performed on 12 nonpregnant Lacaunes ewes (mean age of 2.2 ± 1 years and a mean weight of 64 ± 10 kg).

Experimental Protocol

All animals were studied on two separate occasions at 1 wk interval. In the first part of the experiment, awake animals received, via the jugular vein, a bolus dose of 50 mg of ropivacaine hydrochloride. In the second part of the experiment, anesthetized animals received 20 mg of ropivacaine hydrochloride in the intrathecal space, followed 3 h later by 100 mg of ropivacaine hydrochloride in the epidural space.

The IV study performed in 12 animals was done to determine the plasma pharmacokinetics of ropivacaine required to assess the absolute bioavailability, and the systemic absorption profile after epidural and intrathecal administration.

After insertion of a catheter in the left jugular vein, ropivacaine was administered as a bolus injection (50 mg in 10 mL over 1 min) and blood samples (3 mL) were collected at 0, 1, 2, 3, 5, 8, 10, 15, 20, 30, 45, 60, 90, 120, and 180 min after dosing. After the last sample was collected, the jugular vein catheter was removed, and the animals were allowed to return to the vivarium. After centrifugation for 10 min at 3500g, plasma samples were kept frozen at −20°C until analysis.

The spinal study was performed in 12 animals, and eight animals followed the entire protocol for the determination of intrathecal bioavailability. Four were excluded for dysfunction either of the epidural dialysis probe ($n = 1$) or of the intrathecal probe ($n = 3$). General anesthesia was induced with an IV injection of thiopental (5–8 mg/kg) through a catheter inserted in the right jugular vein. Animals were then tracheally intubated, and ventilation was controlled mechanically (end-tidal CO_2 35 ± 5 mm Hg). Throughout the experiment, anesthesia was maintained with 1%–2% isoflurane in oxygen/air (50%/50%). A second catheter was then inserted in the left jugular vein for blood sampling, and administration of maintenance fluid. Hemodynamic variables (electrocardiogram, invasive

arterial blood pressure) were continuously monitored. Baseline values were recorded approximately 60 min after induction of general anesthesia, before intrathecal administration. When the systolic blood pressure (SBP) decreased to <80 mm Hg, isoflurane administration was reduced, and infusion of 500–1000 mL of hydroxylethyl starch was performed as necessary.

An esophageal thermistor was used to control the animals' body temperature, and a heat lamp was used to maintain body temperature above 37.5°C.

After blunt dissection, a small laminectomy with the removal of a piece of ligamentum flavum was performed at the L5–6 level. The insertion of epidural and intrathecal catheters was performed under visual control by a modified Seldinger technique. In the first step, a puncture of the dura mater was performed with a Tuohy needle (1.5-mm external diameter). Then, after visualization of a free cerebrospinal fluid (CSF) reflux, a guidewire was advanced through the needle over 10 cm into the intrathecal space, and the Tuohy needle was removed. The custom-made catheter (external diameter of 2.0 mm and length of 120 mm), allowing injections around the tip of microdialysis probe, was advanced along the guidewire. After removing the guidewire, the intrathecal microdialysis probe was inserted through catheter only if a CSF return was observed. An epidural catheter was inserted by the same technique to put the tip of the catheter adjacent to the probe in the intrathecal space. An epidural microdialysis probe was introduced in the absence of CSF return. This technique of catheter insertion allowed a good seal between the dura mater and the intrathecal catheter. At the end of surgery, the laminectomy and punction areas were secured with a drop of cyanoacrylate tissue adhesive (Indermil, Tyco Healthcare, Gosport, UK). A small amount of blood was used to occlude the surgical field allowing the control of the flowing back of liquids (i.e., after local anesthetics injection and during the experiment period).

After microdialysis probes insertion, and a 45-min equilibration period for determination of RL of bupivacaine, ropivacaine (20 mg in 3 mL over 1 min) was injected in the intrathecal space and ropivacaine (100 mg in 15 mL over 1 min) was injected in the epidural space 3 h later. In both parts of the experiment, a microdialysis sampling for 1 min was performed every minute for 15 min and for 5 min at 20, 25, 30, 35, 40, 45, 50, 55, 90, 95, 120, 125, 150, 155, 175, and 180 min in both the epidural and intrathecal spaces. In both parts of the experiment, blood samples were collected at 0, 1, 2, 3, 5, 8, 10, 15, 20, 30, 45, 60, 90, 120, and 180 min.

