

REGIONAL ANAESTHESIA

Effect of epinephrine on epidural, intrathecal, and plasma pharmacokinetics of ropivacaine and bupivacaine in sheep

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Background. Local vasoconstriction induced by epinephrine added to epidural local anaesthetics has been shown to improve their quality and duration of action in several clinical reports. There are several assumptions on the mechanisms. This study was designed to evaluate the influence of epinephrine on transmeningeal uptake of epidurally administered ropivacaine and bupivacaine by measuring local anaesthetic concentrations in the epidural and intrathecal spaces and in plasma.

Methods. Ropivacaine (50 mg) and bupivacaine (30 mg) were administered epidurally in sheep with and without epinephrine (75 µg). A microdialysis technique was used to simultaneously measure epidural and intrathecal drug concentrations. Resulting dialysate and plasma concentrations were used to calculate pharmacokinetic parameters for ropivacaine and bupivacaine.

Results. Co-administration of epinephrine decreased epidural clearance for ropivacaine [0.6 (SD 0.1) vs 0.4 (0.1) ml min⁻¹] but not significantly for bupivacaine [1.2 (0.4) vs 0.8 (0.3) ml min⁻¹]. The resultant increase in epidural area under the concentration–time curves (31% for ropivacaine and 52% for bupivacaine) was also observed in the intrathecal space (21% increase for ropivacaine and 37% for bupivacaine). There was no significant influence of epinephrine on ropivacaine plasma pharmacokinetics. Plasma C_{max} for bupivacaine was decreased.

Conclusions. These results show that epinephrine decreases the clearance and distribution processes involved in epidural disposition of ropivacaine and bupivacaine, leading to an increased uptake into the intrathecal space with an apparent more pronounced effect for bupivacaine.

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Epidural administration of local anaesthetics is commonly used for intraoperative anaesthesia and postoperative treatment of pain. The concomitant administration of the vasoconstrictor epinephrine has been reported to improve the onset, duration, and intensity of the sensory and motor block and to decrease plasma concentrations of local anaesthetic responsible for systemic toxicity. These effects were reported with lidocaine, which is less lipophilic and less bound to plasma proteins than bupivacaine.^{1–3} However, the influence of epinephrine on epidural bupivacaine,^{4–6} levo-bupivacaine,⁷ and ropivacaine^{8–10} levels

has led to contradictory results both on pharmacokinetic and pharmacodynamic endpoints.

Although there are several assumptions on the mechanism of the spinal action of epinephrine,¹¹ its effect on epidurally administered drugs remains unclear. The primary action is probably local vasoconstriction that reduces systemic absorption from the site of injection. The maintenance of increased drug concentrations in the epidural space could account for higher transmeningeal uptake into neural tissue, increasing by this way their action and decreasing their plasma concentrations, which are directly responsible for

systemic toxicity. Another explanation is an additive or synergistic analgesic effect *via* activation of α 2-adrenergic receptors.¹² The effect of epinephrine has frequently been assessed from its impact on the plasma concentrations of local anaesthetics. However, such modifications may result from an increase in plasma clearance and in volume of distribution caused by the systemic action of absorbed epinephrine,¹³ and not from a modification of the systemic uptake.

Simultaneous analysis of local anaesthetic concentrations in the epidural and intrathecal spaces, and plasma, could help to clarify the mechanism(s) by which epinephrine improves the action of epidurally administered local anaesthetic. The effect of epinephrine is likely influenced by different factors such as drug physico-chemical characteristics and their concentrations or the site of injection. For that reason, we decided to compare the effects of epinephrine on bupivacaine and ropivacaine disposition, two local anaesthetics with different physico-chemical properties. Compared with ropivacaine, bupivacaine is characterized by higher lipid solubility and a higher uptake into neural tissue.^{14 15} Moreover, ropivacaine has an intrinsic vasoconstrictor effect, in contrast to bupivacaine.^{16–19} The main goal of our study, carried out in a sheep model using simultaneous epidural-intrathecal microdialysis, was to describe the influence of epinephrine on epidural, intrathecal, and systemic local anaesthetic pharmacokinetics.

Methods

Chemicals

Ropivacaine and bupivacaine (Astra Zeneca, Paris, France) were used as the substance of interest and as an internal standard in the microdialysis technique, one being internal standard for the other and vice versa. Etidocaine (Astra Zeneca, Paris, France) was used as a HPLC internal standard for both drugs. Epinephrine was purchased from Aguettant (Lyon, France). Ringer's solution (NaCl 8.6 g litre⁻¹, KCl 0.33 g litre⁻¹, CaCl₂·2H₂O 0.3 g litre⁻¹, pH 7.0) was used as perfusion fluid during the microdialysis experiments. All reagents were of analytical grade.

Microdialysis

Microdialysis was performed using a CMA 102 microinjection pump coupled to a CMA/20 microdialysis probe (membrane length 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).

During the experiments, microdialysis probes were perfused at 1 μ l min⁻¹ with a solution of internal standard (1 mg ml⁻¹ bupivacaine or ropivacaine in a Ringer's solution). After probe insertion in the intrathecal space and

epidural space, an *in vivo* equilibration with determination of relative loss (RL) of internal standard ($n=10$ for each probe tested) was performed over a period of 45 min. Owing to the high sampling frequency in the *in vivo* experiments, an accurate collection of micro-volume dialysates was achieved by immersion of the prolongator of the outlet tubing of microdialysis probe into 100 or 200 μ l of a 1 μ g ml⁻¹ 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 sampling of 1 and 5 μ l of dialysate, respectively.

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

Before and after *in vivo* implantation, the probes were tested *in vitro* in order to verify the lack of significant deterioration by comparison with RL of internal standards. The inter-batch variability among microdialysis probes was low. Indeed, the *in vitro* RL of internal standards checked before *in vivo* implantation was 0.47 (0.06) and 0.49 (0.04) ($n=10$) for ropivacaine and bupivacaine, respectively.

Study design

Twelve non-pregnant Lacaunes ewes with a mean age 2.8 (1) yr and weight 55.6 (3.4) kg were used in this experiment. The experimental protocol was approved by the Local Committee of Laboratory Investigation and Animal Care of our institution and achieved in accordance with the rules and guidelines concerning the care and the use for laboratory animal experiments (agreement no. B35-238-21).

