Pharmacokinetics of Long-Acting Naltrexone in Subjects With Mild to Moderate Hepatic Impairment

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Long-acting naltrexone is an extended-release formulation developed with the goal of continuous naltrexone exposure for 1 month for the treatment of alcohol dependence. The influence of mild and moderate hepatic impairment on naltrexone pharmacokinetics following long-acting naltrexone 190-mg administration was assessed. Subjects with mild (Child-Pugh grade A) and moderate (Child-Pugh grade B) hepatic impairment (n = 6 per group) and matched control subjects (n = 13) were enrolled. Naltrexone and 6β-naltrexol concentrations were determined over a period of 63 days following a single intramuscular dose. Naltrexone and 6β-naltrexol concentrations were detected in all subjects through 28 days. Total exposure ($AUC_{0-\infty}$) of naltrexone and 6β-naltrexol was similar across all groups. The long apparent half-lives of naltrexone and 6β-naltrexol (5-8 days) were attributed to the slow release of naltrexone (long-acting naltrexone exhibits absorption rate-limited elimination or "flip-flop" kinetics); elimination was not altered in subjects with hepatic impairment. Based on pharmacokinetic considerations, the dose of long-acting naltrexone does not need to be adjusted in patients with mild or moderate hepatic impairment.

Keywords: *Naltrexone; long acting; hepatic impairment; alcoholism; LA-NTX*

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Alcohol use disorders are a major public health problem, and worldwide they are the fourth leading cause of disability.[1] Alcohol dependence is present in approximately 4% of the adult population,[2] is common among primary care patients,[3,4] and may contribute to more than 100,000 preventable deaths per year.[5] Naltrexone, an opioid antagonist, reduces the reinforcing subjective or behavioral response to alcohol.[6,7] Although oral naltrexone has been shown to be effective as a maintenance agent in the treatment of alcohol and opiate dependence, a major limitation of its utility has been poor adherence to its daily dosing regimen.[8,9]

Long-acting naltrexone (LA-NTX) is an extended-release formulation intended to provide therapeutic concentrations of naltrexone for approximately 1 month following a single intramuscular (IM) injection, alleviating the need for adherence to daily oral therapy. Long-acting naltrexone is a microsphere-based product composed of naltrexone incorporated into a biodegradable polymer matrix of polylactide-co-glycolide (PLG). Following injection, naltrexone is released from the microspheres by diffusion and erosion as the PLG polymer gradually degrades over a period of several weeks.[10]

Because the liver is an important organ of elimination, disease or impairment of hepatic function may result in altered pharmacokinetics of a drug.[11] In the alcohol-dependent population, approximately 10% to 35% of heavy drinkers develop alcoholic hepatitis, and 10% to 20% develop cirrhosis.[12] Therefore, it is important to understand the impact of liver disease on naltrexone pharmacokinetics.

In healthy subjects, the pharmacokinetics of daily administered oral naltrexone are characterized by

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rapid and near-complete absorption, high first-pass hepatic extraction, and renal elimination of the primary metabolite, 6β-naltrexol; naltrexone, and other minor metabolites.[13,14] Oral bioavailability estimates range from 5% to 40%.[15,16] Following an oral naltrexone dose of 50 mg, plasma concentrations of naltrexone fall below quantifiable limits approximately 8 hours postdose. The oral clearance of 50 mg naltrexone was high (~93 L/h) and approximated liver blood flow.[15] Naltrexone is extensively metabolized to 6β-naltrexol, concentrations of which are typically 10- to 30-fold greater than naltrexone following oral administration.[15,17] 6β-Naltrexol is a biologically active metabolite but appears to be 1/12th to 1/185th as potent as naltrexone in various in vivo animal models.[18] The role that 6β-naltrexol plays in the therapeutic benefit of naltrexone in the treatment of alcohol dependence is unclear.

