Bioequivalence, Dose-Proportionality, and Pharmacokinetics of Naltrexone after Oral Administration

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Healthy male volunteers (N=24) participated in a four-way crossover study to compare the rate and extent of absorption of naltrexone after administration of 50 mg tablets as 50, 100, and 200 mg doses and a 10 mg/ml reference syrup. A high-performance liquid chromatographic method was employed to measure naltrexone and 6-β-naltrexol in plasma and urine. Compared to the syrup, the 50 mg tablets were absorbed more slowly but equally well. There was excellent linearity between the administered dose and the area under the plasma concentration-time profile, as well as total urinary recovery of both drug and metabolite. The mean half-lives for naltrexone and β-naltrexol were approximately 4 and 12 hours, respectively. The fraction of drug reaching the systemic circulation was estimated to be 5% of the administered dose because of extensive first-pass metabolism. Less than 1% of the dose was excreted in the urine as naltrexone after 48 hours, while 25% was recovered as unconjugated β-naltrexol. The renal clearance of naltrexone and β-naltrexol was approximately 127 ml/min and 283 ml/min, respectively. The total systemic clearance for naltrexone was approximately 94 L/hr.
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Naltrexone is an effective narcotic antagonist which is employed in the treatment of opiate dependence. In the study reported here, data were collected to determine the rate and extent of absorption of a 50 mg tablet formulation compared with a reference syrup, and to establish the relationship between the amount of drug administered and the amount of drug absorbed. In addition, the pharmacokinetics of naltrexone after oral administration were determined and compared with the results of earlier studies, which were based on only 5 to 6 subjects.[1-3]

METHOD

Subjects

Twenty-four healthy, white, male volunteers were given a medical history, physical examination, and laboratory evaluation, including blood chemistry, hematology, and urinalysis. The subjects ranged in age from 22 to 33 years and weighed between 60 and 93 kg. All subjects provided written informed consent. Two of the initial subjects withdrew from the study for medical reasons unrelated to the study and were replaced by two additional subjects.

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Drug Administration and Study Protocol

Study dosage forms, provided by Du Pont Pharmaceuticals, consisted of tablets containing 50 mg of naltrexone hydrochloride (Lot No. 820947) and a syrup containing 10 mg/ml of naltrexone hydrochloride (Lot No. NI-2-08031), which was supplied to Du Pont by the National Institute on Drug Abuse.

After an overnight fast, each subject received either naltrexone tablets as single doses of 50 mg, 100 mg, or 200 mg, or 10 ml (100 mg) of the syrup. The tablets were taken with 180 ml of water; syrup was administered by an oral syringe and followed by 180 ml of water. All subjects were required to remain upright for at least 1 hour after drug administration. Water intake was unrestricted throughout the study. No food was permitted for 4 hours after dosing. A standard meal was provided 4 hours and 9-10 hours after dosing. All 24 subjects who completed the study received each of the 4 dosage forms, administered according to a completely balanced crossover design with a 7-day interval between each dose. Subjects were instructed to refrain from taking other drugs during the study, if possible. One subject required two aspirin tablets, one subject took two acetaminophen tablets, and one subject took Afrin Nasal Spray and four doses of aspirin. All subjects were confined to the study site for 12 hours after each dose.

Sample Collections

Blood samples (10 ml) were obtained via indwelling catheters or direct venipuncture prior to each dose, and 20 minutes, 40 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 32 hours after each dose. Plasma was separated by centrifugation and frozen until assay. Urine samples were collected just before drug administration and pooled for periods of 0-6, 6-12, 12-24, 24-32, and 32-48 hours after dosing. All samples were refrigerated until a 20-ml aliquot was withdrawn and frozen for later assay.