Throughout the experiment, the animals were anaesthetized with 1–2% isoflurane in oxygen/air (50/50%). The general anaesthesia was induced with an i.v. injection of thiopental (5–8 mg kg⁻¹) through a catheter inserted in the right jugular vein. Animals were then intubated, and lung ventilation was controlled mechanically [end-tidal CO₂ 35 (5) mm Hg]. Haemodynamic parameters (i.e. ECG and invasive arterial blood pressure) were continuously monitored. When the systolic blood pressure (SBP) decreased to <80 mm Hg, isoflurane administration was reduced, and infusion of 500–1000 ml of hydroxyl-ethyl starch was performed as necessary. An oesophageal thermometer was used to measure 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 L5–L6 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 control of free cerebrospinal fluid (CSF) reflux, a guide wire was advanced through the needle

over 10 cm into the intrathecal space. By sliding it over the guide wire, 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 the microdialysis probe, was advanced along the guide wire. After removal of the guide wire, the intrathecal microdialysis probe was inserted through the catheter only if CSF reflux was observed. An epidural catheter was inserted using the same technique in order to put the tip of the catheter vis-à-vis to that in the intrathecal space. Epidural microdialysis probe was introduced in the absence of CSF reflux. At the end of the surgery, the laminectomy and puncture areas were secured with a drop of cyanoacrylate tissue adhesive (Indermil, Tyco Healthcare, Gosport, UK). Then, a small amount of blood was used to occlude the open surgical site, allowing control of liquid back flow (i.e. after local anaesthetics injection and during the experiment period).

The study was performed on 12 animals, divided into two groups receiving ropivacaine or bupivacaine. Ropivacaine hydrochloride (50 mg) or bupivacaine hydrochloride (30 mg) was diluted in 0.9% sodium chloride to a final volume of 15 ml and was injected through the epidural catheter over a period of 1 min. The ratio of dose between epidural bupivacaine and ropivacaine was close to that used in the previous studies, which were based on the minimal local analgesic concentrations of these drugs.^{20 21} The animals first received the plain drug and then at 2 h intervals the drug with epinephrine (75 µg). A third control injection was performed with one drug (i.e. ropivacaine) and was compared with the first injection to check for the reproducibility of the model (Fig. 1).

Epidural and intrathecal microdialysis sampling after all injections was achieved according to the following schedule: before administration, every minute during the first 15 min and then every 5 min to the end of experiment (120 min). A venous catheter was inserted in the left jugular vein for blood sampling and administration of maintenance fluid. Blood samples were collected before injection and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 30 min and every 15 min until 120 min.

At the end of the experiment, the animals were euthanized with simultaneous i.v. injection of thiopental, potassium chloride, and pancuronium.

The epidural and intrathecal microdialysis probes were removed from their respective catheters to check for the CSF reflux from the intrathecal space and for the lack of the reflux from the epidural space. This allowed confirmation of the good positioning of the probes.

Chromatographic analysis and drug assay

The separation and quantification of the local anaesthetics in the intrathecal or epidural dialysates, and in plasma samples, were carried out using a high-pressure liquid chromatographic with UV 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 and bupivacaine were extracted from plasma according to a previously published method with slight modifications.²² Briefly, 0.5 ml of plasma was alkalized with 50 µl of 1 M NaOH and 3 ml of *n*-heptane was added; after horizontal shaking (3 min) and centrifugation (3 min at 3500 g), the organic phase was transferred to a conical vial containing 50 µl of 0.05 M H₂SO₄. After similar shaking and centrifugation, the organic phase was discarded and the aqueous phase was buffered with 10 µl of 0.5 M K₂HPO₄ and 40 µl were injected onto the chromatographic system. The chromatographic system consisted of a Milton Roy model spectromonitor-3 UV detector (LDC Milton Roy, Riviera Beach, FL, USA), a Waters Model 600 pump, a Waters Model 717 automatic injector, and a Waters Empower-Pro data acquisition system (Waters Assoc., Milford, MA, USA). The analytical chromatographic column was a Lichocart-Lichrospher RP-B Merck cartridge (length 125 mm, internal diameter 3 mm). The flow rate was 0.5 ml min⁻¹, 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 dihydrogen phosphate (23:77).

Data analysis

Maximum plasma, epidural, and intrathecal concentrations (C_{max}), the corresponding time (T_{max}), and the last measured concentrations (C_{last}) of ropivacaine and bupivacaine were derived from raw data. A non-compartmental analysis was applied to the epidural, intrathecal, and plasma concentrations after epidural administration.

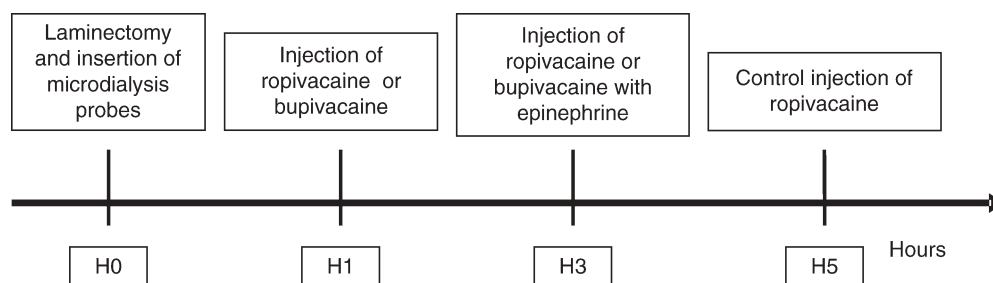


Fig 1 Experimental protocol for the study.

WinNonlin Pro software (Pharsight, USA) was used to determine the area under the concentration–time curve (AUC), volume of distribution (V_{ss}), clearance (Cl), and elimination half-life ($T_{1/2\beta}$). The volume of distribution and clearance are calculated directly if the site of administration and sampling are the same (i.e. in the epidural space). In the intrathecal space and plasma, they can only be calculated when compared with bioavailability; hence, they are expressed as V_{ss}/F and Cl/F , respectively.

