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Arterial and Venous Pharmacokinetics of Ropivacaine with and without Epinephrine after Thoracic Paravertebral Block

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Background: **Animal and volunteer studies indicate that ropivacaine is associated with less neurologic and cardiac toxicity than bupivacaine. Ropivacaine may offer advantages when used for thoracic paravertebral block. This study was designed to describe the pharmacokinetics of ropivacaine after thoracic paravertebral block.**

Methods: **Twenty female patients undergoing elective unilateral breast surgery were randomly assigned to receive a single bolus thoracic paravertebral injection of 2 mg/kg ropivacaine, with or without 5 μg/ml epinephrine. Simultaneous arterial and venous blood samples were obtained for plasma ropivacaine assay. Data were analyzed with NONMEM, using two possible absorption models: conventional first-order absorption and absorption following the inverse gaussian density function.**

Results: **Epinephrine reduced the peak plasma concentrations and delayed the time of peak concentration of ropivacaine in both the arterial and venous blood. The time course of drug input into the systemic circulation was best described by two inverse gaussian density functions. The median bioavailability of the rapid component was approximately 20% higher when epinephrine was not used. The mean absorption times were 7.8 min for the rapid absorption phase and 697 min for the slow absorption phase, with wide dispersion of the absorption function for the acute phase. The half-time of arterial–venous equilibration was 1.5 min.**

Conclusion: **The absorption of ropivacaine after thoracic paravertebral block is described by rapid and slow absorption phases. The rapid phase approximates the speed of intravenous administration and accounts for nearly half of ropivacaine absorption. The addition of 5 μg/ml epinephrine to ropivacaine significantly delays its systemic absorption and reduces the peak plasma concentration.**

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THORACIC paravertebral block produces ipsilateral somatic and sympathetic nerve blockade in multiple contiguous thoracic dermatomes and is effective for anesthesia and analgesia for unilateral surgical procedures in the thorax or abdomen.[1] Bupivacaine is the local anesthetic most commonly used.[1] When a continuous thoracic paravertebral infusion of bupivacaine is used for postoperative analgesia, there is systemic accumulation of bupivacaine,[2,3] and plasma concentrations may exceed the putative safe level (2–4.5 μg/ml) with potential for systemic toxicity. Ropivacaine is a new long-acting amino-amide local anesthetic agent with a chemical structure similar to that of bupivacaine. Ropivacaine has been safely used for nerve blockade *via* different routes, including thoracic paravertebral block.[4] When injected epidurally, ropivacaine produces sensory blockade comparable to that produced by bupivacaine, but the motor blockade is less intense and shorter in duration.[5] Animal and volunteer studies indicate that ropivacaine is safer than bupivacaine in term of its neurologic and cardiac toxicity profile.[6–8] Ropivacaine may therefore offer advantages when used for thoracic paravertebral block. There are no published data describing the pharmacokinetics of ropivacaine after thoracic paravertebral block. We performed this prospective, randomized study to determine the pharmacokinetics of ropivacaine after a single bolus thoracic paravertebral injection and to evaluate whether the addition of epinephrine to ropivacaine had any effect on its pharmacokinetics.

Materials and Methods

After approval from the clinical research ethics committee of the Chinese University of Hong Kong (Hong Kong) and written, informed consent, 20 adult female patients with American Society of Anesthesiologists physical status classifications of I or II, aged younger than 75 yr, scheduled to undergo elective unilateral breast surgery during general anesthesia combined with a thoracic paravertebral block, were randomized by drawing shuffled, coded, opaque envelopes (20 envelopes) to receive a single-bolus thoracic paravertebral injection of 2 mg/kg of either ropivacaine (ropivacaine hydrochloride, 10 mg/ml; AstraZeneca, Södertälje, Sweden) without epinephrine (n = 10) or ropivacaine with epinephrine 1:200,000 (n = 10) diluted in a total volume of 20 ml with normal saline. Patients with known allergy to local anesthetics, infection at the site of block place-

ment, preexisting neurologic or muscular disease, bleeding tendency or evidence of coagulopathy, or deranged liver or renal function were excluded from the study.

Patients fasted preoperatively and were premedicated with 7.5 mg oral midazolam. When patients were in the anesthetic room, routine monitoring was instituted. After local anesthetic infiltration (1% lidocaine), the cubital vein and the radial artery contralateral to the side of the proposed surgery were cannulated using 16- and 20-gauge intravenous cannulas, respectively, to facilitate simultaneous arterial and venous blood sampling for plasma total ropivacaine assay. An intravenous infusion of 0.9% normal saline was commenced *via* the indwelling intravenous cannula, and approximately 500 ml was administered in the time (approximately 15–20 min) until just before the thoracic paravertebral injection. The intravenous infusion was then discontinued for the next 30 min to allow venous blood sampling through the indwelling intravenous cannula. Thereafter, intravenous infusion of normal saline was restarted at 8–10 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of surgery, with it being intermittently stopped for 2–3 min before every subsequent venous blood sample.