Assay Method

Naltrexone and its major metabolite, 6-β-naltrexol, were determined in plasma extracts (pH 9 extraction into toluene/isopropanol and back-extracted into acid) by reversed-phase high-performance liquid chromatography (HPLC) with electrochemical detection and an octyl

FIGURE 1. Mean Plasma Concentrations of Naltrexone (N = 24)

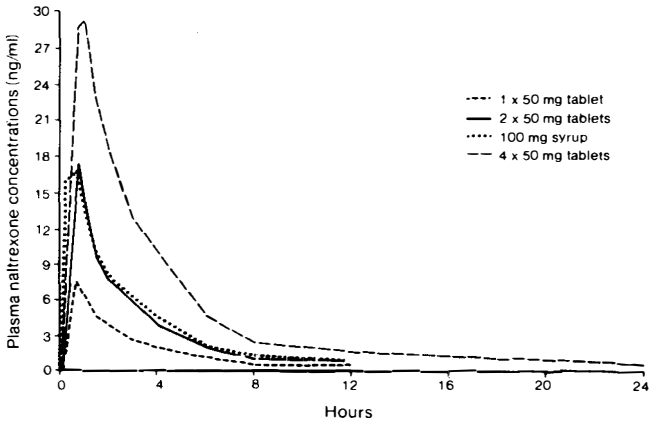
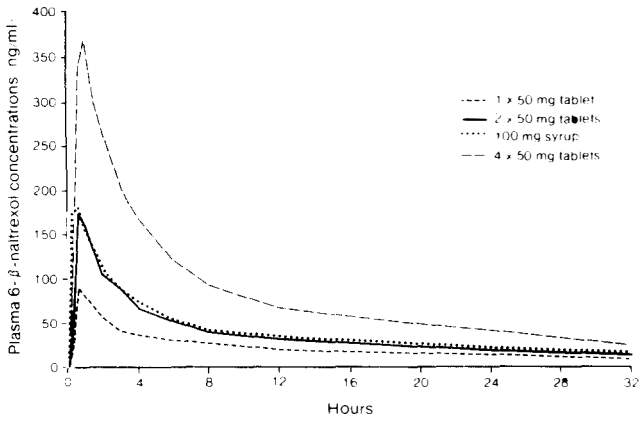


FIGURE 2. Mean Plasma Concentrations of 6-β-Naltrexol (N = 24)



column (Beckman Ultrasphere). Intraday assay coefficients of variation (CV) for naltrexone were 22.5% at 0.2 ng/ml and 0.26% at 100 ng/ml; for naltrexol the CV were 11.8% at 1 ng/ml and 6.1% at 200 ng/ml. Interday assay CV over 4-5 weeks for naltrexone were 10.9% at 0.5 ng/ml and 0.46% at 100 ng/ml; for naltrexol the CV were 22.5% at 3 ng/ml and 0.51% at 500 ng/ml. Extraction recoveries were 96% for naltrexone, 45% for naltrexol, and 88% for the internal standard, an N-cyclopentylmethyl analog of nalbuphine. Both naltrexone and naltrexol were stable in frozen plasma for at least 4 weeks. The limits of detection were 0.2 ng/ml for naltrexone and 0.5 ng/ml for naltrexol, using 2 ml of plasma.

The urine assay was essentially the same as the plasma assay, except that naltrexone and 6-β-naltrexol were determined separately in two HPLC systems because of the large differences in the concentrations of the two components. Intraday urine assay CV for naltrexone ranged from 0.53% to 3.88% over the concentration range of 1 to 20 μg/ml. The intraday assay CV for naltrexol ranged from 0.21% to 2.01% at 5–100 μg/ml. Interday assay CV over 9 weeks for naltrexone were 9.8% at 0.05 μg/ml and 1.3% at 1 μg/ml; for naltrexol the CV were 5.6% at 5 μg/ml and 0.63% at 100 μg/ml. Extraction recoveries were greater than 92% for naltrexone and 86% for naltrexol, and 100% for the internal standard. Both naltrexone and naltrexol were stable in frozen urine for at least 19 weeks. The limits of detection were 0.01 μg/ml for both naltrexone and naltrexol in 0.2 ml of urine.