At the end of the experiment, the animals were killed with IV injection of thiopental, potassium chloride, and pancuronium. A control of the positioning of the catheters was performed on 10 animals either by surgical dissection or by radiography (i.e., anteroposterior and frontal view) using a metal guide introduced through the catheters. Additionally, in all animals, after the removal of the microdialysis probes (but leaving the catheter in place), we controlled the CSF leakage from the intrathecal space and not from the epidural space. The removed catheters confirmed good positioning if they had no distortions.

Chromatographic Analysis and Drug Assay

The assay of local anesthetics in the intrathecal or epidural dialysates, and in plasma samples was performed using a high-pressure liquid chromatographic method with ultraviolet absorbance detection ($\lambda = 205$ nm). Aliquots of 20 or 50 μL (for intrathecal or epidural samples, respectively) of the dialysate dilutions were immediately injected onto the chromatographic system. Ropivacaine was extracted from plasma according to a published method with slight modifications (13). Briefly, 0.5 mL of plasma sample was alkalinized by 50 μL of 1 M NaOH and 3 mL of n-heptane was added, after horizontal shaking (3 min) and centrifugation (3 min at 3500g), the organic phase was transferred to a conical vial containing 50 μL of 0.05 M H_2SO_4. After similar shaking and centrifugation, the organic phase was discarded, and the aqueous phase was buffered with 10 μL of 0.5 M K_2HPO_4, and 40 μL was injected onto the chromatographic system. The chromatographic system consisted of a Milton Roy model spectromonitor-3 ultraviolet detector (LDC Milton Roy, Riviera Beach, FL), a Waters Model 600 pump, a Waters Model 717 automatic injector, and a Waters Empower-Pro data acquisition system (Waters Assoc., Milford, MA). The analytical chromatographic column was a Lichrocart-Lichrospher RP-B Merck cartridge (length 125 mm, internal diameter 3 mm). The flow rate was 0.5 mL/min, and the temperature was maintained at 30°C. The mobile phase consisted of a mixture of acetonitrile and pH 2.1, 0.01 M sodium dihydrogenphosphate (23:77).

Quality Control of Analytical Methods

In plasma, the ropivacaine and etidocaine recoveries were 89.3% ± 6.4% and 84.6% ± 7.6%, respectively. The lower limit of quantification of ropivacaine was set at 3.8 ng/mL. The linearity was checked from 5 to 500 ng/mL ($r^2 > 0.9976 \pm 0.0282$). The interday assay precisions checked at 10 and 100 ng/mL were 15.1% and 4.8%, and the accuracies at these concentrations were 106.5% and 101.4%, respectively.

In dialysate, the lower limit of quantification of ropivacaine with a 5-min sampling in a 100-μL dilution was set at 0.8 μg/mL.

The linearity of ropivacaine and bupivacaine concentrations was checked from 0.05 to 10 μg/mL ($r^2 = 0.9997 \pm 0.0003$ and 0.9998 ± 0.0003, respectively). The interday assay precisions for ropivacaine dialysate concentrations of 1 and 2000 μg/mL were 4.0% and 0.5%, and the accuracies at these concentrations were

98.8% and 99.6%, respectively. The interday assay precisions for bupivacaine dialysate concentrations of 0.5 and 1000 μg/mL were 6.3% and 0.6%, and the accuracies at these concentrations were 93.3% and 99.8%, respectively.

Data Analysis

A compartmental analysis with a first-order elimination from the central compartment was applied to the plasma concentrations after IV administration, to the intrathecal concentrations after intrathecal administration, and to the epidural concentrations after epidural administration using the software package WinNonlin Pro (Pharsight, USA). Clearance parameters are CL_E defined as the elimination clearance and CL_I defined as the intercompartmental distribution clearance. V_1 and V_{ss} are the central and the steady-state volume of distribution, respectively. K_{12} and K_{21} are the distribution rate constants and K_{10} the elimination rate constant. $T_{1/2\alpha}$ and $T_{1/2\beta}$ are the apparent distribution and elimination half-life.

A noncompartmental analysis assuming a first-order elimination was applied to the plasma concentrations after intrathecal and epidural administration, the intrathecal concentrations after epidural administration, and the epidural concentrations after intrathecal administration. The peak plasma concentration (C_{max}) and corresponding time to peak concentration (T_{max}) were derived from raw data. The absolute systemic bioavailability after intrathecal or epidural administration, and the intrathecal bioavailability after epidural administration were calculated from the zero-to-infinite area under the curve (AUC). Individual absorption-time plots were estimated from deconvolution analysis. The percentage absorbed is expressed as relative to the fraction absorbed.

