Influence of Hepatic and Intestinal Cytochrome P4503A Activity on the Acute Disposition and Effects of Oral Transmucosal Fentanyl Citrate

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Background: Oral transmucosal fentanyl citrate (OTF) was developed to provide rapid analgesia and is specifically approved for treating breakthrough cancer pain. Fentanyl in OTF is absorbed across the oral mucosa, but a considerable portion is swallowed and absorbed enterally. Fentanyl metabolism is catalyzed by cytochrome P4503A (CYP3A). The role of intestinal or hepatic first-pass metabolism and CYP3A activity in OTF disposition is unknown. This investigation examined the influence of hepatic and intestinal CYP3A activity on the disposition and clinical effects of OTF.

Methods: Healthy volunteers (n = 12) were studied in an Institutional Review Board-approved, randomized, balanced, four-way crossover. They received OTF (10 µg/kg) after hepatic/intestinal CYP3A induction by rifampin, hepatic/intestinal CYP3A inhibition by troleandomycin, selective intestinal CYP3A inhibition by grapefruit juice, or nothing (control). Plasma fentanyl and norfentanyl concentrations were determined by mass spectrometry. Fentanyl effects were measured by dark-adapted pupil diameter and subjective self-assessments using visual analog scales.

Results: Peak plasma fentanyl concentrations, time to peak, and maximum pupil diameter change from baseline were unchanged after rifampin, troleandomycin, and grapefruit juice. Fentanyl elimination, however, was significantly affected by CYP3A alterations. After control, rifampin, troleandomycin, and grapefruit juice decreased fentanyl elimination rates by 31%, 22%, and 16%, respectively.

Discussion: Peak plasma fentanyl concentrations and clinical effects after OTF were minimally affected by altering both intestinal and hepatic CYP3A activity, whereas fentanyl metabolism, elimination, and duration of effects were significantly affected; selective intestinal CYP3A inhibition had minimal effects. This suggests that first-pass metabolism minimally influences OTF bioavailability. When treating breakthrough pain, with careful attention to maximal mucosal absorption and minimal swallowing, CYP3A variability and drug interactions are unlikely to affect the onset or magnitude of OTF analgesia; however, duration may be affected.

CANCER pain is a devastating problem that remains undertreated despite numerous recent advances. Approximately one third of cancer patients have pain at diagnosis and 70–90% suffer pain with advanced disease. Despite the major urgings and guidelines of the World Health Organization, numerous reviews, and "cancer pain initiatives," there persists a significant prevalence of inadequate cancer pain treatment.

In addition to their persistent pain, cancer patients frequently experience breakthrough pain, "a transitory exacerbation of pain to severe or excruciating levels that occurs on a background of otherwise stable mild or moderate pain in a patient receiving chronic opioid therapy." Breakthrough cancer pain is common (40–80% prevalence, depending on methodology, with a median of four episodes daily) and has a rapid onset (43% have maximal pain intensity within 3 min) and a brief duration (median 30 min). Approximately 75% of breakthrough pain episodes are unpredictable.

Cancer breakthrough pain is associated with poor outcome, low patient satisfaction, diminished functioning, and depression. Nonmalignant breakthrough pain is also problematic, with an incidence, frequency, and duration similar to that of cancer-related breakthrough pain. In short, breakthrough pain is sudden, severe, and usually unpredictable.

Conventional approaches to treating breakthrough pain are inadequate. Increasing the dose of regularly scheduled opioid until either a favorable response is achieved or intolerable side effects occur (sedation, nausea, constipation) usually results in the latter. A preferential approach is to treat the breakthrough episode with rescue opioids administered on demand. Ideal rescue opioids have a rapid onset and short duration of action, obviate intravenous access or nursing care, and are patient-administered.

Oral transmucosal fentanyl citrate (OTF) was designed to achieve rapid analgesia and is the first drug specifically approved for treating breakthrough cancer pain. OTF is effective (>90% response), has a rapid onset (mean 10 min) and short duration, and allows increased patient activity with improved well-being. OTF provides faster analgesia, better pain relief, and greater patient satisfaction than conventional rescue opioids.