Pharmacokinetic Analysis

The area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) was calculated by summing the area determined by the linear trapezoidal rule and the extrapolated area (obtained by dividing the last measured plasma level by the terminal rate constant). The apparent elimination half-life ($T_{1/2}$) was determined by linear regression of the terminal log-concentration data points. The maximum plasma concentration value (C_{MAX}) was the highest concentration of naltrexone or naltrexol observed during the study. The time to maximum plasma concentration (T_{MAX}) was the time at which the highest concentration of naltrexone or naltrexol was observed during the sampling procedure.

Cumulative amounts of unconjugated naltrexone and naltrexol excreted in the urine were calculated from the concentrations and volumes of each urine sample. In those few cases where urine samples were not collected, concentrations were estimated from plots of the log of excretion rate versus the midpoint of the collection period.

The renal clearance (Cl_R) observed for each of the four dosages was estimated from the four mean values for the total amount of naltrexone or naltrexol recovered at 48 hours from urine, divided by the corresponding mean $AUC_{0-\infty}$.[4] The fraction of administered dose reaching the systemic circulation (f) was also estimated from the mean data, using the method of Vaughan.[5] The total clearance (Cl_T) was estimated from the mean data, using the relationship $Cl_T = fD/AUC_{0-\infty}$, where D is the administered dose.[6] The dose-proportionality relationship was determined by using linear regression for both individual and mean data for the $AUC_{0-\infty}$ of naltrexone and naltrexol, as well as the total 48-hour urine recovery of both substances.

RESULTS

Bioavailability

Figures 1 and 2 illustrate the mean plasma concentrations for naltrexone and naltrexol, respectively, after each of the four doses. As previously observed,[1,7] the naltrexol plasma concentrations were about 10- to 30-fold greater than the corresponding naltrexone concentrations. Table 1 summarizes the mean values for the peak plasma concentration (C_{MAX}), the time of peak concentration (T_{MAX}), the area under the plasma concentration-time curve to 32 hours (AUC_{0-32}) and extrapolated to infinite time $AUC_{0-\infty}$, and the total urinary recovery (Σmg) for both naltrexone and naltrexol.

One objective was to determine how well the tablet was absorbed, with the syrup used as a reference standard at a

TABLE 1. Mean Bioavailability Parameters for Naltrexone and 6-β-Naltrexol

	One 50 mg Tablet		Two 50 mg Tablets		100 mg Syrup		Four 50 mg Tablets	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Naltrexone								
C_{MAX}(ng/ml)	8.55	4.84	19.59	17.91	20.73	9.80	36.10	19.54
T_{MAX}(hr)	0.95	0.39	0.99	0.55	0.57	0.35	1.05	0.45
AUC_{0-32}(ng•hr/ml)	22.74	13.81	47.42	36.95	51.97	26.08	104.32	76.42
$AUC_{0-\infty}$(ng•hr/ml)	24.82	14.56	49.76	37.07	54.88	28.07	108.82	75.85
Σ Urine (mg)	0.13	0.06	0.33	0.26	0.37	0.22	0.66	0.38
6-β-Naltrexol								
C_{MAX}(ng/ml)	99.3	30.23	206.77	78.08	206.15	77.77	444.31	140.2
T_{MAX}(hr)	0.91	0.37	1.0	0.49	0.6	0.54	1.08	0.43
AUC_{0-32}(ng•hr/ml)	642.7	189.1	1152.9	282.8	1202.0	257.7	2617.0	441.1
$AUC_{0-\infty}$(ng•hr/ml)	765.0	244.6	1381.1	301.1	1411.6	328.8	3066.6	543.2
Σ Urine (mg)	11.78	2.55	24.73	4.33	24.63	4.50	52.81	9.16

