

PHARMACOKINETICS OF INTRAVENOUS AND EPIDURAL ROPIVACAINE IN THE RHESUS MONKEY

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ABSTRACT

Ropivacaine is a new long-acting amide local anesthetic which is possibly less cardiotoxic than bupivacaine. The absorption and disposition of ropivacaine were characterized in six rhesus monkeys in an open two-way crossover study following intravenous and epidural administration. For these studies, animals were anesthetized for placement of intravenous and intraarterial catheters. For the epidural studies, a PE-10 catheter was also inserted 3 cm into the lumbar epidural space. After recovery from anesthesia, animals received ropivacaine 1 mg kg⁻¹ intravenously over 1 min or 10 mg of ropivacaine epidurally (two 1 ml doses of 0.5%, 5 min apart), and arterial blood samples were obtained over 5 h. Serum ropivacaine concentrations were determined by gas chromatography with NP detection. Concentration-time data following i.v. and epidural administration were fitted simultaneously. Initial parameter estimates were obtained by analyzing each route separately. Input rates and their corresponding extent of absorption were estimated using deconvolution.

Mean (\pm SD) disposition parameters included: $V_{ss} = 1.11 \pm 0.198$ l kg⁻¹; $CL = 0.711 \pm 0.158$ l h⁻¹ kg⁻¹; $t_{1/2,z} = 2.07 \pm 0.438$ h. Mean (\pm SD) absorption parameters included: $F_1 = 0.506 \pm 0.221$; $t_{1/2,k_{a1}} = 0.060 \pm 0.078$ h; $F_2 = 0.444 \pm 0.182$; $t_{1/2,k_{a2}} = 6.45 \pm 11.09$ h. Ropivacaine's biphasic absorption and bioavailability are similar to those of other amide local anesthetics. The biphasic absorption may be related to partitioning into fat or regional changes in blood flow induced by the drug.

KEY WORDS Ropivacaine Pharmacokinetics Ropivacaine absorption Ropivacaine disposition Ropivacaine deconvolution Ropivacaine epidural Ropivacaine primate

INTRODUCTION

Ropivacaine is a new long acting amide local anesthetic. Early *in vitro* and *in vivo* laboratory studies demonstrated a duration of sensory and motor blockade of ropivacaine similar to that of bupivacaine.^{1,2} Ropivacaine is prepared as the

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S(-) enantiomer only, unlike its cogener bupivacaine which is a racemic mixture.³ Much of the interest in ropivacaine is the result of *in vitro* and *in vivo* studies suggesting that it is less cardiotoxic than bupivacaine.³⁻⁶

Studies examining the pharmacokinetics of intravenous ropivacaine have been performed in dogs and humans.^{7,8} However, no studies have yet been performed to fully characterize the rate and extent of ropivacaine absorption following epidural administration. The purpose of this study was to investigate the absorption and disposition profile of ropivacaine in rhesus monkeys following intravenous and epidural administration.

METHODS AND MATERIALS

Six adult rhesus monkeys (*Macaca mulata*) weighing 8.1 ± 0.7 kg were studied using a two-way crossover design protocol. Animal care and use committee approval was obtained and AAALAC guidelines for the care and use of laboratory animals were followed throughout the study. The study consisted of two periods: in period 1 (i.v. study), following an overnight fast, each animal was sedated with intramuscular ketamine (10 mg kg^{-1}) and then anesthetized with $\text{N}_2\text{O}/\text{O}_2$ and halothane prior to placement of 22 g venous and PE-50 arterial catheters. All monkeys were then placed in a sitting position in a primate restraint chair and allowed 1.5 h to recover from anesthesia. After recovery from anesthesia (as evidenced by alertness and response to tactile stimuli), the animals were administered 1 mg kg^{-1} ropivacaine i.v. over 1 min. Arterial blood samples were obtained immediately prior to administration and at 5, 10, 15, 20, 30, 60, 120, 180, 240, and 300 min after administration. Blood was replaced with prewarmed normal saline at 3 ml/(1 ml blood). Following completion of the intravenous study, each primate was given a minimum 6 week rest period prior to participation in the next period of the project.