Intrathecal, epidural, and plasma drug concentrations after the second and the third injection were corrected by subtraction of the residual concentrations resulting from the previous administrations. Residual concentrations were extrapolated from the last sample point on the basis of the terminal elimination half-life.

Statistics

All data are presented as mean (SD). Student's paired *t*-test was performed to compare the effect of epinephrine on pharmacokinetic parameters of ropivacaine and bupivacaine. Differences in pharmacokinetic parameters between both drugs were analysed in the epidural space using a Student's *t*-test. A *P*-value of <0.05 was considered as statistically significant.

Results

Haemodynamic data

No visual CSF leakage was recorded after catheter placement or during the procedure. Compared with baseline haemodynamics determined just before injection (i.e. 60 min after induction of general anaesthesia), no significant differences were observed between groups (bupivacaine *vs* ropivacaine) with or without epinephrine before epidural administration (Table 1).

After epidural administration of local anaesthetics, SBP and diastolic blood pressure (DBP) decreased slightly, with a significant effect only on DBP after ropivacaine injection. No medical intervention was necessary to restore haemodynamics during the entire procedure, and no significant difference was observed with subsequent administrations of local anaesthetics.

At baseline, there was no difference in heart rate between animals receiving epidural ropivacaine or bupivacaine either with or without epinephrine (Table 2). A slight decrease in heart rate was observed after injection of local anaesthetics with a significant effect only after the first ropivacaine injection [maximum decrease observed at 10 min: 91 (15) beats min^{-1}].

Influence of epinephrine on pharmacokinetics of ropivacaine and bupivacaine

Epidural space

The individual and mean epidural concentration–time profiles of ropivacaine and bupivacaine after epidural administration with and without epinephrine are presented in Figure 2. The corresponding pharmacokinetic parameters are listed in Table 3. The epidural concentration–time curves showed a low scatter and displayed important differences in the epidural profiles between both drugs. Ropivacaine epidural clearance and volume of distribution were significantly lower than those observed with bupivacaine. Interestingly, the terminal elimination half-life ($T_{1/2\beta}$) from the epidural space was lower for ropivacaine than for bupivacaine [73.1 (47.8) and 142.5 (67.8) min, respectively].

Pharmacokinetic analysis was performed on six animals for each drug. However, we noticed that in the ropivacaine group, one sheep had atypical values for the volume of distribution (very low without epinephrine and very high with epinephrine). The reason for such feature is unknown, and all others parameters such as clearance and $T_{1/2\beta}$ were close to that obtained for other animals. Adding epinephrine decreased significantly the epidural clearance of ropivacaine and the volume of distribution of bupivacaine. Hence, co-administration of epinephrine increased the epidural AUC of both drugs. Ropivacaine AUC showed a 31% increase ($P<0.03$) and bupivacaine AUC a 52% increase ($P<0.002$). Similarly, the last concentrations at 120 min (C_{last}) were also significantly higher compared with both drugs alone. There was no difference in C_{max} with or without epinephrine for ropivacaine and bupivacaine.

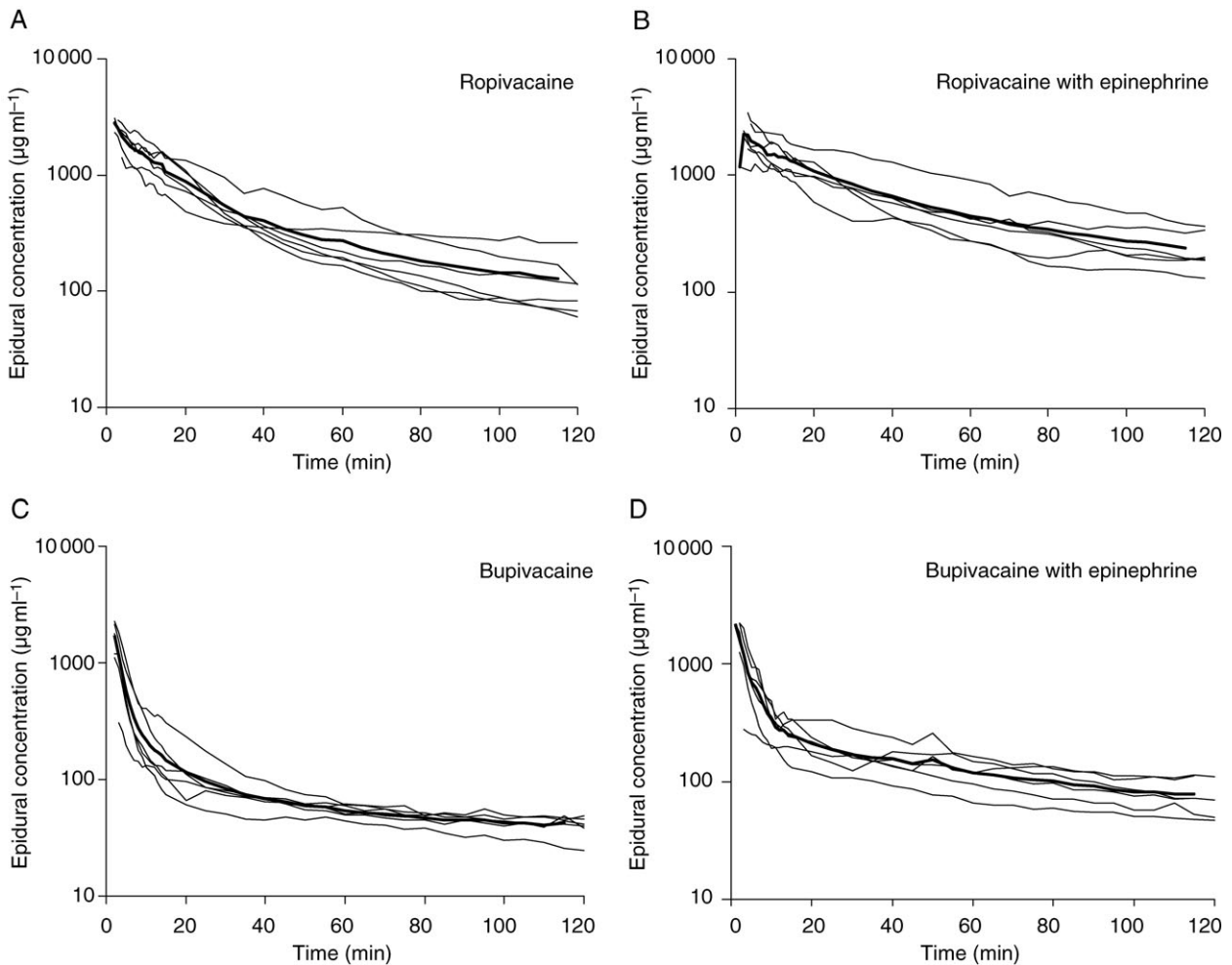
The epidural AUC obtained after the third injection (plain ropivacaine) was not statistically different to that obtained after the first injection [53 609 (15 709) *vs* 61 516 (12 765) $\mu\text{g min ml}^{-1}$], indicating that epidural