Intrathecal, epidural, and plasma ropivacaine concentrations after the second (epidural) injection were corrected by subtraction of the residual concentrations resulting from the first (intrathecal) injection. Residual concentrations were extrapolated from the last sample point on the basis of $T_{1/2\beta}$.

Statistics

All data are presented as mean ± SD. Student's t-test was used to compare individual means. $P < 0.05$ was considered as statistically significant. A one-way analysis of variance with Dunnett's method was used.

RESULTS

Surgical Procedure

No visual evidence of CSF leakage was recorded after catheter placement nor throughout the experiments. Compared with the baseline values (145 ± 27 mm Hg and 115 ± 26 mm Hg), respectively, for SBP and diastolic blood pressure (DBP), there was no significant difference in data measured before epidural administration (144 ± 40 mm Hg and 104 ± 27 mm Hg for SBP and DBP, respectively). A decrease in

SBP was observed after intrathecal administration (mean maximum decrease = 6% at 19 min; 132 ± 28 mm Hg and 103 ± 28 mm Hg for SBP and DBP respectively, $P < 0.05$) and after epidural administration (mean maximum decrease 17% at 12 min; 118 ± 41 mm Hg and 86 ± 34 mm Hg for SBP and DBP respectively, $P < 0.05$) (supplemental figure available at http://www.anesthesia-analgesia.org). The decrease in SBP and DBP was significantly higher after epidural injection ($P < 0.01$). After each epidural administration, a medical intervention was necessary to maintain hemodynamics whereas a medical intervention was necessary in only about 50% of the animals after intrathecal administration.

After hemodynamic correction, no significant differences were observed between intrathecal (125 ± 14 and 95 ± 10 mm Hg for SBP and DBP, respectively) and epidural experiments (123 ± 17 and 97 ± 20 mm Hg for SBP and DBP, respectively). There was no difference in heart rate before intrathecal administration (124 ± 15 bpm) and epidural administration (123 ± 14 bpm).

Plasma Pharmacokinetics

IV Administration

Plasma concentration time-course of ropivacaine after IV administration showed a very low interindividual variability with an extrapolated area of 5.9% ± 2.3% (Fig. 1A). The time-course displayed a biphasic pattern characterized by a rapid $T_{1/2\alpha}$ (6.6 ± 4.4 min) and a $T_{1/2\beta}$ of 64 ± 27 min. Clearance and distribution parameters (Table 1) were close to those previously reported (14).

