Pharmacokinetics of Ropivacaine in Patients with Chronic End-stage Liver Disease

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Background: Ropivacaine is mainly eliminated by hepatic metabolism. The authors studied the effect of chronic end-stage liver disease on the pharmacokinetics of ropivacaine.

Methods: Thirteen patients with chronic end-stage liver disease and eight healthy volunteers received a single dose of 0.6 mg/kg ropivacaine intravenously over 30 min. Ropivacaine, 3-hydroxyropivacaine, and 2,6’-pипе́колоксилидиде were measured in venous plasma and urine.

Results: Peak ropivacaine plasma concentrations were similar. Patients with chronic end-stage liver disease had, on average, 60% lower total (P = 0.001) and 56% lower unbound plasma clearance (P = 0.002), 59% higher steady state volume of distribution (P = 0.03), and 4.2-fold longer half-life (P < 0.001) of ropivacaine. Of the variation in total ropivacaine clearance, 69% was accounted for by variation in albumin, 57% in proalbumin, 25% in international normalized ratio of plasma thromboplastin time, and 24% in galactose half-life. The patients excreted a larger fraction of the original dose as unchanged ropivacaine (2.1% vs. 0.3%; P < 0.001) and a smaller fraction as 3-hydroxyropivacaine (11% vs. 27%; P = 0.001). The fraction excreted as 2,6’-pипе́колоксилидиде (4.7% vs. 5.0%) was similar.

Conclusions: Ropivacaine clearance is decreased in chronic end-stage liver disease. A normal dose can be considered for a single block in patients with liver impairment, because the peak plasma concentrations were essentially similar. When using a postoperative ropivacaine infusion in a patient with end-stage liver disease, the lowest effective dose should be used for the shortest possible time and the patient should be monitored closely, because systemic toxicity cannot be ruled out. Because of wide interindividual differences in pharmacokinetics in patients with liver disease, no definitive dosing instructions can be given.

ROPIVACINE, \((\sim)\)-1-propyl-2,6’-пипе́колоксилидиде, a long-acting local anesthetic with a structure homologous to that of bupivacaine, is extensively metabolized in humans, and the major metabolic route is aromatic hydroxylation, with approximately 1% of an intravenous dose excreted unchanged in urine. Ropivacaine is metabolized to 3-hydroxyropivacaine mainly by CYP1A2 and to 2,6’-пипе́колоксилидиде mainly by CYP3A4. These two major metabolites, identified in the urine, account for approximately 37% and 3%, respectively, of the original single intravenous dose to healthy volunteers. A total of 71% of the dose has been identified or characterized in a supplementary analysis of samples from the study by Halldin et al., where additional metabolites have been identified or characterized (Eva Klasson Wehler, Ph.D., Director, Development DMPK & Bioanalysis, AstraZeneca R&D, Södertälje, Sweden; May 2006; oral and AstraZeneca internal written communication). The most abundant metabolite (38% of the dose) is 3-hydroxyropivacaine and is excreted in the urine conjugated to sulfate and glucuronic acid. Further metabolism occurs primarily by oxidation in the aliphatic moiety and results in a large number of metabolites in trace amounts. Clinical studies support the role of CYP1A2 and CYP3A4 in the metabolism of ropivacaine. During epidural ropivacaine infusion, the urinary excretion of 3-hydroxyropivacaine decreases, and that of 2,6’-пипе́колоксилидиде increases over time.

The liver is the main organ responsible for the metabolism of drugs. In liver disease, absorption, distribution, and elimination of drugs may be changed. Absorption of local anesthetics is directly related to local blood flow and inversely related to local tissue binding in proteins and adipose tissue at the injection site. Distribution can be influenced by changes in the total body water and plasma proteins, and elimination can be altered by abnormal liver blood flow and impaired metabolic capacity. The effect of changes in hepatic blood flow, enzyme activity, and drug plasma protein binding on the clearance of a drug is dependent on its hepatic extraction ratio. Because ropivacaine has a relatively low hepatic extraction ratio (approximately 40%), its total clearance is not very susceptible to changes in the hepatic blood flow and depends mostly on hepatic enzyme activity and plasma protein binding. The unbound (intrinsic) clearance depends only on the enzyme activity. Enzymes responsible for the metabolism of ropivacaine, CYP1A2 and CYP3A4, constitute approximately 13% and 30%, respectively, of the total amount of CYP enzymes in the liver. These enzymes are situated...
The aim of this study was to assess the effect of chronic end-stage liver disease on the pharmacokinetics of ropivacaine. Because we assumed that chronic end-stage liver disease mainly affects ropivacaine disposition, rather than absorption, an intravenous route of administration was chosen to better characterize the distribution and elimination kinetics and to avoid the risks involved in regional anesthesia.

