Systemic Absorption and Block after Epidural Injection of Ropivacaine in Healthy Volunteers

Britt-Marie K. Emanuelsen, M.Sc. Pharm., Ph.D.,¹ Jan Persson, M.D.,† Christina Alm, R.N.,‡ Agneta Heller, R.N.,† Lars L. Gustafsson, M.D., Ph.D. ‡

Background: For local anesthetics, the process of removal from the site of administration influences the duration of anesthesia and the risk for systemic toxicity to develop. The systemic absorption of epidural ropivacaine and the time profile of sensory and motor block were studied in healthy volunteers.

Methods: Nine persons simultaneously received 150 mg ropivacaine hydrochloride (7.5 mg/ml) epidurally and 40 mg deuterium-labeled ([1H₆]ropivacaine hydrochloride (0.25 mg/ml) intravenously. Peripheral arterial and venous plasma samples were collected, and assessments of sensory and motor block were made.

Results: The arterial plasma concentrations increased faster than the venous concentrations, with 50% higher maximum concentrations after both intravenous and epidural administration. The absorption was biphasic. A correlation was seen between the duration of sensory block and the slower absorption half-life; that is, the longer the half-life, the longer the duration. The extent of spread varied among the volunteers, with the median upper block level not exceeding T12. The motor block (Bromage score 1) was of slower onset (median, 0.4 h) and of shorter duration (median, 4.1 h) than the sensory block (onset, 0.2 h; duration, 6.5 h at 1.2 medians).

Conclusions: As much as 50% differences were seen in the arteriovenous plasma concentrations of ropivacaine during the first hour, which has implications for the interpretation of systemic toxic plasma concentrations. The absorption into the general circulation was biphasic, with a correlation between the sensory block and the slower absorption half-life. A faster onset and a longer duration of sensory compared with motor block was seen. (Key words: Anesthesia, epidural ropivacaine. Pharmacokinetics: disposition; elimination; isotope technique.)

FOR local anesthetics, the process of removal from the tissues at the site of administration governs the duration of sensory and motor block and the risk for adverse events to develop. Even though the most common reason for systemic toxicity is accidental intravascular injections, the potential for these drugs to elicit systemic side effects (at correct administration) will be influenced by the rate of absorption and the disposition (distribution and elimination). In general, the tolerability threshold decreases with increased injection rate,¹ such that intravenous injection can be thought of as an instantaneous absorption. Large arteriovenous concentration differences have been observed,² which have implications for the interpretation of systemic drug concentrations and for effects on the central nervous system. Arterial concentration is considered to be the best indicator of the drug concentration at the sites of toxicity in well-perfused organs.

The aim of the present study was to examine the systemic absorption (rate and extent) and the disposition of the new local anesthetic ropivacaine³⁻⁶ after epidural administration and to determine how these factors relate to the blockade. Although no surgery was performed as healthy volunteers were included, the time profile of the sensory and motor block was assessed. Because no difference has been shown in the disposition of the isotope-labeled and the unlabeled forms of ropivacaine,⁷ using stable isotopes made it possible to do a two-arm crossover study as a single procedure,⁸ thereby avoiding intraindividual variation, which is a drawback in classical longitudinal studies.
Materials and Methods

Study Design
This was an open study, with a simultaneous crossover design involving nine men, aged 24-43 yr, with body weights ranging from 70-95 kg. They were judged healthy based on the results of a routine physical examination, laboratory screening, and electrocardiogram. The study was approved by the ethics committee at Huddinge Hospital, Karolinska Institutet, Huddinge, Sweden, and all volunteers gave their written informed consent.

