Single- and Multiple-Dose Pharmacokinetics of Long-acting Injectable Naltrexone

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Background: Oral naltrexone is effective in the treatment of alcohol dependence; however, a major limitation of its clinical utility is poor patient adherence to the daily dosing schedule. A biodegradable, long-acting naltrexone microsphere formulation was developed to achieve continuous naltrexone exposure for 1 month in the treatment of alcohol dependence.

Methods: The single- and multiple-dose safety and pharmacokinetics of a long-acting naltrexone microsphere preparation were evaluated in healthy subjects. One group of subjects ($n = 28$) received a single dose of oral naltrexone 50 mg followed by a single gluteal intramuscular (IM) injection of long-acting naltrexone 190 or 380 mg or placebo. A different group of subjects ($n = 14$) received oral naltrexone 50 mg daily for 5 days, followed by IM long-acting naltrexone 380 mg or placebo every 28 days for a total of 4 doses. A 7-day washout period separated oral and IM administrations. Blood samples were collected to determine plasma concentrations of naltrexone and the primary metabolite, 6β-naltrexol.

Results: After a single IM injection of long-acting naltrexone 380 mg, naltrexone plasma concentrations were measurable in all subjects for at least 31 days postdose. The pharmacokinetics were proportional to the dose and multiple dose observations were consistent with single dose observations. Mean apparent elimination half-lives for naltrexone and 6β-naltrexol ranged from 5 to 7 days. Exposure to 6β-naltrexol was reduced with IM injection compared with that oral administration. No serious adverse events occurred.

Conclusions: This study demonstrated that the long-acting naltrexone formulation was well tolerated, displayed predictable pharmacokinetics, and resulted in no meaningful drug accumulation upon multiple dosing. Intramuscular administration avoids first-pass metabolism and changes the exposure ratio of 6β-naltrexol to naltrexone compared with oral administration. By providing continuous exposure to naltrexone for several weeks following IM injection, this long-acting naltrexone formulation may offer therapeutic benefit to those patients who experience difficulty adhering to the daily administration schedule necessitated by oral naltrexone therapy.

Key Words: Naltrexone, Extended-Release Preparation, Pharmacokinetics, Long-acting Injectable.

ORAL NALTREXONE WAS approved by the United States Food and Drug Administration in 1994 for the treatment of alcohol dependence after the medication was shown to reduce the number of drinking days, reduce craving for alcohol, and reduce the risk of relapse in alcohol-dependent patients (O'Malley et al., 1992; Volpicelli et al., 1992). Naltrexone, an opioid antagonist, is thought to exert its therapeutic benefit by reducing the reinforcing subjective or behavioral response to alcohol (Davidson et al., 1999; McCaul et al., 2001). More recently, the effects of naltrexone have been explored using clinical laboratory models (Drobes et al., 2003; O'Malley et al., 2002). Researchers in these studies found that naltrexone reduced the amount of alcohol consumed in non–treatment-seeking alcoholics. An extension of these findings suggests that the reduction in alcohol consumption may be somewhat dependent on the pattern of alcohol consumption (Anton et al., 2004).

Although oral naltrexone has been shown to be effective in the treatment of alcohol dependence, a major limitation of its clinical utility has been poor patient adherence to the daily dosing schedule (Volpicelli et al., 1997). Reasons for nonadherence include poor motivation, cognitive impairment (Rinn et al., 2002), and adverse effects of the medication, which may result in interrupted therapy or premature discontinuation (Croop et al., 1997; Oncken et al., 2001; Rohsenow et al., 2000). Nonadherence may also result from the ability of alcohol to disrupt behavioral control and an individual's capacity to recognize that

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he/she has an illness requiring treatment (Leshner, 2003). Thus, alcohol dependence itself contributes to the adherence difficulties encountered by individuals who suffer from the disease. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) raised concerns about adherence on the basis of its extensive review of the literature, concluding that patient adherence to the oral naltrexone regimen appears to be a crucial factor in the pharmacological treatment of alcohol dependence (Litten et al., 2005). Additionally, at least 3 reports have found that only those subjects who maintain a high rate of adherence with daily oral naltrexone obtain greater drinking reductions and reduced relapse than with placebo (Chick et al., 2000; Monti et al., 2001; Volpicelli et al., 1997). A recent review has also identified the need for "strategies to improve adherence to naltrexone treatment" (Srisurapanont and Jarusuraisin, 2005).

