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Company: ALZA Corporation **Investigational Product:** Fentanyl citrate **Active ingredient:** Fentanyl citrate		

Protocol No.: FEN-P01-101 CR003253

Title: Pharmacokinetics of Fentanyl Citrate 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: 8 May 2003 Last subject completed: 29 May 2003	**Phase of Development:** 1
Objective: To evaluate the pharmacokinetics of fentanyl citrate following intravenous and oral routes of administration in healthy subjects.	
Methodology: This was a single-center, randomized, open-label, two-treatment, two-period, crossover study. Subjects were randomly assigned to one of two 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. Prior to the first treatment period, each subject was challenged with naloxone to ensure that he/she was not dependent on opioids. Each subject received a 50 mg naltrexone tablet as an opioid antagonist, starting 14 hours before dosing and then twice daily ending 24 hours post-dose.	
Number of subjects (enrolled and analyzed): Enrolled n=18, Completed n=16	
Diagnosis and main criteria for inclusion: Healthy male and female subjects between 18 and 45 years of age who provided written consent, and who did not have a history or show presence of drug or alcohol dependence or abuse, and who met inclusion/exclusion criteria, were included in the study.	
Test product, dose and mode of administration, batch number:	

	Treatment A	Treatment B
Dose	300 μg fentanyl citrate administered intravenously over 15 minutes	1 mg fentanyl citrate solution administered orally
Mode of administration	Intravenous	Oral
Lot number	03C05/584	03C05/584
Fentanyl content	300 μg	1 mg
Duration of treatment	15 minutes	Single ingestion
Duration of individual participation	Approximately 2½ weeks	
Duration of trial	Approximately 3 weeks	

Reference therapy: IV administration was the reference therapy for absolute bioavailability following oral administration	
Additional drugs per protocol:	Naltrexone hydrochloride, 50 mg, twice daily Naloxone hydrochloride 0.8 mg, once (challenge test)

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Criteria for evaluation:

Pharmacokinetics: Blood samples were collected from each subject pre-dose and at the following time points, in hours, post-dose administration:

IV: 0.08, 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, 36.0

Oral: 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, 36.0

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

Statistical methods:

Pharmacokinetics: Descriptive statistics were calculated for fentanyl pharmacokinetic parameters (C_{max}, T_{max}, k, $t_{1/2}$, AUC_t, and AUC_{inf}) for each treatment. Serum fentanyl concentrations as a function of time, following the two treatments, were compared. Absolute bioavailability was calculated for subjects who completed both treatments, and the 95% confidence interval for mean oral bioavailability was computed.

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

Pharmacokinetic Results:

Mean (SD) values for serum fentanyl pharmacokinetic parameters for the 16 subjects who completed both treatment periods are summarized below.

Parameter	**Fentanyl Citrate IV 300 µg (n=16)**	**Fentanyl Citrate Oral 1 mg (n=16)**
C_{max} (ng/mL)	4.05 (1.74)	1.39 (0.59)
T_{max} (h)	0.25 (0.01)	1.36 (0.55)
$t_{1/2}$ (h) [a]	11.5 (3.3)	10.3 (3.4)
AUC_t (ng.h/mL)	6.25 (1.64)	6.68 (3.63)
AUC_{inf} (ng.h/mL)	6.71 (1.92)	7.08 (3.91)
% Bioavailability 95% CI	Reference	31.5 (12.3) 26-37
Dose normalized AUC_{inf} Ratio 90% CI (Log scale using ANOVA model)	Reference	29.2 24.4 – 35.0

[a] Oral (n=14)

Source: Tables 11.1.2.1 – 11.1.2.6

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Pharmacokinetic Results (continued):

Following the IV infusion, peak serum fentanyl concentrations were observed in most subjects when the infusion was stopped at 15 minutes post-initiation. The decline in serum-concentration profile appears to be tri-exponential. The mean terminal half-life was 11.5 hours and mean clearance was 47.3 L/h. The three-compartment disposition model best described the observed IV fentanyl concentration-time profile. Clearance estimates following compartmental (47.7 L/h) and non-compartmental analyses (47.3 L/h) were similar and consistent with values reported in the literature. The estimates of V1 (central compartment) and Vss (steady state) based on compartmental analysis were 46.9 and 532.9 L, respectively. After oral dosing, serum fentanyl concentrations rose fairly rapidly, reaching a peak concentration of 1.39 ng/mL in 1.4 hours. The mean half-life value (10.3 hours) was similar to that observed following IV treatment.

Mean absolute bioavailability after oral administration was estimated to be 31.5% with intersubject variability of 39%. The dose normalized AUC_{inf} ratio was estimated to be 29.2% using log transformed values in the ANOVA model. The estimated disposition parameters from the three compartment IV model for each individual were fixed and the absorption parameters (Absorption rate constant [Ka], absorption lag time) and bioavailability [F] were estimated. The estimates were 1.4 $hours^{-1}$, 0.626 hours, and 29.8%, respectively. The bioavailability estimate was also similar following non-compartmental analysis, and consistent with the value reported in the literature.

Safety results:

No serious adverse events and no discontinuations due to AEs occurred in this study.

At least one AE was reported by 9 (50.0%) of 18 subjects during the fentanyl IV treatment period and by 8 (50.0%) of 16 subjects during the oral treatment. Most of the AEs reported were of mild or moderate severity and tended to be those known to be associated with fentanyl or naltrexone. The most frequently reported AEs (≥10% of subjects) after IV treatment were nausea (5 subjects, 27.8%), headache, diarrhea (3 subjects each, 16.7%), and syncope, vomiting, and dizziness (2 each, 11.1%). Headache and nausea (3 subjects each, 18.8%) were reported by ≥10% of subjects after the oral treatment. The investigator attributed these AEs to the study antagonist naltrexone, based on the timing of their occurrence, or an intercurrent illness. Two AEs, both of mild severity, were assessed by the investigator as possibly related to fentanyl treatment: an increase in AST and ALT values after oral treatment, and a shortened PR interval after IV treatment. Both normalized after study completion.

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Conclusions:

Following IV administration of fentanyl, serum concentration decline appears to be tri-exponential with a mean total clearance of 47.3 L/h and mean terminal half-life of 11.5 hours. Clearance estimates following compartmental and non-compartmental analyses were similar and consistent with the value reported in the literature. The estimates of V1 (central compartment) and Vss (steady state) were 46.9 and 532.9 L, respectively After oral administration, the mean terminal half-life of 10.3 hours was similar to that of IV administration, and the mean absolute bioavailability was estimated to be 31.5%. Bioavailability estimates were also similar following compartmental and non-compartmental analyses and consistent with the value reported in the literature.

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

Date of the report: 19 August 2003

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