The pharmacokinetics of OTF are variable and incompletely understood. The OTF lozenge is placed be-
between the cheek and lower gum and rubbed against the mucosal surface. Approximately 25% undergoes oral transmucosal absorption, whereas a significant portion (75%) is swallowed, absorbed intestinally, and subject to first-pass metabolism (two thirds of the swallowed dose). Hence overall bioavailability is 50% (25% each from transmucosal absorption and swallowed fentanyl escaping first-pass metabolism).22

Fentanyl is cleared systemically by hepatic biotransformation, with minimal urinary excretion of unchanged drug,23 and N-dealkylation to norfentanyl is the major route of metabolism in humans in vivo and in vitro. Cytochrome P4503A4 (CYP3A4) is the predominant enzyme responsible for human fentanyl metabolism by liver microsomes in vitro24,25 and in vivo.26 In addition, fentanyl is also metabolized by human intestinal microsomes, specifically by CYP3A4.25 Thus the swallowed portion of OTF is susceptible to CYP3A4-mediated intestinal and hepatic first-pass metabolism. Interindividual variability in OTF bioavailability may result from heterogeneity in CYP3A4 activity or CYP3A4 drug interactions.27 Because fentanyl administered transmucosally has a narrow therapeutic index,14 variable absorption and drug interactions are clinically important. Nevertheless, the role of intestinal and hepatic CYP3A4 activity on OTF disposition and clinical effect is unknown. This investigation tested the hypothesis that altered CYP3A4 activity would influence the pharmacokinetics and clinical effects of OTF.

Materials and Methods

Clinical Protocol

The investigation was approved by the University of Washington Institutional Review Board and carried out in accordance with the Declaration of Helsinki, and each subject provided written informed consent. Twelve healthy subjects (six men, six women; aged 26 ± 6 yr, weighing 69 ± 15 kg) were studied. Eligibility criteria were age 18–40 yr within 30% of ideal body weight. Exclusion criteria included a history of liver or renal disease, pregnancy or nursing, taking drugs or herbs known to induce or inhibit CYP3A enzymes (including oral contraceptives), a history of addiction to alcohol or drugs (previous or current addiction or treatment for addiction), and access to and routine handling of addicting drugs in the regular course of subjects’ professional duties. Subjects were instructed to abstain from grapefruit products (except per protocol) for at least 5 days before and during each study session, to abstain from alcohol and caffeine for at least 24 h before and during each study session, and to fast for a minimum of 8 h before opioid administration.

The design was a randomized, balanced, four-session (control and three active pretreatments) crossover. Each subject served as their own control. They were instructed to take rifampin (600 mg orally) in the morning for 5 consecutive days before the study session (hepatic and intestinal CYP3A induction). Rifampin was not taken the morning of OTF dosing. On another occasion, they took troleandomycin (500 mg orally) approximately 3 h before OTF administration and again 9 h later (hepatic and intestinal CYP3A inhibition). On a third occasion, subjects took 250 ml regular strength grapefruit juice the night before the study and 100 ml of double strength grapefruit juice 1 h before OTF (selective intestinal CYP3A inhibition). Subjects received no pretreatment before a fourth, control, session. The order of the four sessions was randomized and separated by at least 1–2 weeks, except that the troleandomycin session was always last because it required a longer washout period.

For each study session, peripheral intravenous catheters were inserted in separate arms for drug administration and blood sampling. All subjects (recumbent) were monitored via electrocardiogram, blood pressure, and pulse oximeter. If oxyhemoglobin saturation decreased to less than 94%, the subject was prompted to breathe deeply. Supplemental oxygen (2–3 l/min nasal prongs) was given if saturation did not increase to 94% or if the subject was prompted more than three times within any 5 min period. All subjects received ondansetron (4 mg, intravenously). Thirty minutes later, they received OTF (target dose 10 μg/kg, as either a 600 or 800 μg lozenge). The OTF dose was 600 and 800 μg in eight and four subjects, respectively, and each subject received the same dose in all sessions (average dose 9.8 ± 1.0 μg/kg). Subjects were advised to rub the medication across the buccal mucosa and to not bite, suck, or chew the lozenge. Subjects were monitored to pace dissolution of the medication over exactly 15 min. The start of OTF administration was time zero. Venous blood samples were obtained at baseline, every 5 min during dosing, and 5, 10, 15, 20, 30, 45, 60, 90, 120, 240, 360, 480, and 600 min after completion of OTF administration. Plasma was separated and stored at −20°C for later analysis. Dark-adapted pupil diameters were determined coincident with blood sampling, as described previously,28 except that a Pupilscan Model 12A pupillometer (Keeler Instruments Inc., Broomall, PA) was used. Nausea or vomiting were treated with ondansetron (4 mg intravenous or 8 mg orally) as needed.