One strategy to improve adherence to naltrexone treatment involves use of a long-acting formulation that would provide continuous exposure to naltrexone for several weeks following a single administration. Extended release preparations of naltrexone have been in development for a number of years. One method of achieving extended release is to embed or encapsulate naltrexone in a biodegradable polymer comprising lactic and/or glycolic acid. Once injected or implanted, the polymer in these preparations slowly degrades to its monomer constituents and releases naltrexone into the surrounding tissue. The monomer constituents are further metabolized and eliminated as carbon dioxide and water. The pharmacokinetics of several such preparations have been described following subcutaneous implantation or injection in humans (Chiang et al., 1984; Galloway et al., 2005; Heishman et al. 1993; Hulse et al., 2004a, 2004b; Kranzler et al., 1998).

A long-acting naltrexone formulation that releases naltrexone for 1 month was developed using Medisorb® technology, an injectable, microsphere-based sustained release drug delivery system (Bartus et al., 2003). In this long-acting formulation, naltrexone microspheres (~100 μm) are manufactured using a polylactide-coglycolide (PLG) polymer and administered by deep intramuscular (IM) injection. Recently, a double-blind, randomized, placebo-controlled, clinical trial demonstrated this formulation, in conjunction with psychosocial treatment, significantly reduced heavy drinking among treatment-seeking alcohol-dependent patients during 6 months of therapy (Garbutt et al., 2005).

Described here are results of a clinical study evaluating the pharmacokinetics and tolerability of single and multiple doses of a long-acting naltrexone formulation based on the Medisorb® delivery system in healthy subjects. For comparative purposes, the pharmacokinetics of oral naltrexone following single and multiple doses were also evaluated.

METHODS

Subjects

Nonsmoking men and women aged 18 to 50 years were eligible for enrollment provided they were in good health as determined by physical examination, electrocardiogram (ECG), clinical laboratory evaluations, and medical history. An equal number of men and women were enrolled and randomized across treatments. Subjects were excluded if they had a history of alcohol and/or opioid dependence or anticipated the need for narcotic analgesia during the study period. Women of child-bearing potential were required to have a negative serum pregnancy test result before receiving study medication and were to use appropriate contraception throughout the study. All subjects were required to refrain from other prescription or over-the-counter medications (with the exception of prescription oral contraceptives) for 2 weeks before and throughout the study.

Study Design

This was a single-center, randomized, double-blind, parallel-group study in 2 panels of subjects (A, B). Subjects received either single or multiple doses of both oral naltrexone and long-acting naltrexone or placebo for long-acting naltrexone according to the scheme in Fig. 1.

All subjects in Panel A ($n = 28$) received a single dose of oral naltrexone 50 mg on day 1. Following a 7-day wash-out period, subjects received either a single IM injection of long-acting naltrexone 190 mg ($n = 12$) or 380 mg ($n = 12$) or placebo ($n = 4$). Subjects remained in the Clinical Research Unit (CRU) for 24 and 48 hours, after oral and IM treatments, respectively. All subjects in Panel B ($n = 14$) received oral naltrexone 50 mg daily for 5 days. Subjects arrived at the CRU in the morning for administration of the first 4 doses and were admitted to the CRU in the evening before the fifth oral dose. Beginning 7 days after the last oral dose, subjects received a total of 4 doses of IM long-acting naltrexone 380 mg ($n = 12$) or placebo ($n = 2$) administered every 4 weeks. Subjects were confined to the CRU for 48 hours following the first and fourth IM injections; the second and third injections were administered on an outpatient basis.

The study protocol was reviewed and approved by an independent institutional review board before subject enrollment and was conducted in accordance with principles originating in the Declaration of Helsinki. Written informed consent was obtained from each study participant after having been informed of the purpose of the study, participation conditions, and risks and benefits.

Dose Administration. Oral naltrexone (ReVia®, Dupont Pharma, Wilmington, DE) was administered with 240 mL water following an overnight fast; food was permitted 4 hours after oral drug administration. Long-acting naltrexone microspheres (Alkermes, Cambridge, MA), containing 34% w/w naltrexone, were supplied as a dry powder and suspended in an aqueous diluent before gluteal IM injection (~2 mL for the 190-mg dose and ~4 mL for the 380-mg dose). Placebo for long-acting naltrexone contained only the PLG polymer. The diluent volume used for placebo administration was matched to the volume of the corresponding active treatment. Repeat injections were administered to alternating sides of the buttocks.