Table 1. Characteristics of Patients with End-stage Liver Disease

| Patient No. | Sex | Age, yr | Weight, kg | Type of Liver Disease | Medication* | Alb, g/l | Prealbumin, mg/100 ml | INR | Galactose t½, min | Bilirubin, µM | AAG, µg/ml | Child-Pugh Class | Cl, ml/min | Clu, l/min | Vss, l | l, t½, h |
|-------------|-----|---------|------------|----------------------|-------------|---------|----------------------|------|--------------------|-------------|-----------|----------------|-----------|-----------|---------|----------|--------|
| 1           | F   | 67      | 58         | PBC                  |             | 33      | 88                   | 1.1  | 28                 | 95          | 15        | B              | 100       | 1.7       | 91      | 12.5     |
| 2†          | M   | 48      | 55         | PSC                  |             | 26      | 103                  | 1.7  | 31                 | 248         | 23        | C              | 102       | 3.3       | 41      | 5.0      |
| 3           | M   | 25      | 76         | AIH                  |             | 29      | 71                   | 1.5  | 40                 | 92          | 8         | B              | 246       | 2.9       | 118     | 7.1      |
| 4           | F   | 47      | 65         | PBC                  |             | 20      | 119                  | 1.2  | 27                 | 214         | 20        | C              | 104       | 2.5       | 75      | 9.3      |
| 5           | F   | 58      | 70         | PBC                  |             | 15      | 72                   | 2.2  | 48                 | 372         | 17        | C              | 69        | 1.5       | 97      | 16.7     |
| 6††         | F   | 47      | 53         | Cryptogenic cirrhosis|             | 38      | 78                   | 2.0  | 28                 | 116         | 17        | C              | 86        | 2.3       | 50      | 7.3      |
| 7§          | M   | 44      | 80         | Chronic alcohol liver disease | P10 | 26      | 94                   | 1.4  | 54                 | 51          | 13        | C              | 170       | 3.7       | 93      | 7.9      |
| 8           | M   | 46      | 86         | PSC                  |             | 32      | 101                  | 1.8  | 36                 | 55          | 8         | C              | 271       | 4.7       | 109     | 5.9      |
| 9           | F   | 40      | 50         | PBC                  |             | 28      | 108                  | 1.3  | 13                 | 143         | 21        | B              | 137       | 4.5       | 43      | 3.8      |
| 10#         | F   | 21      | 69         | Familial biliary cirrhosis | P20 | 22      | 58                   | 1.0  | 20                 | 232         | 27        | B              | 69        | 2.9       | 57      | 9.8      |
| 11          | M   | 32      | 71         | Cirrhosis post hepatitis | P30, F150 | 25      | 55                   | 1.9  | 24                 | 15          | 10        | B              | 63        | 1.4       | 124     | 27.6     |
| 12**        | F   | 42      | 47         | PBC                  |             | 24      | 103                  | 1.3  | 15                 | 265         | 18        | C              | 194       | 3.7       | 101     | 8.8      |
| 13††        | M   | 36      | 91         | Cirrhosis post hepatitis | P60, C1000 | 19      | 67                   | 1.5  | 41                 | 88          | 10        | C              | 99        | 1.3       | 160     | 19.2     |
| Mean        |     | 42      | 67         |                      |             | 26      | 86                   | 1.5  | 31                 | 153         | 16        | C              | 131       | 2.8       | 89      | 10.8     |
| SD          |     | 12      | 14         |                      |             | 6       | 20                   | 0.4  | 12                 | 105         | 6         | C              | 68        | 1.1       | 35      | 6.7      |

* Concomitant drug therapy that could potentially have an effect on the pharmacokinetics of ropivacaine, within 7 days before, or during, the study day. † Diagnoses of cholangiocarcinoma 1 week after the study. †† Clinically cirrhotic, no cirrhosis in biopsy. Also, albumin was transfused up to 2 days before the study. § Patient with hepatoportal syndrome; smoked 15 years, 5–20 cigarettes/day. ††† Patient with hepatopulmonary syndrome. ** Patient with insulin dependent diabetes mellitus. ‡‡ Patient also received once orally 400 mg fluconazole 3 days before the study.

AAG = α1-acid glycoprotein; AIH = autoimmune hepatitis; Alb = serum albumin; C1000 = 500 mg ciprofloxacin twice daily; Cl = ropivacaine plasma clearance; Clu = free ropivacaine plasma clearance; F150 = 150 mg fluconazole daily; Galactose t½ = galactose half-time (< 15 min is considered normal); INR = international normalized ratio of plasma thromboplastin time; NA = not available; P10 = 10 mg propranolol daily; P20 = 20 mg propranolol twice daily; P30 = 10 mg propranolol three times daily; P60 = 20 mg propranolol three times daily; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; Prealbumin = serum prealbumin; t½ = ropivacaine elimination half-life; Vss = ropivacaine steady state volume of distribution.

Table 2. Characteristics of Healthy Volunteers

<table>
<thead>
<tr>
<th>Healthy Volunteer No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Oral Contraceptives</th>
<th>Galactose t½, min</th>
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<tr>
<td>1</td>
<td>F</td>
<td>21</td>
<td>59</td>
<td>150 µg desogestrel plus 20 µg ethinyl estradiol</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
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<td>66</td>
<td>No</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>21</td>
<td>51</td>
<td>150 µg desogestrel plus 20 µg ethinyl estradiol</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>22</td>
<td>61</td>
<td>75 µg gestodene plus 30 µg ethinyl estradiol</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>26</td>
<td>83</td>
<td>No</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>24</td>
<td>54</td>
<td>50/70/100 µg gestodene plus 30/40/30 µg ethinyl estradiol</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
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<td>SD</td>
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<td>2</td>
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Galactose t½ = galactose half-time.

Materials and Methods

This was an open, parallel-group study of 13 patients with chronic end-stage liver disease evaluated for liver transplantation (table 1) and 8 healthy volunteers (table 2). The study protocol was approved by the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland, and by the Finnish National Agency for Medicines, and was conducted according to the revised Declaration of Helsinki. Before entering the study, written informed consent was obtained from all subjects.
Sixteen patients with chronic end-stage liver disease were originally enrolled in the study. However, one patient underwent liver transplantation and another withdrew from the study because of back pain (vertebral fracture) before receiving the study drug, and one was excluded because of technical difficulties in venous sampling soon after the start of the ropivacaine infusion. Also, urinary data for one patient with failed bladder control was discarded because of incompleteness. After all, plasma data were obtained from 13 and urinary data from 12 patients.

Twelve of the 13 patients underwent hepatic transplantation 8–97 days (median, 31 days) after participating in the study. One patient was diagnosed with cholangiocarcinoma 1 week after the study and was separated within 2 h and stored at −20°C until analysis. Urine was collected before and in intervals of 0–4, 4–8, 8–12, 12–16, and 16–24 h after the start of the ropivacaine infusion. Urine volumes were measured and aliquots were taken from each fraction and stored at −20°C until analysis.

**Drug Analysis**

The analysis of samples for ropivacaine base, 3-hydroxyropivacaine, 2′,6′-pipecoloxylidide, and α1-acid glycoprotein was performed at Quintiles AB, Uppsala, Sweden. Total plasma concentrations of ropivacaine were determined in all samples by gas chromatography with a nitrogen-sensitive detector. The quantitation limit of the method was 2.7 μg/l, with an interday coefficient of variation of 8.7% (n = 10).