In an investigation by Bertolotti et al,[19] the pharmacokinetics of naltrexone following administration of a single 100-mg oral dose was determined in subjects with compensated (Child-Pugh grade A or B) and decompensated (Child-Pugh grade C) liver disease. The systemic availability of naltrexone in subjects with liver disease was markedly increased compared with healthy controls. Naltrexone exposure in subjects with compensated and decompensated disease was approximately 4- and 8-fold higher, respectively, relative to control values. 6β-Naltrexol exposure was not significantly altered in these subjects, but peak concentrations were delayed compared with healthy controls. The metabolite/parent ratio decreased with increasing severity of liver disease, but no significant differences in the elimination half-lives of parent and metabolite were detected between the different groups.[19]

In a recent clinical study in alcohol-dependent subjects, LA-NTX, in conjunction with psychosocial treatment, significantly reduced heavy drinking during 6 months of therapy.[20] The pharmacokinetics of LA-NTX following single and repeat administration in healthy subjects has been described.[21] The current study evaluated the pharmacokinetics and safety of a single IM dose of LA-NTX in subjects with mild or moderate hepatic impairment and matched healthy subjects.

METHODS

Study Design

This was an open-label, parallel-group study designed to evaluate the pharmacokinetics of LA-NTX in subjects with mild or moderate hepatic impairment compared with healthy subjects. Subjects between the ages of 18 and 70 years old with stable hepatic impairment classified as mild (Child-Pugh grade A) or moderate (Child-Pugh grade B) attributable to alcoholic cirrhosis (according to medical history and liver biopsy), as well as healthy subjects, were enrolled in the study in 4 groups. Subjects who were pregnant, had a body mass index of >35 kg/m^2, had a creatinine clearance <60 mL/min, had current drug or alcohol dependence at time of enrollment, or were on prescribed opiate therapy were excluded from the study.

Healthy subjects were matched to subjects with hepatic impairment by gender (1:1), age (±5 years), and weight (±15%). Six eligible subjects with mild hepatic impairment (group 1) were enrolled; healthy subjects (group 2) were matched to group 1. Following an interim safety evaluation 2 weeks after administration of LA-NTX to groups 1 and 2, 6 subjects with moderate hepatic impairment (group 3) were enrolled and dosed; healthy subjects (group 4) were matched to group 3. Prior to study initiation, subjects provided written informed consent and agreed to follow study procedures. The study duration for each subject was approximately 13 weeks and included a screening visit; a 4-night inpatient stay for screening, dosing, and monitoring following study drug administration; and 11 outpatient visits. Safety evaluations during the study included vital signs, physical examinations, liver examinations, injection site assessments, hematology and blood chemistry laboratory testing, urinalysis, and monitoring of adverse events. The study was approved by the Southern Institutional Review Board, Inc (Miami, Fla) and conformed with the Declaration of Helsinki. The study was conducted at a single site (SFBC International, Miami, Fla).

A single dose of LA-NTX 190 mg was administered to all subjects as a deep, gluteal IM injection. Blood samples (4 mL) for pharmacokinetic analysis were collected into polypropylene EDTA tubes at the following times: predose; 1, 2, 4, 8, 12, 24, 36, 42, 48, and 72 hours; and 5, 7, 14, 21, 28, 35, 42, 49, 56, and 63 days postdose. The plasma was separated by centrifugation (2000 rpm for 15 minutes at 4°C) and stored at −20°C until analysis.

Bioanalytical Methods

Samples were analyzed for naltrexone and 6β-naltrexol according to a validated assay. Briefly, the internal standard naloxone (final concentration ~10 ng/mL) was added to a 0.5-mL aliquot of the sample prior to mixing with an organic solvent under alkaline conditions. Following centrifugation, the upper organic layer was removed and evaporated before being recon-

stituted in mobile phase. An aliquot of the extract was injected onto a SCIEX API 3000 LC-MS-MS equipped with a cyano high-performance liquid chromatography (HPLC) column. Peak areas of the m/z 342 → 324 naltrexone product ion and the m/z 344 → 326 6β-naltrexol product ion were measured against the m/z 328 → 310 product ion of the internal standard. Quantitation was performed using weighted linear least squares regression analyses generated from fortified plasma calibration standards prepared immediately prior to each run. Chromatography was captured using Mass Chrom (Version 1.1); data integration was accomplished using Analyst (Version 1.3.1; Applied Biosystems/MDS SCIEX, Foster City, Calif/Concord, Ontario) for the SCIEX 3000.

The assay was validated for a range of 0.200 to 100 ng/mL for naltrexone and 0.500 to 250 ng/mL for 6β-naltrexol. Accuracy, based on the absolute deviation of the theoretical concentration of quality control samples at 3 concentrations (low, mid, high) across the calibration range, ranged from 0.5% to 5.5% for naltrexone and 6β-naltrexol. Precision, expressed as the percent coefficient of variation (%CV) for quality control samples assayed during sample analysis, was <12% for both analytes.