A total dose of 190 mg ropivacaine hydrochloride was given as 150 mg ropivacaine hydrochloride 7.5 mg/ml by the epidural route and 40 mg (3H)ropivacaine hydrochloride 0.25 mg/ml by the intravenous route. (3H)ropivacaine hydrochloride (molecular weight, 313.9) is similar to ropivacaine hydrochloride (molecular weight, 310.9), except for the substitution of hydrogen with deuterium on a CH3 group on the xylidine ring, resulting in a C2H group. The administration of unlabeled and labeled ropivacaine started simultaneously as a 5-min epidural infusion and a 30-min intravenous infusion, respectively. A 30-min infusion time for the intravenous dose was chosen based on previous clinical experience showing that adverse reactions occur at higher infusion rates/plasma concentrations and pharmacokinetic simulations. A Harvard apparatus syringe pump 92 was used for the intravenous infusion, and the epidural infusion was administered manually by the same anesthesiologist throughout the study. The volunteers were recumbent during administration and the ensuing 7 h or longer if necessary because of sensory or motor block.

The epidural puncture was performed in the morning, starting with skin infiltration using 2 ml prilocaine infused at 10 mg/ml (Citanest; Astra, Södertälje, Sweden), and the epidural block was initiated with a 16-gauge Tuohy needle at the L2-L3 interspace. The midline approach with the volunteer in the lateral decubitus (left) position was used and the epidural space was identified using the loss-of-resistance technique with saline. Provided that neither cerebrospinal fluid nor blood was obtained on aspiration, 20 ml ropivacaine was given as a continuous infusion through the 16-gauge Tuohy needle fixed by the anesthesiologist during the infusion period. The rate of infusion was 4 ml/min over 5 min; that is, 30 mg/min. The patient was then turned to the supine position. The deuterium-labeled (3H)ropivacaine hydrochloride at 2.5 mg/ml was diluted to 0.25 mg/ml (range, 0.229 to 0.253 mg/ml; please refer to the assay method below) with saline just before the start of the intravenous infusion, which was given at a constant rate of 1.3 mg/min (5.3 ml/min) over 30 min. Each volunteer received 160 ml solution, corresponding to total doses of 36.6 to 40.5 mg (3H)ropivacaine hydrochloride. All participants had fasted, and before the induction of anesthesia 300 ml Ringer-acetate solution was given intravenously. After the participants were turned to the supine position, their legs were placed on a "psoas leg rest," in which 90° flexion in the hips and knees was maintained to decrease the risk of hypotension.

Blood Samples and Assays
Peripheral arterial and venous blood samples were simultaneously taken for 8 h after the start of the infusions, although venous blood sampling continued for 30 h. The venous blood samples were collected from an antecubital vein in the arm contralateral to that used for intravenous infusions ((3H)ropivacaine and crystals) just before the start of the infusions (blank) time = 0, and 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 min and 2, 3, 4, 6, 8, 10, 12, 22, 24, and 30 h after the start of the infusions. The arterial blood samples were taken from the radial artery in the same arm as the venous samples, using a catheter inserted under local anesthesia (<2 ml prilocaine 10 mg/ml). The catheter was flushed continuously under pressure with physiologic saline at a rate of 3 ml/h. In the sampling procedures, the first 0.5 ml of blood was discarded to avoid contamination or dilution from the previous sample or saline. The venous and arterial blood samples were taken at exactly the sampling times (drawn by two nurses).

Assays of ropivacaine base and (3H)ropivacaine base in plasma as well as the (3H)ropivacaine hydrochloride concentration in the injected solutions were made using gas chromatography and chemical ionization mass-spectrometry. 9 The limits of quantification were set at 9 μg/l for both ropivacaine and (3H)ropivacaine, with an inter-assay coefficient of variation of 12% at 300 μg/l.

Clinical and Safety Assessments
Assessments of the sensory and the motor block were made frequently during the first hour (at 2, 5, 10, 15, 20, 25, 30, 40, 50, and 60 min) after the start of the drug infusions and then every 30 min until the block

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had worn off. Upper and lower (down to dermatome S2) spread of sensory analgesia was assessed by pin-prick testing using a short bevel needle to test for loss of sharp sensation. Motor blockade was assessed according to a modified Bromage scale with 0 = no paralysis (full flexion of knees and feet), 1 = inability to raise the extended leg (but able to move knees), 2 = inability to flex the knee (able to flex the ankle joint) and 3 = inability to move the lower limb (unable to flex the ankle joint or knee). All assessments of sensory and motor block were performed by the same examiner.

