

Anesthesiology
2000; 92:665-73
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Multiple Dose Pharmacokinetics of Oral Transmucosal Fentanyl Citrate in Healthy Volunteers

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Background: Oral transmucosal fentanyl citrate (OTFC) is a solid form of fentanyl that delivers the drug through the oral mucosa. The clinical utility of multiple doses of OTFC in the treatment of "breakthrough" cancer pain is under evaluation. The aim of this study was to test the hypothesis that the pharmacokinetics of OTFC do not change with multiple dosing.

Methods: Twelve healthy adult volunteers received intravenous fentanyl (15 µg/kg) or OTFC (three consecutive doses of 800 µg) on separate study sessions. Arterial blood samples were collected for determination of fentanyl plasma concentration by radioimmunoassay. The descriptive pharmacokinetic parameters (maximum concentration, minimum concentration, and time to maximum concentration) were identified from the raw data and subjected to a nonparametric analysis of variance. Population pharmacokinetic models for all subjects and separate models for each subject were developed to estimate the pharmacokinetic parameters of fentanyl after multiple OTFC doses.

Results: The shapes of the profiles of plasma concentration versus time for each dose of OTFC were grossly similar. No change was noted for maximum concentration or time to maximum concentration over the three doses, while minimum concentration did show a significantly increasing trend. Terminal half-lives for intravenous fentanyl and OTFC were similar. A two-compartment population pharmacokinetic model ade-

quately represented the central tendency of the data from all subjects. Individual subject data were best described by either two- or three-compartment pharmacokinetic models. These models demonstrated rapid and substantial absorption of OTFC that did not change systematically with time and multiple dosing.

Conclusions: The pharmacokinetics of OTFC were similar among subjects and did not change with multiple dosing. Multiple OTFC dosing regimens within the dosage schedule examined in this study can thus be formulated without concern about nonlinear accumulation. (Key words: Opioid; nonintravenous; pharmacologic modeling.)

ORAL transmucosal fentanyl citrate (OTFC) was initially introduced for clinical use as a single, one-time premedication dose before surgery or painful procedures. The clinical utility of this transmucosal delivery technology for fentanyl is a function of three elements. First, OTFC is noninvasive, eliminating the need for direct access to the patient's circulation with an intravenous catheter or hypodermic needle. Second, clinical effect is achieved rapidly because the absorption process is faster and more complete (*i.e.*, there is increased bioavailability) compared with oral administration. Finally, the fact that the drug is on a handle may enable the patient or clinician to titrate the drug as needed; if excessive drug effect is produced, the remaining dose can be removed from the mouth.

The clinical pharmacology of OTFC after a single dose has been extensively studied in the perioperative setting in both adults and children. Pharmacodynamically, with appropriate dosage, OTFC produces analgesia and sedation if used as an anesthetic premedication.^{1,2} Pharmacokinetically, OTFC is rapidly absorbed with high bioavailability and has a systemic disposition similar to intravenous administration.³

Because of OTFC's rapid absorption characteristics, noninvasive means of administration, and potential for titration, the utility of OTFC in the treatment of breakthrough pain in patients with cancer and other chronic painful conditions is being extensively studied. OTFC treatment of breakthrough cancer pain of course man-

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Received from the Department of Anesthesiology, University of Utah, Salt Lake City, Utah. Submitted for publication November 6, 1997. Accepted for publication October 7, 1999. Supported in part by Anesta Corporation, Salt Lake City, Utah. Presented in preliminary form at the annual meeting of the American Society of Anesthesiologists, Washington, DC, October 8-13, 1993.

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dates the use of multiple doses. Whether or not OTFC exhibits time-dependent pharmacokinetics with multiple dosing is unknown. The aim of this study was to examine the pharmacokinetics of OTFC if administered in multiple doses using an open-label design in healthy adult volunteers. Based on the extensive knowledge of fentanyl's pharmacokinetics if administered intravenously,⁴ we hypothesized that multiple doses of OTFC would not show any time-dependent changes.

Materials and Methods

After approval by the Human Institutional Review Board at the University of Utah Health Sciences Center, informed written consent was obtained from 12 healthy adult male and female volunteers. Eligible subjects were nonsmokers, 18–50 yr of age, whose weight deviated no more than 15% from ideal body weight. They had no history of drug or ethanol abuse and were not taking any pain medications.

Each volunteer completed two randomized study sessions, once receiving intravenous fentanyl and once receiving OTFC. A period of at least 2 weeks separated the study sessions. All volunteers were scheduled to complete both study sessions within 3 months.

