Dose Proportionality and Pharmacokinetics of Oral Transmucosal Fentanyl Citrate

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Background: The pharmacokinetics of a single dose (15 μg/kg) of oral transmucosal fentanyl citrate (OTFC) have been characterized. A range of doses may eventually be used in clinical practice. The goal of this study was to determine if the pharmacokinetics of OTFC are dose proportional for doses ranging from 200 to 1,600 μg.

Methods: Twelve healthy male volunteers were studied on four different occasions, receiving 200, 400, 800, and 1,600 μg OTFC in a double-blind, randomized protocol. Venous blood samples were collected at selected times during and after dosing for a 24-h period and assayed for fentanyl using a radioimmunoassay. Maximum concentration, time to maximum concentration, area under the curve, and elimination half-life were determined for each dose administered. In addition, respiratory rate, need for verbal prompting to breathe, and supplemental oxygen requirements were noted.

Results: Mean fentanyl concentration time curves were similarly shaped with increasing doses. Both peak concentrations and area under the curve increased linearly with an increase in dose, whereas time to reach peak serum concentrations did not vary significantly between doses. Except for the 200-μg dose, the apparent elimination half-life remained relatively constant (358–386 min). The incidence of low respiratory rate, supplemental oxygen requirement, and number of breathing prompts significantly increased with increasing doses.

Conclusions: Oral transmucosal fentanyl citrate exhibits dose-proportional pharmacokinetics over the dose range of 200–1,600 μg. (Key words: Cancer pain management; transmucosal drug delivery.)

ORAL transmucosal fentanyl citrate (OTFC) is a solid dosage form designed to deliver fentanyl noninvasively through the oral mucosa. As the dosage unit is consumed, fentanyl is absorbed directly through the oral mucosa into the systemic circulation. Some fentanyl is swallowed and undergoes gastrointestinal and hepatic metabolism as it is absorbed. The pharmacokinetics of a single dose of OTFC, 15 μg/kg, have been characterized before.1

Clinical trials investigating OTFC to treat cancer pain are ongoing. Because patients with cancer are often opioid tolerant, they may require higher doses of OTFC than have been previously studied. The purpose of this study, therefore, was to determine whether OTFC pharmacokinetics are dose proportional at doses ranging from 200 to 1,600 μg.

Materials and Methods

After Institutional Review Board approval of the protocol, informed written consent was obtained from 12 healthy male volunteers, aged 19–34 yr, who were within 20% of their ideal body weight. Before starting the study, each participant had a medical history taken and was given a physical examination and routine blood and urine tests. At the screening visit, the volunteer consumed an identically shaped, placebo OTFC unit so that a uniform consumption time (15 min) could be learned.

Each volunteer was studied during four different 24-h periods. Doses of OTFC of 200, 400, 800, and 1,600 μg were administered in a double-blind, randomized protocol. These study sessions were separated by a minimum of 3 days and a maximum of 28 days.

After an overnight fast, the participant arrived in the
early morning to the study site. Each person was observed for a minimum of 12 h for each day of the study. A venous catheter was placed in a large forearm or hand vein for blood sampling, and a pulse oximeter and noninvasive blood pressure cuff were attached. Then the volunteer assumed a semirecumbent position.

The volunteers paced themselves, with observation from the study personnel, to consume the OTFC unit in approximately 15 min. Blood samples were taken from the venous catheter before, every 5 min for the first half hour; every 10 min for the second half hour; and at 90, 120, 240, 480, and 720 min after the start of OTFC administration. Volunteers returned after 24 h for their final blood sample (direct venipuncture). Finger pulse oximetry was monitored continuously and heart rate, respiratory rate, and blood pressure were measured before OTFC administration and every 15 min during the first hour, and then 120, 240, 720, and 1,440 min after administration.

If, during the study, the volunteer’s oxyhemoglobin saturation decreased to less than 90%, he was prompted to breathe. Nasal oxygen was administered if the oxyhemoglobin saturation did not increase to more than 90% with prompting or if he required more than three prompts within a 5-min period.

All blood samples were injected into glass clot tubes and placed immediately on ice. After allowing time for the blood to clot, the serum was separated from erythrocytes with a refrigerated centrifuge, placed into polypropylene tubes using a pipette, and frozen at −20°C until analyzed for fentanyl. Plasma fentanyl concentrations were determined by radioimmunoassay (Harris Laboratories, Lincoln, NE). The assay was sensitive to 0.2 ng/ml and was linear in the range of 0.1–4.8 ng/ml. The interday coefficient of variation was 10.2% at 0.3 ng/ml, 7.6% at 1 ng/ml, and 10.2% at 3.6 ng/ml.