In the safety evaluation, cardiovascular effects were monitored over time. To avoid effects of urinary retention, the urinary bladder was palpated repeatedly (until spontaneous micturition occurred). If necessary, catheterization was to be performed. Throughout the study, the volunteers were asked nonspecifically whether they were experiencing any adverse events.

Pharmacokinetic Calculations
All the pharmacokinetic calculations were performed on individual data. The arterial and venous plasma concentrations of ropivacaine (R) and (H)ropivacaine ([H]-R) were characterized by the maximum plasma concentration and the time at which the maximum plasma concentration occurred. The terminal half-life (t1/2) was calculated from the terminal slope by linear regression. The total plasma clearance and the total apparent plasma clearance were calculated as clearance = dose/area under the curve (AUC) after intravenous and epidural administration, respectively. The AUC was calculated as the total area under the plasma concentration-time curve, using the linear trapezoidal rule up to the last data point plus the residual area up to infinity calculated by integration. The fraction of dose absorbed into the general circulation (F) was calculated by comparing dose-corrected areas using the equation

\[ F = \frac{AUC_d}{AUC(\text{H})} \cdot \frac{\text{dose}(\text{H})}{\text{dose}_d} \]

F as a function of time after the epidural administration (based only on venous plasma data) was also determined using point-area deconvolution as described by Igla et al.\(^\text{10}\). The intravenous disposition data of (H)ropivacaine, used in the deconvolution procedure, were obtained from the best fits in compartmental analysis, using the nonlinear regression program PCNONLIN, version 4.2.\(^\text{11,12}\) Assuming first-order absorption, a biexponential function was fitted to the obtained absorption rates versus time data, using least-squares nonlinear regression analysis, to calculate the absorption half-lives (t1/2,1, t1/2,2). The calculated AUC represents the total fraction absorbed into the general circulation, where f1 and f2 are the fractions absorbed during the initial phase and the second phase, respectively.

The volume of distribution at steady state (Vss) was estimated for (H)ropivacaine using the equation

\[ V_{ss} = \left( \frac{(k_0 \cdot T \cdot \text{AUMC})/\text{AUC}^2}{(k_0 \cdot T^2)/2 \cdot \text{AUC}} \right) \]

where k0 is the infusion rate, T is the infusion time, and AUMC is the area under the first-moment curve calculated by the linear trapezoidal rule up to the last data point and the residual area by integration.

The doses of ropivacaine base, 152.4 mg, and (H)ropivacaine base, 32.4 to 35.8 mg, corresponding to 150 mg ropivacaine hydrochloride and 36.6 to 40.5 mg (H)ropivacaine hydrochloride, respectively, were used to calculate clearance, total apparent plasma clearance, and Vss.

Evaluation of Sensory and Motor Block
The time of onset and the duration of sensory block and motor block, defined as a motor block score of 1 (or above 1, 2, or 3) on the modified Bromage scale, were calculated from the start of the epidural infusion of ropivacaine.

Statistics
The basic pharmacokinetic parameters are expressed as means ± SD. The differences in the pharmacokinetics based on arterial and venous drug concentrations and between ropivacaine and (H)ropivacaine were estimated by calculating 95% confidence intervals (CI) based on the Wilcoxon signed-rank statistic.\(^\text{13}\) Sensory block and motor block were analyzed using descriptive graphs.

Results
Figure 1 shows the mean venous and arterial plasma concentration-time profiles of (H)ropivacaine and ropivacaine. The arterial plasma concentrations increased faster than the venous concentrations, with higher levels detected in the samples taken up to about 60 min after the start of drug administration. The arterial and venous plasma levels at that time reached equilibrium, with the venous...
plasma levels thereafter being slightly higher than the arterial ones and the concentrations declining in parallel over time. The arteriovenous concentration differences after the epidural administration were smaller than the differences after the intravenous infusion.