Subjects fasted overnight before each study session. At the start of each session, an 18-gauge catheter was inserted into a peripheral vein for maintenance fluid administration (lactated Ringer's solution at the rate of $1.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and a 20-gauge catheter was inserted into a radial artery for blood sampling. Safety monitors included a noninvasive automatic blood pressure cuff, a pulse oximeter and an electrocardiogram.

During the OTFC sessions, each subject received three 800- μg doses of OTFC, with 6-h intervals between doses. Subjects were instructed to place each OTFC unit (800 μg) in the buccal pouch and suck on it, pacing themselves (with instruction from the investigator) so that the unit was consumed in 15 min. During the intravenous sessions, fentanyl was infused at a constant rate of 50 $\mu\text{g}/\text{min}$ to a total of 15 $\mu\text{g}/\text{kg}$.

Blood Sampling and Fentanyl Assay

Blood samples (4 ml) were obtained from the arterial catheter just before drug administration and at frequent intervals thereafter. For intravenous administration, samples were obtained every 2 min during the infusion. After termination of the infusion, samples were obtained at 1, 2, 3, 4, 5, 6, 8, 10, 15, 30, 45, 60, and 120 min, and

then every 2 h for 24 h. During OTFC administration blood samples were obtained every 4 min during consumption; after consumption, they were obtained at 16, 18, 20, 22, 24, 26, 28, 30, 35, 40, 50, 60, 70, 80 and 90 min, and 2, 4, and 6 h after the start of the first and second doses, and every 2 h for an additional 18 h after the third dose.

All blood samples were injected into uncoated glass tubes and left to clot for 1 h. The serum was then separated from the red cells in a refrigerated centrifuge, placed in polypropylene tubes, and frozen at -20°C until analysis.

Serum fentanyl concentrations were determined by radioimmunoassay. The assay was sensitive to 0.2 ng/ml, with coefficients of variation of 10% at 0.2 ng/ml, 4% at 0.8 ng/ml, and 2% at 1.7 ng/ml.⁵

Pharmacokinetic Analysis

The raw pharmacokinetic data were analyzed using three different methods. First, a model independent analysis of the descriptive pharmacokinetic parameters was undertaken. Second, to estimate typical pharmacokinetic parameters and to show that the pharmacokinetic system could be adequately described by a single pharmacokinetic model, a nonlinear, mixed-effects population compartmental analysis was completed. Finally, to gain more insight into the pharmacokinetic behavior of multidose OTFC, a compartmental analysis of each individual was completed that allowed each individual to have his or her own "best" model. The results of each of these analysis techniques were examined for evidence of time dependency.

Descriptive Pharmacokinetic Parameter Analysis. Peak (C_{max}) and trough (C_{min}) plasma fentanyl concentrations after each OTFC dose were identified by inspection of the data. The C_{min} was set at 360 min after administration for a consistent trough. The time to C_{max} (T_{max}) after each OTFC dose was also identified by inspection of the data. The half-life of the terminal slope of the plasma decay curve from the intravenous dose ($T_{1/2_{\text{iv}}}$) and from the third OTFC dose ($T_{1/2_{\text{tm}}}$) were also estimated by linear regression of the log-transformed data (after visual identification of the terminal portion).

Considering the small sample size, summary statistics for C_{max} , C_{min} , and T_{max} for each OTFC dose were the sample median with 95% confidence intervals. Hodges-Lehmann estimation was used to obtain the sample median and an exact 95% confidence interval.

This being a repeated-measures experiment (one within factor at three levels: first, second, and third

dose), a nonparametric repeated-measures test analogous to analysis of variance was applied to C_{\max} , C_{\min} , and T_{\max} . Two tests were used: The Quade test has as an alternative hypothesis that at least one pairwise inequality is demonstrated. If we let τ_1 , τ_2 , and τ_3 represent the treatment effect of the first, second, and third OTFC doses, then for the Quade test the null hypothesis of no treatment effect is formally stated as $H_0: \tau_1 = \tau_2 = \tau_3$, with the alternative hypothesis being $H_a: \tau_i \neq \tau_j$ for at least one (i,j) pair. The Page test is appropriate for treatments that have a natural ordering. Using the same nomenclature, the null hypothesis is identical as for the Quade test with a different alternative hypothesis $H_a: \tau_1 \geq \tau_2 \geq \tau_3$ or $H_a: \tau_1 \leq \tau_2 \leq \tau_3$, in which at least one of the inequalities is strict. A natural ordering is a reasonable assumption for C_{\max} and C_{\min} .