One of the investigators prepared the study drug, performed the thoracic paravertebral block, and conducted the general anesthesia. The calculated dose of ropivacaine for injection was prepared under aseptic precautions by diluting ropivacaine 1.0% in 20 ml normal saline. Patients randomized to receive ropivacaine with epinephrine had 100 μg epinephrine (1 ml of 1:10,000 epinephrine solution) added to the ropivacaine before diluting it in normal saline. A research nurse blinded to the drug administered assessed the dermatomal distribution of loss of sensation to cold stimulus (ice), recorded hemodynamic parameters, collected procedural data, and performed venous blood sampling for ropivacaine assay at predetermined intervals. A second research nurse, also blinded to the drug administered, simultaneously performed arterial blood sampling. The laboratory technical officer performing the plasma analysis for ropivacaine was also blinded to the drug administered, before the assay.

Thoracic paravertebral block was performed under aseptic precautions at the T3 or T4 thoracic level with the patient in the sitting position. The skin and subcutaneous tissue was infiltrated with 2–3 ml lidocaine, 1%, and an 8-cm, 22-gauge Tuohy needle (B. Braun Medical Inc., Bethlehem, PA) was introduced 2.5 cm lateral to the most cephalad aspect of the spinous process and advanced perpendicular to the skin in all planes until the transverse process of the vertebra below was located. When the transverse process was located, the needle was withdrawn to the subcutaneous tissue and readvanced in a cephalad direction to the depth at which it had previously contacted bone. If bone was not encountered, a glass syringe with approximately 4 ml air was attached to the needle and gently advanced until there was a loss of resistance to the injection of air, indicating that the needle tip had traversed the superior costotransverse ligament into the thoracic paravertebral space. After negative aspiration through the needle, the study drug was injected slowly over 2–3 min in aliquots, after which the patient was returned to the supine position. The time at completion of the thoracic paravertebral injection was noted and recorded as time 0. Blood pressure (systolic blood pressure, diastolic blood pressure, and mean blood pressure) and heart rate were recorded before and at 5-min intervals for the next 30 min, with the patient undisturbed. Dermatomal distribution of loss of sensation to cold stimulus (ice) over the ipsilateral and contralateral thorax, abdomen, and axilla was assessed after 30 min. Discomfort experienced during the block was also assessed using a visual analog scale from 0 to 100 mm (0 = no discomfort and 100 = worst imaginable discomfort). Any adverse events, clinical signs suggestive of local anesthetic toxicity, or complications during the study were also recorded.

Both study groups then had general anesthesia induced as per a standardized protocol. This included fentanyl (100 μg) and propofol (2–3 mg/kg). Tracheal intubation was facilitated using rocuronium (0.5 mg/kg). Anesthesia was maintained with nitrous oxide (70%) and oxygen supplemented with isoflurane (end-tidal concentration, 0.5–1%). Standard monitoring, which included pulse oximetry, electrocardiography, end-tidal carbon dioxide, agent monitoring, blood pressure, and nasopharyngeal temperature, was used intraoperatively. Mechanical ventilation of the lung was adjusted to maintain normocapnia (end-tidal carbon dioxide concentration, 34–36 mmHg). Fentanyl was administered for supplementary analgesia in doses deemed necessary to obtund cardiovascular reflexes (greater than 20% of preincisional baseline) during surgery. Intraoperative blood loss was estimated, and venous hemoglobin was measured using a Hemocue hemoglobinometer (Hemocue AB, Angelholm, Sweden) before and after completion of surgery. At the end of surgery, anesthesia was discontinued, neuromuscular blockade was reversed, and the patient was tracheally extubated when awake. The patient was then transferred to the postanesthesia care unit, where she was observed for 1 h or until all arterial blood sampling was completed. Arterial pH (arterial blood gas) was also measured intraoperatively and in the postanesthesia care unit before removal of the arterial catheter.

For measuring arterial and venous plasma concentrations of total ropivacaine, 1.5-ml blood samples were simultaneously obtained from the indwelling arterial and intravenous cannula (cubital vein), before and at predetermined intervals (1, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 30, 40, 50, 60, 70, 80, 90, 120, 150, and 180 min) and in the postoperative period only venous blood samples were obtained at 6 and 24 h after the thoracic paraver-

tebral injection. The blood samples were collected into prelabeled lithium heparin tubes and mixed gently before being placed into ice. In the sampling procedure, the volume of blood more than the dead space of the system was aspirated and excluded before each sample to avoid contamination or dilution by the previous sample or saline. The blood samples were centrifuged at 3,000 rpm for 10 min at room temperature; the plasma was separated and transferred into clean 1.5-ml Eppendorfs before being stored at −70°C until assay as a batch at a later date.