Total plasma concentrations of unconjugated 3-hydroxyropivacaine and 2′,6′-pipecoloxylidide were assayed in samples taken at 2, 5, 10, 12, 18, and 22 h (patients) or at 2, 5, 8, 10, and 12 h (healthy volunteers) after the start of the ropivacaine infusion. A simple sample preparation technique involving acidification with phosphoric acid and ultrafiltration with a cutoff of 20,000 Da was applied. The ultrafiltrate was preconcentrated on a C8 precolumn with a mobile phase consisting of 2% methanol in 100 mM ammonium formate buffer (pH 3.8), before separation on a reversed phase column (YMC basic, Kyoto, Japan) with gradient elution. Mobile phase A consisted of 10% acetonitrile in 10 mM ammonium formate buffer (pH 3.9), and mobile phase B consisted of 80% methanol in 10 mM ammonium formate buffer (pH 3.9). For detection, a mass spectrometer with electrospray ionization with m/z M + 1 was used. The m/z was 291.1 for 3-hydroxyropivacaine and 233.2 for 2′,6′-pipecoloxylidide. The quantitation limit was 2.9 μg/l for 3-hydroxyropivacaine and 2.3 μg/l for 2′,6′-pipecoloxylidide, and the coefficient of variation was 8.4% (n = 12) for 3-hydroxyropivacaine and 9.7% (n = 12) for 2′,6′-pipecoloxylidide.

Unbound (free) concentrations of ropivacaine and 2′,6′-pipecoloxylidide were assayed in plasma samples taken at ½, 5, 8, 10, 12, 18, and 22 h (patients) or at ⅓, 2, 5, 8, 10, and 12 h (healthy volunteers) after the start of the ropivacaine infusion. A sample preparation technique involving pH-adjusting with carbon dioxide gas to pH 7.4 at 37°C and thereafter ultrafiltration (cutoff 30,000 Da) at 2,000g and 37°C for 15 min was used. The ultrafiltrate was acidified with phosphoric acid before injection into the chromatographic system. The same chromatographic system and detection as for total concentration of unconjugated 3-hydroxyropivacaine and 2′,6′-pipecoloxylidide was used. The m/z was 275.2 for ropivacaine and 233.2 for 2′,6′-pipecoloxylidide. The quantitation limit was 2.7 μg/l for ropivacaine and 2.3 μg/l for 2′,6′-pipecoloxylidide, with a coefficient of variation of 3.9% (n = 6) for ropivacaine and 5.3% (n = 6) for 2′,6′-pipecoloxylidide.
The urinary excretion of ropivacaine, 3-hydroxyropivacaine, and 2',6'-pipecoloxylidide was assayed by liquid chromatography and mass spectrometry.\textsuperscript{18} The 3-hydroxyropivacaine in urine was determined after acid hydrolysis. Acidic hydrolysis and solid phase extraction was used for sample preparation.\textsuperscript{19} The quantitation limits were 27, 200, and 70 μg/l, and the interday coefficients of variation were 3.5, 3.5, and 4.4% (n = 12) for ropivacaine, 3-hydroxyropivacaine, and 2',6'-pipecoloxylidide, respectively.

Samples for determination of plasma \( \alpha_4 \)-acid glycoprotein concentration were taken at \( \frac{1}{2}, 5, 8, 10, 12, 18, \) and 22 h after the start of the ropivacaine infusion. \( \alpha_4 \)-Acid glycoprotein was determined by an immunoturbidimetric method with a quantitation limit of 0.12 g/l; the coefficient of variation was 1.5–3.8% (at 0.31–1.59 g/l).

Pharmacokinetic Analysis Using Noncompartmental Methods

The peak plasma ropivacaine, 2',6'-pipecoloxylidide, and 3-hydroxyropivacaine concentrations (\( C_{\text{max}} \)) and corresponding peak times (\( t_{\text{max}} \)) were observed directly from each plasma concentration-time profile. The area under the total ropivacaine plasma concentration-time curve (AUC) was estimated by means of the linear trapezoidal rule up to the \( t_{\text{max}} \), after which the logarithmic trapezoidal rule was used, with extrapolation to infinity. For each subject, the terminal log-linear phase of the plasma ropivacaine, 2',6'-pipecoloxylidide, and 3-hydroxyropivacaine concentration-time curve was identified visually, and the terminal elimination rate constant (\( k_{\text{el}} \)) was determined by regression analysis. The terminal half-life (\( t_{\frac{1}{2}} \)) was then calculated from the equation \( t_{\frac{1}{2}} = \ln 2/k_{\text{el}} \). The total (Cl) and unbound (Cl\textsubscript{u}) plasma clearance of ropivacaine were computed from Cl = dose/AUC and Cl\textsubscript{u} = Cl/f\textsubscript{u}, where \( f\textsubscript{u} \) is the individual mean free fraction of ropivacaine in plasma, and the renal clearance (Cl\textsubscript{r}) was calculated from Cl\textsubscript{r} = \( f\textsubscript{u} \times \) Cl, where \( f\textsubscript{u} \) is the cumulative fraction of unchanged ropivacaine excreted in the urine in 24 h. The steady state volume of distribution (\( V_{\text{ss}} \)) was obtained from \( V_{\text{ss}} = \text{mean residence time} \times \) Cl. Mean residence time was calculated as AUMC/AUC - \( t_{\text{2}} \), where \( t \) is the infusion time (0.5 h), and AUMC is the area under the first moment of the ropivacaine plasma concentration-time curve, calculated by the logarithmic trapezoidal rule with extrapolation to infinity.

Excretion of the metabolites in the urine (fraction metabolized, \( f_{\text{m},3-\text{OH}} \) and \( f_{\text{m},\text{PPX}} \)) was calculated by \( A_{\text{u}} \)/dose (in micromoles), with \( A_{\text{u}} \) being the total amount excreted in the urine during the collection period.

The pharmacokinetic calculations on plasma data were performed using WinNonlin (version 3.3; Pharsight Corporation, Palo Alto, CA). Evaluations of other data were performed using SAS (version 8.2; SAS Institute, Cary, NC) under Windows NT (Microsoft Corporation, Redmond, WA).

