Pharmacokinetics of Ropivacaine and Bupivacaine for Bilateral Intercostal Blockade in Healthy Male Volunteers

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Background: Intercostal blockade produces the highest serum local anesthetic concentrations of all regional anesthetic techniques. The purpose of this study was to determine the pharmacokinetic properties of ropivacaine and bupivacaine after bilateral intercostal blockade.

Methods: The pharmacokinetics of ropivacaine (n = 7) and bupivacaine (n = 7) were determined in adult human volunteers from venous samples drawn over 24 h after bilateral intercostal blockade of T5–T11 with 140 mg of either drug (0.25% plain solutions, 56 ml). Sensory (pinprick, temperature, and touch) and motor blockade (RAM-test and integrated electromyography) were assessed every 2 h.

Results: There was no significant difference between the maximum plasma concentrations (Cmax) obtained for either drug (ropivacaine 1.1 ± 0.4 µg/ml, bupivacaine 0.9 ± 0.2 µg/ml, P = 0.39), and there were no toxic signs observed in the obtained plasma concentration ranges. Plasma concentrations tended to peak (tmax) earlier with ropivacaine (21 ± 9 versus 30 ± 8 min, P = 0.09). The terminal half-life (t1/2b) of ropivacaine (2.3 ± 0.8 h) was significantly less than that for bupivacaine (4.6 ± 2.6 h, P = 0.04).

Sensory blockade measured by pinprick was of shorter duration with ropivacaine (6.0 ± 2.5 h versus bupivacaine 10.0 ± 3.0 h, P < 0.001). Likewise, motor blockade was less intense and of shorter duration for ropivacaine by RAM-test (P = 0.02).

Conclusions: The results of this pharmacokinetic study indicate that 0.25% ropivacaine and 0.25% bupivacaine (56 ml, 140 mg) produce peak plasma levels less than those considered toxic when used in bilateral intercostal blockade. Studies of ropivacaine for intercostal blockade in surgical patients are necessary before the optimum concentration for efficacy and anesthetic/analgesic duration is identified. (Key words: Anesthetic techniques: intercostal nerve block. Anesthetics, local: bupivacaine, ropivacaine. Pharmacokinetics, local anesthetics: bupivacaine, ropivacaine.)

ROPIVACAINE is a new long-acting amide local anesthetic structurally similar to bupivacaine. Ropivacaine has pharmacokinetic properties resembling bupivacaine in studies of epidural anesthesia in animals or humans.1–4 However, when these drugs are infused intravenously to healthy volunteers, ropivacaine has a higher clearance and a smaller volume of distribution than bupivacaine (ropivacaine t1/2b < bupivacaine t1/2b).1,4 Although intercostal blockade produces plasma local anesthetic concentrations greater than those after epidural anesthesia,5,6 no studies have been performed using ropivacaine for intercostal nerve blockade in humans.

The primary objective of this study was to compare the pharmacokinetic parameters of ropivacaine and bupivacaine after intercostal neural blockade. A secondary objective was to evaluate the clinical efficacy of ropivacaine for intercostal blockade in human volunteers when compared with bupivacaine.

Methods

Fourteen healthy male ASA physical status 1 volunteers participated in the study after Institutional Review Board approval and written informed consent were obtained. Subjects did not eat or drink for 8 h before the start of the study and refrained from alcohol consumption for 48 h before. Volunteers with a history of local anesthetic sensitivity, any concomitant drug therapy, or a history of blood donation within 4 months were excluded. General health was documented by history, physical examination, hematology, clinical chemistry,
and electrocardiography within 3 weeks before the day of the study.

Each participant received a 16-G peripheral intravenous catheter for infusion of maintenance fluids and as access for any possible therapeutic medications and a separate 16-G peripheral intravenous catheter in the contralateral arm for venous blood sampling. No premedicating or sedative medications were given.

In a randomized, double-blind manner, bilateral intercostal blockade from T5 to T11 was performed using either 0.25% ropivacaine or 0.25% bupivacaine (n = 7 each, both without epinephrine, 4 ml per intercostal space, 14 intercostal spaces per subject, total = 56 ml (140 mg)) with the volunteer in the prone position. Volunteers entered the study protocol at 15-min intervals, allowing all assessments and specimens to be collected by the same investigators within a single 30-h period.