In period 2 (epidural study), each animal was anesthetized and had venous and arterial catheters placed as described for period 1. In addition, a 20 g Tuohy needle was placed in the epidural space using the loss of resistance technique at the L45 or L56 interspace. A 23 g polyethylene catheter was then inserted 3 cm into the epidural space through the Tuohy needle. Epidural catheter placement was confirmed radiographically following injection of 2 ml Omnipaque. After recovery from anesthesia, each animal received 10 mg of 0.5% ropivacaine epidurally (two 1 ml doses given 5 min apart; each dose administered over 60 s) while restrained in a sitting position. Epidural dosing was divided as a precautionary safety measure. Arterial blood samples were obtained at the same times as in period 1. Time zero following epidural administration was defined as the midpoint between the two injections. Following epidural ropivacaine, if the resulting neural blockade (as evidenced by lower extremity motor weakness) was not bilateral, animals were anesthetized after completion of the study and radiographs obtained following a 2 ml epidural injection of Omnipaque to

confirm that the catheter had remained in the epidural space throughout the data collection period.

Analytical method

Serum samples were analyzed for ropivacaine by using a two-step extraction method, followed by gas chromatography using a temperature gradient and a nitrogen-phosphorous detector.⁹ The percentage of ropivacaine by extraction was $97 \pm 2\%$ and the limit of quantitation was 10 ng ml^{-1} . The coefficient of variation at 0.5 mcg ml^{-1} was 8.7% .

Pharmacokinetic methods

The following equations were simultaneously fitted to serum concentration-time data following intravenous (C_{iv}) and epidural (C_{epi}) administrations, respectively.¹⁰⁻¹⁴

$$C_{iv} = \sum_{i=1}^n \frac{C_i}{\lambda_i \times \text{TI}} (1 - e^{-\lambda_i b}) e^{-\lambda_i t_a} \quad (1)$$

$$C_{epi} = \sum_{j=1}^k \sum_{i=1}^n \frac{K_{aj} C_i F_j D_{epi}}{(K_{aj} - \lambda_i) D_{iv}} e^{-\lambda_i (t - \text{TL}_j)} - \sum_{j=1}^k \sum_{i=1}^n \frac{K_{aj} C_i F_j D_{epi}}{(K_{aj} - \lambda_i) D_{iv}} e^{-K_{aj} (t - \text{TL}_j)} \quad (2)$$

where n is the number of exponentials necessary to characterize the serum concentration-time profile following intravenous administration; C_i is the i th coefficient; λ_i is the i th exponential corresponding to the i th coefficient; t is the time after the start of administration; TI is the duration of infusion; b is a second independent variable equal to t during the infusion and equal to TI after the infusion; t_a is the time after the end of the infusion; k is the number of absorption rate constants characterizing the input function; D_{iv} is the intravenous dose size used to determine the coefficients and exponents; D_{epi} is the epidural dose size; K_{aj} is the j th first-order absorption rate constant; F_j is the fraction of the administration dose appearing in systemic circulation corresponding to the j th absorption rate; and TL_j is the lag time for the j th absorption rate.

Initial disposition parameter estimates were obtained using curve stripping¹⁵ and subsequent non-linear regression analysis¹⁰ of the data obtained following intravenous administration. Absorption rate-time profiles were obtained by deconvolution.¹⁶⁻¹⁸ Initial estimates of the absorption rate constants were obtained by curve stripping and subsequent non-linear regression. An estimate for the overall extent of absorption was obtained by area analysis.¹¹ The extent of absorption corresponding to each absorption rate constant was estimated from the percentage of the total area under the serum concentration-time curve corresponding to each absorption rate constant. Various weightings of the observed serum concentrations (1 , $1/C^{0.5}$, $1/C$ and $1/C^2$) were used in the

data analysis. Decisions on the appropriate weighting and the number of exponentials/absorption rate constants required to characterize the serum concentration–time data were based on visual inspection of the randomness of scatter of the observed data about the fitted line and the sum of weighted squared residuals.¹⁹ Volumes of distribution, total clearance, mean residence time and terminal disposition half-life were obtained from the disposition coefficients and exponents using standard equations.^{11,20,21}

RESULTS

Ropivacaine was well tolerated in all animals following both intravenous and epidural administration. None of the animals showing unilateral motor weakness following epidural ropivacaine demonstrated any displacement of the epidural catheter on post-study radiographic analysis.