Blood Sample Collection. Venous blood samples (4 mL) were obtained predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, and 48 hours following the first oral dose in Panel A and the fifth oral dose in Panel B. For IM administration, blood samples were collected predose, 1, 2, 4, 8, 12, 24 hours and 1.5, 1.75, 2, 3, 5, 7, 10, 14, 17, 21, 24, 28, 31, 35, 42, 49, and 56 days after the first dose in Panel A and the fourth dose in Panel B. Additional blood samples were obtained from subjects in Panel B over the 28 days following the first IM dose and immediately before the second and third injections. The samples were collected into ethylenediaminetetraacetic acid (EDTA)-containing tubes and centrifuged for 15 minutes. The resulting plasma was transferred to polypropylene storage tubes and stored at −20 °C until analysis.

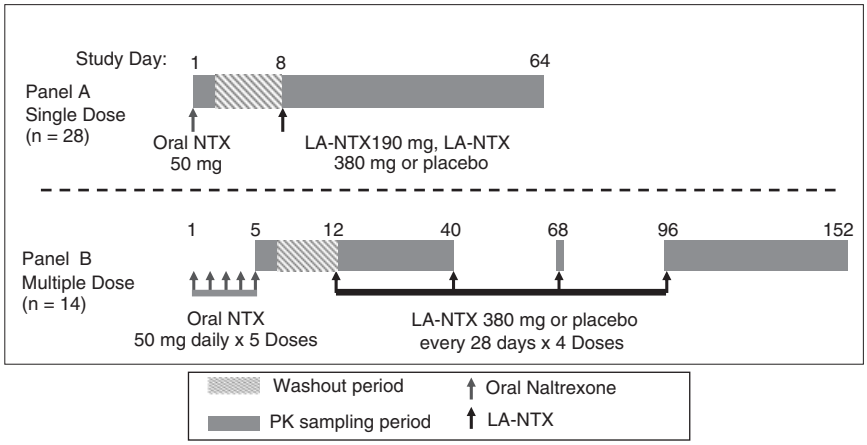

Fig. 1. Study design. NTX, naltrexone; LA-NTX, long-acting naltrexone.

Assessment of Safety and Tolerability. Subjects were monitored throughout the study for the occurrence of clinical and/or laboratory side effects. Reported adverse events were evaluated by the investigator and graded by intensity (mild, moderate, or severe) and relationship to study drug. Intramuscular injection sites were evaluated at each visit following IM drug administration. Twelve lead electrocardiogram (ECG) measurements were obtained at times bracketing the anticipated time of maximal plasma naltrexone concentrations following both routes of administration. QT intervals were adjusted for heart rate using Bazzet's correction (QTcB) and Fridericia's correction (QTcF) (Funck-Brentano and Jaillon, 1993).

Analytical Methodology

Naltrexone and 6β-naltrexol plasma concentrations were determined using a validated high-performance liquid chromatographic (HPLC) assay with tandem mass spectrometry detection. Human plasma (500 μL) containing naltrexone, 6β-naltrexol, and the internal standard (naloxone) was mixed with an organic solvent under alkaline conditions. Following centrifugation, the upper organic layer was removed and evaporated to dryness before reconstitution in mobile phase. An aliquot of the reconstituted sample was injected onto a SCIEX API 3000 LC-MS/MS. Peak areas for the following product ion reactions were measured m/z 342$\rightarrow$324 for naltrexone, m/z 344$\rightarrow$326 for 6β-naltrexol, and m/z 328$\rightarrow$310 for the internal standard. Quantitation was performed using weighted ($1/x^2$) linear least squares regression analyses generated from fortified plasma calibration standards prepared immediately before each run.

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 assayed during sample analysis, 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.