Disposition
The highest mean arterial and venous plasma concentrations of \(^1\text{H}_2\)ropivacaine after intravenous administration were determined to be 1.3 and 0.8 mg/L, respectively (table 1). The highest arterial levels were seen at the end of the infusion, whereas the highest venous plasma levels occurred at 15–40 min, although the infusion lasted for 30 min (table 1). In one participant only the highest venous level was found in the sample taken at the end of the infusion. The elimination \(t_{1/2}\) was calculated to be about 1.7 h, regardless of whether venous or arterial plasma concentrations were used (fig. 1, table 1). The calculated clearance was nearly the same whether based on venous (313 ml/min) or arterial (338 ml/min) plasma concentrations (table 1). The 95% CI for a difference between arterial and venous clearance was 2.5 to 53 ml/min. The mean \(V_w\) was lower when estimated from arterial plasma data, at 36 l, than from venous concentrations, at 43 l (table 1). The 95% CI for a difference between arterial and venous \(V_w\) was $-12$ to $-2$ l.
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Table 1. Pharmacokinetic Characteristics of Ropivacaine after Simultaneous Administration of 40 mg (1H1)Ropivacaine Intravenously (i.v.) and 150 mg Ropivacaine Epidurally

<table>
<thead>
<tr>
<th></th>
<th>(1H1)Ropivacaine (i.v.)</th>
<th>Ropivacaine (epidural)</th>
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<tbody>
<tr>
<td></td>
<td>Venous</td>
<td>Arterial</td>
</tr>
<tr>
<td>C_max (mg/L)</td>
<td>0.82 (0.19)</td>
<td>1.27 (0.17)</td>
</tr>
<tr>
<td>t_max (min)</td>
<td>25 (15–40)</td>
<td>30 (25–30)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.7 (0.3)</td>
<td>1.8 (0.6)</td>
</tr>
<tr>
<td>CL (ml/min)</td>
<td>313 (83)</td>
<td>338 (100)</td>
</tr>
<tr>
<td>CL/F (ml/min)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>V_d (L)</td>
<td>43 (8)</td>
<td>36 (4)</td>
</tr>
<tr>
<td>F (%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>t1/2,kat (min)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>t1/2,ks2 (hr)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>f Kat</td>
<td>—</td>
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<td>f ks2</td>
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C_max = maximum total plasma concentration; t_max = time at which C_max occurred; t1/2 = terminal half-life; CL = total plasma clearance; CL/F = apparent plasma clearance; V_d = volume of distribution at steady state; F = fraction of dose absorbed into the general circulation; t1/2, Kat and t1/2, KS2 = fast and slow absorption half-life; f Kat and f KS2 = fractions absorbed during the fast and slow absorption phases.

* Median (range).
† Calculated by deconvolution.

Absorption

The mean arterial and venous maximum plasma concentration after the epidural administration of ropivacaine were determined to be 1.6 and 1.1 mg/L, respectively, at the maximum plasma concentration times of 20 and 25 min (median; table 1). The terminal t1/2 was calculated to be about 4.3 h from both the venous and the arterial plasma concentrations (fig. 1, table 1). The apparent clearance was calculated to be about 360 ml/min, regardless of whether venous or arterial plasma concentrations were used (table 1). The extent of systemic absorption of ropivacaine was 98% and 87% when calculated from total arterial and venous AUCs, respectively. The 95% CI for a difference in the arterial and venous calculations was 3–17%. Based on venous data, the cumulative fraction absorbed into the general circulation was also calculated by deconvolution to be 84% (fig. 2, table 1). The systemic absorption was biphasic and was well described by two parallel first-order rate processes, initially a fast phase, t1/2, Kat = 14 min, followed by a slower phase, t1/2, KS2 = 4.2 h. The fractions of the dose absorbed (fig. 2) during the different phases were f Kat = 0.52 and f KS2 = 0.48, respectively (table 1).