A high-performance liquid chromatography methodology previously described by our group[9] was used to assay the plasma total ropivacaine concentration. The limit of detection for ropivacaine was 10 ng/ml. The within-day (intraassay) coefficient of variation of the assay varied from 5.3% at 100 ng/ml, 1.4% at 500 ng/ml, and 3.9% at 2,000 ng/ml, and the between-day (interassay) coefficient of variation was 5.7% at 100 ng/ml, 4.4% at 500 ng/ml, and 8.1% at 2,000 ng/ml. The mean relative extraction efficiency ranged from 82.8% to 96% between 50 and 3,000 ng/ml.

Pharmacokinetic Analysis

The peak plasma concentration (C_{max}) and the time to peak plasma concentration (T_{max}) for ropivacaine in individual patients were recorded directly from the measured values. The area under the arterial concentration-*versus*-time curve was calculated using the program KINETICA (Innaphase Corporation, Philadelphia, PA).

The pharmacokinetics of ropivacaine absorption were analyzed based on the intravenous pharmacokinetics of ropivacaine described by Emanuelsson *et al.*[10] Emanuelsson *et al.* gave male volunteers 40 mg intravenous ropivacaine as an infusion over 30 min and measured serial arterial ropivacaine concentrations. The arterial concentration at the end of the infusion was 1.3 μg/ml. They also calculated a half-life of 1.8 h, a clearance of 338 ml/min, and a volume of distribution at steady state of 36 l. From these reported values, it is possible to calculate the pharmacokinetics of a two-compartment mammillary model: V_1, k_{10}, k_{12}, and k_{21}, which are 24 l, 0.014 min^{-1}, 0.0055 min^{-1}, and 0.011 min^{-1}, respectively. We thus modeled the systemic pharmacokinetics of ropivacaine using differential equations for the amounts of ropivacaine in the central compartment (compartment 1) and the peripheral compartment (compartment 2):

$$dx_1/dt = 0.011x_2 - (0.014 + 0.0055)x_1 + I(t)$$

$$dx_2/dt = 0.0055x_1 - 0.011x_2.$$

Emanuelsson *et al.* did not weight adjust their pharmacokinetics. Given that their Swedish male subjects ranged in weight from 70 to 95 kg, whereas our Asian female subjects ranged in weight from 36 to 80 kg, we investigated both weight-invariate and weight-proportional pharmacokinetic models. For the weight-proportional model, we assumed that the average weight in the study reported by Emanuelsson *et al.* was 80 kg.

Two separate input functions were considered, the standard first-order input function,

$$I(t) = Dose \cdot F \cdot k_a \cdot e^{-k_a t},$$

where F is the fraction bioavailable and k_a is the absorption rate constant. The inverse gaussian density function described by Weiss[11] is

$$I(t) = F \cdot (MAT/2\pi CV^2 t^3)^{1/2} \cdot e[-((t-MAT)^2/2CV^2 MAT t)],$$

where F is the fraction bioavailable, MAT is the mean absorption time, and CV^2 is the variance of absorption times. Both absorption models were tested for both one and two absorption phases.

The effects of epinephrine on the arterial pharmacokinetics were evaluated by examining whether the absorption parameters (F and k_a for the first-order absorption model, or F, MAT, and CV^2 for the inverse gaussian density model) were altered by epinephrine. If so, then separate values of the absorption parameters were calculated for the presence or absence of epinephrine.

The venous pharmacokinetics were analyzed assuming a first-order transfer between arterial and venous blood:

$$dC_{venous}/dt = k_{AV}(C_{arterial} - C_{venous}).$$

The pharmacokinetics were analyzed with NONMEM, version V. Interindividual variability was modeled as log-normally distributed. Residual intraindividual variability was also modeled as log-normally distributed, by log transforming the concentrations and then using an additive model for intraindividual error.

Model selection was made using the likelihood ratio test, requiring a decrease in the NONMEM objective function (−2LL) of 3.84 with the addition of a single parameter (chi-square distribution = 3.84 for $P = 0.05$, 1 degree of freedom). Model performance was assessed graphically, comparing plots of measured *versus* predicted concentrations over time, as well as plotting the measured–predicted concentrations over time. Model performance was calculated using the performance error, defined as (measured concentration − predicted concentration) divided by the predicted concentration. The median performance error and the median absolute performance error are measures of bias and inaccuracy in the model.

The data and NONMEM control files are available as a Web Enhancement on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.