For statistical power calculations, a simplified analysis (paired Student t test) was used for the primary outcome variable, the area under the curve (AUC) of plasma fentanyl concentration versus time. Intraindividual variability in fentanyl AUC was not available; hence this could not be used for sample size calculation. However, intraindividual variability in peak fentanyl concentration (Cmax) was known (12 subjects, 3 sessions),29 which showed that the SD of the individuals’ changes (σd = 0.47) was approximately one quarter of the mean of the three sessions (μd = 2.00). Assuming a similar relation-
ship between the mean and SD of changes observed for AUC, studying 12 subjects would provide 90% power, at \( \alpha = 0.0125 \) (0.0125 = .05/4 was considered statistically significant to adequately control type 1 errors for multiple intergroup comparisons), to detect a 25% difference caused by a drug interaction.

**Analytical Methods**

N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide (fentanyl), N-phenyl-N-[4-piperidinyl] propanamide oxalate (norfentanyl), N-(pentadeuterophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide (d5-fentanyl), and N-(pentadeuterophenyl)-N-[4-piperidinyl] propanamide (d5-norfentanyl) were purchased from Cerilliant Corp. (Austin, TX). Methanol and acetonitrile (both HPLC-grade) were from Fisher Scientific (Pittsburgh, PA). Ammonium hydroxide was obtained from J. T. Baker (Phillipsburg, NJ). Trifluoroacetic acid (TFA) was from Fluka (Milwaukee, WI). Oasis MCX (3 ml, 60 mg) solid-phase extraction cartridges were obtained from Waters Corp (Milford, MA). All stock drug solutions, buffers, and high pressure liquid chromatography mobile phase were prepared using Milli-Q grade water (Millipore, Bedford, MA).

All subject samples (all four sessions) were analyzed together. To plasma (1 ml) in glass tubes was added an internal standard mix (1 ml, containing 1 ng each d5-fentanyl and d5-norfentanyl in 0.1N HCl). Solid-phase extraction cartridges were conditioned with 1 ml methanol then 1 ml 0.1N HCl, loaded with acidified plasma (0.5 ml/min), washed with 1 ml 0.1N HCl then 1 ml methanol, dried under vacuum for 2 min, and then analytes were eluted by gravity with 2 ml of 5% ammonium hydroxide in methanol. Samples were evaporated to dryness under nitrogen at 45°C (TurboVap LV evaporator, Zymark, Hopkington, MA). The residue was reconstituted with 50 μl mobile phase and transferred to autosampler vials.

Fentanyl and norfentanyl were quantified by high pressure liquid chromatography and electrospray mass spectrometry using an Agilent (Palo Alto, CA) 1100 series instrument with a binary solvent delivery system, autosampler (15 μl injections), Zorbax (Agilent) Eclipse XDB-C18 HPLC column (2.1 x 50 mm, 5 μm) and an Eclipse XDB-C8 (2.1 x 12.5 mm, 5 μm) guard column.

The mobile phase was a deionized water (0.05% TFA)–methanol then 1 ml 0.1N HCl, loaded with acidified plasma (0.5 ml/min), washed with 1 ml 0.1N HCl then 1 ml methanol, dried under vacuum for 2 min, and then analytes were eluted by gravity with 2 ml of 5% ammonium hydroxide in methanol. Samples were evaporated to dryness under nitrogen at 45°C (TurboVap LV evaporator, Zymark, Hopkington, MA). The residue was reconstituted with 50 μl mobile phase and transferred to autosampler vials.