The skin was anesthetized at each site with approximately 0.5 ml of 0.5% lidocaine without epinephrine (8 ml, 40 mg total) 10 min before initiation of the intercostal nerve blocks. Two experienced anesthesiologists (one per side) performed the intercostal blocks using standard technique, completing the entire 14 intercostal nerve blocks within 4 min. One minute after completion of the blocks, subjects were turned supine and remained in this position for 3 h, after which they were allowed to ambulate and resume oral intake. Blood pressure was measured at 5-min intervals for 1 h, and the electrocardiograph was monitored continuously for 1 h after injection.

**Drug Concentration and Pharmacokinetic Analysis**

Peripheral venous blood samples (10 ml) were used for determination of both total and free concentrations of ropivacaine and bupivacaine and for determination of alpha-1-acid glycoprotein concentrations. Total concentrations were determined from samples drawn immediately before skin infiltration (control) and at time 0 (immediately after the last intercostal injection), 2.5, 5, 10, 15, 20, 30, 45, and 60 min and 2, 3, 4, 6, 8, 10, 12, 16, 20, 22, and 24 h after the end of intercostal injection. Plasma was immediately separated by centrifugation and stored at -20°C until assay.

Total plasma concentrations of ropivacaine and bupivacaine base were measured by gas chromatography using a nitrogen-sensitive detector, with limits of determination of 10 ng/ml and with coefficients of variation of approximately 5% for either drug (at 0.3 µg/ml). Free concentrations were determined by liquid chromatography after ultrafiltration from those samples taken at 5 and 30 min and 6 and 12 h after blockade. Free concentrations were detected by ultraviolet at 210 nm, with limits of determination of 3 ng/ml for both drugs and coefficients of variation less than 10%. The chromatographic assays were not stereospecific; therefore, isomers of bupivacaine were not separated. Alpha-1-acid glycoprotein concentrations were measured using a radial immunodiffusion technique (NOR-Partigen acid α1,2-glycoprotein commercially prepared kit, Behring, Westwood, MA) from the control and 24-h samples, with a limit of determination of 2 µM/l and a coefficient of variation of 7% at 18 µM/l.

Plasma local anesthetic determinations and pharmacokinetic calculations were performed at Astra Pain Control AB (Södertalje, Sweden). Plasma concentration-time determinations of ropivacaine and bupivacaine were used to estimate the maximum plasma concentration (Cmax), time to reach Cmax (tmax), terminal half-life (t1/2β), and the area under the plasma-concentration-time curve (AUC). The t1/2β was calculated from the terminal slope (time 6–24 h) by linear regression, AUC by the linear trapezoidal rule up to the last data point, and the residual area by integration.

Apparent clearance (CL) was estimated using the equation, CL = dose/AUC, and assumed 100% bioavailability of drug after intercostal administration. Free fraction (f0) was calculated by f0 = C0/C, where C0 is the free concentration and C is the total concentration at each sampling time.

**Clinical Assessments**

Anesthesia was tested in each of the four quadrants of the abdomen (approximately the T7 and T10 dermatomes bilaterally) by a trained observer at time 0 (immediately after the last intercostal injection) and every 2 h until complete resolution of blockade. Three methods of testing sensory anesthesia were used: pinprick (pain), alcohol wipe (temperature perception), and having each volunteer lightly touch their own abdomens (subjective touch).

Testing of abdominal motor blockade was performed every 2 h after blockade by two techniques. The RAM-test method, in which a subject’s ability to sit up from a supine position is qualitatively graded on a five-point scale, is felt to be a more appropriate test for measuring motor function of the abdominal muscles than the Bromage scale, which evaluates motor function of the hips and legs. Integrated electromyography (IEMG)

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recorded from surface electrodes is a quantitative method of assessing the degree and duration of motor blockade by measuring electrical activity generated during attempted contracture of the abdominal muscle(s). A mean IEMG value for the abdominal muscle-lature was generated by averaging values at the T7 and T10 levels. IEMG was defined as having returned to baseline when 90% of the control measurement had returned.

After complete resolution of blockade, volunteers were asked a series of questions, including, "In retrospect, how long do you think you had any effect from the intercostal blockade?"