The maximum fentanyl concentration (Cmax) and the time to reach this concentration (Tmax) were obtained from direct observation of the serum concentration versus time curves. The area under the serum fentanyl concentration versus time curve (AUC) was calculated from the time of administration of fentanyl to the last measurable serum concentration, using the linear trapezoid method with linear interpolation when concentrations were increasing, and log-linear interpolation when concentrations were decreasing. Extrapolation of the AUC from the time of the last measurable fentanyl concentration to infinity was calculated by dividing the last serum concentration by the first-order rate constant of the terminal phase of the profile. This first-order rate constant was determined by linear regression of the terminal phase of the log-transformed serum fentanyl concentration data after visually identifying the terminal portion. The sum of these two components was the estimate of the total AUC. The terminal elimination half-life of fentanyl was calculated from the first-order rate constant of the terminal phase of the serum concentration versus time profile.

**Statistical Analysis**

The effect of dose on Cmax and AUC was tested by unbalanced (with one volunteer completing only two doses), repeated measurement multivariate analysis of variance. Because the observations at the four doses for each volunteer may be correlated, an unstructured covariance matrix was used to model this correlation. Linear and quadratic dose effects were included in the alternative hypothesis. Restricted maximum likelihood estimation rather than maximum likelihood estimation was used to adjust for the number of parameters being estimated. Statistical software was the ID and 5V modules of BMDP (1990 Ultronix Version, SPSS, Chicago, IL). Statistical significance was asserted for \( P < 0.05 \).

The analysis of frequency data (side effects and respiratory events) for OTFC dose effect was by exact non-parametric inference using the Page Test. The Page Test compares K correlated observations for N samples when there is a natural ordering of the repeated measurement design factor. In this experiment, n = 12 and the repeated measurement design factor (K = 4) is the ordering of dose (200, 400, 800, and 1,600 μg). The null hypothesis specifies equality across doses while the alternative hypothesis is one of ordered dose effect. Statistical estimation was by Monte Carlo estimation using StatXact 3 for Windows (Cytel Software, Cambridge, MA). Significance was asserted for two-tailed tests with \( P < 0.05 \).

**Results**

Eleven participants completed all four doses whereas one participant completed just the 200 and 1,600 μg doses. The age and weight of the volunteers were 25.3 ± 4.3 yr (means ± SD) and 77.9 ± 10.6 kg, respectively. The mean dose (μg/kg) for each treatment is shown in table 1.

Individual and mean serum fentanyl concentration versus time profiles for each dose are shown in figures 1A–D. The mean concentrations are directly compared in figure 2. The curves for each dose are similar in shape with increasing doses producing...
proportionally increasing fentanyl concentrations. Peak serum concentrations ($C_{\text{max}}$) increased linearly with an increase in doses (table 1, fig. 2). Individual peak concentrations ranged from 0.2 - 0.6 ng/ml in the 200-µg dose, 0.3 - 1.3 ng/ml in the 400-µg dose, 1.0 - 2.6 ng/ml in the 800-µg dose and 1.72 - 3.58 ng/ml in the 1,600-µg dose. There were no differences between doses in the time at which these peak concentrations occurred ($T_{\text{max}}$). Finally, there were no differences in the dose normalized AUCs across in-

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>200 µg (n = 12)</th>
<th>400 µg (n = 11)</th>
<th>800 µg (n = 11)</th>
<th>1,600 µg (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng·ml$^{-1}$)</td>
<td>2.6 ± 0.3</td>
<td>5.2 ± 0.7</td>
<td>10.5 ± 1.4</td>
<td>20.9 ± 2.6</td>
</tr>
<tr>
<td>AUC (ng·ml$^{-1}$·min$^{-1}$)</td>
<td>0.4 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>1.6 ± 0.5</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>AUC (dose normalized*)</td>
<td>172 ± 96</td>
<td>400 ± 363</td>
<td>887 ± 859</td>
<td>1,508 ± 1,360</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>172 ± 96</td>
<td>200 ± 181</td>
<td>222 ± 215</td>
<td>188 ± 170</td>
</tr>
<tr>
<td>Median $T_{\text{max}}$ (min)</td>
<td>193 ± 93</td>
<td>386 ± 443</td>
<td>381 ± 211</td>
<td>358 ± 162</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

$C_{\text{max}}$ = maximum fentanyl concentration; AUC = area under the curve; $t_{1/2}$ = half-life; $T_{\text{max}}$ = time when $C_{\text{max}}$ occurs.

* Normalized to the 200-µg dose.

Fig. 1. Individual and mean (bold line) serum fentanyl concentrations after 200 (A), 400 (B), 800 (C), and 1,600 µg (D) oral transmucosal fentanyl citrate. The y axis is expanded in A and B to better illustrate the serum concentrations.
increasing doses (table 1, fig. 3). The apparent elimination half-life after the 200 μg dose was statistically shorter than the other three doses (table 1).

The most common opioid-related side effects are summarized in table 2. Pruritus was observed universally, whereas the incidence of nausea, headache, vertigo, bradycardia, and vomiting tended to increase with increasing doses. Similarly, the frequency of respiratory events (table 3) significantly increased with increasing doses (Page Test, \( P < 0.001 \)).