Epidural and Intrathecal Administration

The plasma concentration time-course of ropivacaine after epidural and intrathecal administration is displayed in Figures 1B and C with extrapolation areas of 40% ± 16% and 22% ± 12%, respectively. The corresponding pharmacokinetic parameters are presented in Table 1. C_{max} after epidural administration (100 mg) and intrathecal administration (20 mg) was 282 ± 191 μg/L and 89 ± 29 μg/L. T_{max} after epidural and intrathecal injection was very close (17 ± 10 min and 12 ± 7 min, $P = 0.16$). The absolute bioavailability of ropivacaine after epidural and intrathecal administration was 70% ± 22% and 93% ± 36%, respectively ($P = 0.06$). The absorption-time plots (Figs. 2A and B) showed a large variability in systemic absorption after both intrathecal and epidural administration, with an apparent faster absorption after intrathecal administration (80% absorption in 37.9 and 85.3 min, respectively). $T_{1/2\beta}$ after epidural administration was higher than after intrathecal administration (162 ± 88 min and 90 ± 36 min, $P < 0.05$). After epidural administration, $T_{1/2\beta}$ was higher than after IV dosing ($P < 0.0001$), suggesting an absorption rate-limited elimination from the epidural space.
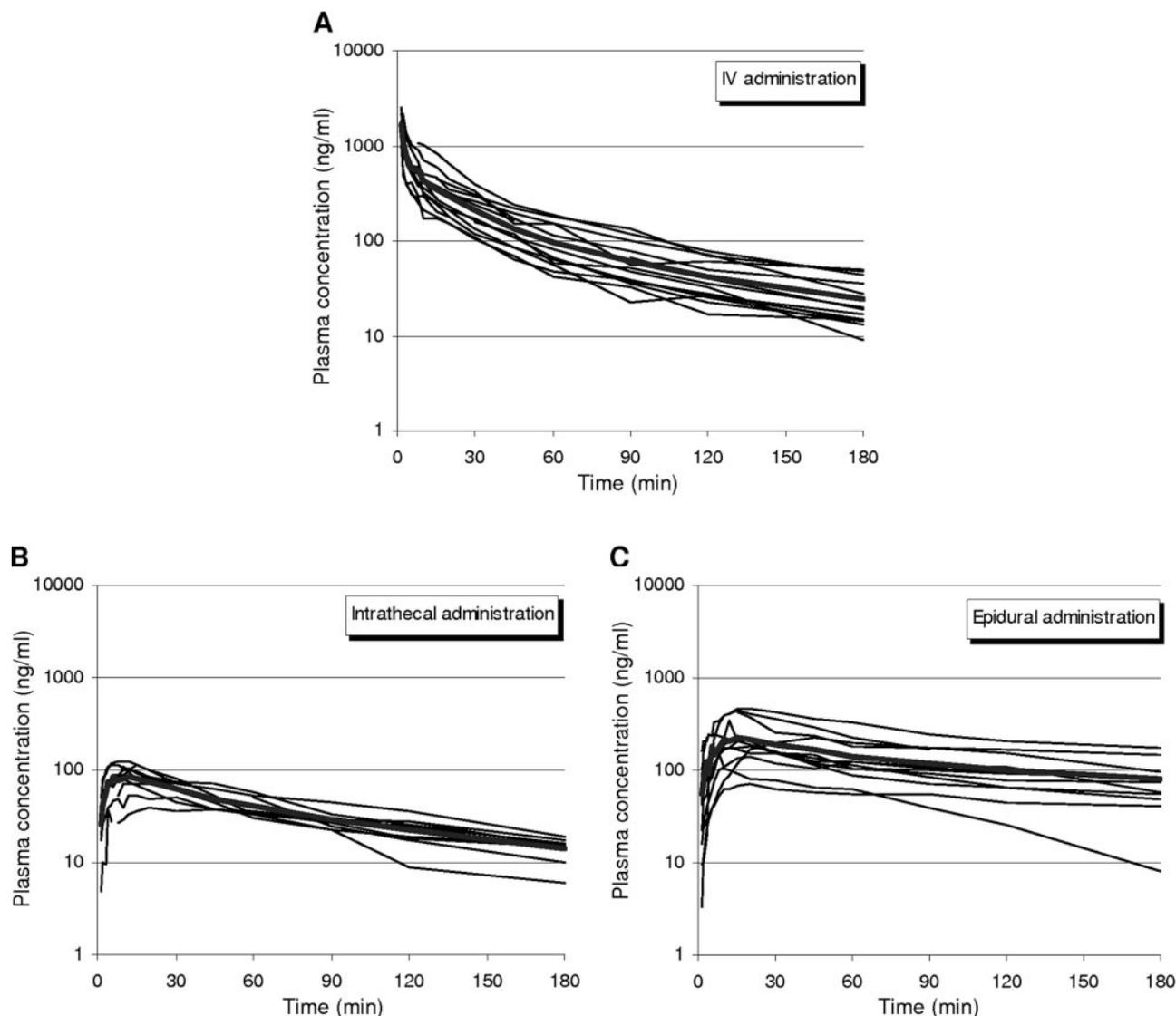
Figure 1. Individual plasma concentration time-course and mean plasma concentration time-course of ropivacaine after IV administration (50 mg) (A), intrathecal administration (20 mg) (B), and epidural administration (100 mg) (C). (C) The concentrations after the subtraction of the residual concentrations from the previous intrathecal administration.

Table 1. Plasma Pharmacokinetic Parameters of Ropivacaine After Intravenous (50 mg), Epidural (100 mg), and Intrathecal (20 mg) Administration in Sheep

Administration	Intravenous	Intrathecal	Epidural
N	12	9	11
C_{max} (ng/mL)	—	89 ± 29	282 ± 191
T_{max}	—	12 ± 7	17 ± 10
F (%)	—	93 ± 28	70 ± 22
CLE (L/min)	2.095 ± 0.810	—	—
V_1 (L)	41 ± 21	—	—
V_{ss} (L)	121 ± 53	—	—
K_{12} (min^{-1})	0.114 ± 0.146	—	—
K_{21} (min^{-1})	0.038 ± 0.030	—	—
K_{10} (min^{-1})	0.063 ± 0.038	—	—
$T_{1/2\alpha}$ (min)	6.6 ± 4.4	—	—
$T_{1/2\beta}$ (min)	64.1 ± 26.9	90 ± 36.5^a	$162 \pm 88^{b,c}$
MRT (min)	56 ± 12.1	125 ± 47.2	232 ± 115