Statistical Analysis

Unless otherwise specified, continuous data are expressed as mean ± SD. Demographic data, pharmacokinetic parameters, and duration of sensory and motor blockade between the two local anesthetic agents were analyzed using unpaired Student's t test. χ² analysis was used to compare success of blockade by abdominal region (quadrant), local anesthetic used, and operator performing the block. Differences between methods of measuring sensory blockade duration were analyzed using the analysis of variance (ANOVA). Motor blockade (RAM-test and IEMG) data were analyzed using the Mann-Whitney U-test and repeated measures ANOVA, respectively. Regression analysis was used to correlate pharmacokinetic parameters (t₁/₂) with duration of sensory blockade and the measures of motor blockade. A P value <0.05 was chosen as significance.

Results

All volunteers completed the study, and no major adverse events requiring treatment occurred. The age, weight, and height of subjects were similar between groups (ropivacaine 33.7 ± 4.6 yr vs. bupivacaine 30.4 ± 1.9 yr, ropivacaine 74.0 ± 10.4 kg vs. bupivacaine 77.6 ± 12.0 kg, and ropivacaine 174.0 ± 7.1 cm vs. bupivacaine 175.4 ± 16.2 cm; P = 0.11, 0.56, and 0.83, respectively). No important hemodynamic alterations were recorded during the study. Three volunteers (two in the bupivacaine group, one in the ropivacaine group) described transient minor symptoms (dizziness, "depersonalization," and headache) that possibly were related to local anesthetic absorption, although these symptoms did not correspond with their maximum venous local anesthetic concentration.

Individual plasma concentration-time curves were all within the same general range. Ropivacaine was detected in samples from two volunteers and bupivacaine from five volunteers at 24 h (fig. 1). Three volunteers (fig. 1, subjects 2, 8, and 12) receiving ropivacaine had secondary peaks in their plasma concentrations. For volunteer 12, this secondary peak (1.02 μg/ml at 244 min) was greater than the initial peak plasma level (0.94 μg/ml at 24 min) and was used in calculating Cₘₐₓ, but the time of the initial peak (table 1,*) was used in calculating tₘₐₓ.

Derived pharmacokinetic parameters are shown (table 1). The t₁/₂ of ropivacaine was significantly shorter than for bupivacaine (fig. 2, P = 0.04). There was no correlation between the t₁/₂ and the duration of sensory blockade (r = 0.67, P = 0.06). There was no statistical difference in Cₘₐₓ (P = 0.39) or tₘₐₓ (P = 0.09) between the agents. No differences in AUC or CL were observed between the agents (P = 0.13 and 0.14, respectively). There is a moderate correlation between the amount of injected local anesthetic (mg/kg) and the resultant peak plasma concentration (fig. 3, ropi-

Fig. 1. Individual plasma concentration curves after bilateral intercostal blockade (T5–T11) with 140 mg ropivacaine (· · · ·) or bupivacaine (---).

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Table 1. Pharmacokinetic Variables Derived from Plasma Concentrations after 140 mg Ropivacaine or Bupivacaine for Bilateral Intercostal Blockade

<table>
<thead>
<tr>
<th>Volunteer</th>
<th>C_{max} (µg/ml)</th>
<th>t_{max} (min)</th>
<th>t_{1/2b} (h)</th>
<th>AUC (mg·min/L)</th>
<th>CL (ml/min)</th>
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<tr>
<td>Ropivacaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.06</td>
<td>24</td>
<td>3.3</td>
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<td>344</td>
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<tr>
<td>2</td>
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<td>14</td>
<td>3.4</td>
<td>289</td>
<td>428</td>
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<tr>
<td>4</td>
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<td>1.9</td>
<td>262</td>
<td>472</td>
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<tr>
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<td>231</td>
<td>534</td>
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<tr>
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<td>1.7</td>
<td>218</td>
<td>566</td>
</tr>
<tr>
<td>12</td>
<td>1.02</td>
<td>24*</td>
<td>1.9</td>
<td>374</td>
<td>330</td>
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<td>14</td>
<td>1.84</td>
<td>12</td>
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<tr>
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<td>21</td>
<td>2.3</td>
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<td>0.8</td>
<td>75</td>
<td>104</td>
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<tr>
<td>Bupivacaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>25</td>
<td>2.1</td>
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<tr>
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<td>34</td>
<td>5.7</td>
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<td>550</td>
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<tr>
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<tr>
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<td>3.6</td>
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<td>547</td>
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<tr>
<td>Mean</td>
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<td>30</td>
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<td>243</td>
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<tr>
<td>SD</td>
<td>0.22</td>
<td>8</td>
<td>2.6</td>
<td>69</td>
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</table>

* See text for explanation.