**Discussion**

When a wide range of doses of a drug is used in clinical practice, it is important to know if the drug's pharmacokinetics are dose independent. Without this knowledge, escalating doses may lead to toxicity when, for example, a drug inhibits its own metabolism and results in greater than dose-proportional drug concentrations with increasing doses. On the other hand, if a drug decreases its own absorption, lower than expected concentrations with escalating doses may result in lack of efficacy. Thus, dose proportionality should be established for the range of doses used in clinical practice. Dose proportionality simply means that if the dose is doubled, the resulting concentrations in the blood also double.

The results of our study show that the kinetics of OTFC are dose proportional for the range of 200 to 1,600 μg. This is true because \( C_{\text{max}} \) and AUC values (table 1) increased proportionately with increases in dose. In addition, there were no significant differences between doses in dose-normalized AUCs (fig. 5) or terminal elimination half-lives (other than the 200 μg dose; figs. 1 and 2).

The apparent terminal elimination half-life after the 200-μg dose was lower than the other doses. This proba-

| Table 2. Opioid-related Side Effects after Four Increasing Doses of Oral Transmucosal Fentanyl Citrate |
|---------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                                       | 200 μg (n = 12) | 400 μg (n = 11) | 800 μg (n = 11) | 1,600 μg (n = 12) |
| Pruritus                                               | 10              | 11              | 11              | 11              |
| Nausea                                                | 1               | 4               | 6               | 10              |
| Headache                                               | 2               | 6               | 5               | 8               |
| Vertigo                                                | 1               | 1               | 2               | 6               |
| Bradycardia                                            | 1               | 1               | 2               | 5               |
| Vomiting                                               | 0               | 1               | 2               | 4               |
| Total                                                  | 15              | 24              | 28              | 44              |

| Table 3. Number of Subjects with Respiratory Events after Four Increasing Doses of Oral Transmucosal Fentanyl Citrate |
|----------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Respiratory rate < 6 breaths/min*                                                                                  | 2               | 5               | 10              | 12              |
| Requires supplemental oxygen*                                                                                      | 1               | 3               | 7               | 10              |
| Occurrence of \( \text{SpO}_2 \) < 90%*                                                                             | 5               | 9               | 11              | 12              |

* \( P < 0.001 \), Page Test, ordered dose effect.

Anesthesiology. V 88, No 2, Feb 1998
DOSE PROPORTIONALITY OF OTFC

bly represents an artifact of assay sensitivity because fentanyl values decreased to below the limit of detection in many of the samples drawn at the end of the 8-h study. Inspection of the raw data suggests there was no actual difference. The apparent terminal elimination half-lives determined after 400, 800, and 1,600 µg were similar to that reported in a previous study of OTFC pharmacokinetics. 1

Serum fentanyl concentrations after OTFC result from combined processes of absorption, distribution, and elimination. In a previous study it was shown that both intravenous and transmucosal fentanyl administration result in similar fentanyl distribution and elimination. 1 Fentanyl administered intravenously, has been shown to be dose proportional and follow linear pharmacokinetics. 4 Thus, because serum concentrations remained dose proportional after OTFC, it can be concluded that the absorption process did not affect the linearity of the system; that is, the absorption process was not affected over the range of OTFC doses studied. In contrast, increasing doses of oral transmucosal etomidate produce less than a proportionate increase in blood concentrations of etomidate. 5

One criticism of this study is the use of venous rather than arterial samples. Arterial samples are generally preferred for pharmacokinetic studies because they are thought to more accurately reflect the concentration of drug being delivered to the organ of interest. 6 Differential uptake of a drug as it passes through various tissues make venous samples less desirable. Further, venous sampling always results in a lower estimation of Cmax and a longer estimation of Tmax. Arteriovenous differences in drug concentration are usually greatest when a drug is given as an intravenous bolus, because arterial concentrations decline rapidly as venous concentrations may continue to increase during the first minutes of sampling. Because absorption of fentanyl from OTFC is relatively slow compared with an intravenous bolus, we could speculate that these arteriovenous differences should be limited in this study. Furthermore, we did not think it was appropriate to subject the volunteers to four arterial catheters in a relatively short period of time.

Another limitation of our study was that no conclusions regarding the systemic clearance of fentanyl across doses can be drawn. Clearance is determined by dividing AUC by the dose administered. Unfortunately, it is impossible to determine the actual dose administered in this study because the bioavailability of fentanyl from OTFC varies. 1 We could have determined bioavailability if we had also determined intravenous kinetic parameters in the same volunteers, but that was beyond the scope of this study.

As expected, dose-related increases in the incidence of respiratory events occurred. Even at the lowest dose of OTFC, 200 µg, 5 of 12 (42%) volunteers exhibited decreases in oxyhemoglobin saturation less than 90%. In contrast, in patients receiving higher doses (400 and 800 µg) before minor dermatologic surgery, only 7% exhibited oxyhemoglobin saturations less than 90%. 7 This discrepancy can be explained by the fact that we studied volunteers in a quiet, unstimulated environment rather than patients who were having a surgical procedure.

In conclusion, the results of this study show that the pharmacokinetics of OTFC for the range of 200 to 1,600 µg are dose proportional. The extent of fentanyl absorption from OTFC does not appear to change over the dose range studied.

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References