Effects of liver disease on the disposition of the opioid antagonist nalmefene

Objectives: The pharmacokinetics of nalmefene and its glucuronide metabolite were investigated in 12 patients with liver disease (four patients with mild, five patients with moderate, and three patients with severe liver disease) and 12 age-, weight-, and gender-matched control subjects.

Methods: Subjects received a single intravenous bolus 2.0 mg dose of nalmefene. Multiple blood and urine samples were collected for 48 hours. Within 1 week of nalmefene administration, antipyrine and galactose clearances were determined as general markers of hepatic metabolism and effective liver plasma flow, respectively. Plasma concentrations of nalmefene were determined by radioimmunoassay.

Results: The antipyrine and galactose clearance values were 56% and 33% lower, respectively, in the patients with liver disease compared with the normal healthy control subjects. The systemic clearance of nalmefene was reduced by 32% (0.61 ± 0.21 versus 0.90 ± 0.27 L/hr/kg [mean ± SD]) and the terminal elimination half-life was increased by 31% (10.5 ± 1.9 versus 8.0 ± 2.2 hours) in the patients with liver disease. This was primarily the result of a 31% reduction (0.181 ± 0.067 versus 0.263 ± 0.072 L/hr/kg) in nalmefene glucuronide formation clearance. There were no significant differences in nalmefene volumes of distribution or protein binding. There was a significant inverse relationship between nalmefene clearance and Pugh score (r = -0.57; p = 0.004), indicating decreasing nalmefene clearance with increasing severity of liver disease.

Conclusions: The clearance of nalmefene was significantly reduced in the presence of liver disease. However, because nalmefene will be primarily used in the acute care setting for reversal of opioid-induced effects, it is not likely that these alterations will necessitate a dosage modification. (Clin Pharmacol Ther 1997;61:15-23.)

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Nalmefene hydrochloride (Revex) is a specific opioid antagonist that possesses high affinity to multiple central opioid receptor subtypes. Nalmefene was recently approved by the U.S. Food and Drug Administration after it showed effective reversal of opioid-induced postoperative respiratory depression and opioid overdose following parenteral administration. Results from clinical trials indicate that nalmefene, which is structurally similar to naltrexone, has a much longer elimination half-life (t1/2) and thus pharmacodynamic duration of action than naloxone.

Nalmefene is predominately eliminated by conjugation with glucuronic acid to form a pharmacologically inactive ether glucuronide metabolite. After intravenous administration, approximately 40% of nalmefene is eliminated in the urine and 20% is eliminated in the feces as the glucuronide metabolite. About 10% of nalmefene is eliminated renally unchanged, and 10% or less is N-dealkylated. Nalmefene is widely distributed, with an average steady-state volume of distribution (Vss) of approximately 8 L/kg in normal healthy volunteers. The total body clearance (CL) approaches 1100 ml/min, and the terminal elimination t1/2 ranges between 8 and 10 hours in healthy middle-aged volunteers.

The longer duration of action and enhanced effectiveness of nalmefene in reversing opioid induced respiratory depression and sedation is likely a result of its longer terminal elimination t1/2 relative to naloxone, which has a t1/2 of approximately 1 hour.
Numerous investigations have documented the influence of liver disease on drug disposition. It is generally accepted that liver disease impairs the elimination of drugs that undergo metabolic oxidation. For example, alcoholic liver disease or cirrhosis has been associated with decreases in the clearance of general in vivo probe drugs such as antipyrine (phenazone), theophylline, and caffeine. However, liver disease does not appear to have a comparable effect on the glucuronidation of drugs. The objective of this study was to examine the influence of liver disease on the disposition of nalmefene and its primary metabolite nalmefene glucuronide.