Data Analysis and Statistical Evaluation

The mean naltrexone and 6β-naltrexol concentrations were determined at each sampling time point. Concentrations reported as below the lower limit of quantitation of the assay were set equivalent to 0 for this calculation. Pharmacokinetic parameters for naltrexone and 6β-naltrexol were calculated for each subject using standard noncompartmental methods. The maximum plasma concentration (C_{max}) and the time of its occurrence (t_{max}) were obtained directly from the concentration-time data. Area under the curve ($AUC_{0-\infty}$) was calculated using the linear trapezoidal method up to the last measured concentration plus the remaining extrapolated area, determined as the ratio of the last measured concentration and k, where k is the terminal elimination rate constant estimated from the log-linear portion of the concentration-time curve. The extrapolated area was <15% for all subjects included in the statistical analysis. Elimination half-life ($t_{1/2}$) was calculated as ln(2)/k. Note: due to the prolonged release of naltrexone from the depot site, k and $t_{1/2}$ reflect an apparent terminal elimination rate and half-life, respectively. The metabolite/parent ratio was calculated as the ratio of 6β-naltrexol AUC_∞ to the corresponding naltrexone AUC. The ability to evaluate pharmacokinetic data from subjects who did not complete all pharmacokinetic sampling procedures was assessed on a case-by-case basis. Pharmacokinetic calculations were determined using WinNonlin Professional Version 4.1 (Pharsight Corporation, Mountain View, Calif).

An analysis of variance (ANOVA) model including hepatic function as a fixed effect and subject as a random effect was used to compare naltrexone and 6β-naltrexol pharmacokinetic parameters between each group with impaired hepatic function and the respective matched control group. The 4 groups were considered totally independent in the ANOVA model. A secondary analysis was conducted to compare each impaired hepatic function group to all healthy subjects combined. The values for C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$ were logarithmically transformed prior to analysis. Point estimates and 90% confidence intervals (CIs) for the difference between each of the hepatically impaired groups and the control group were constructed. The point estimates and CIs on the log-scale were back transformed to give estimates for the ratio comparisons (ie, moderate hepatic impairment vs normal hepatic function and mild hepatic impairment vs normal hepatic function). In addition to the parameters above, the ratio of 6β-naltrexol $AUC_{0-\infty}$ to naltrexone $AUC_{0-\infty}$ was also compared between hepatic impairment and healthy groups. A nonparametric method was used to analyze t_{max}. Each of the impaired hepatic function groups was compared with the respective matched control group using a Wilcoxon rank sum test. Statistical comparisons were calculated using SAS Version 8.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Subject Demographics

Of the 25 subjects enrolled, 23 subjects completed the study and 2 discontinued. One subject in group 4 who discontinued before day 7 was replaced. A second subject in group 4 discontinued after day 14 and was not replaced. Pharmacokinetic observations of t_{max} and C_{max} for this subject were included in the statistical analysis. Subject demographics are summarized in Table I.

Pharmacokinetic Results

Mean naltrexone and 6β-naltrexol concentration versus time plots for subjects with mild and moderate hepatic impairment are presented in Figures 1 and 2, respectively. Naltrexone and 6β-naltrexol plasma concentrations were measurable in all subjects through 28 days postdose and fell below the limit of the analytical assay in most subjects by 49 days postdose. Mean

Table I Demographic Data

Variable	Group 1: Mild Hepatic Impairment		Group 2: Healthy Subjects[a]		Group 3: Moderate Hepatic Impairment		Group 4: Healthy Subjects[b]	
Gender, n (%)								
Male	4	(67)	4	(67)	3	(50)	4	(57)
Female	2	(33)	2	(33)	3	(50)	3	(43)
Race, n (%)								
Caucasian	5	(83)	1	(17)	3	(50)	1	(14)
Hispanic	1	(17)	5	(83)	3	(50)	6	(86)
Age (years)								
Mean (SD)	58.2	(9.4)	58.0	(9.0)	55.0	(8.6)	51.7	(7.4)
Range	51-76		47-73		47-71		43-67	
Body mass index (kg/m^2)								
Mean (SD)	28.6	(5.6)	29.6	(3.7)	27.8	(4.7)	26.9	(2.1)
Range	18-35		25-34		24-34		24-31	

a. Matched to group 1.
b. Matched to group 3.