Table 1 Blood pressure after epidural ropivacaine and bupivacaine with and without epinephrine. SBP and DBP at the baseline and at the time of maximum decrease (at about 10 min). * $P<0.05$ different comparing with baseline

Parameters (mm Hg)	Ropivacaine						Bupivacaine			
	First injection plain		Second injection with epinephrine		Third injection plain		First injection plain		Second injection with epinephrine	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Baseline value	141 (10)	114 (25)	133 (20)	93 (25)	129 (10)	102 (10)	144 (15)	110 (20)	150 (15)	120 (15)
Value at time of maximal decrease	110 (21)	82 (20)*	109 (20)	66 (10)*	114 (10)	83 (9)*	123 (17)	91 (21)	140 (20)	110 (24)

Table 2 Cardiac frequency after epidural ropivacaine and bupivacaine with and without epinephrine. Cardiac frequency at baseline and at the time of maximum decrease (between 10 and 14 min). * $P < 0.05$ different comparing with baseline

Cardiac frequency	Ropivacaine			Bupivacaine	
	First injection plain	Second injection with epinephrine	Third injection plain	First injection plain	Second injection with epinephrine
Baseline (beats min^{-1})	116 (16)	104 (19)	119 (40)	114 (25)	122 (25)
At time of maximal decrease (beats min^{-1})	91 (15)*	93 (11)	108 (45)	110 (16)	110 (18)

**Fig 2** Mean (bold) and individual concentration–time profiles in epidural space after epidural administration of ropivacaine (50 mg) and bupivacaine (30 mg) with and without epinephrine.

drug disposition had returned to normal (without epinephrine).

Intrathecal space

Figure 3 reports the individual and mean CSF concentrations of ropivacaine and bupivacaine after epidural administration with and without epinephrine. CSF non-compartmental pharmacokinetic parameters are listed in Table 4. The observed T_{max} in the intrathecal space did not show any significant difference between ropivacaine and bupivacaine [15.2 (8.2) and 13.5 (3.7) min, respectively]. Co-administration of epinephrine influenced the

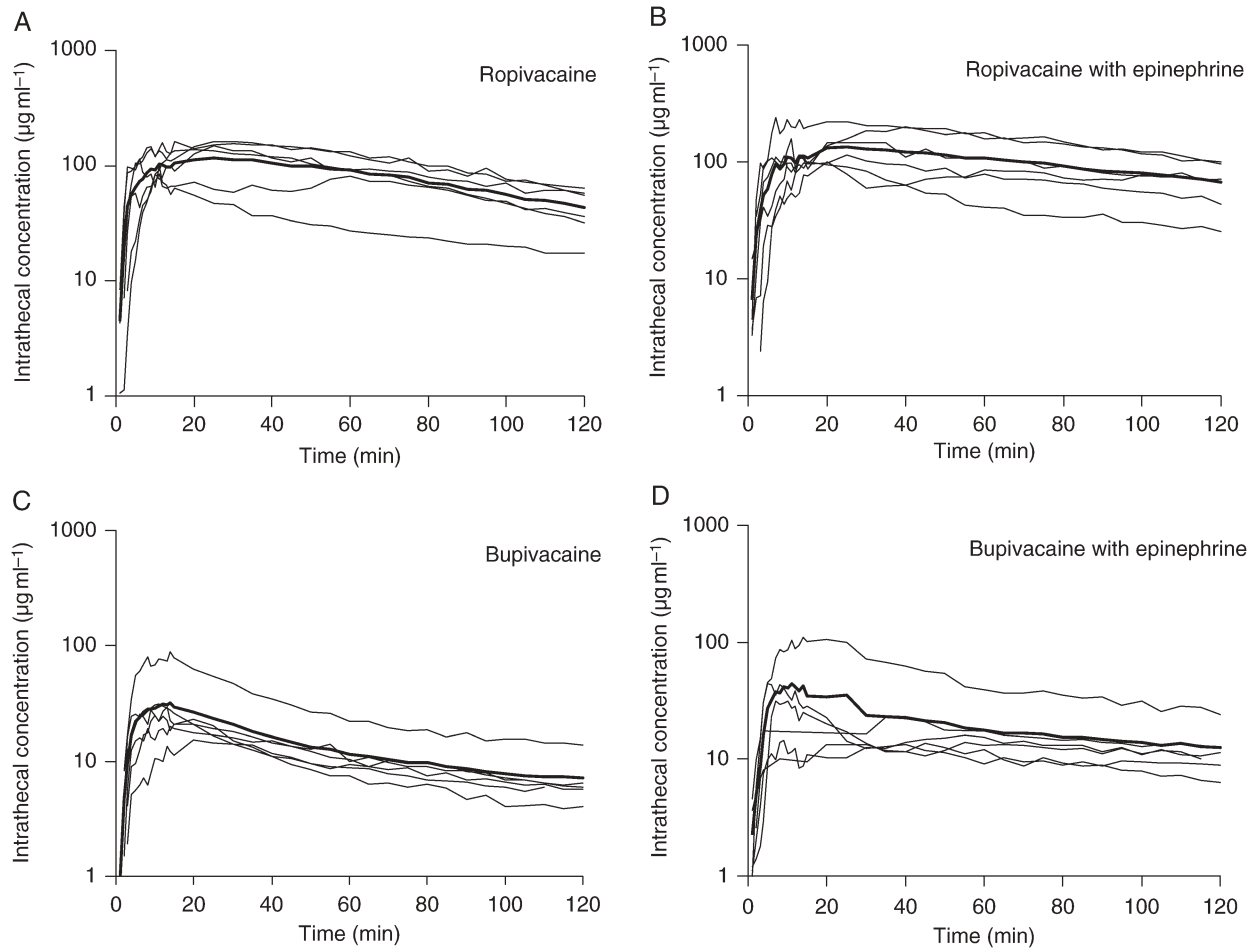
intrathecal pharmacokinetics of both drugs. The AUC and the clast of ropivacaine and bupivacaine were higher with epinephrine. The increase in intrathecal AUC was 21% for ropivacaine ($P < 0.05$) and 37% for bupivacaine ($P = 0.07$). The co-administration of epinephrine also increased the apparent $T_{1/2\beta}$ of bupivacaine in the intrathecal space.