For $T_{1/2_{iv}}$ and $T_{1/2_{tm}}$, median values with exact 95% confidence intervals were obtained by Hodges-Lehmann estimation. $T_{1/2_{iv}}$ and $T_{1/2_{tm}}$ were compared by the Wilcoxon signed rank test.

The statistical software for estimation and hypothesis testing was StatXact 4 for Windows (Cytel Software, Cambridge, MA). Alpha for the rejection of the null hypothesis was set at 0.05; two-sided tests were used.

Nonlinear, Mixed-effects Population Model Analysis. The measured concentrations for all subjects from both the intravenous and OTFC limbs were combined with dosing information to produce the dataset for population analysis using the nonlinear mixed-effects modeling program NONMEM.⁶ The combined (intravenous and oral) dataset for simultaneous fitting contained 1,113 records, including 1,065 observation and 48 dosing events from 12 patients. Fentanyl concentrations less than 0.5 ng/ml were not included.

A two-compartment mamillary model with a first-order absorption rate constant was used. The model was parameterized in terms of an absorption rate constant (k_a), bioavailability (F), systemic clearance (CL_e), central and peripheral volumes of distribution, and intercompartmental flow rate. Intersubject variability of the pharmacokinetic parameters was modeled using an exponential error model. The distribution of random residual errors was described by a constant coefficient of variation model. Initial parameter estimates were guided by our prior work and the work of others.^{3,7} The theoretic and applied aspects of NONMEM have been reviewed extensively elsewhere.⁸

Individual Compartmental Model Analysis. Each subject's intravenous and OTFC concentration-time data were combined with dosing information to produce the

dataset for estimation of each individual's "best" model using the pharmacokinetic parameter estimation program ADAPT II.⁹ Using the general form of the two-compartment model described previously for the population analysis, individual models for each subject were built by simultaneously fitting the OTFC data with systemic pharmacokinetic parameters shared by both transmucosal and intravenous routes of administration.

Some subjects required a three-compartment pharmacokinetic model, and therefore the system of equations was appropriately expanded. For each subject unique values of k_a and F were estimated for each dosing interval if it improved the fit; otherwise their values were held constant across all dosing intervals.

For the purposes of this analysis, the swallowed fentanyl was modeled as parallel drug loss, and fentanyl concentrations less than 0.5 ng/ml were not included.¹⁰ A one-way analysis of variance was performed to compare k_a , F, CL_e and volume of distribution at steady-state (V_{ss}) values.

Results

Twelve volunteers were enrolled (7 male, 5 female). Eleven were Caucasian and one was of Asian ancestry. Their mean age was 27.8 yr (SD = 3.8). Mean weight was 74.4 kg (SD = 11.1). All 12 subjects completed the study.

In general, the volunteers tolerated the study protocol well. There were no serious adverse events. No volunteer received naloxone in the treatment of an adverse event.

The most common adverse events were nausea (10 volunteers in the OTFC group, 9 in the intravenous group) and decreased oxygen saturation as measured by pulse oximetry (7 in the OTFC group and 8 in the intravenous group), complications that were expected as part of this protocol. All subjects in the intravenous group required supplemental oxygen, whereas five subjects in the OTFC group received oxygen. There were no episodes of significant muscle rigidity in the OTFC group.

Pharmacokinetic Analysis

The profiles of concentration *versus* time observed in this study are typical of those generally observed for OTFC.³ These profiles are characterized by rapid attainment of C_{\max} (compared with oral administration), indicating rapid absorption of transmucosally administered