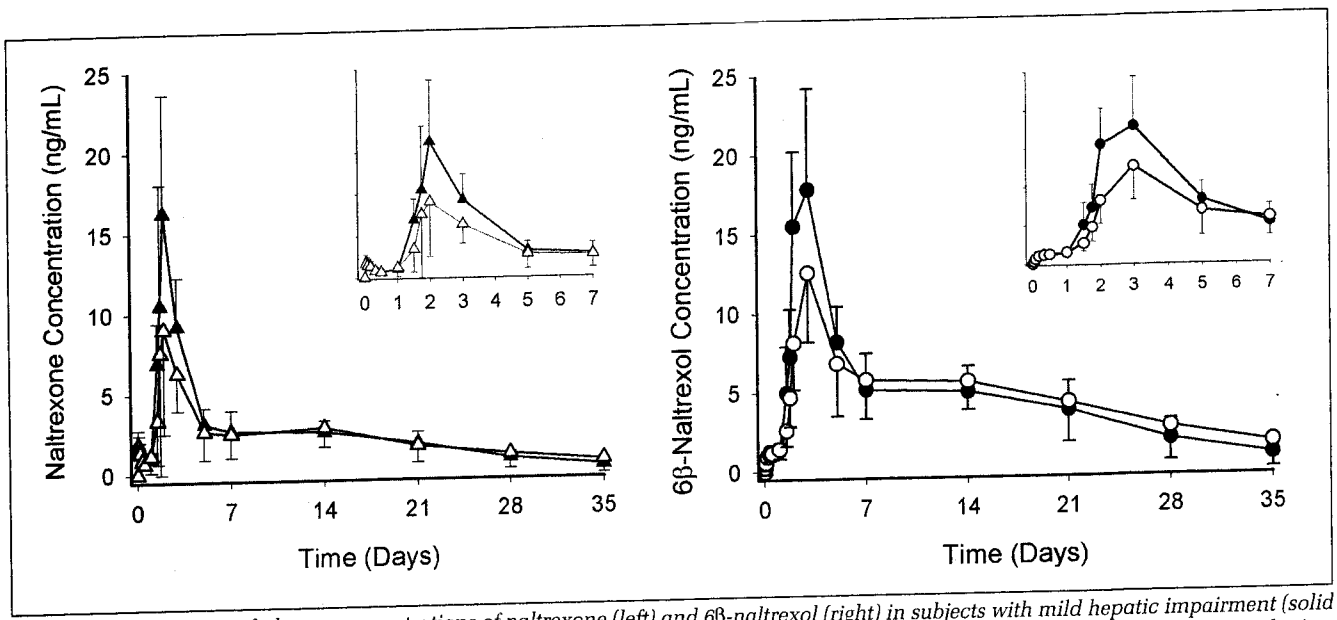

Figure 1. Time course of plasma concentrations of naltrexone (left) and 6β-naltrexol (right) in subjects with mild hepatic impairment (solid symbols) and healthy matched controls (open symbols) after administration of long-acting naltrexone (LA-NTX) 190 mg. Inset: Early time course (days 0-7). Data represent mean ± SD (n = 6).

naltrexone concentrations in subjects with mild hepatic impairment were higher or equal to those of matched healthy control subjects, whereas mean concentraion in subjects with moderate hepatic impairment were lower or equal to those of the respective healthy control group. In general, the shape of the 6β-naltrexol concentration-time profile was similar to that of naltrexone.

Naltrexone and 6β-naltrexol pharmacokinetic parameters following administration of LA-NTX are summarized in Table II by study group. C_{max} variability in healthy subjects (group 2) and subjects with moderate hepatic impairment (group 3) tended to be greater than variability observed within groups 1 and 4. Total naltrexone exposure ($AUC_{0-\infty}$) was similar across all groups. Scatter plots of naltrexone C_{max} and $AUC_{0-\infty}$ are presented in Figure 3. Mean C_{max} values of 6β-naltrexol were reflective of differences observed with naltrexone, whereas $AUC_{0-\infty}$ was similar across all study groups. Median t_{max} and mean $t_{1/2}$ values were