Pharmacokinetic parameters following i.v. administration of ropivacaine are summarized in Table 1. Serum concentration–time profiles following intravenous administration of ropivacaine were best described by a biexponential equation and a weighting factor of either $1/C^{0.5}$ or $1/C^2$. Mean (SD) parameters included: central volume of distribution (V_c), 0.405 (0.1189) l kg⁻¹; volume of distribution at steady state (V_{ss}), 1.111 (0.1977) l kg⁻¹; total clearance (CL), 0.7109 (0.1576) l h⁻¹ kg⁻¹; terminal phase volume of distribution ($t_{1/2,z}$), 2.066 (0.4379) h.

Table 2 summarizes the absorption parameters following epidural administration of ropivacaine. Absorption data from all animals were best characterized

Table 1. Parameters following 1 mg kg⁻¹ single dose i.v. ropivacaine in primates

Primate	Weight (kg)	Weighting method	V_c (l kg ⁻¹)	V_{ss} (l kg ⁻¹)	V_z (l kg ⁻¹)	CL (l h ⁻¹ kg ⁻¹)	MRT (h)	$t_{1/2,z}$ (h)
1	8.5	1/y	0.4471	1.147	2.513	0.9140	1.254	1.906
2	8.4	1/y2	0.4825	0.8808	1.943	0.5305	1.660	2.538
3	7.3	1/y2	0.2353	0.9487	1.955	0.8736	1.086	1.583
4	9.4	1/y	0.3679	1.113	1.792	0.7379	1.509	1.684
5	7.8	1/y	0.3285	1.128	2.366	0.6210	1.816	2.641
6	7.4	1/y2	0.5688	1.449	1.737	0.5882	2.464	2.047
Median	8.1	—	0.4075	1.121	1.949	0.6631	1.382	1.977
Mean	8.1	—	0.4050	1.111	2.051	0.7109	1.632	2.066
SD	0.8	—	0.1189	0.1977	0.3158	0.1576	0.4865	0.4379

V_c = central volume of distribution.

V_{ss} = volume of distribution at steady state.

V_z = volume of distribution during terminal phase.

CL = total clearance.

MRT = mean residence time.

$t_{1/2,z}$ = terminal phase elimination half-life.

Table 2. Parameters following 10 mg single dose epidural ropivacaine in primates

Primate	F	$t_{1/2,k_{a1}}$ (h)	F_1	$t_{1/2,k_{a2}}$ (h)	F_2
1	0.8006	0.0518	0.3494	2.2573	0.4512
2	0.8444	0.0275	0.7211	28.4483	0.1233
3	1.2973	0.2163	0.7047	7.1940	0.5926
4	1.1285	0.0361	0.6944	0.5594	0.4341
5	0.6929	0.0052	0.2747	0.1508	0.4182
6	0.9376	0.0239	0.2941	0.2540	0.6435
Median	0.8191	0.0318	0.5215	1.408	0.4425
Mean	0.950	0.060	0.506	6.477	0.444
SD	0.225	0.078	0.221	11.089	0.182

F = Overall extent of bioavailability.

$t_{1/2,k_{a1}}$ = half-life of absorption corresponding to first phase.

$t_{1/2,k_{a2}}$ = half-life of absorption corresponding to second phase.

F_1 = extent of absorption corresponding to first phase.

F_2 = extent of absorption corresponding to second phase.

by biphasic absorption. Mean (SD) bioavailability following epidural administration of ropivacaine was 0.950 (0.225). Absorption rate parameters indicated that approximately 50% of ropivacaine is absorbed during an initial phase of rapid absorption (mean $t_{1/2,k_{a1}} = 0.03$ h) and 50% is absorbed during a subsequent slower phase (mean $t_{1/2,k_{a2}} = 6.5$ h).

Representative serum concentration-time profiles following i.v. and epidural administration are illustrated in Figures 1 and 2.