Sensory and Motor Block

The segmental spread of the sensory block was symmetrical in all participants, with a median upper block level at T11 at 1–2 h. Some participants had a sensory block up to T6 to T8 during the initial hours only. The time to onset (loss of sharp sensation) was 5–20 min

Fig. 2. Individual (n = 9) cumulative fractions of ropivacaine absorbed into the general circulation as a function of time after 150 mg given epidurally. Calculation based on venous plasma data. (Inset) Cumulative fractions absorbed during the first 60 min after start of drug administration.
at the dermatomes where the needle was placed (L2/L3) during the epidural infusion (fig. 3A), and it was longer at more rostral dermatomes. The duration of sensory block at L2 (fig. 3B) varied from 4–8 h (median, 6.5 h) and was slightly lower at the L1 level. Figure 4 shows that the duration of the sensory block at L3 is a function of the slow absorption phase half-life (t1/2,ka,2), with a calculated correlation coefficient of 0.37. A motor block score of 31 was obtained in both legs for all participants within 15–40 min (figs. 3C and 3D). A complete motor block (Bromage score 3) was not established until 40–90 min after the start of the epidural infusion and was seen in six of the nine participants. The duration of motor block was 3–6 h (median, 4 h).

Safety
Blood pressure and heart rate were stable during the actual treatment period for all volunteers (fig. 5). Spontaneous micturition occurred in all of them, and none needed to be catheterized. The volunteers reported no adverse events related to systemic concentrations of ropivacaine/\(^{2}H_{1}\) ropivacaine.

Discussion
Local anesthetics do not depend on the general circulation for transport to their sites of action as in the case of most other drugs, such as general anesthetics.
Fig. 4. Individual data on duration of sensory block at dermatome L3 (site of injection, L2/L3) as a function of the slow absorption half-life (t_{1/2ka2}); correlation coefficient = 0.37.

However, the systemic uptake is largely responsible for the duration of the local anesthetic when used in regional anesthesia and for determining the risk of systemic toxicity that is of concern in clinical practice. In the present study, the absorption of ropivacaine from the epidural space into the general circulation was biphasic, with an initial rapid phase (t_{1/2ka1}=14 min) followed by a slower phase (t_{1/2ka2}=4.2 h). Biphasic absorption previously was reported for bupivacaine, lidocaine, and etidocaine, and Katz et al. recently reported the same for ropivacaine after epidural administration in monkeys. All plasma concentrations were less than the maximum tolerated total arterial plasma concentration of 4.3 mg/l (range, 3.4 to 5.3 mg/l) ropivacaine. In a similar study using 102 mg epidural bupivacaine (over 20 s), a mean venous maximum plasma concentration of 0.73 mg/l was determined, which is comparable to our results considering the difference in dose. However, bupivacaine was given more rapidly, which probably increased its peak concentration. Peak plasma concentrations after epidural administration have been reported to be higher after ropivacaine compared with bupivacaine in patients but not in volunteers.

It is noteworthy that we found a correlation between the duration of sensory block and the t^{1/2} of the slower absorption phase (fig. 5). We found a median duration of the sensory block of 6.5 h and 5 h at the L2 and L1 interspaces, respectively, and a shorter duration of the motor block. The median duration of a motor block corresponding to a Bromage score of 1 was 4 h. Our results correspond with those of many studies of patients showing a shorter duration of the motor than the sensory block after epidural administration of ropivacaine. We found a twofold variation in the duration of both sensory and motor block. One factor responsible for the variability in duration is probably the differences in the rate of absorption of ropivacaine from the epidural space. Our group of healthy volunteers was homogeneous and it is likely that the variability in duration would be more pronounced in patients. Our results show how the duration of an epidural block using ropivacaine can be reflected by the rate of absorption from the epidural space. The limited spread of sensory block that we found, with most of the volunteers not achieving a level sufficient for lower abdominal surgery, requires comment. First, our volunteers were quite young, a factor that per se entails a more limited spread. Second, our rate of epidural injection, 5 min, was considerably slower than in most other studies.