The gradient (solvent A (0.05% TFA in water), solvent B (0.05% TFA in acetonitrile)) was 15% B for 1 min, increased to 35% over 2.5 min, held at 35% for 1.5 min, increased to 45% over 1.5 min, maintained for 1.5 min, increased to 90% over 0.5 min, and maintained at 90% B for 1.5 min before decreasing down to 15% over 0.5 min and holding for 3 min for column equilibration. Retention times were 3.6 and 5.7 min, respectively, for fentanyl and norfentanyl. The mass spectrometer parameters were as follows: positive electrospray mode, nitrogen drying gas 350°C at 9 l/min, nebulizer pressure 25 psig, and capillary voltage 3500 V. Ions monitored were m/z 233.1 and 238.1 (d0- and d5-norfentanyl) and m/z 337.1 and 342.1 (d0- and d5-fentanyl). The fragmentor voltage was 70 V for norfentanyl and 90 V for fentanyl. Selected ion mode resolution was set to low for both groups.

Fentanyl and norfentanyl were quantified using standard curves of peak area ratios versus analyte concentration. Calibration curves were obtained by analyzing plasma containing 0.1–25 ng/ml fentanyl and 0.05–15 ng/ml norfentanyl. Quality control samples (0.4, 1, 4 ng/ml fentanyl; 0.6, 2, 8 ng/ml norfentanyl) were prepared from separate dilutions of stocks than those used for the calibration curves. Interday coefficients of variation were 5%, 2%, and 5% (0.4, 1, 4 ng/ml fentanyl); 6%, 5%, and 5% (0.6, 2, 8 ng/ml norfentanyl). Extraction recovery exceeded 88% for fentanyl and 57% for norfentanyl. The limit of quantification was the lowest point on the standard curve.

**Clinical Effects**

Subjective self-assessment of fentanyl effect was quantified by visual analog scales. Attributes assessed (scored from 0 to 100) included level of alertness/sedation (almost asleep to wide awake), energy level (no energy to full of energy), confusion (confused to clear headed), clumsiness (extremely clumsy to well coordinated), anxiety (calm/relaxed to extremely nervous), and nausea (no nausea to worst nausea).

**Data Analysis**

Plasma fentanyl and norfentanyl data were analyzed using a noncompartmental model with extravascular input (WinNonlin 4.01, Pharsight Corp, Mountain View, CA). Pupil diameter data were also analyzed using noncompartmental methods, as described previously. Concentration-effect data were analyzed by nonparametrically collapsing the hysteresis loops to determine the value of \( k_{e0} \), the first order rate constant for transfer between plasma and the effect compartment, using the program ke0obj.§ One-way repeated measures analysis of variance followed by the Student-Newman-Keuls test for multiple comparisons was used to assess the significance of differences between groups for pharmacodynamic and effect parameters using SigmaStat (SPSS Science, Chicago, IL). Visual analog scores were analyzed by two-way repeated measures analysis of variance. All results are reported as the mean ± SD. Statistical significance was assigned at \( P < 0.05 \).


Anesthesiology, V 101, No 3, Sep 2004

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Results

For human subject safety considerations, antiemetic prophylaxis was administered before OTF. Some antiemetics, such as droperidol, which is an α-adrenergic antagonist in addition to being a dopamine D2 antagonist, can influence pupil diameter. Therefore, a pilot investigation assessed the miotic effect of ondansetron. Ondansetron had no effect on dark-adapted pupil diameter (fig. 1) and thus is not a confounder of pupil diameter measurements.

Plasma concentrations of fentanyl and norfentanyl after OTF, and the influence of CYP3A modulation, are shown in figure 2. Plasma fentanyl concentrations showed an early (0.4 h) and, in some subjects, a later (2 h) peak. Secondary peaks were apparent in some controls (7 of 12 subjects) and even more apparent in subjects pretreated with grapefruit juice and troleandomycin (10 of 12 subjects each). Nevertheless, fentanyl concentrations of the secondary peak were not greater than those of the first peak (table 1). CYP3A inhibition by either troleandomycin or grapefruit juice did not significantly affect the timing of these secondary peaks. Rifampin pretreatment completely abolished the secondary fentanyl peak in all subjects. None of the pretreatments, however, significantly altered the initial fentanyl Cmax or time to peak fentanyl concentration. No secondary peak was observed for plasma norfentanyl concentrations.