TABLE 2. Linear Regression For Dose-Proportionality

	Naltrexone		6-β-Naltrexol	
Regression	$AUC_{0-\infty}$	48 hr Urine	$AUC_{0-\infty}$	48 hr Urine
Individual data (N = 96)				
Slope	0.55	0.00351	15.56	0.275
Intercept	−4.71	−0.0377	−77.75	−2.267
r^2	0.34	0.39	0.86	0.89
Mean data (N = 4)				
Slope	0.621	0.00382	17.30	0.305
Intercept	−3.532	−0.0183	−102.42	−2.47
r^2	0.998	0.992	0.997	0.999

100 mg dose. Since there were no significant differences ($p > .05$) between the tablet and the syrup in terms of AUC or Σmg for naltrexone or naltrexol, it can be concluded that an equivalent amount of drug is absorbed from both dosage forms. The only significant difference ($p \leq .05$) noted in this comparison was for the T_{MAX} values, with the syrup being absorbed slightly more rapidly than the tablet. The mean 48-hour urinary recovery of naltrexone and naltrexol was less than 1% and about 25%, respectively, which is similar to previously reported data.[1,8,9]

Dose Proportionality

Since naltrexone appears to exhibit a substantial first-pass metabolism and is primarily eliminated from the body by metabolism,[1,8,9] it is important to determine if the observed systemic availability is proportional to the administered dose. In the absence of such proportionality (which could result if one or more metabolic steps were saturable), the adjustment of a patient's dosage regimen for optimal response could be more difficult. Fortunately, there is an excellent linear relationship between the administered dose and the mean $AUC_{0-\infty}$ or urinary recovery (Σmg) for both naltrexone and naltrexol (Table 2). The lower correlation coefficients for naltrexone from individual subject data result from the considerable intersubject variability and from much lower plasma concentrations for naltrexone than for naltrexol. These data clearly show that the systemic availability and renal elimination of both naltrexone and its major metabolite, naltrexol, are linearly related to the administered dose. Mulé[7] also noted an approximately proportional increase in naltrexone and naltrexol plasma concentrations during chronic administration of naltrexone with doses of 100–800 mg/day.

Pharmacokinetics

Pharmacokinetic parameters were derived from the mean data, and the mean terminal half-lives were determined from individual subject data (Table 3). The mean half-lives for the elimination of naltrexol ranged from 12.2 to 13.9 hours for the 4 doses. Other workers have reported naltrexol half-lives ranging from 7.7[3] to 12.7 hours.[1] The mean half-lives for naltrexone ranged from 3.7 to 4.8 hours; the lack of significant differences among the half-lives for the 4 doses further indicated a lack of dose dependency in the elimination process. The estimated half-lives were quite variable within each subject. The highest mean half-life (N = 4 doses) for any subject was 6.5 hours (1.72–11.65 hours) and the lowest mean half-life was 2.27 hours (1.6–2.9 hours). Earlier reports in small numbers of subjects indicated a wide range of half-lives for naltrexone: A mean of 1.1 hours has been obtained from urinary excretion data;[8] means have been reported of 2.7 hours and 8.9 hours after intravenous and oral administration, respectively,[3] and 10.3 hours and 9.7 hours after acute and chronic oral administration, respectively.[1] There are several possible causes for the apparent difference in reported half-lives. Verebey et al.[1] administered 100 mg oral doses of naltrexone to 4 male postaddict subjects and observed an apparent biexponential decay in naltrexone plasma concentrations. They reported initial and terminal half-lives of 2–4.1 hours and 7.3–14.7 hours, respectively. Similar data are shown in Figure 3 for those subjects with the longest half-life for a given dose.