Pharmacokinetic Modeling Using Compartmental Methods

In an attempt to predict the concentrations of unbound ropivacaine and 2',6'-pipecoloxylidide in plasma during continuous administration of ropivacaine, a compartmental pharmacokinetic model was constructed that was specified in terms of four differential equations. The metabolite 2',6'-pipecoloxylidide was incorporated in the model because it is the major known active metabolite of ropivacaine. Although 2',6'-pipecoloxylidide only accounts for 3% of ropivacaine elimination after single dose administration, it is known to accumulate and become the major active metabolite in plasma during postoperative continuous epidural and peripheral infusion.\textsuperscript{10,20} With the chosen sampling scheme, it was possible to capture a biphasic plasma concentration-time profile of ropivacaine (fig. 1), which could be well described by a two-compartment model with zero-order input into the central plasma compartment and first-order elimination of ropivacaine from the central compartment via dual routes, directly and via metabolism into a 2',6'-pipecoloxylidide plasma compartment with further urinary elimination (fig. 2). The model parameters were volume of the central compartment (\( V_{\text{c}} \)), volume of the peripheral compartment (\( V_{p} \)), volume of distribution for 2',6'-pipecoloxylidide (\( V_{\text{D}} \)), distribution clearance between central and peripheral compartments (\( Cl_{\text{p}} \)), elimination clearance of ropivacaine to 2',6'-pipecoloxylidide (\( Cl_{\text{PO}} \)), renal 2',6'-pipecoloxylidide clearance (\( Cl_{\text{PO}} \)), and elimination clearance of ropivacaine via other routes than transformation to 2',6'-pipecoloxylidide (\( Cl_{\text{L}} \)). Four differential equations (equations 1–4) described the rates of change of ropivacaine concentrations in the central and peripheral compartments (\( \text{Ropi}_{\text{C}} \) and \( \text{Ropi}_{\text{P}} \)), dual routes, directly and via metabolism into a 2',6'-pipecoloxylidide plasma compartment with further urinary elimination (fig. 2). The model parameters were volume of the central compartment (\( V_{\text{c}} \)), volume of the peripheral compartment (\( V_{p} \)), volume of distribution for 2',6'-pipecoloxylidide (\( V_{\text{D}} \)), distribution clearance between central and peripheral compartments (\( Cl_{\text{p}} \)), elimination clearance of ropivacaine to 2',6'-pipecoloxylidide (\( Cl_{\text{PO}} \)), renal 2',6'-pipecoloxylidide clearance (\( Cl_{\text{PO}} \)), and elimination clearance of ropivacaine via other routes than transformation to 2',6'-pipecoloxylidide (\( Cl_{\text{L}} \)). Four differential equations (equations 1–4) described the rates of change of ropivacaine concentrations in the central and peripheral compartments (\( \text{Ropi}_{\text{C}} \) and \( \text{Ropi}_{\text{P}} \)), dual routes, directly and via metabolism into a 2',6'-pipecoloxylidide plasma compartment with further urinary elimination (fig. 2). The model was fitted simultaneously to plasma concentration-time data of total ropivacaine and 2',6'-pipecoloxylidide, and cumulative urinary excretion-time data of 2',6'-pipecoloxylidide by means of a user defined model in WinNonlin (version 4.0; Pharsight Corporation). Data were weighted according to the reciprocal of the predicted value. Goodness of fit was based on residual analysis, and as shown in figure 3, the observed plasma concentrations of ropivacaine and 2',6'-pipecoloxylidide as well as the urinary excretion of 2',6'-pipecoloxylidide in each subject were well predicted by the chosen model. Other models (e.g., one-compartment) and different weighting schemes were also tested, but none were found to improve overall goodness of fit. The model was then used to predict individually the concentrations of total ropivacaine and 2',6'-pipecoloxylidide in plasma during a continuous 72-h intravenous infusion of ropiva.
Fig. 1. Individual plasma concentrations of total (continuous lines) and unbound (dashed lines) ropivacaine, and total and unbound 2',6'-pipocloxyldide (PPX) in 13 patients with chronic end-stage liver disease (left) and 8 healthy volunteers (right) after the start of a 30-min intravenous infusion of 0.6 mg/kg ropivacaine.
caine at 28-mg/h input rate. The corresponding unbound concentrations were obtained by multiplying the predicted total ropivacaine and 2′,6′-pipecoloxylidide concentrations with individually determined free fraction ($f_u$) values. Because the central nervous toxicity of unbound 2′,6′-pipecoloxylidide in rats is approximately one twelfth of that of unbound ropivacaine (Magnus M. Halldin, M.Sc.Pharm., Ph.D., Senior Principal Scientist, Global Development DMPK & Bioanalysis, AstraZeneca R&D, Södertälje; April 1998; oral and AstraZeneca internal written communication), we also calculated the sum of the unbound concentration of ropivacaine and one twelfth of that of 2′,6′-pipecoloxylidide to illustrate the potential central nervous system toxicity of ropivacaine plus its major active metabolite 2′,6′-pipecoloxylidide.

\[
\text{d}Ropi_{C}/\text{d}t = \left(\text{Input} + \text{Cl}_{D} \cdot Ropi_{F} - \text{Cl}_{D} \cdot \text{Ropi}_{C} - \text{Cl}_{E} \cdot \text{Ropi}_{C}\right)/\text{V}_{C} \tag{1}
\]

\[
\text{d}Ropi_{T}/\text{d}t = \left(\text{Cl}_{D} \cdot \text{Ropi}_{C} - \text{Cl}_{D} \cdot \text{Ropi}_{T}\right)/\text{V}_{T} \tag{2}
\]

\[
\text{d}PPX/\text{d}t = \left(\text{Cl}_{PO} \cdot \text{PPX}\right)/\text{V}_{O} \tag{3}
\]

\[
\text{d}PPX_{Excr}/\text{d}t = \text{Cl}_{PO} \cdot \text{PPX} \tag{4}
\]

**Safety Assessment**

A three-lead electrocardiogram, heart rate, and noninvasive blood pressure were monitored for 1 h after the start of the ropivacaine infusion, and adverse events were assessed using standard questioning.
LIVER DISEASE AND ROPIVACAINE PHARMACOKINETICS

Table 3. Mean Pharmacokinetic Variables of 0.6 mg/kg Intravenous Ropivacaine in Patients with Chronic End-stage Liver Disease and Healthy Volunteers, Based on a Noncompartmental Model