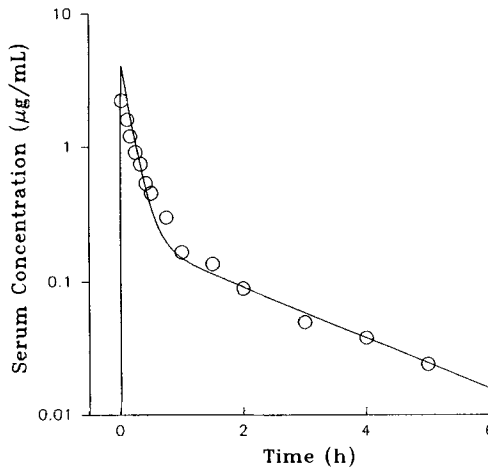


Figure 1. Observed and predicted serum concentration-time curves for ropivacaine following intravenous administration in primate 3

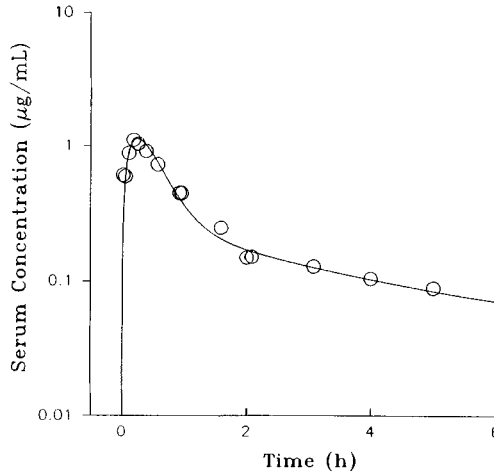


Figure 2. Observed and predicted serum concentration-time curves for ropivacaine following epidural administration in primate 3

DISCUSSION

Ropivacaine is a long acting local anesthetic currently undergoing clinical trials for epidural and perineural administration in humans. Using equivalent doses, the neural blockade produced by ropivacaine in humans has been found to be similar in onset and duration to that of the currently used long acting local anesthetic, bupivacaine.^{22,23} Interest in ropivacaine, however, is based on data demonstrating it to be less cardiotoxic than bupivacaine.^{4,6} Studies in pigs and rabbits showed higher serum concentrations of ropivacaine were required relative to bupivacaine to produce changes in cardiac conduction and contractility.^{4,24}

The primate model was chosen for this study in part because of previous literature using this model.^{25,26} It was also believed that the general structure of the primate spinal canal more closely resembles that of man relative to other species, so absorption of drugs from the epidural space would also better correlate to man. While distribution and elimination half-lives correlate well between primate and man, a higher clearance in the primate of intravenous lidocaine (and probably other local anesthetics) is due to the higher basal heart rate in the primate of about 200 beats min^{-1} , while differences in volume of distribution have been previously observed for local anesthetics when performing interspecies comparisons.²⁵

The method of parameter determination in the present study differs from that of most other studies of extravascular drug uptake. Disposition parameters are commonly estimated by analyzing only the data following intravenous administration. Absorption is then estimated either by fitting an empirical equation to the serum concentration-time profile following extravascular

administration or by using deconvolution and disposition parameters to estimate both the rate and extent of absorption. However, since both intravenous and epidural data contain information on disposition, data from both routes of administration in the present study were simultaneously fitted in order to obtain a better estimation of the pharmacokinetic parameters.

Previous studies of local anesthetics in the primate allow comparison to the present primate data regarding ropivacaine. Following intravenous administration, ropivacaine demonstrated a clearance and MRT similar to that following intravenous administration of bupivacaine in the primate.²⁶ However, compared to bupivacaine, ropivacaine's larger V_{ss} with its similar serum protein binding suggests more extensive tissue binding of ropivacaine. Following epidural administration of lidocaine in primates and of lidocaine and bupivacaine in humans, other studies have shown complete absorption of both drugs.²⁵⁻²⁷ The present study also demonstrated complete absorption of ropivacaine following epidural administration in primates as evidenced by the high bioavailability. There are no studies published of which we are aware that have examined the pharmacokinetics of bupivacaine in the primate following epidural administration, but a study of the absorption of epidurally administered lidocaine in primates has demonstrated a biphasic pattern of absorption similar to that observed in the present study—an initial period of relatively rapid absorption followed by a second phase of slower absorption.²⁸

The present intravenous data were compared to those of previous studies of intravenous ropivacaine in humans. Following a single dose of intravenous ropivacaine in human volunteers, the elimination $t_{1/2}$ was 111 min, similar to the 118 min $t_{1/2,z}$ found in the present study following intravenous administration of ropivacaine.⁷ The human data also demonstrated a $V_{d,ss}$ of 59 l versus about 9 l in the present study.⁷ The large difference in $V_{d,ss}$ could be the result of differences in body fat content between humans and primates.

