SYNOPSIS

(PAGE 1 OF 5)

Company: ALZA Corporation **Investigational Product:** Naltrexone HCl 50 mg tablet and naltrexone HCl 1 mg solution **Active ingredient:** Naltrexone HCl		

Protocol No.: FEN-P01-102 CR003256

Title: Pharmacokinetics of Naltrexone Hydrochloride Following Intravenous and Oral Routes of Administration in Healthy Subjects	
Investigator(s)/Study Center: Annemie Mertens, MD, AZ Jan Palfijn, Clinical Pharmacology Unit, Merksem, Belgium	
Publication (reference): none	
Study period: First subject treated: 2 June 2003 Last subject completed: 13 June 2003	**Phase of Development:** 1
Objective: To evaluate the pharmacokinetics of naltrexone hydrochloride (HCl) following intravenous and oral routes of administration in healthy subjects.	
Methodology: This was a single-center, randomized, open-label, 2-treatment, 2-period crossover study in healthy subjects. Subjects were randomly assigned to 1 of 2 treatment sequences (AB or BA) with a washout period of 6 to 14 days between treatments. The washout period commenced the day of dosing, after drug administration.	
Number of subjects (planned and analyzed): Planned n=18; Enrolled n=18; Completed n= 18	
Diagnosis and main criteria for inclusion: Healthy male or female subjects between 18 and 45 years of age. All subjects had to provide written consent, have no history of or show the presence of drug or alcohol dependence or abuse, and meet inclusion/exclusion criteria.	

Test product, dose and mode of administration, batch number:

Treatment	**Treatment A**	**Treatment B**
Dose	1 mg naltrexone HCl	50 mg naltrexone HCl
Mode of administration	Intravenously over 15 minutes	Oral
Lot number	341982 341734	TEA442AB
Duration of treatment	Single dose	Single dose
Duration of trial	11 days	

Reference therapy: IV administration was reference therapy for absolute bioavailability following oral administration.

Criteria for evaluation:

Pharmacokinetics: Blood samples were collected from all subjects at predose and at 0.08 (after IV only), 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 15.0, 22.0, 24.0, 26.0, 30.0, and 34.0 hours post dose administration. Blood samples were analyzed for serum naltrexone and 6-β-naltrexol (naltrexone's major metabolite) concentrations.

Safety: Adverse events (AEs) and vital signs (blood pressure, temperature, pulse, and respiratory rate) were monitored.

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Statistical methods:

Pharmacokinetic Measures: Descriptive statistics for the pharmacokinetic parameters (C_{max}, T_{max}, k, $t_{1/2}$, AUC_t, and AUC_{inf}) were calculated for each treatment for both naltrexone and its major metabolite, 6-β-naltrexol. Absolute bioavailability of naltrexone following the oral route of naltrexone administration was calculated for subjects who completed both treatments. The 90% CIs for mean oral bioavailability are presented. Dose-normalized 6-β-naltrexol AUC ratios after IV and oral naltrexone treatments were calculated for subjects who completed both treatments, and the 90% CIs for the mean AUC ratios were presented. Serum 6-β-naltrexol/naltrexone concentration ratios at different time points and 6-β-naltrexol/naltrexone AUC ratios following naltrexone IV and oral treatments were also summarized.

Safety Measures: Data were summarized and descriptive statistics were calculated.

Pharmacokinetic results:

Naltrexone*:* Mean (SD) values for serum naltrexone pharmacokinetic parameters are summarized below for both treatment periods. Following the IV infusion, as expected, peak serum naltrexone concentrations were observed in most subjects when the infusion was stopped at 15 minutes post-initiation. The decline in serum-concentration profile generally appears to be biexponential. The mean terminal half-life was 2.5 hours.

After oral dosing, serum naltrexone concentrations rose fairly rapidly, reaching a peak concentration by 0.86 hours. Half-life values were greater after oral dosing (mean 5.8 hours) than those observed following IV treatment (mean 2.5 hours). Secondary peaks were observed between the 2- and 12-hour time points after oral dosing, possibly due to biliary recycling, which has been reported in the literature for naltrexone (Kleber 1985). Mean absolute bioavailability after oral administration was estimated to be 5.3%. The dose-normalized AUC_{inf} ratio was estimated to be 4.9% using log-transformed values in the ANOVA model.