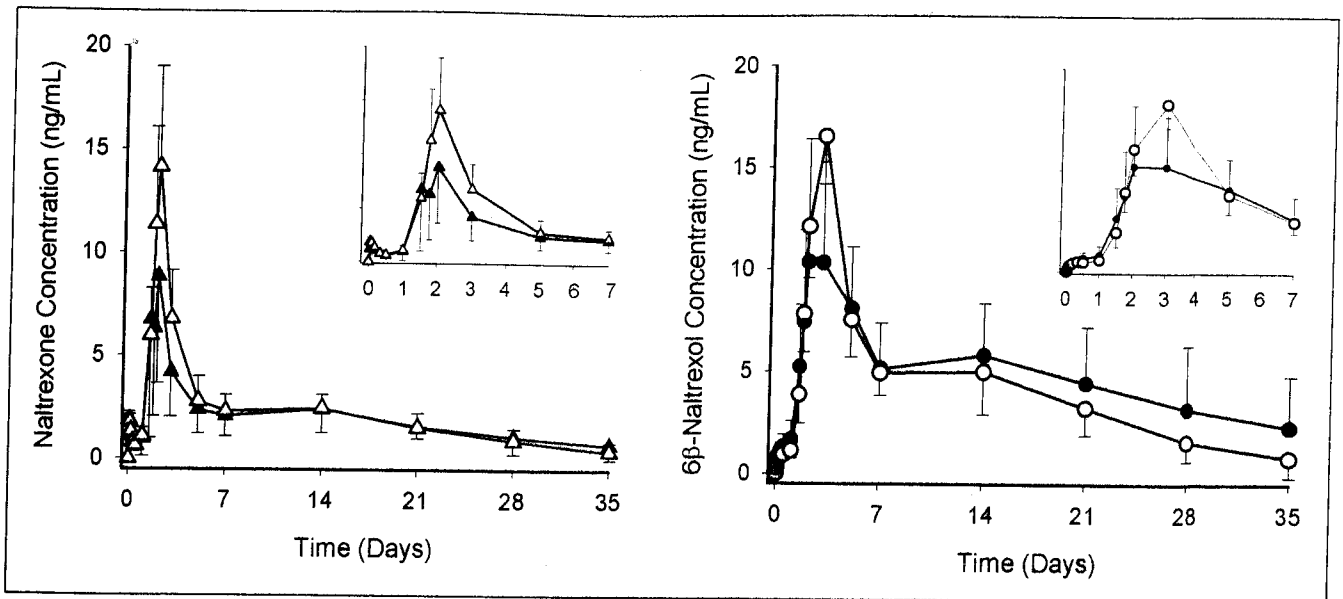

Figure 2. Time course of plasma concentrations of naltrexone (left) and 6β-naltrexol (right) in subjects with moderate hepatic impairment (solid symbols) and healthy matched controls (open symbols) after administration of long-acting naltrexone (LA-NTX) 190 mg. Inset: Early time course (days 0-7). Data represent mean ± SD (n = 6, moderate hepatic impairment; n = 5, healthy subjects).

Table II Mean Pharmacokinetic Parameters Following a Single Intramuscular Dose of Long-Acting Naltrexone (190 mg) in Subjects With Hepatic Impairment and Matched Healthy Subjects

Analyte and Parameter	Group 1: Mild Hepatic Impairment		Group 2: Healthy Subjects[a]		Group 3: Moderate Hepatic Impairment		Group 4: Healthy Subjects[b]	
Naltrexone								
C_{max}, ng/mL	16.3 ± 7.3		9.7 ± 6.8		9.0 ± 5.3		14.2 ± 4.9	
t_{max}, days	2.0	(2.0-3.0)	2.0	(1.8-14.0)	2.0	(1.5-2.0)	2.0	(1.8-2.0)
$AUC_{0-\infty}$, ng•d/mL	87 ± 27		82± 27		79 ± 19		82 ± 20[c]	
$t_{1/2}$, days	6.0 ± 1.7		5.6 ± 1.4		7.1 ± 2.0		7.8 ± 1.7[c]	
6β-Naltrexol								
C_{max}, ng/mL	18.0 ± 6.2		12.6 ± 4.4		12.3 ± 5.2		16.5 ± 2.3	
t_{max}, days	3.0	(2.0-3.0)	3.0	(3.0-3.0)	3.0	(2.0-14.0)	3.0	(3.0-3.0)
$AUC_{0-\infty}$, ng•d/mL	165 ± 58		176 ± 53		199 ± 93		150 ± 28[c]	
$t_{1/2}$, days	6.9 ± 1.6		6.5 ± 1.6		7.2 ± 1.7		8.8 ± 5.4[c]	

Data are expressed as arithmetic mean ± SD (n = 6; unless otherwise noted), except for t_{max}, for which median values and range are reported. $AUC_{0-\infty}$, area under the curve extrapolated to infinity; C_{max}, maximum plasma concentration; t_{max}, time to reach maximum plasma concentration; $t_{1/2}$, terminal elimination half-life.

a. Matched to group 1.

b. Matched to group 3.

c. n = 5.

similar across all subjects and groups for both naltrexone and 6β-naltrexol. Exposure to 6β-naltrexol was generally 2-fold greater than naltrexone across the study groups (range, 1.86-2.34).