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<tr>
<th></th>
<th>Patients</th>
<th>Healthy volunteers</th>
<th>95% Confidence Limits</th>
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<tbody>
<tr>
<td>Ropivacaine</td>
<td></td>
<td></td>
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<tr>
<td>( C_{\text{max}} ), mg/l</td>
<td>13 0.71 0.17</td>
<td>8 0.87 0.20</td>
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<td>( C_{\text{max}} ), ( \mu )g/l</td>
<td>13 37 11</td>
<td>8 41 8</td>
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<tr>
<td>AUC, mg · l(^{-1}) · h</td>
<td>13 5.5 2.7</td>
<td>8 1.9 0.4</td>
<td>1.3 6.5 0.000</td>
</tr>
<tr>
<td>( V_{\text{ss}} ), l</td>
<td>13 131 68</td>
<td>8 331 113</td>
<td>295 110 0.001</td>
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<tr>
<td>( t_{\text{max}} ), h</td>
<td>13 2.8 1.1</td>
<td>8 6.3 2.7</td>
<td>6.1 1.2 0.002</td>
</tr>
<tr>
<td>( C_{\text{mean}} ), mg/l</td>
<td>12 2.8 1.9</td>
<td>8 1.1 0.7</td>
<td>0.4 2.5 0.015</td>
</tr>
<tr>
<td>( t_{\text{1/2}} ), h</td>
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<td>8 56 19</td>
<td>0.9 60 0.033</td>
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<td>( \text{MRT} ), h</td>
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<td>8 0.3 0.2</td>
<td>1.1 2.5 0.000</td>
</tr>
<tr>
<td>( 2',6')-Pipocoloxylidide</td>
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</tr>
<tr>
<td>( C_{\text{max}} ), ( \mu )g/l</td>
<td>13 19 8</td>
<td>8 26 12</td>
<td>18 4 NS</td>
</tr>
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<td>( t_{\text{max}} ), h</td>
<td>13 16.3 6.7</td>
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<td>5.0 17.2 0.000</td>
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<tr>
<td>( f_m,\text{PPX} ), %</td>
<td>12 4.7 2.8</td>
<td>8 5.0 2.8</td>
<td>3.4 2.4 NS</td>
</tr>
<tr>
<td>( f_\text{u} ), %</td>
<td>13 59 14</td>
<td>8 52 6</td>
<td>4.1 21.2 NS</td>
</tr>
<tr>
<td>3-Hydroxyropivacaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ), ( \mu )g/l</td>
<td>1 4 NA</td>
<td>8 15 7</td>
<td>21 5 0.000</td>
</tr>
<tr>
<td>( t_{\text{max}} ), h</td>
<td>1 2.0 NA</td>
<td>8 2.0 0.06</td>
<td>0.3 7.2 NS</td>
</tr>
<tr>
<td>( f_m,3)\text{-OH} ), %</td>
<td>12 11 5</td>
<td>8 27 7</td>
<td>22 9.5 0.001</td>
</tr>
<tr>
<td>AAG</td>
<td></td>
<td></td>
<td>3.2 7.2 NS</td>
</tr>
</tbody>
</table>

AAG = \( \alpha \)-acid glycoprotein; AUC = area under the drug plasma concentration–time curve with extrapolation to infinity; \( Cl \) = plasma clearance; \( Cl_{i} \) = renal plasma clearance; \( Cl_{u} \) = free plasma clearance; \( C_{\text{max}} \) = peak (or highest measured for the metabolite) plasma concentration; \( C_{\text{mean}} \) = mean concentration; \( C_{\text{u,max}} \) = peak free (unbound) plasma concentration; \( t_{\text{u}} \) = fraction of unchanged ropivacaine excreted in urine; \( t_{m,3\text{-OH}} \) = fraction metabolized to 3-hydroxyropivacaine; \( f_{m,\text{PPX}} \) = fraction metabolized to \( 2',6'\)-pipocoloxylidide; \( f_{\text{u}} \) = free (unbound) fraction of ropivacaine or \( 2',6'\)-pipocoloxylidide in plasma; MRT = mean residence time; NA = not applicable; NS = not significant; \( t_{\text{i}} \) = elimination half-life; \( t_{\text{max}} \) = time to \( C_{\text{max}} \); \( t_{\text{1/2}} \) = steady state volume of distribution.

Statistical Analysis

The results are expressed as mean ± SD. The Mann–Whitney U test was used for comparisons of all pharmacokinetic parameters between the patients and healthy volunteers. No correction for multiple tests was used, and the exact \( P \) values and the 95% confidence limits for the group differences are given in table 3. Differences were regarded as significant if \( P < 0.05 \). The Pearson product–moment correlation coefficient was used to investigate the possible relation between the ropivacaine CI and the galactose half-life, serum albumin, serum prealbumin, and international normalized ratio of plasma thromboplastin time.

Results

Ropivacaine

The mean peak total (\( C_{\text{max}} = 0.71 \) vs. 0.87 mg/l) and unbound (\( C_{\text{u,max}} = 37 \) vs. 41 \( \mu \)g/l) ropivacaine plasma concentrations (fig. 1) and the mean free fraction of plasma ropivacaine (\( f_u = 4.8\% \) vs. 5.7\%) were similar in the patients with chronic end-stage liver disease and in the healthy volunteers (table 3). The patients had 60% lower mean total ropivacaine plasma clearance (\( Cl = 131 \) vs. 331 ml/min; \( P = 0.001 \)), 56% lower unbound plasma clearance (\( Cl_{u} = 2.8 \) vs. 6.3 l/min; \( P = 0.002 \)), 59% higher volume of distribution (\( V_{\text{ss}} = 89 \) vs. 56 l; \( P = 0.03 \)), fourfold longer ropivacaine half-life (\( t_{\text{i}} = 10.8 \) vs. 2.6 h; \( P < 0.001 \)), fivefold longer mean residence time (13.8 vs. 2.9 h; \( P < 0.001 \)), and threefold higher AUC (5.5 vs. 1.9 mg · l\(^{-1}\) · h; \( P < 0.001 \)) of ropivacaine compared with the healthy volunteers.

Only a small fraction of the original ropivacaine dose was excreted unchanged in urine (fig. 4). The patients with liver disease excreted sevenfold more ropivacaine compared with the healthy volunteers (\( f_u = 2.1\% \) vs. 0.3\%; \( P < 0.001 \)) and also had a significantly higher renal clearance of ropivacaine (\( Cl_{u} = 2.8 \) vs. 1.1 ml/min; \( P = 0.02 \)).

In the linear regression analysis, 69% of the variation in total clearance of ropivacaine was accounted for by variation in albumin (\( r^2 = 0.69, P < 0.001 \)) and 57% by variation in prealbumin (\( r^2 = 0.57, P < 0.001 \); fig. 5). Based on a negative correlation, 25% of the variation in total clearance of ropivacaine was accounted for by variation in international normalized ratio of plasma thromboplastin time (\( r^2 = 0.25, P = 0.02 \)), and 24% was accounted for by variation in galactose half-life (\( r^2 = 0.24, P = 0.02 \); fig. 5). Patient 6 received albumin before

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the study and was excluded from the ropivacaine clearance versus serum albumin analysis. Of the variation in unbound ropivacaine clearance, 56, 51, 27, and 27%, respectively, were explained by variations in the previously mentioned laboratory values.