The f_{0} of ropivacaine was significantly greater than that of bupivacaine (7.1 ± 2.8% vs. 5.2 ± 1.7%, P = 0.003). The range of alpha-1-acid glycoprotein levels was not different between the two groups or when comparing samples 24 h after blockade from control (control 17.0 ± 3.3 mm/l versus 17.8 ± 2.8 mm/l at 24 h, P = 0.49). There were no differences in alpha-1-acid glycoprotein levels between those volunteers receiving ropivacaine and those receiving bupivacaine (17.5 ± 2.6 vs. 17.3 ± 3.5, P = 0.85).

Sensory blockade appeared rapidly with both agents, although onset time was not specifically measured. All volunteers were able to discern the onset of some blockade while turning from the prone position (5 min after initiation of block, 1 min after completion). Anesthesia to pinprick was demonstrable in 84% (47/56) of the abdominal quadrants tested—all four abdominal quadrants in eight volunteers, three quadrants in four volunteers, two quadrants in one volunteer, and one quadrant in one volunteer. Quadrants without demonstrable anesthesia were excluded from analysis of duration of sensory anesthesia. There was no statistical difference in presence of blockade between the sides of the abdomen or between the upper and lower abdominal quadrants (χ² P = 0.27 and 0.06). There also was no correlation between either the local anesthetic used (ropivacaine 25/28 quadrants = 89%, bupivacaine 22/28 quadrants = 79%) or the operator performing the block and the presence of anesthesia by quadrant (χ² P = 0.27 and 0.71, respectively).

Time to complete resolution of sensory anesthesia (pinprick, maximum duration) of all quadrants was significantly longer with bupivacaine than with ropivacaine (fig. 4). The average duration of all anesthetized abdominal quadrants (pinprick, temperature, and touch) also was significantly longer with bupivacaine (fig. 5). This difference was particularly pronounced in the upper quadrants. The duration of anesthesia to pinprick correlated with the duration of anesthesia to temperature and the duration of anesthesia to touch (r = 0.87 and 0.86 respectively, P < 0.001 for both). There was no difference in duration of anesthesia between these different methods of measurement (ANOVA, P = 0.52). Duration of anesthesia to temperature was longer in the upper quadrants than in the lower quadrants of the abdomen, regardless of local anesthetic agent used. However, statistical significance was not

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Fig. 2. Mean plasma concentration after bilateral intercostal blockade (T5-T11) with 140 mg ropivacaine (- - -) or bupivacaine (---).
Fig. 3. Plot of injected dose of local anesthetic (mg/kg) versus resultant maximum plasma concentration (Cmax) for ropivacaine and bupivacaine after bilateral intercostal blockade (T5–T11).

attained for pinprick or subjective touch testing (fig. 5). No difference in duration of anesthesia was detectable between the right and left sides.

When asked after complete resolution of blockade “how long do you think you had any effect from the intercostal blockade?”, volunteer responses were relatively similar between the agents (ropivacaine 9.5 ± 1.3 h, bupivacaine 9.9 ± 1.6 h, \( P = 0.65 \)).

Some degree of motor blockade developed in all volunteers. Motor blockade was of greater intensity and longer duration with bupivacaine compared to ropivacaine when measured by the RAM-test technique but no different by the IEMG technique (figs. 6 and 7). Duration of motor blockade for each drug was similar when measured by the RAM-test (ropivacaine 5.1 ± 1.1 h, bupivacaine 6.9 ± 2.0 h) or by IEMG (ropivacaine 3.5 ± 2.2 h, bupivacaine 6.0 ± 2.2 h, \( P = 0.11 \) and 0.46, respectively). The correlation coefficient between RAM-test scores and IEMG measurements was 0.63 (\( P < 0.001 \)).