**METHODS**

Twelve patients with liver disease and 12 age-, gender-, and weight-matched healthy volunteers participated in this investigation after each gave written informed consent. The study was approved by the University of Pittsburgh Biomedical Institutional Review Board (Pittsburgh, Pa.). All patients and volunteers who were enrolled completed the study. The average age of the patients with liver disease was 47.3 years (age range, 25 to 75 years; two women and 10 men); the average age of the healthy volunteers was 47.5 years (age range, 21 to 73 years; two women and 10 men; Table I). The Child's-Pugh score was used at screening to categorize the degree of hepatic impairment. Four patients had mild liver disease (Pugh score, 5 to 6; Child's class A), five patients had moderate liver disease (Pugh score, 7 to 9; Child's class B), and three patients had severe liver disease (Pugh score, 10 to 15; Child's class C). Cirrhosis was confirmed by biopsy in all patients with Child's class B or C. The causes of liver disease included hepatitis C (seven patients), hepatitis B (one patient), chemically induced (one patient), alcoholic cirrhosis (two patients), and cryptogenic cirrhosis (one patient). Study participants were asked to abstain from alcohol or caffeine intake for 48 hours before and during each study visit. All of the study participants were nonsmokers. None of the patients or normal volunteers were receiving any medications known to modulate metabolizing enzyme activity. All normal volunteers were healthy as confirmed by medical history, physical examination, blood chemistries, and urinalysis.

Antipyrine was administered to all study participants within 7 days of nalmefene administration to provide an independent estimate of oxidative metabolic capacity. The pharmacokinetics of antipyrine were assessed after the oral administration of 1000 mg antipyrine in solution the morning after an overnight fast. Saliva was collected after stimulation by chewing parafilm before drug administration and at 1, 2, 4, 8, 12, 24, 32, and 48 hours after administration. Additional samples were collected at 56 and 72 hours after antipyrine administration in patients with liver disease. Saliva samples were centrifuged and the supernatant was transferred to polypropylene tubes and stored at −20°C until analyzed.

The clearance of galactose was used as an estimate of effective hepatic plasma flow and was assessed within 7 days of nalmefene administration to provide an independent estimate of oxidative metabolic capacity. The pharmacokinetics of antipyrine were assessed after the oral administration of 1000 mg antipyrine in solution the morning after an overnight fast. Saliva was collected after stimulation by chewing parafilm before drug administration and at 1, 2, 4, 8, 12, 24, 32, and 48 hours after administration. Additional samples were collected at 56 and 72 hours after antipyrine administration in patients with liver disease. Saliva samples were centrifuged and the supernatant was transferred to polypropylene tubes and stored at −20°C until analyzed.
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Study participants were admitted to the Clinical Research Center the evening before nalmefene administration. They fasted overnight and continued to fast for 4 hours after the intravenous bolus administration of 2.0 mg nalmefene over 30 seconds. Blood samples were collected into heparinized tubes before nalmefene administration and at 5, 10, 15, 30, and 45 minutes and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 36, and 48 hours after administration. An additional blood sample was collected 1 hour after dosing for the determination of nalmefene protein binding. All urine was collected from 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, and 36 to 48 hours after nalmefene administration. Creatinine clearances were determined during the last 24-hour period. Vital signs were measured at 5, 15, and 30 minutes and at 1, 2, 4, 6, 8, 12, 18, 24, 30, 36, 40, and 48 hours after nalmefene dosing.

Analytical methods

Antipyrine and galactose. The concentration of antipyrine in saliva was determined by a modification of the HPLC method of Danhof et al.14 The concentration of galactose in infusate and plasma was determined by a previously described automated fluorometric assay method.15

Nalmefene. The concentrations of nalmefene and its ether glucuronide in plasma and urine were determined by a specific radioimmunoassay (RIA) procedure as previously described by Dixon et al.16 The unconjugated nalmefene and total nalmefene (unconjugated nalmefene plus conjugated nalmefene) present after hydrolysis with β-glucuronidase were quantitated by RIA. The nalmefene glucuronide concentration was determined as the difference between nalmefene and total nalmefene obtained after hydrolysis. Nalmefene was detected by rabbit antiserum to naltrexone-6-(carboxymethyl)oxime conjugated to bovine serum albumin. The assay was linear over the range from 0.0625 to 2 ng/ml in plasma and 1.25 to 40 ng/ml in urine. If necessary, samples were diluted until the measured concentrations were in the appropriate range. The interday coefficient of variation over the concentration range from 0.375 to 30 ng/ml in plasma ranged from 6.2% to 11.3%. The interday coefficient of variation in urine over the concentration range from 3.75 to 300 ng/ml ranged from 2.6% to 5.5%. The intraday coefficients of variation ranged from 3% to 7% in both biological fluids.

The percentage of nalmefene bound to plasma proteins was determined at the 1-hour plasma sample time. Plasma (0.5 ml) was placed in a Centrifree filtration device (molecular weight cutoff, 30,000; Amicon, Beverly, Mass.) and centrifuged for 30 minutes in a fixed-angle centrifuge. The filtrate was collected and then analyzed as described for plasma.