The comparison of naltrexone and 6β-naltrexol pharmacokinetic parameters between subjects with hepatic impairment and healthy matched subjects is presented in Table III. Naltrexone C_{max} was 86% higher in subjects with mild hepatic impairment and 45% lower in subjects with moderate hepatic impairment compared with matched healthy subjects. Similar results were observed for 6β-naltrexol C_{max}.

Hepatic impairment did not appear to affect naltrexone $AUC_{0-\infty}$ (treatment comparison ratios were 0.97 and 1.08 for mild and moderate impairment, respectively, relative to healthy subjects). Although subjects with mild hepatic impairment had similar 6β-naltrexol exposure compared with healthy subjects,

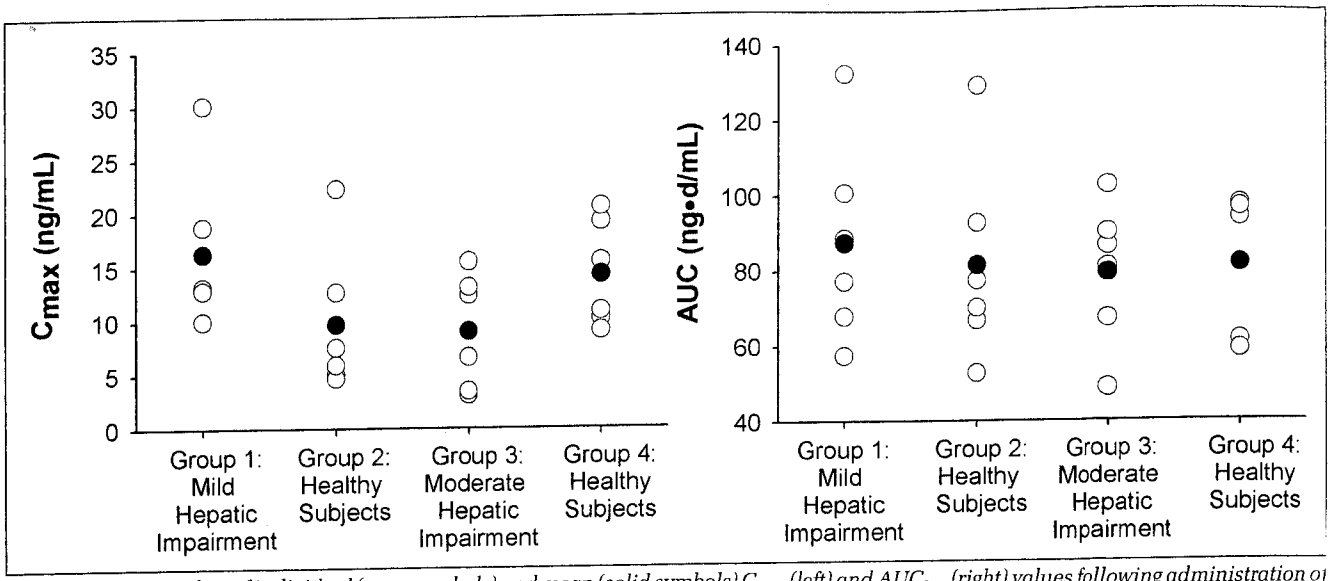

Figure 3. Scatter plots of individual (open symbols) and mean (solid symbols) C_{max} (left) and $AUC_{0-\infty}$ (right) values following administration of long-acting naltrexone (LA-NTX) 190 mg.