Pharmacokinetic Analyses

Pharmacokinetic parameters for naltrexone and its major metabolite, 6β-naltrexol, following single and multiple oral and long-acting naltrexone doses were calculated for each subject using standard noncompartmental methods (WinNonlin Professional Ver 4.01, Pharsight Corporation, Mountain View, CA). The maximum plasma concentration (C_{max}) and the time of its occurrence (t_{max}) were obtained directly from the concentration–time data. Following single oral and IM doses, area under the curve (AUC_∞) 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 according to the analysis software algorithm. Area under the curve over a dosing interval ($AUC_{1\ day}$ for oral and $AUC_{28\ days}$ for IM) was calculated following multiple oral and IM doses. Elimination half-life ($t_{1/2}$) was calculated as ln(2)/k. The metabolite:parent ratio was calculated as the ratio of 6β-naltrexol AUC (AUC_∞, $AUC_{28\ days}$, or $AUC_{1\ day}$) to the corresponding naltrexone AUC.

Statistical Analyses

Naltrexone and 6β-naltrexol pharmacokinetic parameters were analyzed with respect to dose proportionality, time dependency, accumulation, and achievement of steady state. Dose proportionality (evaluated using C_{max} and AUC_∞ following single doses of long-acting naltrexone 190 and 380 mg), time invariance (evaluated using AUC and $t_{1/2}$ following a single dose compared with steady state), and accumulation (evaluated using $AUC_{28\ days}$ following the fourth IM dose compared with $AUC_{28\ days}$ following the first IM dose) were assessed using an analysis of variance (ANOVA) model with treatment as a fixed effect and subject as a random effect. The ratio of geometric least squares means (obtained by exponentiating the difference between log-transformed parameters) and 90% confidence intervals (CIs) were determined. Results were interpreted in the context of whether or not the CIs included the value of 1.0 (2.0 in the case of dose proportionality). Statistical tests were performed using the mixed effects model (PROC MIXED) procedure in SAS, version 8.2.

Achievement of steady state following IM dosing was assessed by using concentrations before Doses 2, 3, and 4 and 28-days postdose following Dose 4. The 90% CI for the slope of the linear regression through the log-transformed values was estimated. A CI, that contained 0 indicated that steady state was achieved.

The effect of gender on $AUC_{28\ days}$ and C_{max} was explored using an ANOVA model including gender as a fixed effect and subject as random effect.

RESULTS

Subject Demographics and Baseline Characteristics

The extended elimination half-life of naltrexone resulting from administration of the long-acting preparation made a cross-over study design impractical; therefore, the

single and multiple dosing arms of this study were conducted in different panels of subjects. Demographic information on enrolled subjects is presented in Table 1. Within each panel, an equal number of men and women were enrolled; however, they were not matched for weight, age, or race. A total of 42 subjects (Panel A, $n = 28$; Panel B, $n = 14$) were enrolled in the study, and 40 subjects completed all evaluations. Two subjects in Panel B who discontinued the study early (1 was lost to follow-up and 1 withdrew consent) were not replaced. In subjects who received a single dose of long-acting naltrexone 380 mg (Panel A), males weighed approximately 15% more on average [76 (67–90) kg; mean (range)] than females [66 (56–71) kg]. In this same group, males were approximately 10 years younger on average [31 (24–42) years old] than females [41 (34–44) years old].

Table 1. Demographics of Study Participants

	LA-NTX			
	Panel A[a] (mg)		Panel B[b] (mg)	
Variable	190	380	380	All[c]
Gender, *n* (%)				
Male	6 (50)	6 (50)	6 (50)	21 (50)
Female	6 (50)	6 (50)	6 (50)	21 (50)
Age (years)				
Mean (SD)	36.3 (8.8)	35.8 (7.5)	39.1 (7.4)	36.9 (7.9)
Range	20 to 49	24 to 44	23 to 48	20 to 49
Weight (kg)				
Mean (SD)	75.7 (8.5)	71.0 (8.7)	69.3 (10.8)	72.2 (9.2)
Range	59 to 89	56 to 90	54 to 85	54 to 90
Race, *n* (%)				
Hispanic	9 (75)	11 (92)	11 (92)	37 (88)
Caucasian	2 (16.7)	0 (0)	0 (0)	2 (5)
African American	1 (8.3)	1 (8)	1 (8)	3 (7)

[a]Subjects also received a single dose of oral naltrexone 50 mg.
[b]Subjects also received oral naltrexone 50 mg daily for 5 days.
[c]Includes 6 subjects who received placebo injections.
LA-NTX, long-acting naltrexone; SD, standard deviation.