Data analysis

Antipyrine pharmacokinetics. The pharmacokinetics of antipyrine were determined by noncompartmental methods. The elimination rate constant was obtained by nonlinear least-squares regression of the terminal concentration-time data. The area under the concentration-time curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity. Antipyrine oral clearance was determined as follows: Dose/AUC(O−∞).

Galactose clearance. The clearance of galactose was used as an estimate of effective hepatic plasma flow.17,18 The plasma clearance of galactose was calculated from the galactose infusion rate (R0) and the mean observed steady-state plasma concentrations, which was adjusted by subtracting the basal level at time (C0): $\text{CL}_{\text{Gal}} = \frac{R_0}{(C_{\text{SS}} - C_0)}$.17

Nalmefene pharmacokinetic analysis. The pharmacokinetic parameter estimates of nalmefene were determined by compartmental analysis. The data were fitted to both two- and three-compartment pharmacokinetic models by weighted ($1/y^2$) nonlinear regression analysis with use of PC-NONLIN (Statistical Consultants, Inc., Apex, N.C.). Model selection was based on the Akaike information criterion and the coefficients of variation of the parameter estimates.19,20 On the basis of these criteria, the two-compartment model provided the best fit to the data. Therefore only these parameters are presented. The pharmacokinetic parameters that were estimated include the initial and terminal disposition rate constants (α and β, respectively) and γ-intercepts (A and B), area under the plasma concentration time curve to infinity [AUC(0−∞)], first moment of the concentration versus time curve (AUMC), and the maximum plasma concentration (Cmax). The terminal elimination t1/2 (t1/2β) was calculated as 0.693/β. The central compartment volume of distribution (Vc) was derived from the ratio of dose and Cmax, and the total body clearance (CL) of nalmefene was determined from the quotient of dose and AUC(0−∞). The mean residence time (MRT) was...
calculated as \( \text{AUMC}/\text{AUC}(0-\infty) \), and the steady-state volume of distribution \( (V_{ss}) \) was calculated as the product of \( CL \) and \( MRT \).

The pharmacokinetic parameter estimates of nalmefene glucuronide were calculated by non-compartmental methods. The terminal elimination rate constant \( (\lambda_e) \) of nalmefene glucuronide was determined by nonlinear regression analysis of the terminal portion of the nalmefene glucuronide concentration–time data. The terminal elimination \( t_{1/2} \) \( (t_{1/2e}) \) was calculated as \( 0.693/\lambda_e \). The AUC was calculated by the linear trapezoidal rule with extrapolation to infinity. The \( C_{\text{max}} \) and \( t_{\text{max}} \) were determined by visual inspection of the plasma concentration–time data. The rate of formation of nalmefene glucuronide was expressed as the formation clearance \( (CL_f) \) and was calculated as follows:

\[
CL_f = \frac{\text{Ae}(0-48)}{\text{AUC}(0-48)}
\]

in which \( \text{Ae}(0-48) \) is the amount of nalmefene glucuronide excreted in urine from 0 to 48 hours and \( \text{AUC}(0-48) \) is the nalmefene plasma AUC over the same time frame. The renal clearance \( (CL_R) \) of nalmefene and nalmefene glucuronide was calculated as the quotient of the total amount recovered in the urine and the AUC from 0 to 48 hours.

**Statistical analysis.** The demographic characteristics of the control subjects and the patients with liver disease were compared with use of an unpaired Student \( t \) test. Antipyrine and galactose clearance values observed in each group were compared with the Mann Whitney \( U \) test. The nalmefene pharmacokinetic parameter estimates were assessed for normality of distribution with the Wilks-Shapiro test. Parameter estimates that were non-normally distributed were log-transformed before statistical comparisons. Comparisons of nalmefene pharmacokinetic parameters between the control subjects and patients with liver disease were made with the unpaired \( t \) test. The relationship between the clearances of nalmefene, antipyrine, or galactose and Pugh score was assessed by Spearman’s rank correlation. The healthy volunteers were assigned a Pugh score of 4 for this analysis. The relationship between nalmefene clearance and antipyrine or galactose clearance was assessed by linear regression. Computations were performed with version 6.10 of Statistical Analysis Software (SAS Institute, Cary, N.C.), and \( p < 0.05 \) was considered to be statistically significant.