Statistical Analysis

SPSS® for Windows version 11 (SPSS Inc., Chicago, IL) was used for statistical analysis. The Kolmogorov-Smir-

Table 1. Patient Characteristics with Clinical Parameters

	Ropivacaine (n = 10)	Ropivacaine with Epinephrine (n = 10)
Age, yr	38.9 (10.9) [20–53]	49.4 (9.7) [35–63]*
Weight, kg	54.9 (12.6) [36–80]	56.5 (11) [41–75]
Height, cm	156.6 (6.5) [146.5–168]	158.7 (3.9) [153–164]
ASA I/II	1/9	5/5
Time to perform block, min	10.8 (2.5) [6–14]	11.4 (3.6) [7–19]
Discomfort score during needle placement (VAS 0–100)	20 [0–70]	20 [0–50]
Number of ipsilateral anesthetized dermatomes	6.1 (2.2) [4–10]	5.4 (2.4) [3–10]
Time from paravertebral injection to surgical incision, min	34.3 (8.7) [20–45]	38.4 (8.5) [25–46]
Hb (preoperative), g/dl	11.9 (1.7) [7.5–13.6]	12.9 (2.3) [9.7–18.1]
Hb (postoperative), g/dl	11.4 (1.8) [7.7–14.5]	11.8 (1.7) [9–15.1]
Body temperature (preoperative), °C	36.3 (0.5) [35.2–37.1]	36.1 (0.2) [35.8–36.4]
Body temperature (postoperative), °C	36.5 (0.5) [35.8–37.4]	36.3 (0.4) [35.8–36.8]
pH (preoperative)	7.42 (0.03) [7.35–7.46]	7.41 (0.03) [7.36–7.49]
pH (postoperative)	7.37 (0.02) [7.35–7.42]	7.37 (0.04) [7.31–7.47]
Blood loss, ml	100 [30–120]	100 [80–300]

Data are expressed as mean (SD) [range], except discomfort score during needle placement and blood loss, which are expressed as median [range], and American Society of Anesthesiologists (ASA) physical status, which is expressed as frequency.

* Intergroup difference, $P = 0.03$.

Hb = hemoglobin; VAS = visual analog scale.

nov test was used to test the normality of the data recorded. Results are presented as mean (SD) [range] when normally distributed or as median [range, minimum–maximum] when not normally distributed. Appropriate parametric (two-tailed Student *t* test) and nonparametric tests (Wilcoxon signed ranks test or Mann–Whitney U test) were used for intragroup (arteriovenous difference) and intergroup comparison (arterial or venous difference). Fisher exact test was used to test the proportional differences in American Society of Anesthesiologists physical status between the two study groups. Changes in hemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate) were compared using repeated-measures analysis of variance for intragroup comparison and multiple *t* tests for intergroup comparison at different time intervals. A *P* value less than 0.05 was considered statistically significant.

Results

The dose of ropivacaine (2 mg/kg) used for the thoracic paravertebral block in this study was well tolerated by our patients. Patients randomly assigned to ropivacaine with epinephrine were older than those receiving ropivacaine without epinephrine ($P = 0.03$; table 1). Otherwise the two study groups were comparable with respect to weight, height, American Society of Anesthesiologists physical status, the time it took to perform the block, discomfort experienced during block placement, number of ipsilateral anesthetized dermatomes, time from paravertebral injection to surgical incision, body temperature, hemoglobin concentration, pH, and total amount of blood loss (table 1). No significant changes in heart rate or blood pressure were noted in either group after the paravertebral injection (data not provided).

There were no technical complications or clinical evidence of local anesthetic toxicity before the induction of general anesthesia or at the times that the C_{max} was attained. However, one patient who received ropivacaine with epinephrine had transient development of involuntary muscular activity resembling shivering at 15 min after the paravertebral injection, which was close to the time that the arterial C_{max} was attained (C_{max} 1.17 μg/ml, T_{max} 12.5 min) in this patient. The patient was conscious throughout this episode, which aborted spontaneously. Ipsilateral Horner syndrome developed in one patient, and ipsilateral vasodilatation seen as a well demarcated reddish coloration of the skin or flush over the anesthetized thoracic dermatomes was seen in two patients who received ropivacaine without epinephrine.

Figure 1 shows the mean time profiles for the first 120 min for the arterial and venous concentrations in the presence and absence of epinephrine. Epinephrine decreased peak concentration in both the arterial and venous blood by approximately 20%. The time lag between arterial and venous concentrations is also evident. Arterial C_{max}, T_{max}, and cumulative area under the curve at 30, 60, 120, and 180 min are reported in table 2.