Rifampin induction of intestinal and hepatic CYP3A activity increased plasma norfentanyl Cmax, AUC, and the norfentanyl/fentanyl AUC ratio while significantly increasing fentanyl apparent oral clearance and elimination rate and decreasing AUC and apparent oral bioavailability. Selective inhibition of intestinal CYP3A activity decreased norfentanyl Cmax but had no effect on norfentanyl AUC or the norfentanyl/fentanyl AUC ratio and similarly had no effect on any parameter of fentanyl disposition.

OTF effects were characterized using dark-adapted pupil diameter (fig. 3), and miosis versus time data were analyzed similarly to drug concentration versus time data to obtain effect parameters (table 2). The time course of OTF miosis (fig. 3) strongly resembled the time course of plasma fentanyl concentration (fig. 2). Maxi-
Table 1. Oral Transmucosal Fentanyl Citrate Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Rifampin</th>
<th>Grapefruit Juice</th>
<th>Troleandomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>0.74 ± 0.34</td>
<td>0.76 ± 0.33</td>
<td>–</td>
<td>0.82 ± 0.25</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.42 ± 0.08</td>
<td>0.48 ± 0.09</td>
<td>0.41 ± 0.09</td>
<td>0.43 ± 0.10</td>
</tr>
<tr>
<td>Kel (l/h)</td>
<td>1.9 ± 0.5</td>
<td>2.0 ± 0.9</td>
<td>2.4 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>AUC_{0-10} (h · ng/ml)</td>
<td>3.62 ± 1.95</td>
<td>1.84 ± 0.75*</td>
<td>3.96 ± 1.91</td>
<td>5.42 ± 3.89*</td>
</tr>
<tr>
<td>AUC_{0-30} (h · ng/ml)</td>
<td>5.87 ± 3.74</td>
<td>2.20 ± 0.84*</td>
<td>5.79 ± 3.31</td>
<td>10.4 ± 8.9*</td>
</tr>
<tr>
<td>Kel (l/h)</td>
<td>0.127 ± 0.046</td>
<td>0.236 ± 0.109</td>
<td>0.152 ± 0.064</td>
<td>0.118 ± 0.056</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>153 ± 78</td>
<td>343 ± 133*</td>
<td>141 ± 59</td>
<td>104 ± 63</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>1238 ± 401</td>
<td>1715 ± 791</td>
<td>1057 ± 468</td>
<td>922 ± 312</td>
</tr>
<tr>
<td>Bioavailability†</td>
<td>0.50 ± 0.25</td>
<td>0.19 ± 0.06*</td>
<td>0.50 ± 0.22</td>
<td>0.87 ± 0.63*</td>
</tr>
</tbody>
</table>

AUC_{0-10} = area under the curve of plasma concentration versus time from 0–10 h; AUC_{0-30} = area under the curve of plasma concentration versus time from zero extrapolated to infinity; CL/F = apparent oral clearance; Cmax = maximum plasma concentration; Kel = terminal elimination rate constant; Tmax = time of maximum plasma concentration; V/F = apparent volume of distribution.

* Significantly different from control (P < 0.05). † Secondary peaks were observed in some subjects. For these subjects (n in parentheses), results for the second peak are also provided. ‡ Apparent bioavailability was calculated using data from a previous investigation of intravenous fentanyl disposition in an analogous young healthy population.* Bioavailability was calculated as (AUC_{0-10, 0.1% Dose_{OTF}}) / (AUC_{0-10, iv fentanyl/Dose_{iv fentanyl}}).

The experimental protocol was safely conducted without serious adverse events. Significant respiratory depression, defined as an oxygen saturation <94% and need for supplemental oxygen, occurred in 1, 1, 1, and 2 subjects in the control, rifampin, grapefruit juice, and troleandomycin groups, respectively. Treatment of nausea or vomiting was required in 1, 1, 1, and 2 subjects in the control, rifampin, grapefruit juice, and troleandomycin groups, respectively.