**RESULTS**

The hepatically impaired patients and the control subjects were similar with regard to age, gender, race, weight, and creatinine clearance (Table I). Antipyrine was used in this study to assess total oxidative capacity because it is metabolized by multiple CYP enzymes and provides an index for comparison to previous work. As expected, the median clearance of antipyrine was significantly lower \( (p = 0.0012) \) in the patients with liver disease \( (0.23 \text{ ml/min/kg}) \) than in the control subjects \( (0.52 \text{ ml/min/kg}) \), confirming that total metabolic activity was reduced in these patients with liver disease. The median plasma clearance of galactose, an estimate of effective hepatic plasma flow, was also significantly greater \( (p = 0.03) \) in the control subjects \( (17.6 \text{ ml/min/kg}) \) than in the patients with liver disease \( (11.8 \text{ ml/min/kg}) \). These data indicate that there are significant reductions in hepatic function in the patients with liver disease evaluated in this study.

Mean concentration–time profiles for nalmefene and nalmefene glucuronide for both study groups are shown in Fig. 1, A and B, respectively. The nalmefene pharmacokinetic parameter estimates are summarized in Table II. The \( t_{1/2} \) of nalmefene in the patients with liver disease was significantly longer than that observed in the control subjects \( (10.5 \pm 1.9 \text{ versus } 8.0 \pm 2.2 \text{ hours, respectively; } p = 0.008) \). Because there were no changes in either the \( V_{ss} \) or \( V_C \) values in patients with liver disease, the increased \( t_{1/2} \) is secondary to a decreased clearance in patients with liver disease compared with the control subjects \( (0.61 \pm 0.21 \text{ versus } 0.90 \pm 0.27 \text{ ml/min/kg; } p = 0.003) \). The renal function of the two groups as estimated by creatinine clearance and the \( CL_R \) of nalmefene were not significantly different (Tables I and II). The total recovery of unchanged nalmefene in urine as a percentage of dose was not significantly different between the groups \( (9.6\% \pm 4.9\% \text{ in control subjects versus } 10.9\% \pm 4.6\% \text{ in patients with liver disease}) \). The percentage of nalmefene bound to plasma proteins was also not significantly different between the two groups and approximated 35%.

The disposition of nalmefene glucuronide was similar between patients with liver disease and control subjects (Table III). The maximum observed plasma concentration was similar between the two groups; however, the time at which this concentration was achieved tended to be much later in the patients with liver disease \( (3.4 \pm 5.1 \text{ hours}) \) than in the control subjects \( (0.61 \pm 0.40 \text{ hours}) \). This did not achieve statistical significance. The \( t_{1/2e} \) of
Fig. 1. Nalmefene (A) and nalmefene glucuronide (B) plasma concentration–time profiles after intravenous bolus administration for healthy control subjects (open squares) and patients with liver disease (open circles).

Table II. Pharmacokinetic parameter estimates for nalmefene in normal volunteers and patients with liver disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Liver disease</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>17.3 ± 6.3</td>
<td>16.9 ± 7.6</td>
<td>0.896</td>
</tr>
<tr>
<td>A (ng/ml)</td>
<td>15.1 ± 6.0</td>
<td>14.6 ± 7.4</td>
<td>0.862</td>
</tr>
<tr>
<td>B (ng/ml)</td>
<td>2.2 ± 0.8</td>
<td>2.3 ± 0.6</td>
<td>0.689</td>
</tr>
<tr>
<td>AUC(0-∞) (ng · hr/ml)</td>
<td>30.2 ± 10.9</td>
<td>42.1 ± 13.8</td>
<td>0.016</td>
</tr>
<tr>
<td>CL (L/hr/kg)</td>
<td>0.90 ± 0.27</td>
<td>0.61 ± 0.21</td>
<td>0.003</td>
</tr>
<tr>
<td>α (hr⁻¹)</td>
<td>3.0 ± 1.6</td>
<td>3.1 ± 2.2</td>
<td>0.749</td>
</tr>
<tr>
<td>t1/2α (hr)</td>
<td>0.30 ± 0.19</td>
<td>0.43 ± 0.47</td>
<td>0.380</td>
</tr>
<tr>
<td>β (hr⁻¹)</td>
<td>0.094 ± 0.03</td>
<td>0.068 ± 0.012</td>
<td>0.009</td>
</tr>
<tr>
<td>t1/2β (hr)</td>
<td>8.0 ± 2.2</td>
<td>10.5 ± 1.9</td>
<td>0.008</td>
</tr>
<tr>
<td>Vc (L/kg)</td>
<td>1.6 ± 0.5</td>
<td>1.6 ± 0.8</td>
<td>0.984</td>
</tr>
<tr>
<td>Vss (L/kg)</td>
<td>8.0 ± 1.8</td>
<td>7.3 ± 1.1</td>
<td>0.225</td>
</tr>
<tr>
<td>CLα (L/hr/kg)</td>
<td>0.078 ± 0.041</td>
<td>0.058 ± 0.021</td>
<td>0.147</td>
</tr>
<tr>
<td>CLβ (%)</td>
<td>34.4 ± 13.6</td>
<td>35.9 ± 17.9</td>
<td>0.758</td>
</tr>
<tr>
<td>Plasma binding (%)</td>
<td></td>
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<td></td>
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</tbody>
</table>