Pharmacokinetic Model

Initial exploration with the model demonstrated that two absorption phases were required, and the inverse gaussian density function was hugely superior (by several hundred points in the NONMEM objective function) to the conventional first-order absorption model. The weight-adjusted adjusted version of the ropivacaine pharmacokinetics reported by Emanuelsson *et al.*[10] resulted in a significant improvement of the model ($P < 0.01$) over the weight-invariant pharmacokinetics. Epinephrine was a significant covariate of the bioavailability

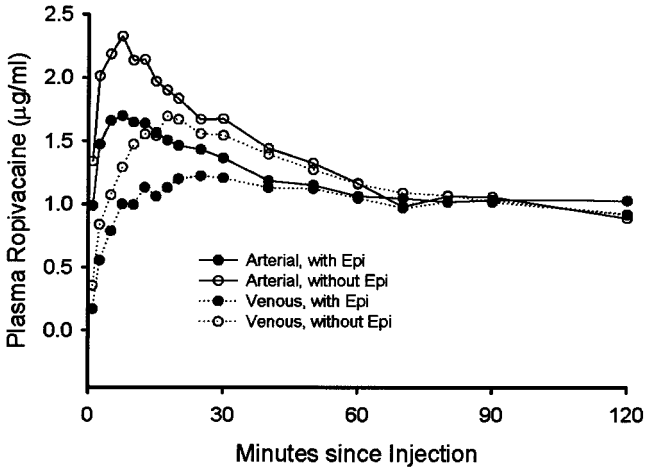

Fig. 1. Mean plasma concentration of ropivacaine during the 120 min after the thoracic paravertebral injection of ropivacaine (2 mg/kg) with or without epinephrine (Epi) 1:200,000, showing the lower concentrations and delay in peak concentration observed when epinephrine is added to the solution.

of the first absorption phase ($P < 0.01$). There was a trend toward epinephrine resulting in a longer MAT for the first absorption phase, but it was not statistically significant. Weight, age, and height were not covariates of any model parameters.

The final model was arrived at in an unconventional manner. The "typical parameters" of the population model did not fit the data well, even though the *post hoc* Bayesian estimates of the parameters for each individual patient described that patient's data quite well. Therefore, median parameters were calculated from the *post hoc* Bayesian estimates for individual subjects. These median parameters fit the population data well and were used as "fixed" values of the structural model in the final NONMEM analyses. The interindividual variability about these parameters was then estimated by NONMEM, and new *post hoc* Bayesian estimates of the parameters for individual were developed. "First-order" and "first-order conditional" estimation approaches were explored. In general, the results with the first-order approach better described the data than the first-order conditional approach.

Figure 2 shows the results of the pharmacokinetic modeling. The upper graph in figure 2 shows all of the

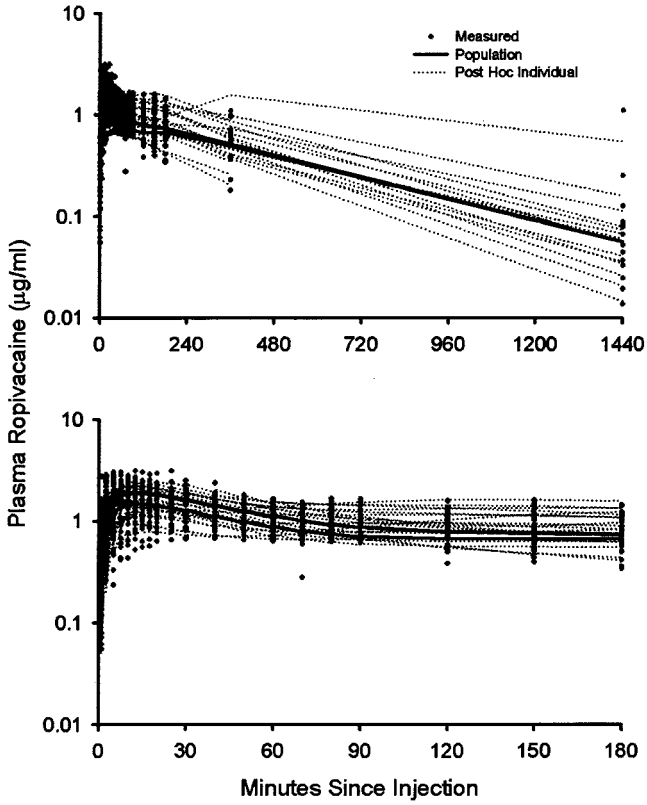

Fig. 2. Observed concentrations (*points*), population pharmacokinetic models (*solid lines*), and individual *post hoc* Bayesian pharmacokinetic models (*dotted lines*). The *upper graph* shows all data, while the *lower graph* expands the first 180 min. There are two models for the population fit, reflecting the effects of epinephrine on bioavailability.

observations (both arterial and venous), as well as the final model. The solid lines show the population estimate. There are two lines for the population estimate, reflecting different predictions for the presence or absence of epinephrine in the solution. The dotted lines show the individual *post hoc* Bayesian pharmacokinetics. The lower graph is identical to the upper graph, except that the time axis has been expanded to show the first 180 min.