Values mean $\pm$ SD.
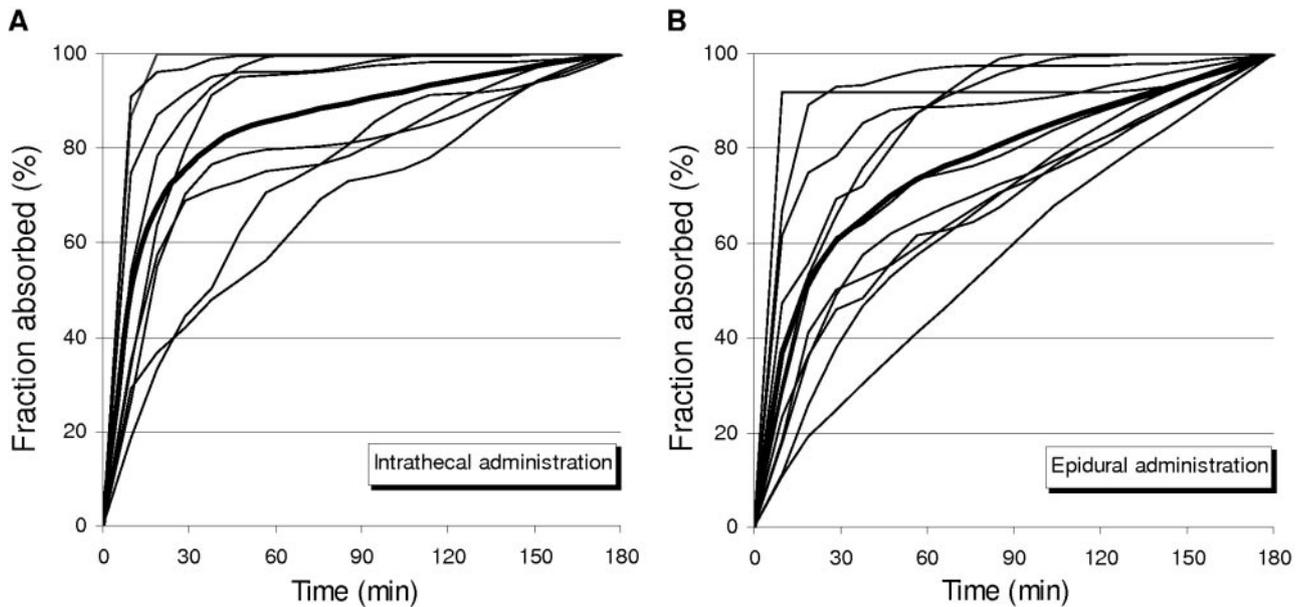
[a] Difference between IV and intrathecal.

[b] Difference between IV and epidural.

[c] Difference between intrathecal and epidural.

Epidural and Intrathecal Pharmacokinetics

The intrathecal and epidural concentration time-course of ropivacaine after intrathecal and epidural administration is displayed in Figures 3A and C with extrapolated areas of 23% $\pm$ 12% and 13% $\pm$ 7%, respectively. The corresponding pharmacokinetic parameters are presented in Table 2. The mean residual concentration from intrathecal injection in the intrathecal space was 22 $\pm$ 17 µg/mL.

The ropivacaine concentration time-course in the space where the drug was injected (either epidural or intrathecal) displayed a much lower interindividual variability than after transmeningeal diffusion (Figs. 3B and D). Both epidural and intrathecal profiles displayed a biphasic pattern with rather similar apparent distribution and elimination half-lives. After intrathecal and epidural administration, the mean extrapolated AUC was 4.4% $\pm$ 5.8% and 14.2% $\pm$ 8.1%, respectively, indicating that the sampling schedule was suitable. CL_E from the intrathecal space was

Figure 2. Ropivacaine systemic cumulative fraction absorbed after intrathecal administration (A) and after epidural administration (B).

less than from the epidural space (0.337 ± 0.140 vs 0.899 ± 0.302 mL/min). The difference between the intrathecal and epidural space was more pronounced for CL_I (0.099 ± 0.132 vs 0.858 ± 0.680 mL/min).

The intrathecal and epidural concentration time-course of ropivacaine after epidural and intrathecal administration, respectively, is displayed in Figures 3B and D, with extrapolation areas of $23\% \pm 12\%$ and $13\% \pm 7\%$, respectively. The corresponding pharmacokinetic parameters are presented in Table 3. These profiles displayed moderate interindividual variability, especially in the epidural space after intrathecal dosing. T_{max} and C_{max} were similar in both spaces, whereas $T_{1/2\beta}$ in the epidural space was higher than in the intrathecal space.