Data are mean values ± SD.

nalmefene glucuronide was not different between the patients with liver disease and the control subjects. However, the CLα of the glucuronide metabolite was significantly smaller in patients with liver disease (0.181 ± 0.067 L/hr/kg) compared with control subjects (0.263 ± 0.072 L/hr/kg). This suggests that the clearance through this conjugation pathway was reduced in patients with liver dis-
Table III. Pharmacokinetic parameter estimates for nalmefene glucuronide in normal volunteers and patients with liver disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Liver disease</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cm (ng/ml)</td>
<td>8.3 ± 4.0</td>
<td>8.1 ± 7.3</td>
<td>0.916</td>
</tr>
<tr>
<td>tmax (hr)</td>
<td>0.61 ± 0.40</td>
<td>3.4 ± 5.1</td>
<td>0.077</td>
</tr>
<tr>
<td>t1/2CL (hr)</td>
<td>1.7 ± 2.8</td>
<td>10.6 ± 2.6</td>
<td>0.315</td>
</tr>
<tr>
<td>AUC(0-∞) (ng * hr/ml)</td>
<td>85.4 ± 30.8</td>
<td>90.9 ± 59.7</td>
<td>0.780</td>
</tr>
<tr>
<td>CLf (L/hr/kg)</td>
<td>0.263 ± 0.072</td>
<td>0.181 ± 0.067</td>
<td>0.008</td>
</tr>
<tr>
<td>CLr (L/hr/kg)</td>
<td>0.114 ± 0.036</td>
<td>0.107 ± 0.040</td>
<td>0.608</td>
</tr>
</tbody>
</table>

Data are mean values ± SD.

Cm, peak plasma concentration; tmax, time to reach Cmax; t1/2CL, terminal elimination half-life; AUC(0-∞), area under the concentration-time curve from zero to infinity; CLf, formation clearance; CLr, renal clearance.

The total recovery of nalmefene glucuronide in urine expressed as a percentage of dose was similar: 32.0% ± 6.6% in control subjects compared with 31.4% ± 9.4% in patients with liver disease.

Statistically significant relationships were observed between the Pugh score and both antipyrine clearance (r = -0.79; p = 0.0001) and galactose clearance (r = -0.48; p = 0.018). The clearance of nalmefene was also inversely related to the Pugh score (r = -0.57; p = 0.004), indicating that the clearance of nalmefene decreased as the severity of liver disease increased (Fig. 2). Significant relationships were also observed between nalmefene clearance and antipyrine clearance (r = 0.73; p < 0.0001) or galactose clearance (r = 0.87; p < 0.0001).

DISCUSSION

The results of this study indicate that the disposition of nalmefene and its primary metabolite nalmefene glucuronide are significantly influenced by the presence of liver disease. The total body clearance of nalmefene was reduced by approximately 30%, whereas the terminal elimination t1/2 was increased to a similar extent. The Vc, VSS, and the protein binding of nalmefene were not affected by liver disease. Although the amount of nalmefene glucuronide recovered in the urine was similar between the groups, the fractional metabolic clearance to nalmefene glucuronide was significantly reduced in patients with liver disease. Thus it appears that the reduced clearance of nalmefene in the patients with liver disease is primarily the result of impaired formation of the glucuronide metabolite.