Discussion

OTF disposition in this group of volunteers was similar to that described previously. Specifcally, peak plasma fentanyl concentrations and AUCs were somewhat smaller compared with some, but not all, investigations, whereas time to peak fentanyl concentration was comparatively invariant. This may reflect methodological differences. For example, subjects in previous studies were instructed to place OTF in a buccal pouch and actively suck on it, whereas those in the present investigation actively rubbed OTF across the oral mucosa and were encouraged not to swallow. These differences may have enhanced the amount of transmucosal absorption and diminished the amounts of intestinal absorption of swallowed drug compared with previous investigations. In addition, plasma fentanyl concentrations were greater in those previous investigations using radioimmunoassay, whereas those using mass spectrometry reported lower concentrations that were closer to those found in the present study. Although OTF bioavailability in the present subject group was assessed using intravenous fentanyl data from different healthy young subjects, the estimated bio-

None of the pretreatments caused a change in the overall shape of the hysteresis loops or, specifically, collapse of the ascending and descending limbs that would have reflected enhanced fentanyl transfer to the site of action. The pretreatments did not significantly change the fentanyl k_{e0} for miosis (table 2).

miosis was not affected by CYP3A modulation, whereas grapefruit juice moderately and troleandomycin significantly delayed miosis time to peak fentanyl concentration. Rifampin induction of intestinal and hepatic CYP3A activity significantly decreased the miosis AUC and increased the effect clearance and elimination. Troleandomycin inhibition of intestinal and hepatic CYP3A activity increased the miosis AUC. Effect clearance was diminished but did not reach statistical significance.

OTF effects were also characterized by subject self-assessment using visual analog scales. Visual analog scores for sedation are shown in figure 4. Compared with controls, CYP3A modulation had no influence on subject self-assessment of sedation. Similar negative results were obtained for visual analog scores for energy, confusion, anxiety, clumsiness, and nausea (not shown).

Fentanyl concentration-effect relationships after OTF were evaluated using miosis. Although there was some scatter, a general sigmoidal log concentration-effect relationship is apparent (fig. 5), and miotic effects were not saturated at the OTF doses used. There was counterclockwise hysteresis observed in the concentration-effect relationship (fig. 6), indicating a transit delay from plasma to the effect compartment. The half-life for equilibration between venous plasma and effect compartment concentrations (t_{1/2} k_{e0} for miosis) averaged 7 min. None of the pretreatments caused a change in the overall shape of the hysteresis loops or, specifically, collapse of the ascending and descending limbs that would have reflected enhanced fentanyl transfer to the site of action. The pretreatments did not significantly change the fentanyl k_{e0} for miosis (table 2).
availability (50%) was identical to that reported previously (50%) in healthy young volunteers.\textsuperscript{22}

The primary purpose of this investigation was to assess the role of intestinal and hepatic CYP3A4 activity on OTF disposition. Rifampin is a highly effective inducer of CYP3A isoforms in liver and intestine, increasing protein expression severalfold and increasing the clearance of intravenous and, especially, CYP3A substrates substantially.\textsuperscript{34} Troleandomycin is an effective, selective, mechanism-based inhibitor of intestinal and hepatic CYP3A4, and it decreases the clearance of intravenous and (more so) oral CYP3A substrates, including fentanyl.\textsuperscript{26,28,35} Grapefruit juice selectively inhibits intestinal, but not hepatic, CYP3A4 activity.\textsuperscript{36–38}

Only a small portion (25%) of OTF undergoes oral transmucosal absorption, whereas a significant portion (75%) is swallowed, absorbed intestinally, and subject to first-pass metabolism (two thirds of the swallowed dose).\textsuperscript{22} First-pass metabolism may occur in the intestine as well as the liver, as fentanyl is metabolized by CYP3A in both intestinal and liver microsomes.\textsuperscript{24,25} The present results suggest that OTF undergoes first-pass metabolism in both the intestine and liver. Plasma fentanyl concentrations showed an early peak consistent with a portion undergoing rapid oral mucosal absorption and a later