Plasma

Figure 4 shows the mean and individual plasma concentrations of ropivacaine and bupivacaine after epidural administration with and without epinephrine. The corresponding pharmacokinetic parameters are presented in Table 5.

Table 3 Epidural pharmacokinetic parameters after epidural administration. * $P < 0.05$ difference between plain ropivacaine and ropivacaine with epinephrine and between plain bupivacaine and bupivacaine with epinephrine. † $P < 0.05$ difference between ropivacaine and bupivacaine. ‡ $P < 0.05$ difference between ropivacaine with epinephrine and bupivacaine with epinephrine

	Ropivacaine (50 mg)		Bupivacaine (30 mg)	
	Plain	With epinephrine	Plain	With epinephrine
AUC ₀₋₁₂₀ ($\mu\text{g min ml}^{-1}$)	61 516 (12 765)	80 846 (28 555)*	15 989 (5677)	24 326 (7801)*
C _{max} ($\mu\text{g ml}^{-1}$)	2534 (617)	2287 (770)	1472 (745)	1552 (794)
Cl (ml min^{-1})	0.6 (0.1)†	0.4 (0.1)*‡	1.2 (0.4)	0.8 (0.3)
V _{ss} (ml)	77.8 (60.2)†	117.0 (67.7)‡	150 (100)	88.7 (42.5)*
T _{1/2β} (min)	73.1 (47.8)†	110.6 (75.3)	142.5 (67.8)	111.9 (75.6)
C _{last} ($\mu\text{g ml}^{-1}$)	117 (75)	236 (95)*	40 (8)	74 (25)*

**Fig 3** Mean (bold) and individual concentration–time profiles in intrathecal space after epidural administration of ropivacaine (50 mg) and bupivacaine (30 mg) with and without epinephrine.

Venous plasma concentration time plots are characterized by a biphasic pattern with a rather significant scattering. The observed T_{max} in plasma did not show any significant difference between ropivacaine and bupivacaine [12 (5) and 13 (4) min, respectively]. Adding epinephrine did not influence plasma pharmacokinetics of ropivacaine. In contrast, the C_{max} of bupivacaine with epinephrine was significantly lower than that observed with plain bupivacaine [28 (12) and 45 (21) $\mu\text{g ml}^{-1}$, respectively]. There was also a trend to decreasing the AUC of bupivacaine with co-administration

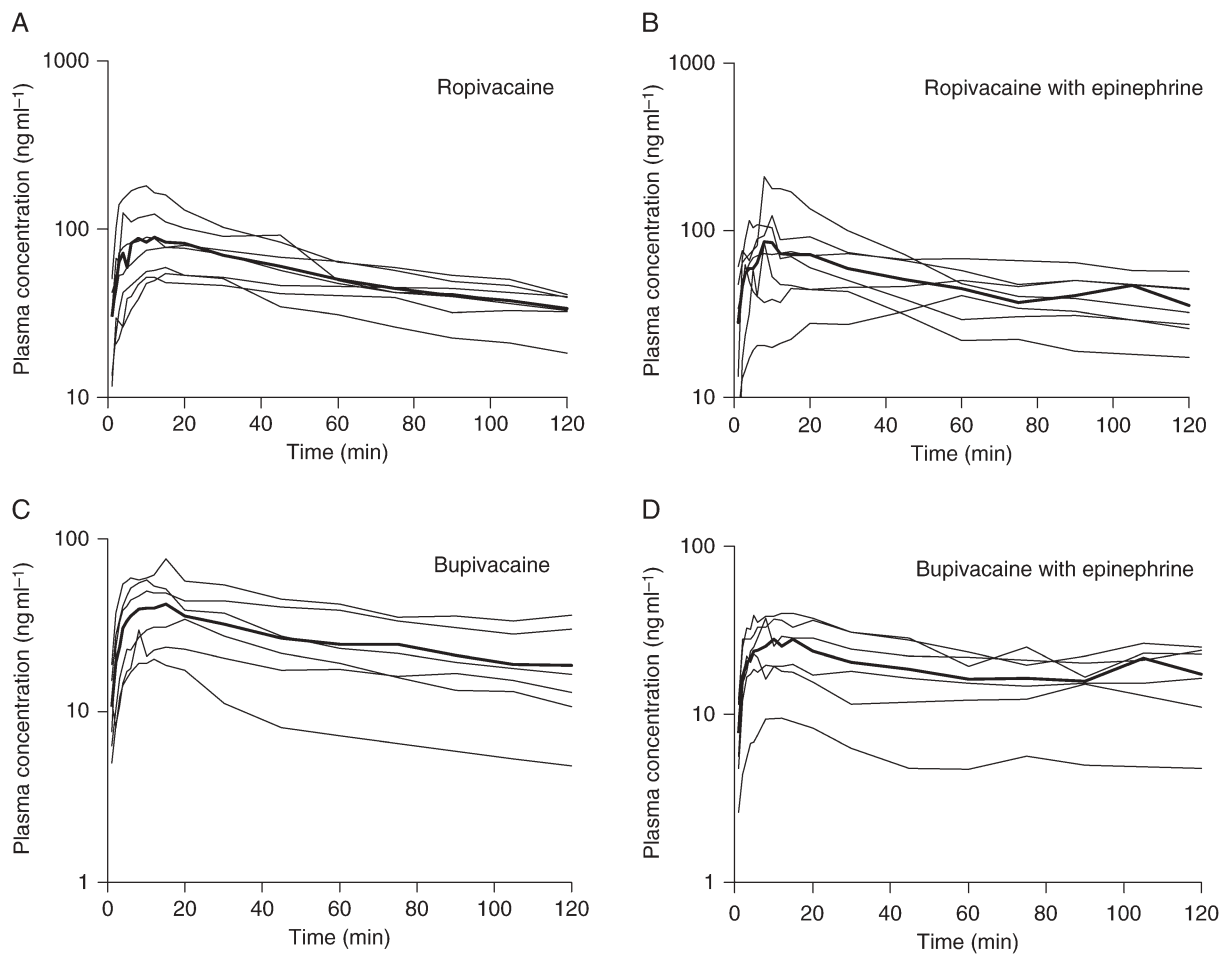
of epinephrine ($P=0.06$). The bupivacaine total clearance (Cl/F) was lower and apparent T_{1/2 β} was higher when co-administrated with epinephrine ($P < 0.05$), but T_{max} was unaffected.