Figure 3 shows the same data as in figure 2, but expanded for the first 180 min. The arterial and venous data are shown separately. The curves are shown for the population model, reflecting the slightly different mod-

Table 2. Noncompartmental Pharmacokinetic Parameters

	Ropivacaine	Ropivacaine with Epinephrine
C_{max}, μg/ml	2.47 (0.5) [1.7–3.13]	1.85 (0.7) [1.05–2.86]*
T_{max}, min	7.5 [2.5–25]	11.25 [2.5–120]*
AUC 30 min, $\mu g \cdot ml^{-1} \cdot min$	57 (14.2) [38.7–82.5]	44.5 (14.9) [26.4–70.3]
AUC 60 min, $\mu g \cdot ml^{-1} \cdot min$	98.8 (25.3) [63.2–143]	80 (23.8) [51.1–122]
AUC 120 min, $\mu g \cdot ml^{-1} \cdot min$	159.6 (40.1) [101–217.4]	141.9 (39.6) [94.5–206]
AUC 180 min, $\mu g \cdot ml^{-1} \cdot min$	209.8 (56.4) [137–306.4]	192.5 (52.8) [135.8–281.9]

Arterial data are presented. Data are expressed as mean (SD) [range], except T_{max}, which is expressed as median [range].

* $P < 0.05$ for difference between solutions with *vs.* without epinephrine.

AUC = area under the curve; C_{max} = peak plasma concentration; T_{max} = time to peak plasma concentration.

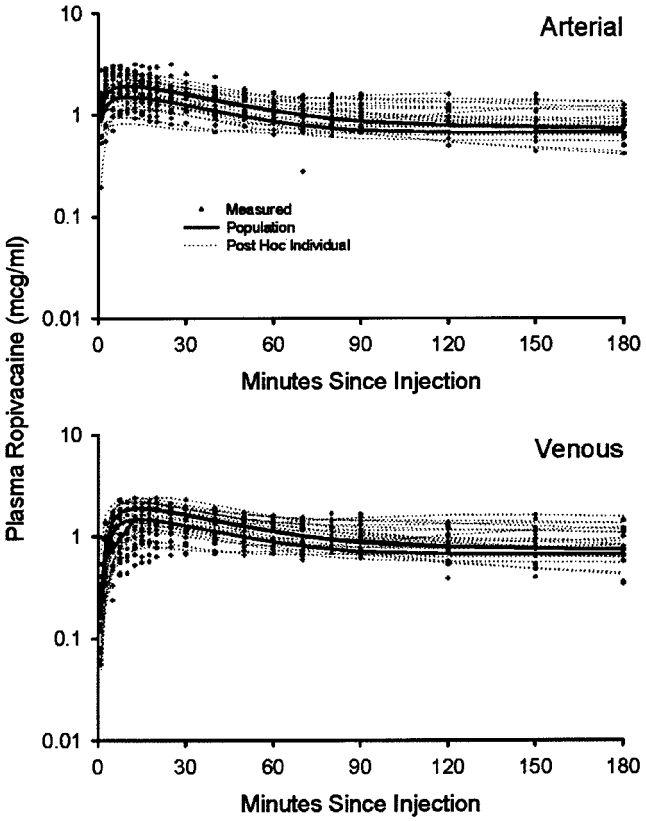

Fig. 3. Model fits for arterial (*upper graph*) and venous (*lower graph*) data. There is systematic model misspecification for the population model (*solid lines*) approximately 90 min after drug administration. The individual *post hoc* Bayesian models describe the distribution of data well (median absolute performance error = 11%), without evidence of model misspecification.

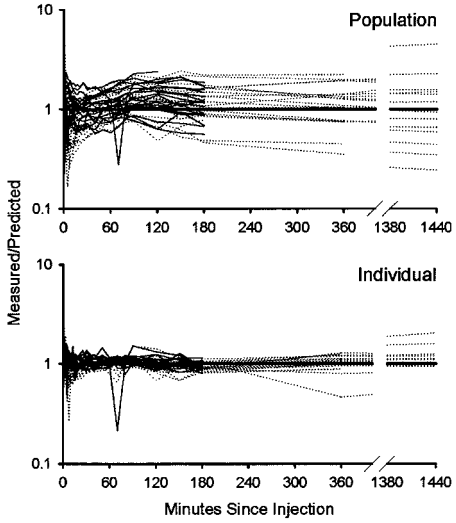

Fig. 4. Graphs of measured–predicted concentrations for the population model (*upper graph*) and the individual fits (*lower graph*). Arterial concentrations for individual subjects are connected by *solid lines*, and venous concentrations for individual subjects are connected with *dotted lines*. The population model shows systemic misspecification at around 90 min after drug administration. However, there is no such misspecification in the individual fits. The individual fits in the first 15 min show a divergence of the arterial concentrations from the venous concentrations, reflecting the failure of the model of arterial–venous equilibration to fully explain the lower concentrations observed in the venous blood.

els depending on whether the solution contained epinephrine. Overall, the population model runs through the center of the data, although there is a modest bias in the models around 90 min after drug administration. The individual *post hoc* Bayesian predictions, shown as the dotted lines, follow the observations without a suggestion of bias.