The intrathecal bioavailability after epidural administration was $11.1\% \pm 7.6\%$, ranging from 0.7% to 23.0%. The absorption-time plots showed two groups of animals in which the absorption rate was very different (Fig. 4).

DISCUSSION

The current experiment was designed to create an animal model close to humans, allowing the simultaneous evaluation of epidural and intrathecal disposition after drug administration, by the epidural and intrathecal route, and the intrathecal bioavailability after epidural administration.

Since our microdialysis model of simultaneous epidural and intrathecal drug disposition requires working on animals under general anesthesia, the influence of general anesthesia on the pharmacokinetics of ropivacaine has to be considered. Early studies on lidocaine, a flow-limited hepatic clearance drug with a hepatic extraction ratio higher than 0.9 (15), reported that halothane decreased (16) or had a nonsignificant

effect on its clearance (15), and that isoflurane and sevoflurane have fewer hemodynamic effects (17–19). Considering this information, and that ropivacaine has an intermediate hepatic extraction ratio (14,20), i.e., are thus less affected by changes in hepatic blood flow, we did not expect isoflurane to have a significant influence on ropivacaine's hepatic clearance. A potential shortcoming of the study may arise from a higher volume of IV fluids that were administered in anesthetized animals.

Plasma Pharmacokinetics

The absolute bioavailability of ropivacaine after intrathecal and epidural administration was close to 100% and 70%, suggesting that ropivacaine was in part sequestered (perhaps in the epidural fat), as evidenced by the great difference in the volume of distribution of ropivacaine after epidural administration (Table 2). Evaluation of the absorption kinetics has been performed by deconvolution analysis, which is the most powerful method used (21–23). Indeed, calculating ka by classical pharmacokinetics modeling usually leads to a lack of precision in the determination of the absorption rate constant (K_a) for drugs that have a bicompartmental pharmacokinetics. In our experiment, the absorption-time plots (Figs. 2A and B) showed a large variability in the systemic absorption after both intrathecal and epidural administration, with an apparent faster systemic absorption after intrathecal administration (80% absorption in 38 and 85 min, respectively). This is in agreement with the difference in the elimination rate constants (K_{10}) from the intrathecal and epidural sites. Such a difference was also displayed by the analysis of the percent remaining to be absorbed showing a biphasic absorption with
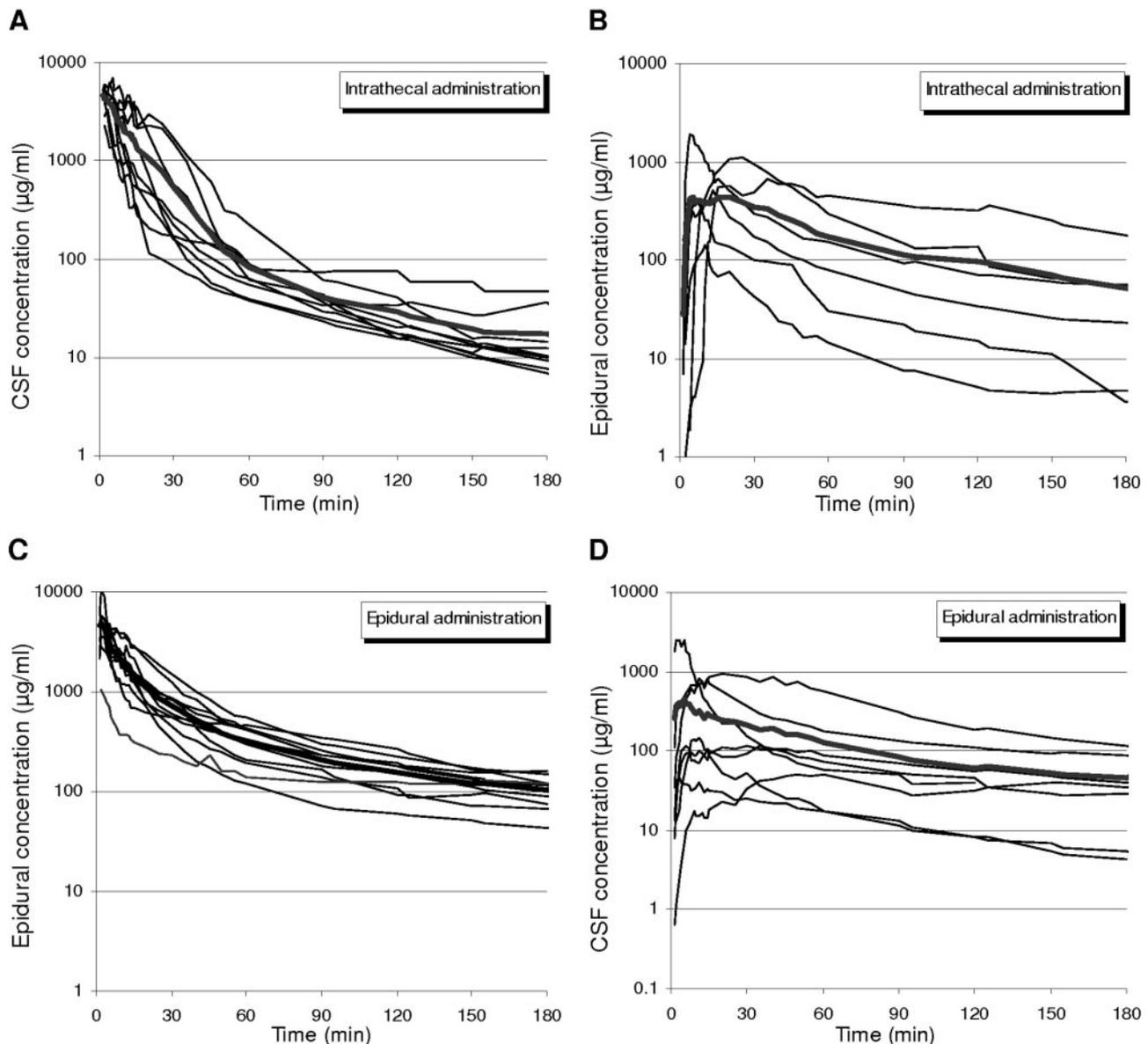
Figure 3. Intrathecal concentration time-course (A) and epidural concentration time-course (B) after intrathecal administration of ropivacaine (20 mg). Epidural concentration time-course (C) and intrathecal time-course (D) after epidural administration of ropivacaine (100 mg). (C) and (D) represent the concentrations after the subtraction of the residual concentrations from the previous intrathecal administration.