2′,6′-Pipecoloxylidide
There were no statistically significant differences in the highest measured plasma concentrations of total (19 vs. 26 μg/l) or unbound (11 vs. 13 μg/l) 2′,6′-pipecoloxylidide between the patients with liver disease and the healthy volunteers (table 3). However, the concentrations of the total and unbound 2′,6′-pipecoloxylidide were still increasing at 2 h in seven and five patients, respectively. 2′,6′-Pipecoloxylidide half-lives could not be estimated reliably either in the patients or healthy volunteers (fig. 1).

Both the patients and healthy volunteers excreted similar amount of 2′,6′-pipecoloxylidide in urine in 24 h ($t_{\text{m}} = 4.7\%$ vs. $5.0\%$; $P = $ not significant; fig. 4), and in both groups, a similar fraction ($f_{\text{u}} = 59\%$ vs. $52\%$; $P = $ not significant) of the plasma 2′,6′-pipecoloxylidide was free.

3-Hydroxyropivacaine
In the patients, 3-hydroxyropivacaine could be detected only in one plasma sample in one patient (4 μg/l at 2 h). In the healthy volunteers, the peak 3-hydroxyropivacaine concentration ($C_{\text{max}} = 15 μg/l$) was reached at 2 h (table 3).

The 3-hydroxyropivacaine plasma half-life in the healthy volunteers was 2.5 h. Patients excreted 59% less 3-hydroxyropivacaine in urine in 24 h than the healthy volunteers did ($f_{\text{m}} = 11\%$ vs. $27\%$; $P = 0.001$; fig. 4).

Simulation of Unbound Ropivacaine and 2′,6′-Pipecoloxylidide Plasma Concentrations during Continuous Intravenous Infusion of Ropivacaine
The individually predicted concentrations of unbound ropivacaine, 2′,6′-pipecoloxylidide, and the sum of ropivacaine and one twelfth of 2′,6′-pipecoloxylidide are shown in figure 6. The pharmacokinetic variables based on the compartmental model are presented in table 4. Two patients were excluded from pharmacokinetic modeling because the initial urinary excretion rates of 2′,6′-pipecoloxylidide were not available. In the patients, the simulated maximum concentration of unbound ropivacaine at the end of the infusion was 155 ± 54 μg/l (range, 89–266 μg/l), and that in the healthy volunteers was 78 ± 31 μg/l (range, 42–116 μg/l). The simulated concentrations of unbound 2′,6′-pipecoloxylidide were 379 ± 176 μg/l (range, 75–660 μg/l) and 211 ± 126 μg/l (range, 47–340 μg/l) in the two groups, respectively. The corresponding concentrations of the sum of ropivacaine and one twelfth of 2′,6′-pipecoloxylidide were 184 ± 56 μg/l (range, 95–292 μg/l) and, in the healthy volunteers, 95 ± 38 μg/l (range, 47–141 μg/l).

The plateau is determined by clearance, which is illustrated by the approximately two- to four-times-higher unbound plasma concentrations of ropivacaine (and even higher for 2′,6′-pipecoloxylidide) in the patients with liver disease compared with those in healthy volunteers (fig. 6). Time to steady state is determined by the half-life, and consequently, the plateau is reached later in those with impaired liver function. Several patients did not reach the plateau of 2′,6′-pipecoloxylidide during the simulated 72-h intravenous infusion (patient 5 regarding ropivacaine and, in order of descending concentration, patients 4, 10, 6, and 5 regarding 2′,6′-pipecoloxylidide).

Safety Assessment
One patient had ventricular extrasystoles during and after the ropivacaine infusion. She had a total ropivacaine $C_{\text{max}}$ of 0.88 mg/l (unbound concentration 0.02 mg/l) at the end of the ropivacaine infusion. There was no clinically relevant change in her heart rate or blood pressure. Another patient experienced a tingling feeling in her tongue 1–2 h after the start of the infusion ($C_{\text{max}}$ 0.82 mg/l and unbound concentration 0.03 mg/l at the end of the infusion).

Discussion
This study was performed in patients with chronic end-stage liver disease who were being evaluated for liver transplantation. Twelve of the 13 patients underwent hepatic transplantation 8–97 days (median, 31 days) after participating in the study. It is reasonable to...
believe that ropivacaine pharmacokinetics are less affected in patients with a less severe liver disease. Although the patients with chronic end-stage liver disease in the current study had, on average, 60% lower ropivacaine clearance and approximately threefold higher AUC values than the healthy volunteers after the intravenous administration of ropivacaine, the patients tended to have somewhat lower peak ropivacaine plasma concentrations than the healthy volunteers. This is due to the larger volume of distribution in the patients. The volume of distribution of many other drugs, e.g., rocuronium,21,22 furosemide,23 and propofol,24 is also increased in liver disease. After an accidental intravenous ropivacaine injection, patients with liver disease would then be expected to have similar (or slightly lower) ropivacaine peak concentrations but a longer half-life than healthy subjects.

Compared with the healthy volunteers, the patients excreted more unchanged ropivacaine, an equal amount of 2',6'-picecoloxylidide, and less 3-hydroxyropivacaine in urine. Because the formation of 2',6'-picecoloxylidide is catalyzed by CYP3A4 and that of 3-hydroxyropivacaine is catalyzed by CYP1A2, it seems plausible to assume that CYP1A2 activity is more affected than CYP3A4 activity in end-stage liver disease. The fact that CYP3A4 is more abundant than CYP1A2 in the liver may be one reason for this.15 Another possible explanation for the preserved 2',6'-picecoloxylidide excretion in patients with liver disease might be reduced further metabolism of 2',6'-picecoloxylidide to 3-OH-PPX by CYP1A2.2

If the absorption of ropivacaine in regional anesthesia is not affected by chronic end-stage liver disease, a single dose of ropivacaine, on a pharmacokinetic basis, seems to be equally safe in patients with and without liver disease.