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Pharmacokinetic results, continued:

Mean (SD) Values for Serum Naltrexone Pharmacokinetic Parameters

	Treatment	
Parameter	**Naltrexone HCl 1 mg IV (n=18)**	**Naltrexone HCl 50 mg Oral (n=18)**
C_{max} (ng/mL)	11.26 (2.87)	8.82 (3.9)
T_{max} (h)	0.25 (0.01)	0.86 (0.5)
$t_{1/2}$ (h)	2.5 (0.5)	5.8 (2)
AUC_t (ng·h/mL)	8.01 (1.3)	20.36 (6.87)
$AUC_{(0-34)}$ (ng·h/mL)	8.05 (1.3)	20.37 (6.87)
AUC_{inf} (ng·h/mL)	8.07 (1.3)	20.61 (7.04)
Mean % bioavailability (SD) 90% confidence interval (CI)	Reference	5.26 (2.2) 4.4 - 6.2
Dose-normalized AUC_{inf} Ratio 90% CI (Log scale using ANOVA model)	Reference	4.94 4.3 - 5.7

A 2-compartment disposition model best described the observed IV naltrexone concentration-time profile. The estimates for clearance were similar for the compartmental (136 L/h) and the noncompartmental analyses (127 L/h). The estimates for V1 (central compartment) and V_{ss} (steady state) were 44 and 216 L, respectively. For each subject, the estimated disposition parameters from the 2-compartment IV model were fixed and the absorption parameters were estimated for oral treatment: absorption rate constant [K_a] 1.17 $hours^{-1}$, absorption lag time 0.24 hours, and bioavailability 4.6%. The bioavailability estimate was similar following noncompartmental analysis.

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Pharmacokinetic results, continued:

6-β-Naltrexol: Mean (SD) values of the pharmacokinetic parameters for serum 6-β-naltrexol are summarized below for both treatment periods. The mean dose-normalized 6-β-naltrexol AUC ratio (oral/IV) was about 93%, indicating that the extent of metabolism from naltrexone to 6-β-naltrexol is similar with both IV and oral treatments. The mean 6-β-naltrexol $t_{1/2}$ value was about 11.4 hours, approximately 5 times that of naltrexone (2.5 hours) after IV administration. These results suggest that the elimination rate of 6-β-naltrexol is slower than its formation rate from naltrexone. As a result, the serum 6-β-naltrexol/naltrexone concentration ratios increase over time following naltrexone treatments. The 6-β-naltrexol/naltrexone AUC ratio was higher with oral than with IV treatment (40 vs 2.1, respectively), suggesting high first-pass metabolism of naltrexone following oral administration.

Mean (SD) Values for Serum 6-β-naltrexol Pharmacokinetic Parameters

	Treatment	
Parameter	**Naltrexone HCl 1 mg IV (n=18)**	**Naltrexone HCl 50 mg Oral (n=18)**
C_{max} (ng/mL)	1.53 (0.52)	122.56 (48.22)
T_{max} (h)	0.82 (0.7)	0.94 (0.5)
$t_{1/2}$ (h)	11.43 (3.07)	11.71 (3.12)
AUC_t (ng·h/mL)	14.59 (3.39)	677.31 (128.1)
$AUC_{(0-34)}$ (ng·h/mL)	14.59 (3.39)	677.31 (128.1)
AUC_{inf} (ng·h/mL)	16.88 (3.97)	775.71 (160.6)
Mean % dose-normalized AUC ratio (SD); 90% CI	Reference	93.1 (12) 88.2 - 98.0
Dose-normalized AUC_{inf} ratio; 90% CI (Log scale using ANOVA model)	Reference	92.38 87.9 - 97.1

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(PAGE 5 OF 5)

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Safety results:

No serious adverse events were reported in this study, and no subjects discontinued from the study. After each naltrexone treatment, 10 subjects (55.6%) reported at least 1 AE, and the AEs tended to be those known to be associated with naltrexone treatment. All but 1 of the AEs was of mild or moderate severity.

Headache was the most frequently reported AE after naltrexone IV (6 subjects, 33.3%) or oral treatment (6 subjects, 33.3%). Other AEs reported by ≥10% of subjects were: dizziness (3, 16.7%) and nausea, thirst, and rash (each 2, 11.1%) after naltrexone IV treatment, and nausea and dizziness (each 3, 16.7%) and asthenia and somnolence (each 2, 11.1%) after naltrexone oral treatment.

Conclusions:

Following IV administration of naltrexone, the serum naltrexone concentration decline appears to be biexponential with a mean half-life of 2.5 hours and total clearance of 127 L/h; the clearance estimate following compartmental analysis was similar. The estimates of V1 (central compartment) and V_{ss} (steady state) were 44 and 216 L, respectively. After oral administration, the mean terminal half-life value (5.8 hours) was greater than that after IV administration. The mean absolute bioavailability values from noncompartmental and compartmental analyses were estimated to be 5.3% and 4.6%, respectively.

The extent of metabolism from naltrexone to 6-β-naltrexol was similar with IV and oral treatments. 6-β-naltrexol's longer half-life (11.4 hours) compared with that of naltrexone after naltrexone IV administration suggests that the elimination rate of the metabolite is slower than its formation rate from naltrexone. The 6-β-naltrexol/naltrexone AUC ratio was higher with oral than with IV administration, suggesting high first-pass metabolism of naltrexone following oral administration.

Both intravenous and oral administrations of naltrexone were well tolerated and no new safety issues were identified in the study population.

Date of the report: 3 November 2003

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