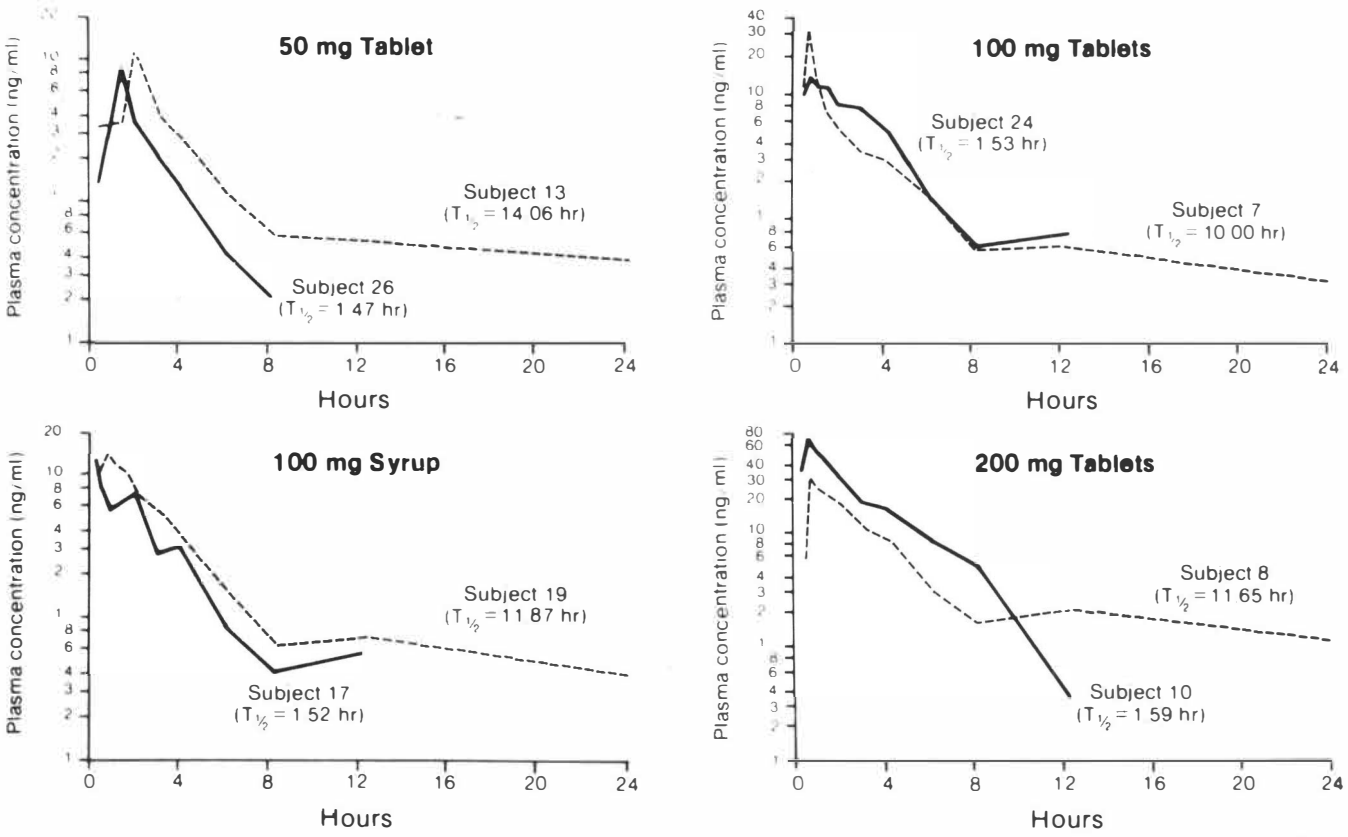
It is possible that some enterohepatic recycling could account for the prolonged phase, since the curvature in the plots occurs after the evening meal. Some evidence for enterohepatic recycling of naltrexone in the guinea pig has been reported by Ludden et al.[10] It is also possible that the terminal portion of the curves with the longest apparent half-lives is seen when the plasma concentrations are ap-

TABLE 3. Pharmacokinetic Parameters for Naltrexone and Naltrexol

Dose	Systemic Availability(f)[a]	Renal Clearance[a]		Total Clearance	Half-Life (±SD)[b]	
		Naltrexone (ml/min)	Naltrexol (ml/min)	Naltrexone (L/hr)[a]	Naltrexone (hr)	Naltrexol (hr)
One 50 mg tablet	0.051	107.0	256.5	92.9	3.57 ± 2.62	12.24 ± 2.43
Two 50 mg tablets	0.052	137.4	298.4	94.3	3.37 ± 2.06	13.89 ± 10.84
100 mg syrup	0.058	138.8	290.7	95.5	3.93 ± 3.00	12.58 ± 4.02
Four 50 mg tablets	0.056	126.1	287.0	93.0	4.83 ± 2.36	12.83 ± 2.02

[a]Calculated using mean data.
[b]Calculated using individual subject data.