**Discussion**

This study was designed to evaluate the differences in systemic uptake, distribution, and elimination between ropivacaine and bupivacaine after intercostal blockade in humans. Therefore, a single concentration and total dosage of the two local anesthetic agents was used. As patients receiving intercostal blockade in the clinical setting (e.g., thoracotomy, upper abdominal surgery) often have coexisting diseases that could dramatically alter pharmacokinetic evaluation (tumor, altered liver blood flow/metabolism), we chose to study healthy volunteers in hopes of eliminating these variables.

The \( t_{1/2} \) of intercostal ropivacaine determined in this study (2.3 h) agrees with the \( t_{1/2} \) reported by Lee et al. after intravenous administration (1.9 h).\(^4\) The calculated \( t_{1/2} \) of bupivacaine (4.6 h), however, was slightly longer than reported earlier (2.7 h) after intravenous administration.\(^1^1\) The \( t_{1/2} \) was estimated to be almost 10 h in subject 5, who was the heaviest subject and had the second smallest clearance of bupiva-
Ropivacaine. This longer t1/2 might be an indication that the elimination of bupivacaine is absorption-dependent after intercostal administration.

The t1/2B of intercostal ropivacaine is somewhat shorter than after epidural injection (>4.5 h). The longer t1/2B probably reflects a greater sequestration of local anesthetic by the epidural fat than by the intercostal perineural tissues and a subsequent slower absorption into the circulation after epidural injection.

Nevertheless, our Cmax after intercostal blockade with 140 mg ropivacaine is comparable to that after epidural anesthesia with 150 mg. The shorter t1/2B for ropivacaine is not unexpected and agrees with previous studies comparing ropivacaine and bupivacaine after intravenous injection in animals and humans. This difference may be explained by the lower tissue and plasma protein binding of ropivacaine, which makes more free drug available for elimination. Our data confirm previous results indicating that protein binding of ropivacaine (94%) is less than bupivacaine (96%). It is also possible that ropivacaine's formulation as a single isomer has different metabolism or absorption than would its racemate, because stereoisomerization has been shown to be important for the elimination other local anesthetic drugs. Differences in protein binding cannot explain differences in t1/2B because alpha-1-acid glycoprotein levels (the predominant element of protein binding of local anesthetic agents) did not differ between groups.

Previous studies evaluating the clinical or pharmacokinetic aspects of intercostal bupivacaine frequently have used solutions containing epinephrine, which is added to decrease the peak plasma levels of the local

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anesthetic. No studies have examined the possible influence of the addition of epinephrine on efficacy, pharmacokinetics, or safety of ropivacaine for intercostal blockade. Previous studies comparing ropivacaine for subclavian perivascular brachial plexus block demonstrated no difference in the pharmacokinetics when epinephrine was added.\textsuperscript{15} In contrast, pharmacokinetic studies of bupivacaine for brachial plexus block (interscalene) and bilateral intercostal block show a marked difference in pharmacokinetics with the addition of epinephrine.\textsuperscript{6,16} One possible explanation is that the inherent vasoconstrictive action of ropivacaine decreases its own absorption and thereby limits peak plasma levels.\textsuperscript{17,18} As local anesthetic agents are absorbed more rapidly after intercostal injection, whether the addition of epinephrine would further limit the absorption of ropivacaine from the intercostal space is yet to be determined.

The mechanism behind a secondary peak in the plasma concentrations of three of the volunteers who

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received ropivacaine remains unclear. Pharmacokinetic evaluations rarely obtain blood samples as frequently during later hours of the study. Thus, it is possible that previous studies missed these secondary peaks. Although this phenomenon has been observed previously in individual patients, these delayed peaks resulted in a "shoulder" in the mean plasma concentration curve for ropivacaine after intercostal block in our study (fig. 2) and in a previous study after subclavian perivascular brachial plexus block.10 This peak has not been observed previously with bupivacaine.

Clinical evaluation of various concentrations of ropivacaine for peripheral nerve block of the ulnar nerve at the elbow demonstrated a 20% failure rate with a 0.25% concentration but only a 9% failure rate when a 0.5% or greater concentration was used.19 Our data suggest 0.25% ropivacaine may not be an ideal agent for single-injection techniques if the longest possible duration of anesthesia is the goal. Though these studies suggest that 0.5% ropivacaine may not be the minimum concentration that is reliably efficacious for peripheral nerve blockade, further studies would be necessary to fully determine the minimum effective concentration and safe maximum total dose of ropivacaine that could be used for intercostal blockade.