The effect of liver disease on drug elimination is thought to be dependent on whether the predominant route of biotransformation is by phase I (oxidation) or phase II (e.g., glucuronidation or sulfation) reactions. In general, the clearance of drugs that are predominately biotransformed by phase I enzymes, such as antipyrine, caffeine, and theophylline, is reduced in patients with liver disease. Each of these drugs is metabolized by multiple CYP enzymes and may thus provide a general index of overall metabolic capacity.

Although oxidative metabolism is often impaired in patients with cirrhosis, biotransformation through conjugation with glucuronic acid was thought to be preserved. This was based on early reports with predominantly conjugated drugs such as oxazepam, lorazepam, temazepam, acetaminophen (paracetamol), and morphine in which no change in clearance was observed in patients with liver disease. This lack of change was initially attributed to the theory that glucuronyltransferases were preserved in liver disease or that there may be significant extrahepatic glucuronidation.

In previous studies with glucuronidated drugs in which no change in clearance was observed, the patients evaluated generally had mild or compensated liver disease. Subsequent studies in patients with more severe disease have shown significant reductions in the clearance of both of these drugs. It appears that this disparity in results with glucuronidated drugs may stem from differences in the chronicity and severity of the liver disease of the patients who were evaluated.

In previous studies with glucuronidated drugs in which no change in clearance was observed, the patients evaluated generally had mild or compensated liver disease. Subsequent studies in patients with more severe disease have shown significant reductions in drug elimination. For example, Sonne, et al. found a 54% reduction in systemic clearance and an 84% reduction in the unbound clearance of oxazepam in patients with severe cirrhosis. This is in contrast to the previous studies in patients with compensated alcoholic cirrhosis or acute viral
hepatitis where oxazepam clearance was unchanged.\(^{21,22}\) The influence of liver disease severity on drug conjugation is further illustrated by studies that examine the disposition of morphine. The clearance of morphine in two studies was similar in control subjects and in patients with compensated alcoholic cirrhosis\(^ {26,33}\) but was decreased from 37% to 59% in patients with severe alcoholic cirrhosis.\(^ {31,32}\)

Further evidence of the role of liver disease severity on morphine clearance was presented by Hoyumpa and Schenker\(^ {34}\) with use of previously published data. The discriminant factor, a clinical index of disease severity that incorporates the prothrombin time and serum bilirubin values, was calculated, and a weak but significant \((r = -0.44; p < 0.05)\) inverse relationship was observed between the discriminant factor and morphine clearance.

The severity of liver disease in the patients in this study ranged from mild to severe disease. Our data support the hypothesis that changes in glucuronida-
tion may only occur with more advanced disease. Indeed, there was an inverse relationship between nalmefene clearance, as well as antipyrine clearance, and the Pugh score, an index of disease severity (Fig. 2). Fig. 2 reveals that if only patients with mild or mild to moderate disease were evaluated (Pugh score \(\leq 8\)), the results would have indicated that liver disease has no effect on nalmefene clearance. When only the patients with mild to moderate disease were considered, nalmefene clearance was not significantly different from control subjects. A differential sensitivity of phase I and phase II reactions to the presence of liver disease is suggested by comparison of the antipyrine and nalmefene data. Results from these drugs indicate that, in these patients, there was a 56% reduction in oxidative metabolism and a 32% reduction in glucuronide conjugation. However, appropriate characterization of this potential differential sensitivity requires further study.
In conclusion, we have shown that the clearance of nalmefene is reduced by approximately 30% in patients with liver disease compared with control subjects. There was no change in nalmefene distribution or protein binding, but the terminal elimination \( t_{1/2} \) was prolonged. The reduced clearance was attributed to reduced \( CL_{\text{int}} \) of the primary metabolite nalmefene glucuronide. Although there were statistically significant alterations in nalmefene disposition in patients with liver disease, nalmefene will be used in the acute care setting for reversal of postoperative respiratory depression or in opioid overdose and thus the dose is titrated to effect. Because these indications require limited doses of nalmefene over a short period of time and because it is likely that the elimination of the opiate will be similarly impaired, no dosage modification is anticipated to be necessary in patients with liver disease as a result of the observed pharmacokinetic differences.

We greatly appreciate the technical assistance of Cheryl Galloway and the assistance of Dr. Jeffrey McVey and the nursing staff of the General Clinical Research Unit. We also thank Dr. Michael Hooks and Beverly Noe, MS, at Emory University for the galactose sample analysis.

References