Table 2. Oral Transmucosal Fentanyl Citrate Effect Parameters

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Rifampin</th>
<th>Grapefruit Juice</th>
<th>Troleandomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum miosis (mm)</td>
<td>4.5 ± 1.1</td>
<td>4.2 ± 1.3</td>
<td>4.5 ± 1.6</td>
<td>4.9 ± 1.3</td>
</tr>
<tr>
<td>T\textsubscript{max} (h)</td>
<td>0.79 ± 0.56</td>
<td>0.69 ± 0.21</td>
<td>1.08 ± 0.64</td>
<td>1.43 ± 0.62*</td>
</tr>
<tr>
<td>AUC\textsubscript{0–10} (mm/h)</td>
<td>18.4 ± 11.3</td>
<td>8.4 ± 4.5*</td>
<td>17.8 ± 10.6</td>
<td>28.2 ± 14.2*</td>
</tr>
<tr>
<td>AUC\textsubscript{0–∞} (mm/h)</td>
<td>22.6 ± 17.5</td>
<td>9.2 ± 5.0*</td>
<td>21.3 ± 15.9</td>
<td>29.2 ± 15.2*</td>
</tr>
<tr>
<td>Kel (l/h)</td>
<td>0.34 ± 0.17</td>
<td>0.88 ± 0.67*</td>
<td>0.35 ± 0.19</td>
<td>0.27 ± 0.19</td>
</tr>
<tr>
<td>CL/F ((\mu g/mm \cdot h))</td>
<td>37.7 ± 20.6</td>
<td>88.4 ± 64.1*</td>
<td>38.3 ± 18.1</td>
<td>26.7 ± 16.7</td>
</tr>
<tr>
<td>k\textsubscript{e0} (h\textsuperscript{-1})</td>
<td>4.8 ± 2.8</td>
<td>5.8 ± 2.0</td>
<td>7.3 ± 1.1</td>
<td>6.1 ± 3.0</td>
</tr>
</tbody>
</table>

AUC\textsubscript{0–10} = area under the curve of pupil diameter change (miosis) versus time from 0–10 h; AUC\textsubscript{0–∞} = area under the curve of miosis versus time from time zero extrapolated to infinity; CL/F = apparent oral effect clearance; Kel = terminal effect elimination rate constant; k\textsubscript{e0} = first order rate constant for transfer between plasma and the effect compartment; T\textsub{max} = time of maximum miosis.

* Significantly different from control (\(P < 0.05\)).
peak consistent with a portion being swallowed, escaping first-pass metabolism, and being absorbed systemically. The secondary peak was not observed in rifampin-treated subjects, consistent with induction of intestinal and hepatic CYP3A activity, increased first-pass metabolism, and minimal amounts of fentanyl escaping first-pass metabolism. Conversely, the secondary peak was enhanced in troleandomycin-treated subjects, consistent with substantial inhibition of intestinal and hepatic CYP3A activity, decreased first-pass metabolism, and a greater proportion of swallowed fentanyl escaping first-pass extraction and reaching the systemic circulation. In subjects treated with grapefruit juice, which selectively inhibits only intestinal CYP3A, the secondary peak was somewhat greater than in controls but not as large as that in troleandomycin-treated subjects. This is consistent with inhibition of intestinal, but not hepatic, CYP3A activity, and moderately decreased first-pass metabolism. Thus selective inhibition of intestinal CYP3A with grapefruit juice, compared with intestinal and hepatic CYP3A inhibition by troleandomycin, can identify a role for intestinal metabolism in overall first-pass extraction.

A second purpose of this investigation was to test the hypothesis that altered CYP3A4 activity would influence the pharmacokinetics and clinical effects of OTF. In general, modulation of intestinal or hepatic CYP3A activity had little meaningful effect on the absorption kinetics of OTF or the onset of clinical effects. The time to and magnitude of (the first) peak plasma fentanyl concentrations were not significantly altered by CYP3A modulation, nor were the onset and magnitude of miosis. The only exception was an apparent delay in miosis in troleandomycin-treated subjects, likely owing to the influence of the large secondary plasma fentanyl peak. In contrast, modulation of CYP3A activity by rifampin and troleandomycin significantly altered the elimination kinetics of fentanyl and the magnitude and duration of clinical effects after OTF. For example, pupil diameters returned to baseline values after 6 h in rifampin-treated subjects but were still miotic at the end of the 10-h measurement period in troleandomycin-treated subjects. These effects are likely mediated primarily by altered hepatic CYP3A activity, as grapefruit juice (selective intestinal CYP3A inhibition) had minimal effects on fentanyl metabolism as measured by norfentanyl AUC, by fentanyl pharmacokinetic parameters, and by apparent oral bioavailability. Troleandomycin effects on elimination of fentanyl after OTF were similar to those after intravenous fentanyl.26