Fig. 5. Ropivacaine plasma clearance in 13 patients with chronic end-stage liver disease and 8 healthy volunteers (after a 30-min intravenous infusion of 0.6 mg/kg ropivacaine) versus serum albumin ($r = 0.83$, $P < 0.001$), serum prealbumin ($r = 0.75$, $P < 0.001$), international normalized ratio (INR; $r = -0.50$, $P = 0.02$), and galactose half-life ($r = -0.49$, $P = 0.02$). One patient (star) received albumin before the study and was excluded from the ropivacaine clearance versus serum albumin analysis. Linear regression lines are included.
disease. However, the effects of absorption kinetics and pharmacodynamics were not assessed in this study. An increase in the absorption speed would theoretically lead to a higher peak plasma concentration after a single extravascular dose. However, the patients with end-stage liver disease had higher volumes of distribution and a tendency toward lower ropivacaine plasma concentrations than the healthy volunteers, so it seems unlikely that a modest increase in the absorption speed would considerably change the peak ropivacaine plasma concentrations in these patients. Any change in the absorption of ropivacaine in the patients with liver disease would most likely not change the time needed to reach a steady state in ropivacaine concentration during a continuous infusion, because even a changed absorption half-life is likely to be shorter than the elimination half-life (mean 11 h) in these patients.

One of the patients had ventricular extrasystoles during the ropivacaine infusion, and another patient experienced a tingling feeling in her tongue 1–2 h after the start of the infusion. The unbound venous plasma concentrations of ropivacaine in these patients at the end of the infusion (at 0.5 h) were 0.02 and 0.03 mg/l, respectively. These concentrations are low to be responsible for the adverse events, especially because the symptoms did not commence at the time of the peak plasma concentrations. Healthy volunteers have tolerated mean 0.56 mg/l (minimum 0.34 mg/l) arterial unbound plasma concentration during an intravenous 10-mg/min infusion of ropivacaine. Generally, the unbound arterial plasma concentrations, rather than the unbound venous concentrations (mean 0.15 mg/l and minimum 0.01 mg/l, respectively), are related to the local anesthetic toxicity during a rapid input of the drug, when there is an arteriovenous concentration difference. After intravenous administration, the arterial plasma concentrations increase faster than the venous concentrations, and equilibrium is reached within 20 min. In the current study, the mean ropivacaine infusion rate was approximately 1.3 mg/min, and peripheral venous sampling was used. In both cases, the unbound ropivacaine plasma concentrations at the end of infusion (0.02 and 0.03 mg/l) were well below the reported threshold for definitive central nervous system toxicity, 0.3 mg/l.

For ethical reasons, a small dose of ropivacaine was administrated intravenously to patients with chronic end-stage liver disease and healthy volunteers.

Table 4. Mean Pharmacokinetic Variables for Ropivacaine and Its Conversion to 2,6'-Pipocelovalidie and Urinary Elimination, Based on a Compartmental Model

<table>
<thead>
<tr>
<th>Patients</th>
<th>Healthy Volunteers</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>$\text{CL}_{E}$, ml/min</td>
<td>11</td>
<td>118</td>
</tr>
<tr>
<td>$\text{CL}_{D}$, l/min</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>$\text{CL}_{P}$, ml/min</td>
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<td>24</td>
</tr>
<tr>
<td>$\text{CL}_{PO}$, ml/min</td>
<td>11</td>
<td>68</td>
</tr>
<tr>
<td>$\text{V}_{O}$, l</td>
<td>11</td>
<td>125</td>
</tr>
</tbody>
</table>

Ropivacaine, 0.6 mg/kg, was administered intravenously to patients with chronic end-stage liver disease and healthy volunteers.

$\text{CL}_{E}$ – elimination clearance of ropivacaine; $\text{CL}_{D}$ – distribution between central and peripheral compartments; $\text{CL}_{P}$ – elimination clearance to 2,6’-pipocecolavlidie; $\text{CL}_{PO}$ – renal 2,6’-pipocecolavlidie clearance; $\text{V}_{O}$ – volume of the central compartment; $\text{V}_{D}$ – volume of distribution for 2,6’-pipocecolavlidie; $\text{V}_{T}$ – volume of the peripheral compartment.
given intravenously as a relatively short (30-min) infusion and considered relevant for the pharmacokinetic evaluation. Because the ropivacaine clearance is decreased in patients with chronic end-stage liver disease, it can be expected that plasma concentration and, thus, the risk of toxicity of ropivacaine are increased if a continuous infusion or repeated doses are to be used. However, because of the longer half-life, the steady state in ropivacaine plasma concentration in patients with liver disease is to be reached later than in healthy subjects. Another issue with continuous administration of ropivacaine is a possible accumulation of the 2′,6′-pipocoloxylidide metabolite because the central nervous toxicity of unbound 2′,6′-pipocoloxylidide in rats is approximately one twelfth of that of unbound ropivacaine (Magnus M. Halldin, M.Sc.Pharm., Ph.D.; April 1998; oral and AstraZeneca internal written communication). In the current study, in the healthy volunteers, 52% of the infused ropivacaine dose was excreted in urine in form of unchanged ropivacaine, 2′,6′-pipocoloxylidide, or 3-hydroxyropivacaine within 24 h after the start of infusion. This is similar to the previous studies in healthy volunteers.6,7,9 In the current study, in the patients with liver disease, only 18% of the original dose was excreted in urine within 24 h. This, together with increasing 2′,6′-pipocoloxylidide plasma concentrations (fig. 1) in many patients at 22 h, suggests that, during a continuous administration of ropivacaine, steady state plasma 2′,6′-pipocoloxylidide levels are higher in patients with liver disease. Higher unbound concentrations of 2′,6′-pipocoloxylidide have been reported during postoperative epidural and interscalene infusion.10,20

To further evaluate the risk of a continuous ropivacaine infusion in patients with liver disease, we used pharmacokinetic modeling to predict the accumulation of ropivacaine and 2′,6′-pipocoloxylidide in plasma during a 72-h intravenous ropivacaine infusion. Ropivacaine pharmacokinetics were assumed to be linear.26 The estimated values for total clearance of ropivacaine using the compartmental approach were similar to clearance values calculated by noncompartmental methods. A dose of 28 mg/h was used for the simulation, because it is the largest dose recommended by the manufacturer for a continuous postoperative epidural infusion.6,20