Table 2. Epidural and Intrathecal Pharmacokinetic Parameters of Ropivacaine After Epidural (100 mg) and Intrathecal (20 mg) Administration in Sheep

Space	Intrathecal	Epidural
Administration	Intrathecal	Epidural
N	9	11
CLE (mL/min)	0.337 ± 0.140	0.899 ± 0.302
CLI (mL/min)	0.099 ± 0.132	0.858 ± 0.680
V_1 (mL)	3.9 ± 3.1	17 ± 5
V_{ss} (mL)	11.4 ± 11.3	57 ± 24
MRT (min)	33 ± 26	63 ± 14
K_{12} (min^{-1})	0.027 ± 0.040	0.057 ± 0.053
K_{21} (min^{-1})	0.014 ± 0.005	0.024 ± 0.021
K_{10} (min^{-1})	0.105 ± 0.054	0.055 ± 0.012
$T_{1/2\alpha}$ (min)	6.6 ± 3.3	7.2 ± 3.6
$T_{1/2\beta}$ (min)	70.3 ± 28.6	82.9 ± 28.2

Values mean $\pm$ sd.

35% and 65% of ropivacaine absorbed during an initial phase of rapid absorption after epidural and intrathecal administration, respectively. The difference was unexpected, given that the absorption process is likely to be influenced by vascularity, and that the epidural space is more extensively vascularized than the intrathecal space.

Epidural and Intrathecal Pharmacokinetics

The transmeningeal diffusion was rather similar after either epidural or intrathecal administration, as suggested by the similarity of C_{max} and T_{max} in these compartments. Such a feature is normal, given that this process is assumed to be a passive phenomenon, and that the concentration of the injected solutions was the same. However, it should be noted that drug disposition in the intrathecal space can be atypical

Table 3. Epidural and Intrathecal Pharmacokinetic Parameters of Ropivacaine After Intrathecal (20 mg) and Epidural (100 mg) Administration in Sheep

Space	Epidural	Intrathecal
Administration	Intrathecal	Epidural
N	6^a	8
AUC	35,776 ± 31,572	31,178 ± 30,818
C_{max} (μg/mL)	786 ± 640	670 ± 898
T_{max}	15 ± 13	12 ± 12
F	—	11.1 ± 7.6
$T_{1/2\beta}$ (min)	70 ± 29	99 ± 34
MRT (min)	78 ± 37	122 ± 59