Discussion

Spinal disposition of local anaesthetics administered by the epidural route has been the subject of much discussion

Table 4 Intrathecal pharmacokinetic parameters after epidural administration. * $P < 0.05$ difference between plain ropivacaine and ropivacaine with epinephrine and between plain bupivacaine and bupivacaine with epinephrine

	Ropivacaine (50 mg)		Bupivacaine (30 mg)	
	Plain	With epinephrine	Plain	With epinephrine
AUC ₀₋₁₂₀ ($\mu\text{g min ml}^{-1}$)	9727 (3547)	11 798 (5004)*	1688 (994)	2314 (1828)
C _{max} ($\mu\text{g ml}^{-1}$)	136 (30)	154 (56)	36 (27)	40 (36)
T _{max} (min)	15.2 (8.2)	18.7 (12.5)	13.5 (3.7)	27.6 (22.0)
Cl/F (ml min^{-1})	3.8 (1.7)	2.4 (1.2)*	13.0 (4.4)	6.9 (3.2)*
V _{ss} /F (ml)	349.5 (263.1)	347.73 (176.1)	1331.6 (355.6)	1335.5 (531.5)
T _{1/2β} (min)	60.7 (17.5)	93.7 (56.9)	73.8 (11.8)	140.3 (58.9)*
C _{last} ($\mu\text{g ml}^{-1}$)	43 (18)	67 (29)*	7 (4)	12 (6)*

**Fig 4** Mean (bold) and individual concentration–time profiles in plasma after epidural administration of ropivacaine (50 mg) and bupivacaine (30 mg) with and without epinephrine.

and speculation. Furthermore, the effect of epinephrine on spinal and systemic concentrations of local anaesthetics has been subjected to debate in preclinical and in clinical studies. Confusion results as a consequence of various data derived either from pharmacodynamic studies^{2 12} suggesting a specific analgesic effect of epinephrine (i.e. α_2 adrenergic effect) or from pharmacokinetic studies^{10 23} based only on plasma concentrations. In this work, we report the first investigation, with a simultaneous epidural–intrathecal

microdialysis, evaluating the influence of the co-administration of epinephrine on the spinal disposition of ropivacaine and bupivacaine after epidural administration.

However, given the fact that our model requires anaesthetized animals, we could not perform a simultaneous evaluation of pharmacodynamic data on sensory and motor block, and this represents a limitation of our study. Moreover, the duration of experiment has to be limited because of the general anaesthesia (around 7 h post-

Table 5 Plasma pharmacokinetic parameters after epidural administration. * $P < 0.05$ difference between plain ropivacaine and ropivacaine with epinephrine and between plain bupivacaine and bupivacaine with epinephrine

	Ropivacaine (50 mg)		Bupivacaine (30 mg)	
	Plain	With epinephrine	Plain	With epinephrine
AUC ₀₋₁₂₀ (ng min ml ⁻¹)	6241 (2113)	5931 (2227)	3085 (1553)	2209 (977)
C _{max} (mg ml ⁻¹)	86 (49)	103 (60)	45 (21)	28 (12)*
T _{max}	13 (4)	17 (21)	13 (4)	10 (4)
Cl/F (ml min ⁻¹)	3.8 (1.8)	3.8 (1.9)	6.1 (4.8)	3.1 (1.5)*
V _{ss/F} (ml)	669 (217)	828 (352)	993 (641)	1746 (1521)
T _{1/2β} (min)	139 (79)	170 (68)	136 (54)	365 (137)*
C _{last} (mg ml ⁻¹)	34 (8)	36 (14)	18 (12)	19 (9)

implantation of the catheters) allowing only two or three consecutive injections. Since we did not know if the effect of epinephrine could be long lasting, we decided to inject first plain drug, and then the drug with epinephrine. A randomized administration would have led to a better protocol, but we did not want to take the risk that our data could be biased by epinephrine from the preceding injection. However, in the ropivacaine experiment which was performed first, we made a third injection with plain drug that showed that the epidural drug disposition returned to normal state (without epinephrine), confirming the validity of our experimental model.

Haemodynamic evaluation

There was no visual evidence of CSF leakage after intrathecal catheter insertion confirming that the intrathecal space remained closed. The lack of a systemic effect (i.e. tachycardia) of epinephrine at a dose usually used clinically (5 μg ml⁻¹) may suggest that the action of epinephrine in this animal model was located mainly in the epidural site. On the other hand, the local action of epinephrine did not lead to increased sympathetic blockade as suggested by the lack of significant haemodynamic difference with or without epinephrine for bupivacaine and ropivacaine.

Pharmacokinetic evaluation

Influence of epidurally co-administered epinephrine was similar for ropivacaine and bupivacaine, although more pronounced for the latter.

After epidural administration of ropivacaine 50 mg, the ratio between epidural AUC and intrathecal AUC was 6.3. A similar ratio (5.7) was found after the administration of 100 mg of ropivacaine²⁴ suggesting that there was no dose-effect on transmeningeal uptake ($P=0.37$).