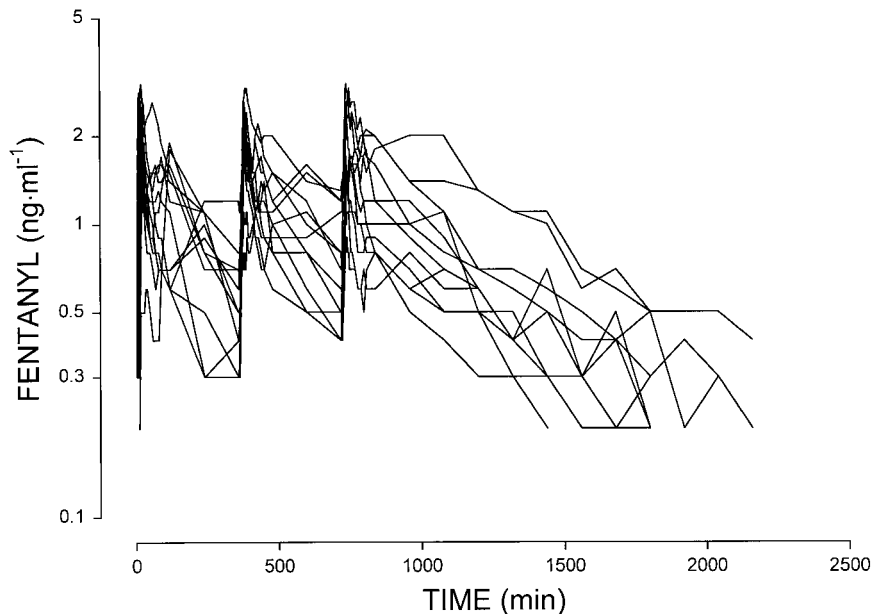


Fig. 1. Fentanyl plasma concentrations in 12 subjects who received 800 μg of oral transmucosal fentanyl citrate administered every 6 h (three doses total).

fentanyl, followed by a gradual decline in plasma concentrations typical of fentanyl administered by any route. The combined raw data for the transmucosal doses are shown in figure 1. There was no obvious trend toward grossly higher peak or trough concentrations with the dosing schedule used in this study.

Descriptive Pharmacokinetic Parameter Analysis. The descriptive pharmacokinetic parameters are displayed in table 1. Although C_{max} showed no change

among the three doses of OTFC, C_{min} did show an increase with successive doses of OTFC as illustrated in figure 2. This was confirmed by the Page test (C_{max} , $P \approx 0.5$; C_{min} , $P \approx 0.005$). There was no difference for C_{max} with the nonordered test. A 360-min sample for plasma fentanyl for subject 12 (first OTFC dose) was not available. A conservative substitution of the value at 240 min was made. Statistical tests were calculated with and without this substitution and were both significant.

Table 1. The Descriptive Pharmacokinetic Parameters

Subject	C_{max} (ng/ml)			C_{min} (ng/ml)			T_{max} (min)			Half-lives (min)	
	1 st	2 nd	3 rd	1 st	2 nd	3 rd	1 st	2 nd	3 rd	OTFC	IV
1	2.5	1.9	3.0	0.5	0.7	1.1	22.0	22.0	20.0	1,198	1,126
2	3.0	2.5	1.7	0.7	0.6	0.7	20.0	24.0	18.0	599	636
3	1.8	0.9	2.0	0.4	1.2	1.1	120.0	30.0	70.0	465	684
4	1.9	2.9	2.9	1.2	1.3	1.4	26.0	24.0	30.0	1,294	1,244
5	1.4	1.1	0.9	0.6	0.5	0.7	26.0	18.0	20.0	1,216	1,225
6	1.8	1.5	1.5	0.3	0.4	0.5	16.0	18.0	24.0	1,422	880
7	2.8	2.3	1.1	0.8	0.8	0.6	12.0	26.0	18.0	927	1,368
8	3.0	2.3	2.7	0.4	0.4	0.4	20.0	20.0	16.0	920	472
9	1.9	2.6	1.6	0.7	0.8	0.8	120.0	22.0	28.0	1,322	1,696
10	1.5	2.2	2.4	0.5	1.1	0.9	24.0	26.0	22.0	956	1,480
11	2.0	2.0	1.3	0.3	0.5	0.5	22.0	22.0	20.0	1,053	1,093
12	1.6	1.8	2.0	*	1.2	2.0	80.0	12.0	240.0	1,168	1,443
Median	2.1	2.1	1.9	0.6	0.8	0.8	24.0	22.0	24.0	1,070	1,125
LB 95% CI	1.7	1.6	1.5	0.4	0.6	0.6	20.0	19.0	19.0	841	865
UB 95% CI	2.5	2.4	2.4	0.8	1.0	1.2	71.0	25.0	49.0	1,245	1,368

Peak (C_{max}), trough (C_{min}) and time to peak (T_{max}) concentration values after the 1st, 2nd and 3rd transmucosal fentanyl doses are shown. Also listed are the terminal half-lives for the intravenous and 3rd transmucosal dose.

CI = confidence interval; IV = intravenous; LB = lower bound; OTFC = oral transmucosal fentanyl citrate; UB = upper bound.

* Not available.