The parameters of the model are given in table 3. As mentioned, epinephrine decreases the bioavailability of the first absorption phase from 0.91 to 0.76, approximately a 15% decrease. The mean absorption time for the rapid phase is 7.8 min, but the dispersion of absorption around that is very large, with a CV^2 of 31. The rapid phase accounts for approximately half of the total absorption. The slower phase has a typical bioavailability of 0.89, with a mean absorption time of 697 min. The dispersion about this time is smaller than for the rapid phase, with a CV^2 of 1.51. The rate constant for arterial–venous equilibration is 0.47 min^{-1}, which corresponds to an equilibration half-time of 1.5 min.

Figure 4 shows the goodness of fit for the population and individual models. The y-axis is the measured–predicted, plotted against time. As observed in the figure 3, figure 4 shows a modest systematic error around 90 min for the population fit. However, that is not reflected in the individual fits, which do not show evidence of systematic error. For the population fit (whose parameters can be found in table 3), the median performance error was 6%, with a median absolute performance error of

Table 3. Derived Pharmacokinetic Parameters

	First Absorption Phase				Second Absorption Phase			
	Bioavailability							
	With Epinephrine	Without Epinephrine	MAT	CV^2	Bioavailability	MAT	CV^2	k_{AV}
Median [range]	0.76 [0.34–1.13]	0.91 [0.61–1.36]	7.8 [2.4–152]	31 [31–31]	0.89 [0.27–4.67]	697.00 [387–1,660]	1.51 [0.98–2.69]	0.47 [0.13–1.55]

Pharmacokinetic parameters estimated for the first and second absorption phases and the rate constant for arterial–venous equilibration (k_{AV}).
CV^2 = variance of absorption times; MAT = mean absorption time.

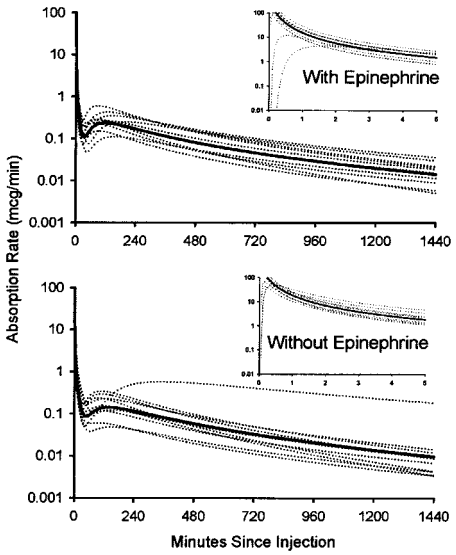

Fig. 5. Absorption rates over time for ropivacaine with epinephrine (*upper graphs*) and without epinephrine (*lower graphs*). Epinephrine decreases the bioavailability of the rapid absorption phase by approximately 15%. However, on a log scale, this decrease is almost impossible to see.

26%. For the individual *post hoc* Bayesian pharmacokinetic estimates (*i.e.*, the parameters individualized for each subject), the median performance error was 1%, and the median absolute performance error was 11%.

Figure 5 shows the absorption functions for the individuals, based on the inverse gaussian distribution and the individual *post hoc* Bayesian estimates (dotted lines) or the population estimates (solid lines; parameters given in table 3). As can be seen, the first input is very rapid for several minutes, but rapidly declines after that. A second input phase is then observed, which peaks at approximately 3 h. The slow terminal phase of the plasma concentrations (fig. 2) is driven by the slow absorption from the injected drug. Note that one individual who did not receive epinephrine had a very high concentration at 24 h (fig. 2). NONMEM assigned this individual a very different terminal input phase, obvious in the lower graph of figure 5, to account for this high concentration at 24 h. The data point is likely an artifact of the assay, and therefore, the high absorption rate seen for a single individual in the lower graph of figure 5 is likely an artifact as well.