The pharmacokinetics of epidural bupivacaine and ropivacaine were in accordance with a previous study of our group carried out in a rabbit model.²⁵ Indeed, after epidural administration, the clearance, V_{ss}, and T_{1/2β} of bupivacaine were higher than that of ropivacaine (Table 3).

The dose-normalized epidural AUC for ropivacaine was 2.3 times higher than that for bupivacaine [1230 (255) vs

532 (189) min μg ml⁻¹]. However, in the intrathecal space, the dose-normalized AUC was 3.5-fold greater for ropivacaine than for bupivacaine [195 (70) vs 56 (33) min μg ml⁻¹]. These proportions were similar when the local anaesthetics were co-administered with epinephrine, suggesting that the action of epinephrine had no intrinsic effect *per se* on transmeningeal diffusion of ropivacaine and bupivacaine.

The differences ($\times 2.3$) in the dose-normalized epidural AUC of these drugs could be explained by the difference in their diffusion into epidural fat, with a two-fold higher diffusion for bupivacaine compared with ropivacaine.¹⁴ The increase in the intrathecal dose-normalized AUC was higher ($\times 3.5$), in favour of ropivacaine. Such a difference in unbound (i.e. pharmacologically active) intrathecal concentrations may result from an increase in the epidural AUC and also from a difference in protein binding. Indeed, CSF contains acid alpha-glycoprotein and the free fraction of ropivacaine in plasma resulting mainly from binding to that protein (8.2%) is higher than that for bupivacaine (4.4%).²⁶

The influence of epinephrine on epidural drug disposition has frequently been studied by measuring plasma concentrations. However, this evaluation is indirect, and only evaluates the influence on absorption into the systemic circulation, and not absorption in the CSF. Moreover, as previously reported, the effect of epinephrine on the systemic uptake of epidural drugs is unclear.^{6 10 23 27 28}

The current evaluation of both epidural and intrathecal concentrations of local anaesthetics brings some new findings to the understanding of the mechanism of action of epidural epinephrine. After epidural administration, local anaesthetics have a low intrathecal bioavailability^{23 24 29} indicating that almost 90% of the administered dose is absorbed directly into the systemic circulation.

Our data showed that the effect of epinephrine was more pronounced on bupivacaine than ropivacaine. Indeed, the increase in epidural AUC was higher for bupivacaine than for ropivacaine (52 vs 31%) and plasma concentrations were only modified for bupivacaine, with a significant decrease in C_{max} (-37.7%) and a trend towards a decrease in AUC (-28.4% , $P=0.06$).

The differences observed between bupivacaine and ropivacaine on epidural and plasma concentrations could be explained by intrinsic vasoconstrictor properties of ropivacaine compared with bupivacaine.^{16–18} In addition, local anaesthetic action on spinal and peripheral vessels was reported to be concentration-dependent.^{17, 19} Recently, in a rat model, it was shown that the combination of ropivacaine and epinephrine did not reduce nerve blood flow to a greater extent than ropivacaine alone.¹⁹ Hence, it may be assumed that, at the concentration used in our experiment, close to that used clinically (0.33%), ropivacaine induced a vasoconstrictor effect that reduced the effect of epinephrine on its systemic uptake.

Although the increase in epidural AUC was different between ropivacaine and bupivacaine, it resulted in a proportional increase in AUC in the intrathecal space. Indeed, the increase in the intrathecal AUC was 21% for ropivacaine and 37% for bupivacaine ($P=0.07$). The increase in epidural AUC resulted from a decrease in epidural clearance and distribution (Table 3), allowing a higher uptake of ropivacaine and bupivacaine into the intrathecal space.

The current data suggest that local vasoconstriction of epidural vessels induced by epinephrine influenced the spinal pharmacokinetics of ropivacaine and bupivacaine. However, the spinal pharmacokinetics of drugs is complex and sometimes not intuitive. After epidural administration, drug fate results from different competitive processes,^{13, 25, 30} such as transmeningeal uptake into the intrathecal space, distribution into epidural fat, and uptake into the systemic circulation. In our study, epidural epinephrine led to a decrease in clearance of ropivacaine and a decrease in distribution of bupivacaine in the epidural space, leading to an increase in uptake into the intrathecal space. The impact on systemic uptake was only apparent for bupivacaine. This could result from the fact that bupivacaine is more lipophilic, and has no vasoconstrictor effect compared with ropivacaine.

For both drugs, intrathecal Cl/F decreased significantly with epidurally co-administered epinephrine (Table 4). Considering that epidural epinephrine should not influence intrathecal clearance of local anaesthetics (significant metabolism of epinephrine by meninges³¹), decreases in Cl/F (from 3.8 to 2.4 ml min⁻¹, around 60%) should reflect the increase in bioavailability (F). We have previously shown that the mean intrathecal bioavailability of epidural ropivacaine was about 11%.²⁴ Hence, intrathecal bioavailability of epidural ropivacaine administered with epinephrine could be extrapolated to 17.6%, suggesting a 60% increase in intrathecal bioavailability. Such an increase may explain the clinical improvement in onset, duration, and intensity of the sensory and motor block of epidural local anaesthetics with epinephrine.

In conclusion, the current work has shown that epidural epinephrine significantly increased the concentrations of ropivacaine and bupivacaine in the epidural space and increased their uptake into the intrathecal space. The action of epinephrine was more pronounced on

bupivacaine than ropivacaine, as a result probably of the intrinsic vasoconstrictor property of ropivacaine.