MULTIPLE DOSE PHARMACOKINETICS OF ORAL TRANSMUCOSAL FENTANYL

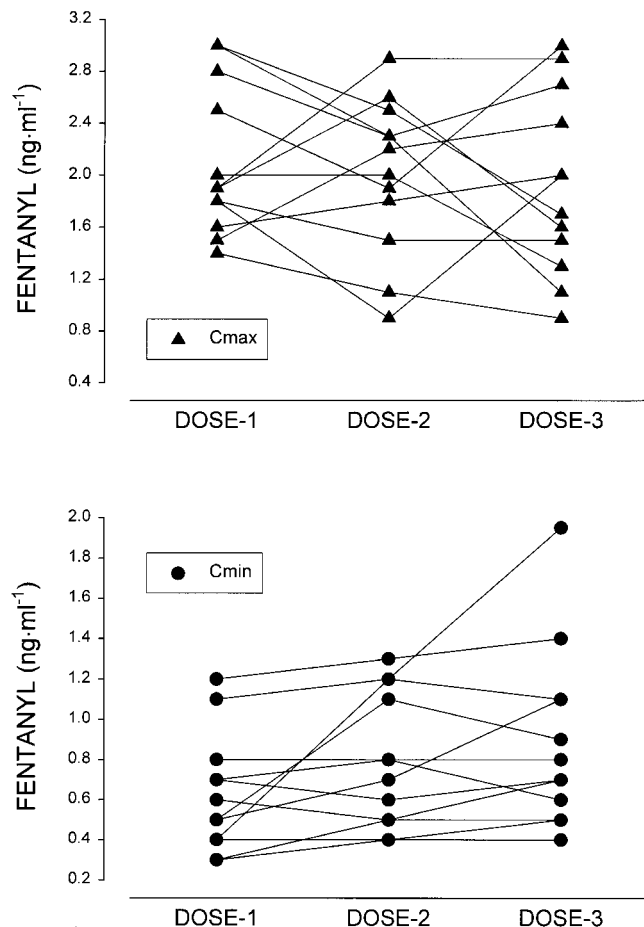


Fig. 2. Peak (C_{max}) and trough (C_{min}) fentanyl plasma concentrations associated with each of the three doses of oral transmucosal fentanyl citrate. Triangles = C_{max} values; circles = C_{min} values.

The median values (exact 95% confidence interval) for the first, second, and third dose T_{max} were 24 (20, 71), 22 (19, 25), and 23.5 (19, 49) min, respectively. These were not different (Quade test, $P \approx 0.5$). The terminal slopes of $T_{1/2iv}$ and $T_{1/2tm}$ were not different (Wilcoxon signed rank test, $P \approx 0.6$).

Nonlinear, Mixed-effects Population Model Analysis. The population pharmacokinetic parameter estimates from NONMEM are displayed in table 2. The estimated typical value of CL_c was 571 ml/min with a reasonable precision (10% standard error of the estimate [SEE]). Similarly, population estimates for central and peripheral volumes of distribution were 17 l (12% SEE) and 261 l (8.4% SEE), respectively. Random residual variability was 35% (30% SEE). The bioavailability of OTFC was 40% (11% SEE). Intersubject variability in F was 29% and estimated with a reasonable precision (34%

SEE). However, between-subject variability in CL_c and central and peripheral volumes of distribution was considerable (60–68%).

The quality of the model fit is represented graphically in figure 3. The agreement between the predicted and observed concentrations and individual weighted residuals indicate that the model adequately represents the central tendency of the data. In other words, this two-compartment population model is a reasonable characterization of the pharmacokinetics of OTFC.

Individual Compartmental Model Analysis

The best simultaneous fittings of the serum concentration-time data for each subject were obtained by using one of the following four systemic pharmacokinetic models, in which the values of F or k_a were allowed to vary at the end of each dosing interval: (1) Three subjects required a two-compartment model in which k_a was common to all dosing intervals but F was allowed to vary at the end of each dosing interval; (2) four subjects required a three-compartmental model in which k_a was common to all dosing intervals but F was allowed to vary at the end of each dosing interval; (3) four subjects required the three-compartment model in which k_a was allowed to vary at the end of each dosing interval but F was common to all dosing intervals; and (4) one subject required a three-compartment model in which both k_a and F were allowed to vary at the end of each dosing interval.

A simultaneous fit of plasma fentanyl concentration-time data for both the intravenous infusion and the OTFC data are shown in figure 4 for a typical subject. In each subject the oral and intravenous profiles showed a parallel decline, which supported the combined fitting of each subject's intravenous and transmucosal data.