Table III Comparison of Pharmacokinetic Parameters Between Subjects With Mild and Moderate Hepatic Impairment and Matched Healthy Subjects

Analyte and Parameter	Ratio: Hepatic Impairment/Healthy			
	Mild Impairment		Moderate Impairment	
Naltrexone				
C_{max}, ng/mL	1.86	(1.1, 3.2)	0.55	(0.3, 0.9)
$AUC_{0-\infty}$, ng•d/mL	1.08	(0.8, 1.4)	0.97	(0.7, 1.3)[a]
t_{max}, days[b]	–0.10	(0.92)	–0.74	(0.46)
$t_{1/2}$, days	1.05	(0.8, 1.4)	0.90	(0.7, 1.2)[a]
6β-Naltrexol				
C_{max}, ng/mL	1.44	(1.0, 2.0)	0.70	(0.5, 1.0)
$AUC_{0-\infty}$, ng•d/mL	0.93	(0.7, 1.3)	1.22	(0.9, 1.8)[a]
t_{max}, days[b]	–1.23	(0.22)	–0.69	(0.49)
$t_{1/2}$, days	1.06	(0.8, 1.5)	0.91	(0.7, 1.2)[a]
6β-Naltrexol/naltrexone				
$AUC_{0-\infty}$ ratio	0.86	(0.6, 1.1)	1.26	(0.9, 1.7)[a]

Data expressed as the ratio of geometric least squares mean values with 90% confidence interval (hepatic impairment/healthy subjects; n = 6/group unless otherwise noted).

a. $n = 5$ for group 4, healthy subjects.

b. Wilcoxon Z score is presented for t_{max} with P value of comparison.

those with moderate hepatic impairment showed an approximate 20% increase. Subjects with moderate hepatic impairment had increased 6β-naltrexol exposure (26%) relative to naltrexone compared with healthy subjects.

Naltrexone and 6β-naltrexol pharmacokinetic parameters were compared between subjects with hepatic impairment and all healthy subjects combined in a secondary analysis (data not shown). The results of this secondary analysis were consistent with the primary analysis. However, the magnitude of the differences for C_{max} and $AUC_{0-\infty}$ between subjects with hepatic impairment and all healthy subjects combined was smaller than that observed in the primary analysis

Safety Results

Long-acting naltrexone was generally well tolerated in all subjects. A total of 17 adverse events was reported in 12 of the 25 enrolled subjects. Adverse events we

more common in subjects with mild hepatic impairment (5 of 6) and moderate hepatic impairment (4 of 6) compared with healthy subjects (3 of 13). Most adverse events were mild in severity (13 of 17 reported adverse events); headache was the most frequently reported adverse event (5 of 25 subjects).

There were no trends or clinically meaningful changes from baseline observed in mean or median clinical laboratory values (including hepatic enzymes), vital signs, or electrocardiogram findings for any of the study groups. Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels did increase 28 days after LA-NTX injection (30.3 and 24 U/L change from baseline, respectively) in subjects with moderate hepatic impairment. This increase primarily reflected changes in 2 subjects whose enzyme levels were variable and likely associated with their underlying medical conditions (hepatitis C and alcohol-induced cirrhosis of the liver).

DISCUSSION

This study was designed to assess the pharmacokinetics of LA-NTX in subjects with mild or moderate hepatic impairment, as many patients who suffer from alcohol dependence also develop varying degrees of hepatic impairment. In this study, healthy subjects were enrolled after subjects with hepatic impairment to ensure a similar distribution of gender, age, and weight between the treatment groups. There was a larger proportion of Hispanic subjects represented in the healthy subject groups (groups 2 and 4) compared to the hepatic impairment groups (groups 1 and 3); however, based on results of the study, it does not appear that differences in race influenced the pharmacokinetics of LA-NTX.

Following a single administration of LA-NTX 190 mg, plasma concentrations of naltrexone were measurable for greater than 30 days in most subjects. Plasma concentrations of 6β-naltrexol were approximately 2-fold greater than corresponding naltrexone concentrations. C_{max} values of naltrexone and 6β-naltrexol were higher in subjects with mild hepatic impairment yet lower in subjects with moderate hepatic impairment compared with their respective control groups. A biological reason for this type of pattern is neither readily apparent nor obvious. The differences in C_{max} values may be attributed to high between-group variability in a small sample size. In a comparison of the 2 groups of healthy subjects, the differences observed in C_{max} values for naltrexone and 6β-naltrexol approximated the differences observed between subjects with hepatic impairment and matched healthy subjects (Table II), suggesting that differences in C_{max} were not necessarily related to hepatic impairment but could be the result of high between-group intersubject variability.