Discussion

This is the first study that systematically evaluates the absorption kinetics of ropivacaine after thoracic paravertebral injection. We compared the pharmacokinetics of ropivacaine after a single-bolus thoracic paravertebral injection of 2 mg/kg with or without epinephrine (1:200,000, 5 μg/ml). As expected, plasma total ropivacaine concentrations were higher in the arterial blood compared with the venous blood during the rapid phase of systemic absorption. This is similar to the arterial–venous differences in plasma local anesthetic concentration reported after intercostal[12] and epidural[10,13] block. A significant arterial–venous difference in plasma ropivacaine concentration was seen up to 15 min in patients who received ropivacaine without epinephrine and 40 min in patients who received ropivacaine with epinephrine. This highlights the importance of arterial blood sampling in assessing local anesthetic toxicity because the arterial blood reflects the concentration delivered to the heart and brain, the sites of local anesthetic toxicity.

In our analysis, the equilibration between the arterial and venous blood was modeled using a single constant, k_{AV}. Although this accounted for the time delay and provided a reasonable prediction of the arterial and venous levels, in separate simulations (not shown), we found that this accounted for only a small part of the reduction in venous concentrations when compared with arterial concentrations. A more complex model of arterial–venous equilibration will be required to fully capture the arterial–venous differences seen in our data.

Epinephrine is often added to local anesthetic agents during regional anesthetic procedures to reduce systemic absorption[14–16] by causing local vasoconstriction. The addition of epinephrine to ropivacaine in this study produced a 25% reduction in mean arterial C_{max} of ropivacaine and delayed both the arterial and venous T_{max}, all of which were statistically significant. The effect of epinephrine was to decrease the bioavailability of the most rapid absorption phase of ropivacaine, with a trend toward increasing the mean absorption time. This is similar to the effects of epinephrine reported after intercostal[16] and interpleural[15] administration of bupivacaine. However, our results differ from those of Snowden *et al.*,[17] who, in a letter to the editor, reported that arterial C_{max} and T_{max} were comparable after thoracic paravertebral injection of bupivacaine (1 mg/kg) with or without epinephrine 1:200,000. Although the median arterial C_{max} of bupivacaine was 23% lower in patients who received bupivacaine with epinephrine, Snowden *et al.*[17] did not find it to be statistically significant. We suspect this is simply a type II statistical error, because the magnitude of the effect reported by Snowden *et al.* is nearly identical to the magnitude of effect that was statistically significant in our study.

Although patients were randomized, there was a statistically significant difference in age between the two study groups (table 1). Using NONMEM, we specifically examined whether age was a covariate of any of the estimated pharmacokinetic parameters. It was not.

Systemic absorption of local anesthetic after extravascular administration is biphasic and related to the relative absorption from the aqueous phase (initial rapid phase) and from the fatty tissue (slow phase) at the site of injection.[18] The arterial C_{max} and T_{max} occur within the rapid phase.[18] The biphasic absorption was well

described using two inverse gaussian distribution functions. This function has been found to be a robust model for drug absorption.[19]

Determination of the absorption function requires knowledge of the systemic pharmacokinetics after intravenous administration. We were fortunate in having such a function available, the report from Emanuelsson *et al.*[10] This function worked quite well, in that we were able to identify a model with seven parameters that predicted the ropivacaine concentrations with a median error of only 10% for each subject (fig. 4, lower graph). The only individualization we performed of the systemic ropivacaine pharmacokinetics was to weight adjusting the Emanuelsson model.[10] The only suggestion of any problem with our use of the Emanuelsson model was the typical bioavailability being larger than 1. This is the expected result if our female patients had a smaller volume of distribution, and hence higher concentrations, than that predicted by the Emanuelsson model for the male volunteers. Therefore, even though we weight adjusted the model, it seems that perhaps the model still overestimated the volume of distribution for systemic ropivacaine in our patients. Nonetheless, the performance of the pharmacokinetic model, with our only estimating the absorption parameters and using a previously published model for the intravenous pharmacokinetics of ropivacaine, was comparable to the 20–30% median absolute performance errors typical of intravenous pharmacokinetics.[20,21]

The dose of ropivacaine (2 mg/kg) used in this study was well tolerated. This is consistent with our clinical experience using the dose of ropivacaine used in this study (2 mg/kg) for thoracic paravertebral block in several hundred patients, both with or without midazolam premedication. Therefore, we believe the dose of 2 mg/kg ropivacaine is safe for thoracic paravertebral block.

In conclusion, a single bolus injection of ropivacaine (2 mg/kg) for thoracic paravertebral block was well tolerated and produced unilateral segmental thoracic anesthesia. The addition of epinephrine (1:200,000) to ropivacaine decreased the C_{max}, delayed the T_{max}, and decreased the bioavailability of the rapid absorption phase. This confirms that epinephrine reduces and delays the systemic absorption of ropivacaine from the thoracic paravertebral space. Therefore, adding epinephrine to ropivacaine may be a useful strategy to reduce systemic ropivacaine toxicity.

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