The mean values of CL_c and V_{ss} , estimated by using one

Table 2. Population Pharmacokinetic Parameters Estimated by Nonlinear Mixed-effects Modeling (NONMEM)

Parameter	Estimate (% SEE)	Intersubject Variability
CL_c (ml/min)	571 (10%)	68%
CL_d (ml/min)	2820 (16%)	—
V_c (l)	17.2 (12%)	67%
V_p (l)	261 (8.4%)	60%
k_a (min^{-1})	0.018 (18%)	—
F	0.40 (11%)	29%
Random residual error	35% (30%)	—

CL_c = systemic clearance; F = bioavailability; k_a = absorption rate constant; SEE = standard error of the estimate; V_c = central volume of distribution; V_p = peripheral volume of distribution.

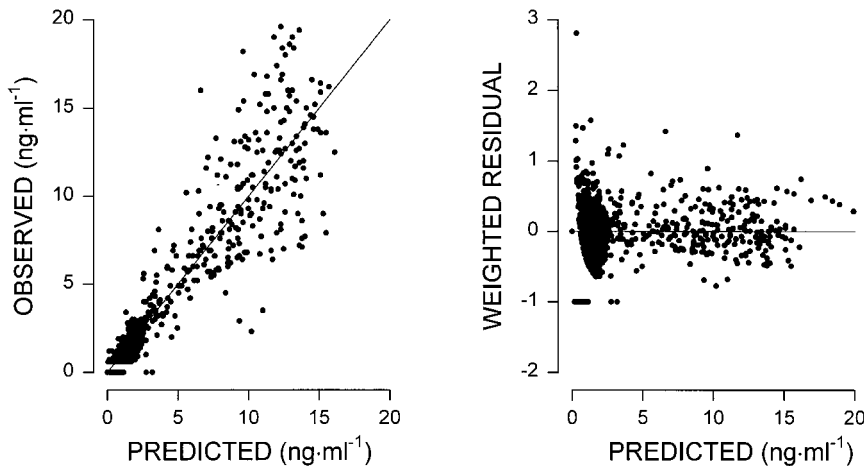


Fig. 3. Results of the population pharmacokinetic analysis using nonlinear mixed-effects modeling. (Left) The predicted versus the observed fentanyl concentrations for the NONMEM model (includes both oral transmucosal fentanyl citrate and intravenous limbs of the experiment). (Right) A plot of the weighted residuals.

of the four systemic pharmacokinetic models, are presented in table 3. The mean CL_c values estimated from the models were 752, 432, 334, and 803 ml/min (table 3). The coefficients of variation of these clearance values ranged from 31 to 52%. The difference in CL_c values was not statistically significant ($P > 0.05$). The mean V_{ss} values estimated from the four models were 274, 277, 596, and 205 l (table 3). These were not significantly different ($P > 0.05$) from each other. The coefficients of variation of these V_{ss} values ranged from 22 to 63%.

The mean F values of fentanyl after three doses of OTFC for each subject estimated from one of the four pharmacokinetic models are also listed in table 3. For subjects fitted to models that allowed F to vary for each

dosing interval, the F remained relatively constant and averaged 40%. The coefficients of variation of these F values are reasonable, ranging from 16 to 51%. For subjects fitted to the model in which F was common to all dosing intervals, the mean value of F was 37%. In these cases the coefficient of variation of F is reasonable at 36%. This value for bioavailability compares favorably with previously published results.³

The mean first-order k_a values for each dosing interval were 0.049, 0.011, and 0.006 min⁻¹. The coefficients of variation of these k_a values are appreciable, ranging from 71 to 139%, mainly because subjects 3 and 7 had very large and small k_a values, respectively (0.152 and 0.0006 min⁻¹). The k_a and F values did not change systemati-