Values mean ± SD.
[a] Epidural profiles after intrathecal dosing in two animals were totally erratic for unexplained reasons and were excluded from analysis and from the corresponding figure.
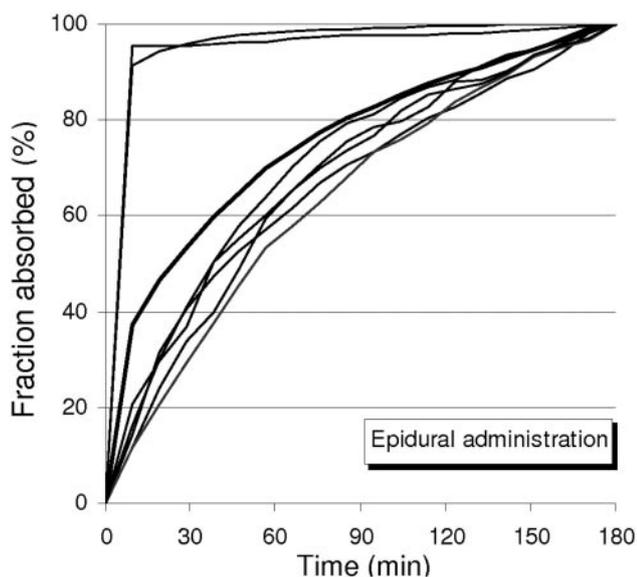
Figure 4. Ropivacaine intrathecal cumulative fraction absorbed after epidural administration.

given the fact CSF is not a well stirred fluid as opposed to blood, in which a drug injected as a bolus is assumed to be quite instantly diluted. Hence, the disposition of drugs in CSF is affected by CSF bulk flow and to a lesser extent by the diffusion of the drug within the CSF (24,25), so that the distance between microdialysis probes and catheter for injection affects the magnitude of the measured concentrations. In our model, microdialysis probes and the catheter for injection were close on both sides of the meninges, thus minimizing the variability that could result from a variation in the distance between injection and sampling sites. However, we cannot be sure that the distance between catheter and probe was the same in all experiments. Hence, the relative position of the catheter of injection and dialysis probes is a variability factor of this model.

Drug dispositions in the epidural and intrathecal compartments were different. In the intrathecal space, CL_E was around three-times higher and less variable than the CL_I, whereas in the epidural space, the relative contribution of CL_E and CL_I to ropivacaine disposition was different, indicating a more pronounced influence of the distribution process. A similar contribution of elimination and distribution process to the intrathecal and epidural disposition of ropivacaine has been described in a rabbit model (6). The intrathecal bioavailability of ropivacaine after epidural administration was close to the values previously reported for clonidine in a sheep model (26) and for ropivacaine in a rabbit model (6), and higher than that reported for opioids in humans (27–31).

The intrathecal bioavailability after epidural administration displayed a significant variability, ranging from 0.7% to 23.0%. It should be noted that one animal had a very low intrathecal bioavailability (0.7%). However, this animal had unusual values for intrathecal AUC either after epidural dosing (eight times lower than the mean) as after intrathecal dosing (two times higher than the mean) that may have resulted from a distant positioning of the administration catheters and microdialysis probes. If this animal is excluded, the variability in the intrathecal bioavailability remained high, ranging from 5.4% to 23.0%. The absorption in CSF showed two groups of animals with different absorption patterns. The very rapid absorption rate observed in two animals may suggest that catheter insertion may have damaged the arachnoid-dura mater meninges.

These results are useful for selecting the respective intrathecal and epidural doses and time between these administrations. For example, approximately 45 min after intrathecal administration (20 mg), the CSF concentrations of ropivacaine are of the same order of magnitude as those obtained at the peak after epidural administration (100 mg). It should be stressed that intrathecal administration led to a smaller variability in CSF concentrations compared with epidural administration.

In conclusion, the intrathecal bioavailability of ropivacaine is approximately 10% after epidural administration. Moreover, the relative importance of the distribution and elimination processes differs between the epidural and intrathecal spaces, and the systemic absorption after intrathecal administration was faster than after epidural administration.

This model can be used to clarify the influence of vasoconstrictors, and of permeation enhancers, as well as the influence of sustained delivery systems on the intrathecal bioavailability of drugs given epidurally.

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