FIGURE 3. Plasma Naltrexone Time Profiles for Two Subjects with Longest and Shortest Half-Life after Each Oral Dose



components are also present in low concentration, they would have little effect on the quantitation of the initial high plasma concentrations, but could affect the accurate measurement of the terminal phase concentrations. A study of the plasma concentrations of naltrexone and naltrexol after a single 100-mg dose and daily chronic 100-mg doses of naltrexone suggested no significant accumulation of naltrexone.[1] Further, while there was an increase in peak naltrexol concentrations during chronic administration, trough levels after 24 hours (just before each additional dose) were quite similar for naltrexol after acute and chronic dosing. Even if the true elimination half-life of naltrexone was similar to that of naltrexol (i.e., approximately 12 hours), the administration of naltrexone as a single daily dose should not result in significant accumulation of the drug or the metabolite in the plasma.

The renal clearance data for naltrexone and naltrexol (Table 3) are based on mean data that have been corrected for a 20% protein-binding.[11] There was no effect of dose on the renal clearance values. Those for naltrexone were somewhat higher than the mean 66.7 ml/min (16.5–107 ml/min) reported by Verebey et al.[1] for 4 subjects, and the values gave no indication of net renal secretion or reabsorption of naltrexone. Renal clearance values for naltrexol were similar to the mean of 318 ml/min (243–405 ml/min) reported by Verebey et al.,[1] suggesting renal tubular secretion of this metabolite. The fraction of administered dose reaching the systemic circulation (f) indicated that approximately 95% of the dose was subject to first-pass metabolism. Previous estimates have indicated a value of 80% for first-pass metabolism in a study of 4 postaddict subjects.[2] In addition, Wall et al.[3] determined the plasma concentrations of naltrexone after a 1 mg intravenous dose and a 50 mg oral dose in 5-6 healthy subjects and reported that the AUC

TABLE 4. Numbers of Subjects Reporting Side Effects

Side Effect	N
Headache	1
Nausea	5
Constipation	2
Lightheadedness	2
Tiredness	3
Faintness	2
Dreams	1
Abdominal cramping	1
Body aches	1
Lack of appetite	2
Malaise	2
Fatigue	1
Diplopia	1
Drowsiness	1

after the oral dose was 60% that of the intravenous dose. The apparently greater systemic availability of naltrexone after oral administration in that study[3] could be the result of different subject populations, differences in assay specificity, or the large difference between the intravenous and oral doses. Further, it was not clear whether the same subjects received both the intravenous and the oral doses.

Total systemic clearance of naltrexone was also estimated from mean data with the method of Vaughan.[5] The calculated values approximate liver blood flow and indicate that naltrexone can be classified as a highly extracted drug. The contribution of renal clearance to total clearance was about 8%, which is in agreement with a urinary recovery of approximately 7% of total systemically available drug after a dose of 100 mg.

There was considerable inter- and intrasubject variability noted in the pharmacokinetic parameters and in the plasma naltrexone and naltrexol concentrations. This has been observed by others[1,7] and is not unexpected for a drug that is subject to extensive first-pass metabolism.

Subject Responses

Side effects were reported by the subjects, with nausea being the most common (Table 4). There were no dose-dependent trends in the numbers of subjects reporting one or more side effects (50 mg tablet, N=3; two 50-mg tablets, N=2; 100-mg syrup, N=4; and four 50-mg tablets, N=4). No subject withdrew from the study because of side effects.

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