Single-Dose Pharmacokinetics of Long-Acting Naltrexone

Mean naltrexone and 6β-naltrexol plasma concentrations versus time following a single dose of long-acting naltrexone 190 and 380 mg are illustrated in Fig. 2. Naltrexone located at or near the surface of the microspheres was immediately released, resulting in an initial peak in plasma concentrations at 1 to 2 hours after dosing. Concentrations declined approximately 12 hours postdose and began to increase again 1 day postdose as naltrexone embedded deeper in the microspheres was released, resulting in a second peak approximately 2 days after dosing. Beginning around Day 14, plasma naltrexone concentrations declined in a log–linear fashion and were measurable in all subjects, although at least 31 days following administration of 190- and 380-mg doses. Mean concentrations remained >1 ng/mL for longer than 35 days at the 380-mg dose level. At both dose levels, the concentrations of 6β-naltrexol exceeded those of naltrexone, but the shape of the profile was similar.

Plasma pharmacokinetic parameters for naltrexone and 6β-naltrexol following a single dose of long-acting naltrexone are summarized in Table 2. Dose-related increases for AUC_∞ were observed, however, C_{max} did not differ substantially between the 190- and 380-mg doses. Owing to the shape of the concentration profile and the sample collection schedule, it is possible that the true C_{max} was not captured in some subjects at the 380-mg dose. Peak naltrexone concentrations were achieved at a median of 2 days following injection, but were delayed in 2 subjects in the 190-mg dose group (17 and 24 days). Time of occurrence of C_{max} for the metabolite typically occurred 1 day later than the parent, although in 2 subjects in the 190-mg dose group and 4 subjects in the 380-mg dose group, t_{max} occurred 14 days or later after dosing. With the exception of 2 subjects, 6β-naltrexol was detected in the plasma at the first sampling timepoint (1 hour postdose), indicating prompt formation of the metabolite. Considering the rapid generation of 6β-naltrexol, the 24-hour delay typically observed for t_{max} was possibly an artifact of the sample collection schedule. Elimination half-lives ($t_{1/2}$) for both naltrexone and 6β-naltrexol were approximately 7 days following single dose administration of 190 mg and approximately 5 days following single dose administration of 380 mg. Exposure to 6β-naltrexol was approximately 2-fold higher than the corresponding naltrexone exposure.

Multiple-Dose Pharmacokinetics of Long-Acting Naltrexone

Mean plasma concentrations of naltrexone and 6β-naltrexol following administration of the first and fourth long-acting naltrexone 380-mg doses to subjects in Panel B are shown in Fig. 3. The concentration profiles following the first and fourth doses to subjects in Panel B were consistent with the profile following a single dose to subjects in Panel A. Summary statistics of pharmacokinetic parameter values are listed in Table 3. Estimated naltrexone and 6β-naltrexol $t_{1/2}$ following multiple doses of long-acting naltrexone 380 mg to subjects in Panel B were in general agreement with those estimated following single dose administration to subjects in Panel A. Naltrexone and 6β-naltrexol concentrations immediately before subsequent doses (i.e., 28 days after each dose of long-acting naltrexone) were relatively constant. A linear regression through these data points indicated that steady state was achieved at the end of the first dosing interval (naltrexone, slope -0.001, 90% CI -0.004, 0.002; 6β-naltrexol, slope 0.000, 90% CI -0.004, 0.003)

Statistical Analysis of Dose Proportionality, Time Invariance, Accumulation, and Gender Effects

Table 4 summarizes the statistical analysis of naltrexone and 6β-naltrexol dose proportionality, time invariance,