The anatomy of the intercostal nerve in its relationship to its overriding rib is predictably constant, which allows significant control of many factors (e.g., distance from site of injection to nerve, composition in intervening tissues) governing the clinical practice of peripheral nerve block and produces highly reliable and reproducible neural blockade. Ideally, a better comparison of the onset and duration of anesthesia of these agents would have been to use one agent on each of the sides and allow each volunteer to be their own control. However, ropivacaine and bupivacaine, although chemically very similar, have widely differing vascular effects.17,18,20 It is not known what influence one anesthetic might have on the uptake, distribution (protein binding), and elimination of the other anesthetic agent, which was the primary intent of the study. Therefore, we chose not to give both anesthetics to each volunteer.

This study also demonstrates that ropivacaine produces significantly less motor blockade than bupivacaine when used for intercostal blockade. Although this difference has been demonstrated in studies of epidural anesthesia comparing these two agents in animals21 and humans22 and is predicted from in vitro studies of these agents,23,24 no other studies in humans have shown ro-

pivacaine to spare motor strength when peripheral nerve blocks were performed. This preferential sparing of motor function could be obviously advantageous in the management of postoperative pain and in the laboring obstetric patient. Increasing intensity and duration of motor blockade, as assessed by isometric muscle force measurement and the Bromage scale, have been demonstrated for epidural ropivacaine as the concentration (and hence, dosage) is increased from 0.5% to 1.0%.25 Further evaluation is necessary to determine whether similar increases in the duration and intensity of motor blockade occur when higher concentrations of ropivacaine are used for intercostal blockade.

As this study used volunteers, direct translation of these data to the surgical patient population is unwarranted. When intercostal blockade is used in surgical patients, 0.25% bupivacaine with epinephrine is sufficient to provide excellent postoperative analgesia. Our inability to detect any evidence of intercostal blockade in 21% and 13% of the abdominal quadrants anesthetized with plain 0.25% solutions of bupivacaine and ropivacaine, respectively, makes one wonder whether this concentration would be sufficient to provide analgesia in a surgical patient, without the addition of epinephrine.

None of the volunteers had experienced intercostal blockade previously. Their retrospective reflections on how long they had an effect from the block is unexplainable. They were unable to detect any significant difference between the agents, unlike the large difference detected by the objective data collected prospectively.

Although it is impossible to isolate the effects on an individual intercostal nerve, because of their overlap of sensory and motor function, averaging 14 nerve blocks in a single patient is likely preferable to evaluating block of a single nerve in 14 patients. Duration of blockade tended to be longer in the upper quadrants compared to the lower quadrants, although statistical significance was not attained. Likewise, a successful block was more common in the left side of the abdomen than in the right, although statistical significance again was not attained. We ascribe this latter finding to the fact that both anesthesiologists were right-handed, and performance of a left-side intercostal block appears to be technically easier and more successful for a right-handed operator.7 This trend is consistent with the previous recommendation that a right-handed anesthesiologist performing bilateral intercostal blockade.
should stand on the patient’s left side and reach over the back to perform the injections on the right side. A longer duration of analgesia from blockade of the upper compared to the lower intercostal nerves has been noted previously but defies easy explanation. Therefore, though bilateral intercostal blockade is an ideal situation for studying the clinical aspects of two agents, it would not seem prudent to study more than two agents in any patient by using different solutions in each quadrant, as has been suggested.

This is the only study, to our knowledge, in which subjects received bilateral intercostal blockade without premedication or sedation. The lack of premedication may be important when comparing this study with previous results. Virtually all sedative/premedicants are known to increase the seizure threshold and produce a greater margin of safety when large or inadvertent intravascular injections of local anesthetics occur. Furthermore, fentanyl and morphine accentuate and prolong the duration of other blocks (spinal and epidural), even when these agents are given intravenously.

In conclusion, ropivacaine can be used without the addition of epinephrine and without intravenous sedation for bilateral intercostal blockade in volunteers, when a 140-mg dose (0.25%) is used. No toxic signs in the obtained plasma concentration range were observed. Sensory blockade is of shorter duration when compared with bupivacaine. Motor blockade is less profound and of shorter duration with ropivacaine.

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