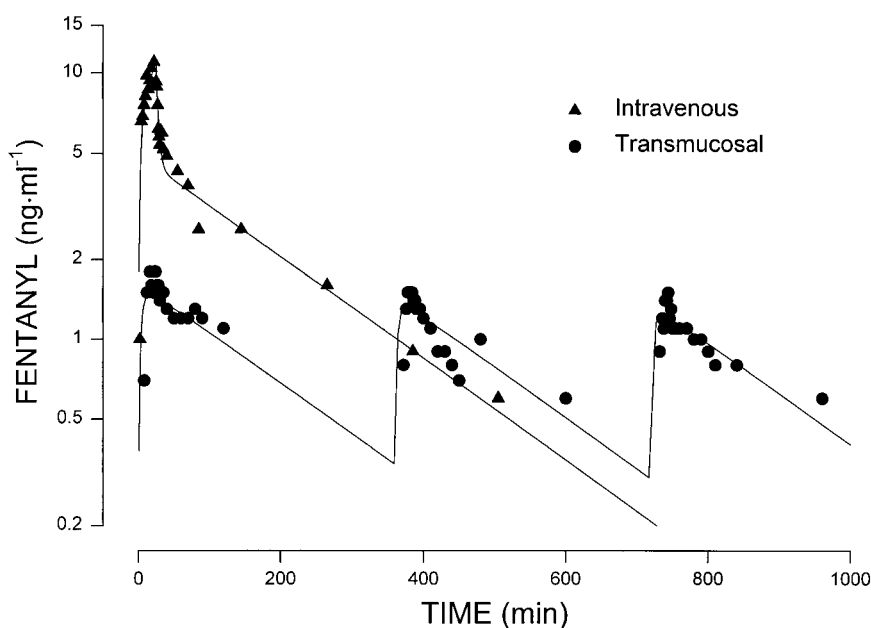


Fig. 4. A typical result of the simultaneous fitting procedure from the individual compartmental model analysis. A single, "best" model was constructed for each subject (with varying bioavailability and absorption for each dose if it improved the model). Circles = transmucosal fentanyl concentrations. Triangles = intravenous concentrations.

MULTIPLE DOSE PHARMACOKINETICS OF ORAL TRANSMUCOSAL FENTANYL

Table 3. Individual Compartmental Pharmacokinetic Parameters

	CL _e (ml/min)	V _{ss} (l)	k _a (min ⁻¹)			F		
			1 st	2 nd	3 rd	1 st	2 nd	3 rd
Two-compartment model with variable F (three subjects)								
Mean	752	274	0.022*	0.022*	0.022*	0.55	0.34	0.37
SD	230	83.1	0.007	0.007	0.007	0.09	0.08	0.17
%CV	30.5	30.3	33.8	33.8	33.8	15.6	22.7	46.1
Three-compartment model with variable F (four subjects)								
Mean	432	277	0.021*	0.021*	0.021*	0.38	0.45	0.33
SD	141	61.1	0.005	0.005	0.005	0.07	0.22	0.12
%CV	32.6	22.1	25.9	25.9	25.9	18.0	50.5	37.8
Three-compartment model with variable k _a (four subjects)								
Mean	334	596	0.049	0.011	0.006	0.37†	0.37†	0.37†
SD	173	374	0.069	0.008	0.004	0.13	0.13	0.13
%CV	51.7	62.9	139	71.2	74.4	35.7	35.7	35.7
Three-compartment model with variable k _a and F (one subject)								
	803	205	0.028	0.028	0.015	0.28	0.30	0.25

Note that a diverse array of models were used so that each subject could assume its own "best model."

* Common to all dosing intervals ($k_{a1} = k_{a2} = k_{a3}$).

† Common to all dosing intervals ($F_1 = F_2 = F_3$).

cally with subsequent doses during multiple dosing. The mean k_a of 0.022 reflects an absorption half-life of 32.5 min and is responsible for the rapid increase in fentanyl concentrations in the blood after OTFC administration (compared to oral administration).

Discussion

This study examined the pharmacokinetics of OTFC during multiple dosing in a healthy adult volunteer population using an open-label study design. The raw data were analyzed by comparison of the descriptive pharmacokinetic parameters and by population and individual compartmental modeling techniques. This study has not revealed any significant time-dependent changes in the pharmacokinetics of OTFC after three doses of 800 μ g. Our hypothesis that the single-dose pharmacokinetics of OTFC are representative of the multidose pharmacokinetics was confirmed.

The raw data provide perhaps the most compelling evidence of OTFC's lack of time-dependent pharmacokinetic changes with multiple dosing. Inspection of the combined raw data shown in figure 1 fails to reveal any obvious alteration in the profile of concentration *versus* time with multiple dosing. Although inspection of the data does not constitute a statistical test, the implications of the raw data are clear. The conclusions based on inspection of the raw data would obviously be more convincing if the experiment had been carried out to near steady state, requiring five or six doses; this was not practical.