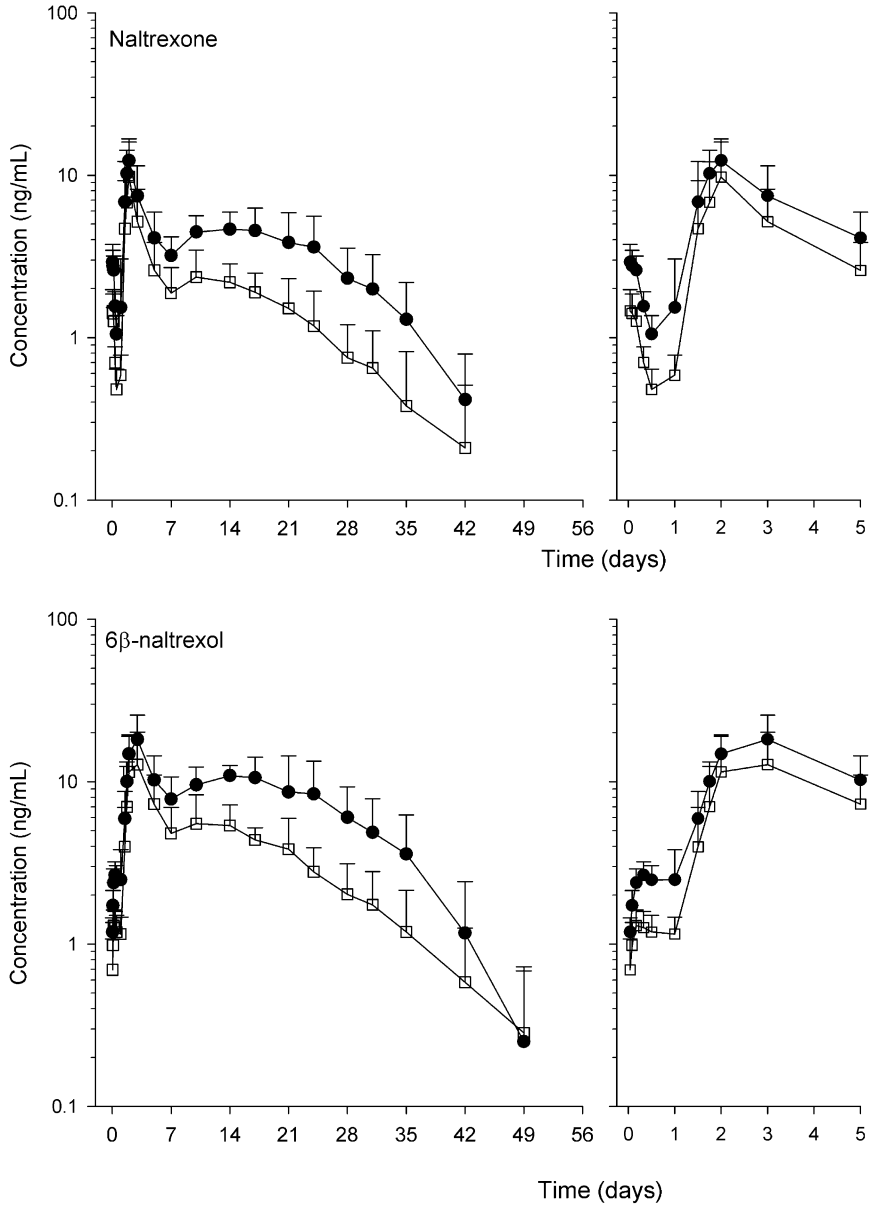

Fig. 2. Mean plasma concentration of naltrexone (*top*) and 6β-naltrexol (*bottom*) following single dose administration of long-acting naltrexone 190 (□) and 380 (●) mg. *Left panel*: Days 0 to 56; *right panel*: Days 0 to 5.

accumulation, and gender effects following long-acting naltrexone administration. Naltrexone and 6β-naltrexol pharmacokinetics appeared dose proportional between the 2 dose levels, with C_{max} exhibiting greater variability compared with AUC. Pharmacokinetic parameters did not change upon repeat dosing, as the AUC and $t_{1/2}$ estimates following multiple doses were in agreement with those from a single dose. Dosing of the long-acting preparation every 28 days resulted in minimal accumulation of naltrexone and 6β-naltrexol (13 and 11%, respectively). Maximum plasma concentration for naltrexone and 6β-naltrexol was approximately 30% lower in females; however, AUC was similar between the genders.

Single- and Multiple-Dose Pharmacokinetics of Oral Naltrexone

Mean naltrexone and 6β-naltrexol plasma concentrations versus time following a single oral dose of naltrexone 50 mg are depicted in Fig. 4. The concentration profiles for both analytes following multiple oral doses were similar to the profiles following a single dose. After oral dosing, peak concentrations of naltrexone were approximately 1/10th of those observed for 6β-naltrexol (Table 5). Elimination of 6β-naltrexol was slower compared with naltrexone. Little or no accumulation of naltrexone or 6β-naltrexol was observed after daily oral dosing. Area under the curve of

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