The sample collection intervals used in this study also may have contributed to variability in C_{max} values of naltrexone, as well as the apparent delay in 6β-naltrexol t_{max}. The metabolic conversion of naltrexone to 6β-naltrexol occurs rapidly following oral administration, with t_{max} values similar or identical to naltrexone.[15,17,20] Therefore, the actual t_{max} of 6β-naltrexol following LA-NTX administration is likely more closely related to naltrexone t_{max} than was observed. Given the limited number of samples collected between 2 and 3 days postdose, the true t_{max} for 6β-naltrexol may not have been captured.

The average total naltrexone exposure, based on $AUC_{0-\infty}$, was comparable between subjects with mild and moderate hepatic impairment and healthy subjects. This result is in contrast to a previous report for oral naltrexone, wherein naltrexone AUC significantly increased for subjects with hepatic impairment.[19] Hepatic disease may reduce first-pass extraction efficiency of drugs with high hepatic extraction such as naltrexone, resulting in significantly increased systemic availability following oral administration.[11] The IM administration of LA-NTX avoids first-pass elimination by the liver. Therefore, unlike oral administration, the systemic availability of naltrexone following LA-NTX administration is not dependent on presystemic hepatic metabolism.

The liver is capable of extracting naltrexone as rapidly as it is presented to the organ[15]; therefore, naltrexone clearance is sensitive to changes in liver blood flow.[11] Unlike oral administration, however, the extended release of naltrexone from the polymer matrix results in gradual delivery of naltrexone to the liver. The hepatic elimination of naltrexone following administration of LA-NTX is absorption rate limited ("flip-flop" kinetics).[21,22] As such, a reduction in blood flow due to hepatic impairment may not result in an apparent alteration in naltrexone clearance following administration of LA-NTX. In the present study, any decrease in hepatic blood flow that may have been present in subjects with hepatic impairment were not sufficient to alter naltrexone clearance and, thereby, systemic exposure.

The impact of liver disease on the expression and activity of the enzymes involved in naltrexone metabolism is not well understood. Although it is recognized that aldehyde dehydrogenases and some cytochrome P450 enzyme activities are reduced in patients with cirrhosis,[23] neither of these enzyme families plays a role in the metabolism of naltrexone.[24,25] Rather, the

aldo-keto reductase enzymes AKR1C1, AKR1C2, and AKR1C4, previously designated as dihydrodiol dehydrogenase enzymes (DD1, 2, and 4), are responsible for the stereospecific reduction of naltrexone to 6β-naltrexol.[24,26] To date, the expression of these enzymes in subjects with hepatic impairment has not been reported. The formation of naltrexone and 6β-naltrexol glucuronide conjugates[13] would likely not be altered, as glucuronidation is mainly preserved in subjects with mild to moderate hepatic disease.[23]

Recognized alterations in protein levels in subjects with hepatic impairment[11] are unlikely to affect naltrexone clearance as the plasma protein binding of naltrexone is reported to be low (21%).[27]

Long-acting naltrexone is intended for use in treatment of alcohol dependence. As the incidence of liver disease within the treatment population is high,[28] the potential for altered naltrexone pharmacokinetics was the rationale behind this study in subjects with mild and moderate hepatic impairment. Patients with severe hepatic impairment were not studied primarily because of the increased potential for coagulation defects in this population.[29]

Long-acting naltrexone was safe and well tolerated in subjects with mild and moderate hepatic impairment. Reported adverse events were similar to those reported following oral naltrexone administration.[16] As previously mentioned, IM injection of LA-NTX avoids the extensive first-pass elimination that occurs following oral naltrexone administration. Thus, monthly hepatic exposure to naltrexone is dramatically reduced following LA-NTX administration compared with oral naltrexone administration (50 mg/d; ~1500 mg/month), adding protection against the risk of hepatotoxicity.

In summary, plasma concentrations of naltrexone were observed for longer than 1 month following a single IM administration of this long-acting naltrexone formulation; total exposure (AUC) to naltrexone and 6β-naltrexol was comparable for subjects with mild and moderate hepatic impairment and matched healthy subjects. Comparison of additional naltrexone and 6β-naltrexol pharmacokinetic parameters did not reveal any differences that would be expected to be of clinical significance. By using IM administration, LA-NTX avoids first-pass metabolism and the potential for increased systemic availability similar to that observed following oral administration in subjects with hepatic impairment. Based on the results of this study, the pharmacokinetics of naltrexone following administration of LA-NTX is not altered in subjects with mild to moderate hepatic impairment.

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