This investigation also demonstrates the utility of miosis as a noninvasive approximate surrogate for plasma fentanyl concentrations. Mean values of the effect parameters maximum miosis, miosis AUC, and miosis fentanyl apparent oral clearance accurately reflected mean values of the fentanyl pharmacokinetic parameters Cmax, AUC, and fentanyl apparent oral clearance across all four treatment groups. Miosis provides results much faster (in real-time) and less expensively than plasma concentration determinations, which are typically performed in a batch at the conclusion of the entire subject enrollment. Thus, fentanyl miosis, like that of alfentanil, methadone, and morphine, is a useful method for assessing opioid drug interactions. Miosis data should be interpreted with the understanding that miosis has greater intrasubject and intersubject variability because it reflects both pharmacokinetic and pharmacodynamic variability and that use as a surrogate to detect pharmacokinetic drug interactions assumes a lack of a pharmacodynamic interaction.

Determination of fentanyl concentrations and miotic effects permitted an evaluation of fentanyl pharmacodynamics and the effects CYP3A modulators (especially

Fig. 6. Influence of CYP3A modulation on oral transmucosal fentanyl citrate pharmacodynamics, shown as a hysteresis plot. Each data point is the mean of 12 subjects, with SD omitted for clarity.
analgesia in mice was significantly increased by the P-gp inhibitor cyclosporine, an increase that was pharmacodynamically mediated because plasma fentanyl concentrations were not changed. In P-gp knockout mice, fentanyl analgesia was significantly increased. Nonetheless, the role of P-gp in fentanyl CNS access in humans is not known. Chronic fentanyl up-regulates P-gp expression, but fentanyl also acutely inhibits P-gp activity. In the present investigation, fentanyl had no apparent effect on fentanyl CNS access, as concentration-effect relationships were unchanged (figs. 5 and 6, table 2). This cannot be attributed to acute fentanyl inhibition of P-gp and masking of potential P-gp induction, as fentanyl was not administered on the day of OTF dosing. Lack of fentanyl effects is consistent with a previous observation that the P-gp inhibitor quinidine also had no effects on fentanyl CNS access. Fentanyl also undergoes transport by other proteins, and fentanyl also modulates the activity of several non-P-gp transporters. Nonetheless the present results do not support a role for P-gp or other fentanyl-sensitive transporters in the CNS access of fentanyl.

There are clinical implications of the results of this investigation. More than 50% of all drugs are metabolized by CYP3A, and hence there is significant potential for CYP3A drug interactions. Nonetheless, when OTF is administered with careful attention to maximizing transmucosal absorption (rather than swallowing), major changes in neither hepatic nor intestinal CYP3A activity affect the acute absorption, peak concentrations, or onset of OTF effects (as measured by miosis). By analogy, onset of analgesia would likely be similarly unaffected.

In summary, alterations in intestinal or hepatic CYP3A activity had little influence on OTF absorption and onset of effect, but did alter fentanyl elimination and duration of effect. OTF drug interactions are unlikely to alter the onset or magnitude of analgesia, but duration may, however, be affected.

We appreciate the support of Lesley Russell, M.B.Ch.B., M.R.C.P. and the monitoring assistance of Mason Gay, Cephalon, Inc. (West Chester, Pennsylvania).

References


Anesthesiology, V 101, No 3, Sep 2004
CYP3A AND TRANSMUCOSAL FENTANYL DISPOSITION


47. Henthusm TK, Liu Y, Mahapatro M, Ng KY: Active transport of fentanyl by the blood-brain barrier. J Pharmacol Exp Ther 1999; 298:1081–9


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