The present epidural data were then compared to data obtained in humans following epidural administration of ropivacaine. In a human study examining the absorption of ropivacaine following epidural administration, MRT was found to decrease as the ropivacaine dose increased.²⁹ Although no data following intravenous ropivacaine administration were obtained in that study, that finding was believed to be due to data from two subjects receiving the lowest dose in which significantly slower absorption contributed to the increased MRT compared to the other subjects.²⁹ Similar variability in epidural absorption between subjects was seen in the present study, with one group of primates showing a $t_{1/2,k_2}$ of less than 1 h and another group with $t_{1/2,k_2}$ of notably larger values. Human studies of epidural absorption of ropivacaine required the utilization of both bi- and triexponential equations to describe the serum concentration-time profiles, while the present study demonstrated biphasic absorption and disposition in all animals, thus requiring a quad-exponential equation to describe epidural absorption.³⁰ However, the human study did not include intravenous administration, which would allow separation of absorption

and disposition parameters. It is also possible in the human study that a vanishing exponent existed in subjects apparently demonstrating monophasic absorption.³¹

In comparing the present primate ropivacaine data to pharmacokinetic studies of absorption and disposition of other local anesthetics in humans (lidocaine, bupivacaine, and etidocaine) following epidural administration, all have shown a biphasic pattern of absorption as observed in the present study.^{32,33} Veering *et al.* recently characterized the biphasic absorption profile of epidurally administered bupivacaine in human subjects.³⁴ Mean (SD) F_1 was 0.2716 (0.0254) and F_2 was 0.6574 (0.0397) while $t_{1/2, k_{a1}}$ was 8.1 (0.9) min and $t_{1/2, k_{a2}}$ was 326 (19) min. Their data indicate a greater fraction of bupivacaine absorbed during the second, slower phase while the present study in primates demonstrates that ropivacaine has a greater fraction absorbed during the initial rapid phase. Assuming that the primate model is appropriate for humans, two possible explanations for differences in the biphasic pattern of absorption between ropivacaine and bupivacaine can be proposed. The first is based on the observation that local anesthetics produce regional vascular changes in the area to which they are administered.³⁴ Bupivacaine in high doses, such as those used in epidural anesthesia, is likely to produce vasodilatation, while decreased epidural blood flow following epidural ropivacaine has been demonstrated in humans.³⁵ Based on those findings, bupivacaine might, therefore, be expected to demonstrate a greater degree of absorption during the first rapid absorption phase than ropivacaine, a pattern which was not found in the present study. We are unaware of any studies of epidural blood flow in primates following epidural administration of ropivacaine. Another possible explanation for the differences in epidural absorption between bupivacaine and ropivacaine is based on local anesthetic partitioning into fat. Possibly as a result of the large amount of fat in the epidural space, local anesthetics with lower lipid solubilities are absorbed more quickly than those with higher lipid solubilities. Lidocaine, for example, has less contribution from the slow absorption phase than the more lipid soluble bupivacaine.³⁶ Ropivacaine's lipid solubility is about half that of bupivacaine, so absorption from the epidural space might be expected to be more dependent on the initial rapid absorption phase than for bupivacaine, which is consistent with the results in the present study.³ It might be proposed, then, that lipid solubility plays a greater role in determining the absorption profile of local anesthetics from the epidural space than local vascular changes induced by the anesthetics.

While these data imply that systemic uptake of ropivacaine from the epidural space may be faster than that of bupivacaine, studies in humans demonstrate no clinically significant differences in duration of sensory blockade nor in peak serum concentrations achieved when similar doses of epidural ropivacaine and bupivacaine are given.²⁹

In summary, ropivacaine has pharmacokinetic profiles following i.v. and epidural administration in the monkey which are similar to those of other local

anesthetics. Intersubject variability in the absorption of ropivacaine is probably the result of either variability in regional blood flow changes induced by the local anesthetic or variability in the amount of epidural fat.

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