Fig. 5. Individual systolic and diastolic blood pressure measured during the first 4 h after the start of administration of 40 mg (1L) ropivacaine given intravenously and 150 mg ropivacaine given epidurally. The data for each volunteer are connected by straight lines.
and certainly slower than in a clinical setting. A slow injection would be expected to generate a lower pressure, which could also limit the spread. Compared with results presented by Finucane et al., our results were similar in the extent of spread of the sensory block, although our dose was 20% lower and our injection time was 2 min longer (the age was in the same range). Their variation in onset time and duration for both sensory and motor block also corresponded to with our results.

The absorption t½ of 4.2 h corresponds well with the terminal t½ of 4.3 h of ropivacaine after epidural administration, indicating that absorption is the rate-limiting step in the elimination. The elimination t½ after the intravenous dose was 1.7 h. The discrepancy between Fven and Farter was unexpected, although F estimated by deconvolution tends to be slightly underestimated.

It is well known from lidocaine, etidocaine, and bupivacaine and from earlier studies with ropivacaine that whole blood concentrations are not interchangeable with plasma concentrations of the drug. A-V differences are also known to occur, as was also seen in this study, especially during the first hour after the start of the infusions. In the terminal phase, when the A-V differences were in equilibrium and the venous concentrations were slightly higher than the arterial ones, the concentrations decreased in parallel with time. A larger ratio of arterial and venous plasma concentrations was seen after the intravenous infusion of (3H)ropivacaine compared with the arterial/venous ratio after the epidural administration of ropivacaine, which corresponds to results reported in the literature. Because the arterial blood carries the drug to body organs and is related to side effects, it would be more logical to use arterial than venous concentrations (obtained from poorly perfused sampling tissues) before distribution equilibrium has been reached. These concentrations would give insight in the relation of toxic reactions of local anesthetics and plasma concentrations. However, from an ethical and practical point of view, arterial blood samples were only collected for 8 h, and later no arteriovenous concentration differences would be expected. However, it should be remembered that the free concentration of the drug crosses membranes and is biologically active and thus should be correlated with systemic effects.

The Vmean, a measure of the extent of distribution, is expected to be overestimated when calculated from venous plasma data for a drug with known arteriovenous concentration differences. The estimate of clearance is, however, expected to be independent of whether it is calculated from venous or arterial plasma data, although a difference was seen in the present study. This may be explained by different sampling periods for arterial and venous blood, which may have influenced the calculations due to different sizes of extrapolated AUC.

The estimated clearance of about 320 ml/min after intravenous administration is less than reported previously, about 500 ml/min, but is of the same magnitude as the apparent clearance after epidural administration. One possible reason for a lower clearance in volunteers with an epidural block might be a consequence of the hemodynamic effect of the block per se. Splanchnic flow resistance has been reported to increase and blood flow to decrease during an epidural block, entailing a decreased hepatic blood flow and a decreased clearance. Ropivacaine is, however, classified as an intermediate clearance drug, which means that decreases in hepatic blood flow probably cannot be the only reason for this decrease in clearance. The decrease in hepatic blood flow may have consequences for the clearance/elimination of high-clearance drugs in connection with continuous epidural infusions or intermittent administration of local anesthetics.

Conclusions

Arteriovenous differences were seen after both intravenous and epidural administration, with equilibrium reached about 1 h. The absorption of ropivacaine into the general circulation after the epidural administration was biphasic, with a rapid initial phase followed by a slower phase. A correlation was seen between the duration of sensory block and the slow absorption t½. The interindividual variation in the extent of spread was large, and the upper block level was low in most participants. The motor block was of slower onset and duration than the sensory block. The clearance of (3H)ropivacaine given intravenously was comparable with the apparent clearance estimated after epidural administration.

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References

21. Finucane BT, Sandler AN, McKenna J, Reid D, Milner A, Friedlander M, Musyka D, O’Callaghan-Enright S, Chan V: A double-blind comparison of ropivacaine 0.5%, 0.75%, 1.0% and bupivacaine 0.5% injected epidurally, in patients undergoing abdominal hysterectomy. Can J Anaesth 1996; 43: 442–9

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