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References

- 1 Sinnott CJ, Cogswell LP III, Johnson A, Strichartz GR. On the mechanism by which epinephrine potentiates lidocaine's peripheral nerve block. *Anesthesiology* 2003; **98**: 181–8
- 2 Sakura S, Sumi M, Morimoto N, Saito Y. The addition of epinephrine increases intensity of sensory block during epidural anesthesia with lidocaine. *Reg Anesth Pain Med* 1999; **24**: 541–6
- 3 Bernards CM, Kopacz DJ. Effect of epinephrine on lidocaine clearance in vivo. A microdialysis study in humans. *Anesthesiology* 1999; **91**: 962–8
- 4 Eisenach JC, Grice SC, Dewan DM. Epinephrine enhances analgesia produced by epidural bupivacaine during labor. *Anesth Analg* 1987; **66**: 447–51
- 5 Wilson CM, Moore J, Ghaly RG, Flynn R, McClean E, Dundee JW. Plasma concentrations of bupivacaine during extradural anaesthesia for caesarean section. The effect of adrenaline. *Anaesthesia* 1988; **43**: 12–5
- 6 Hansen TG, Morton NS, Cullen PM, Watson DG. Plasma concentrations and pharmacokinetics of bupivacaine with and without adrenaline following caudal anaesthesia in infants. *Acta Anaesthesiol Scand* 2001; **45**: 42–7
- 7 Kopacz DJ, Helman JD, Nussbaum CE, Hsiang JN, Nora PC, Allen HW. A comparison of epidural levobupivacaine 0.5% with or without epinephrine for lumbar spine surgery. *Anesth Analg* 2001; **93**: 755–60
- 8 Leonard SA, Flynn R, Kelleher N, Shorten GD. Addition of epinephrine to epidural ropivacaine during labour—effects on onset and duration of action, efficacy, and systemic absorption of ropivacaine. *Int J Obstet Anesth* 2002; **11**: 180–4
- 9 Cederholm I, Anskar S, Bengtsson M. Sensory, motor and sympathetic block during 0.5 and 0.75% ropivacaine with or without epinephrine. *Reg Anesth* 1994; **19**: 18–33
- 10 Lee BB, Kee DN, Plummer JL, Karmaker MK, Wong ASY. The effect of the addition of epinephrine on early systemic absorption of epidural ropivacaine in humans. *Anesth Analg* 2002; **95**: 1402–7
- 11 Bernards CM, Shen DD, Sterlig ES, et al. Epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidural opioids (Part 2) effect of epinephrine. *Anesthesiology* 2003; **99**: 466–75
- 12 Dahl V, Hagen I, Koss KS, Nordentoft J, Reader JC. Bupivacaine 2.5 mg/ml versus bupivacaine 0.625 mg/ml and sufentanil 1 µg/ml with or without epinephrine 1 µg/ml for epidural analgesia in labour. *Int J Obstet Anesth* 1999; **8**: 155–60
- 13 Bernards CM. Epidural and intrathecal drug movement. In: Yaksh TL, ed. *Spinal Drug Delivery*. Amsterdam: Elsevier Science B.V., 1999; 239–52

- 14 Rosenberg PH, Kytta J, Alila A. Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into n-heptane, rat sciatic nerve, and human extradural and subcutaneous fat. *Br J Anaesth* 1986; **58**: 310–4
- 15 McClure JH. Ropivacaine. *Br J Anaesth* 1996; **76**: 300–7
- 16 Kopacz DJ, Carpenter RL, Mackey DC. Effect of ropivacaine on cutaneous capillary blood flow in pigs. *Anesthesiology* 1989; **71**: 69–74
- 17 Kristensen JD, Karlsten R, Gordh T. Spinal cord blood flow after intrathecal injection of ropivacaine and bupivacaine with or without epinephrine in rats. *Acta Anaesthesiol Scand* 1998; **42**: 685–90
- 18 Dahl JB, Simonsen L, Mogensen T, Henriksen JH, Kehlet H. The effect of 0.5% ropivacaine on epidural blood flow. *Acta Anaesthesiol Scand* 1990; **34**: 308–10
- 19 Bouaziz H, Iohom G, Estebe JP, Campana WM, Myers RR. Effects of levobupivacaine and ropivacaine on rat sciatic nerve blood flow. *Br J Anaesth* 2005; **95**: 696–700
- 20 Capogna G, Celleno D, Fusco P, Lyons G, Columb M. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* 1999; **82**: 371–3
- 21 Graf BM, Zausig Y, Zink W. Current status and clinical relevance of studies of minimum local-anaesthetic concentration (MLAC). *Curr Opin Anaesthesiol* 2005; **18**: 241–5
- 22 Reif S, Le Corre P, Chevanne F, Le Verge R. High-performance liquid chromatographic determination of ropivacaine, 3-hydroxy-ropivacaine, 4-hydroxy-ropivacaine and 2',6'-pipecoloxylidide in plasma. *J Chromatogr* 1998; **719**: 239–44
- 23 Van Obbergh LJ, Roelants FA, Veyckemans F, Verbeeck RK. In children, the addition of epinephrine modifies the pharmacokinetics of ropivacaine injected caudally. *Can J Anaesth* 2003; **50**: 593–8
- 24 Rose F-X, Estebe J-P, Ratajczak M, *et al.* Epidural, intrathecal pharmacokinetics and intrathecal bioavailability of ropivacaine. *Anesth Analg* 2007; **105**: 859–67
- 25 Clément R, Malinovsky J-M, Hildgen P, *et al.* Spinal disposition and meningeal permeability of local anesthetics. *Pharm Res* 2004; **21**: 707–17
- 26 McCrae AF, Westerling P, McClure JH. Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour. *Br J Anaesth* 1997; **79**: 558–62
- 27 Arthur GR, Feldman HS, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. *Anesth Analg* 1988; **67**: 1053–8
- 28 Feldman HS, Covino BG. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. *Anesth Analg* 1988; **67**: 1047–52
- 29 Clément R, Malinovsky JM, Le Corre P, Dollo G, Chevanne F, Le Verge R. Cerebrospinal fluid bioavailability and pharmacokinetics of bupivacaine and lidocaine after intrathecal and epidural administrations in rabbits using microdialysis. *J Pharmacol Exp Ther* 1999; **289**: 1015–21
- 30 Clément R, Malinovsky J-M, Hildgen P, *et al.* Spinal biopharmaceutics of bupivacaine and lidocaine by microdialysis after their simultaneous administration in rabbits. *Int J Pharm* 2000; **203**: 227–34
- 31 Kern C, Mautz DS, Bernards CM. Epinephrine is metabolized by the spinal meninges of monkeys and pigs. *Anesthesiology* 1995; **83**: 1078–81