The steady state total ropivacaine plasma concentrations during a postoperative ropivacaine epidural infusion increase to concentrations that are higher than predicted by this model,10,27 because of a postoperative increase in α1-acid glycoprotein, to which ropivacaine is bound. The decrease in the free fraction due to increased protein binding will decrease total clearance and drive an increase in total concentration. However, the unbound ropivacaine clearance is independent of changes in the α1-acid glycoprotein concentration, and the steady state unbound plasma concentration during a postoperative ropivacaine epidural infusion show no time dependency.10,27 Consequently, the predicted steady state unbound concentrations of ropivacaine and 2′,6′-pipocoloxylidide during an intravenous infusion are expected to be similar to those during a long-lasting epidural infusion, because ropivacaine is extensively absorbed from the epidural space.28 During an epidural infusion of 30 mg/h ropivacaine for 72 h after surgery in normal patients,10 the unbound plasma concentrations of ropivacaine and 2′,6′-pipocoloxylidide were of the same order of magnitude as predicted by the intravenous model, although the predicted concentrations were still increasing at the end of infusion in some subjects.

The highest simulated unbound ropivacaine plasma concentration during the 72-h ropivacaine infusion was 0.27 mg/L, which is close to the toxic threshold in healthy volunteers.25 However, the safety limits should be based on the sum of the unbound concentrations of ropivacaine and one twelfth of that of 2′,6′-pipocoloxylidide. That the unbound ropivacaine concentration in one patient and the 2′,6′-pipocoloxylidide concentration in four of the patients were still markedly increasing at 72 h further stresses a potential risk of toxicity of ropivacaine in patients with liver disease.

The patients in this study were evaluated for liver transplantation, and all had severe chronic end-stage liver disease. It is reasonable to believe that the ropivacaine clearance is less affected in patients with less severe liver disease. Some routine laboratory measurements, such as serum albumin and prealbumin, seem to explain approximately 70% and 60%, respectively, of the variation in ropivacaine clearance (fig. 5). The correlation was not improved by a simultaneous regression analysis of serum albumin and prealbumin, which did not explain more of the variation in ropivacaine clearance (70%). Serum albumin was also shown to be the parameter best predicting an increase in drug exposure in a review of hepatic impairment studies by the Swedish regulatory agency (Medical Products Agency, Upplands, Sweden),29 which supports our results.

Because ropivacaine has a relatively low hepatic extraction ratio (approximately 40%),25 6 its total clearance is more susceptible to changes in the hepatic enzyme activity and plasma protein binding than in the hepatic blood flow. Furthermore, changes in protein binding does affect total but not unbound ropivacaine clearance, which fits with the theoretical influence of a low hepatic extraction ratio on pharmacokinetics.10,20,27 However, changes in the hepatic blood flow might to some extent be responsible for part of the variability seen in the ropivacaine clearance. Unfortunately, hepatic blood flow was not systematically measured in this study.

Although renal excretion is only a very minor elimination pathway for ropivacaine, it was interesting to notice...
that the patients with liver disease had a considerably higher renal ropivacaine clearance than the healthy volunteers. An explanation for this might be the increased cardiac output in patients with liver cirrhosis. However, the increased cardiac output does not seem to be associated with increased glomerular filtration rate in cirrhotic patients. The increased renal clearance of ropivacaine could be due to changes in urine pH in chronic liver disease. Unfortunately, the urine pH was not measured in this study. The urinary excretion of cefoperazone, another basic drug, has also been reported to be significantly increased in patients with liver cirrhosis. Renal clearance was calculated as clearance times fraction of ropivacaine excreted in urine in 24 h. Because, especially in the patients, all ropivacaine was not excreted in 24 h, the calculated renal clearance values are somewhat underestimated, and the difference between the patients and controls is likely to be even larger than now computed.

The patients with liver disease were mostly recruited after the healthy controls and were not matched for age. However, differences in CYP content and activity seem to be relatively small in individuals between the ages of 20 and 70 yr. Because of ethical considerations, food intake was not restricted in patients. Because ropivacaine was administered intravenously, this is not likely to invalidate our results. One of the patients and none of the volunteers were smokers, but the effect of smoking on ropivacaine clearance is small. One of the patients had a chronic alcohol liver disease, but none of the subjects were heavy drinkers at the time of participating in this study. Half of the healthy controls were taking oral contraceptives, and four of the patients were taking medicines that might have reduced ropivacaine clearance (tables 1 and 2). Calculated without these subjects, the difference in ropivacaine clearance between the two groups is 66% (P < 0.001).

Venous plasma samples were collected for up to 12 h from the healthy volunteers and up to 22 h from the patients with chronic end-stage liver disease. This was judged to be relevant, considering the ropivacaine elimination half-life of approximately 2 h in healthy subjects. Because the patients with liver disease had a mean half-life of 11 h, however, a collection period even longer than 22 h would have been more appropriate.

Clearance of lidocaine, another amide-type local anesthetic agent also metabolized by CYP1A2 and CYP3A4, is decreased 65% by Child C liver cirrhosis. This is similar to our finding with ropivacaine, even if the hepatic extraction ratio of lidocaine (65%) is much higher than that of ropivacaine (40%). There is little information on the metabolism of a third amide-type local anesthetic agent, bupivacaine. Bupivacaine is structurally related to ropivacaine, approximately 5% of it is metabolized to 2',6'-piperacoloxylide by CYP3A, and it has a hepatic extraction ratio (38%) comparable to that of ropivacaine. Until more precise information is available, it seems reasonable to assume that an end-stage liver disease has roughly a similar impact on both bupivacaine and ropivacaine clearance.

End-stage liver disease has been associated with neuropathy, but to our knowledge, the clinical impact of this on the pharmacodynamics of local anesthetic agents is not known. This study was not designed to evaluate pharmacodynamics.

We conclude that chronic end-stage liver disease decreases ropivacaine clearance, on average, by 60%. But because the peak plasma concentration after a single dose is essentially unaffected by liver impairment, a normal dose can be considered for a single block in patients with liver disease. The risk of ropivacaine toxicity cannot be ruled out, however, for repeated doses or a continuous postoperative infusion. Because of wide interindividual differences in pharmacokinetics in patients with liver disease, no definitive dosing instructions can be given. It is advisable to use the lowest effective dose, for the shortest possible time, and to monitor the patients closely when using a ropivacaine infusion in patients with an end-stage liver disease.

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