Analysis of the descriptive pharmacokinetic parameters, a method that is statistically demonstrable, also provides evidence of OTFC's lack of time-dependent pharmacokinetic changes with multiple dosing. This experiment allowed the comparison of C_{max} , C_{min} , T_{max} , and the terminal slopes (transmucosal *vs.* intravenous) associated with each dose in the same subject. Using this straightforward technique of analysis there is no indication of time-dependent pharmacokinetics.

The results of the population model analysis constructed with NONMEM are also consistent with the conclusion that multiple-dose OTFC does not exhibit time-dependent pharmacokinetic changes. One model with a single bioavailability and absorption rate constant was able to describe the observed data adequately. This model adequately characterizes both the transmucosal and intravenous systemic disposition of fentanyl. This suggests that there are no gross changes in the disposition of OTFC with multiple dosing.

The individual compartmental analysis, although intended by and large as a data-exploration technique that was admittedly not absolutely essential to achieve the goals of the study, nonetheless also demonstrated that no systematic time-dependent changes occurred in fentanyl bioavailability or absorption after multiple doses of OTFC. Although a number of different models were considered optimal or "best" for the individual subjects, there were no obvious systematic changes or trends from dose to dose with these models. It is important to note that the pharmacokinetic parameters estimated by

population modeling were very similar to those estimated individually for each subject.

In general, the aims of this kind of multidose study are traditionally at least twofold. First, multidose studies are intended to determine whether the pharmacokinetics are time-dependent. Second, multidose studies are helpful in determining the concentrations associated with steady state for a given dosage scheme.

These two goals are related. The central issue in multidose studies is accumulation. Some accumulation always occurs with multiple dosing until a steady state is reached, unless the dosing interval is greater than five or six times the terminal half-life (*i.e.*, when the trough concentrations preceding the next dose are essentially zero). Thus, during multiple dosing trough concentrations are indeed expected to increase before the achievement of a steady state. However, if the observed rise is greater than what would be expected from superposition of the individual doses, the pharmacokinetic system is said to be nonlinear (*i.e.*, a doubling of the dosage results in a greater than doubling of the concentration).

Viewed in terms of accumulation, the study goals can be restated as questions. First, to what extent is accumulation dependent upon the timing of a dose—that is, is the pharmacokinetic system nonlinear with multiple dosing? This is an important question, because a nonlinear pharmacokinetic system may predispose to toxicity with repeated dosing. Second, once the rate of accumulation equals the rate of elimination and a steady state is reached, what are the expected concentrations at steady state for a given dosing scheme? Again, this information is important in formulating a nontoxic dosing strategy.

If a drug exhibits some kind of time-dependent nonlinear change in absorption, bioavailability, distribution, or clearance, it is necessary to alter the dosage strategy during multiple dosing for safe and efficacious treatment. Although they are exceptions rather than the rule, there are a number of drugs that behave in this way. For example, the analgesic acetaminophen may exhibit nonlinear accumulation if given in doses greater than 18 mg/kg.¹¹ Similarly, the cholesterol-lowering agent atorvastatin exhibits a more than proportional increase in plasma concentration if given in multiple doses.¹²

There is no evidence in the literature that suggests that fentanyl, if administered by a nonintravenous route, exhibits this kind of nonlinear accumulation. For example, if fentanyl is administered transdermally in multiple doses its pharmacokinetics are known to be linear.¹³ In addition, our group has previously shown that OTFC

pharmacokinetics are linear with respect to dose (*i.e.*, there is dose proportionality).¹⁴

Several limitations of the current study deserve emphasis. First, three doses of OTFC may not have been sufficient to exclude absolutely the possibility of a nonlinear pharmacokinetic system with multiple dosing. Second, it is conceivable that nonlinear accumulation could result with multiple dosing at higher dosages, although this is unlikely because dose proportionality has been demonstrated for single doses up to 1,600 μg .¹⁴ Finally, because a true steady state was not reached during this experiment, we are not able to comment definitively on the expected steady-state concentrations for this dosage regimen.

In summary, the pharmacokinetic profile observed after three OTFC doses of 800 μg does not appear to be substantially different than those observed after a single dose.³ In other words, the previously described single-dose pharmacokinetics of OTFC are predictive of the multidose behavior for this dosage schedule. Furthermore, the concentrations produced by this dosing scheme are in a range shown to produce analgesia.¹⁵ Thus, the results of this study suggest that OTFC could be safely used in multiple doses as an alternative to more invasive administration routes in the treatment of acute and chronic pain.

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MULTIPLE DOSE PHARMACOKINETICS OF ORAL TRANSMUCOSAL FENTANYL

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