A Phase I Pharmacokinetic and Bioavailability Study of a Sublingual Fentanyl Wafer in Healthy Volunteers

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BACKGROUND: The sublingual administration of opioids is a simple and noninvasive method that provides rapid analgesia. In this phase I study we investigated the pharmacokinetics and bioavailability of a fentanyl wafer in healthy volunteers. The principal study objective was to investigate the pharmacokinetic profile of a new sublingual fentanyl wafer and to establish its absolute bioavailability.

METHODS: Twenty-four healthy volunteers, mean age 23 years, were randomly assigned to receive the equivalent of fentanyl 100 μg by both the sublingual and IV routes. Blood samples were collected in sterile polypropylene tubes for 24 hours after each fentanyl administration. The pharmacokinetic parameters were determined by model-independent pharmacokinetic analyses of the plasma fentanyl concentration–time profiles.

RESULTS: The mean absolute bioavailability of the sublingual fentanyl wafer was 78.9% (90% confidence interval [CI] 51.1% to 121.7%). The first detectable plasma fentanyl concentration time ranged from 2 to 10 minutes in all volunteers, and the mean (±SD) time to peak plasma concentration at 0.91 (±0.73) hours after administration.

CONCLUSION: Sublingual administration of fentanyl as a wafer product resulted in rapidly detectable plasma fentanyl concentrations. The absolute bioavailability of 78.9% indicated a high systemic availability of fentanyl and suggests that further development of this wafer is justified. (Anesth Analg 2012;115:554–9)

Because, although they may be deemed effective, their onset is such that the breakthrough pain may have resolved spontaneously.2

Fentanyl is a rapidly acting lipophilic opioid that has peak analgesic effects within a few minutes of IV administration and a duration of action, after small to moderate doses, of 30 to 60 minutes.3 Unfortunately, parenteral administration of fentanyl is usually unsuitable or inconvenient for the patient for the self-management of breakthrough pain, especially in the home environment. Fentanyl has therefore been formulated for administration by a number of alternative routes including transdermal,4 pulmonary,5,6 oral,7–9 oral transmucosal,10–13 and intranasal (IN).14–17 Sublingual (SL) administration is noninvasive, and the transmucosal absorption of lipophilic drugs is rapid.18,19 SL fentanyl appears to be clinically useful. It causes minimal mucosal irritation,13 is devoid of the bitter taste of other opioids,20–23 and avoids presystemic metabolism and the hepatic first-pass effect.24–28

We evaluated a new SL wafer, which was prepared by freeze-drying an aqueous dispersion of fentanyl citrate (equivalent to 100 μg fentanyl base) containing sodium carboxymethylcellulose and amylopectin as matrix formers. The fentanyl wafer dissolves rapidly with no residue when placed under the tongue.29

The lipophilicity of a drug influences its rate of absorption through biological membranes. Fentanyl has a pKa value of 8.4; hence at a pH of 7.0, almost 40% of fentanyl citrate should be present as the nonionized base. The wafer includes sodium bicarbonate to adjust the pH of the release microenvironment to approximately 7.0. The pH of saliva lies between 5.5 and 7.0.28 It was postulated that the nonionized (lipophilic) form of fentanyl would penetrate the SL mucosal membrane rapidly and that the absolute bioavailability of this wafer would exceed 70%.

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The primary aim of this open-label phase I study was to investigate the pharmacokinetic profile of a new fentanyl citrate wafer and to establish its absolute bioavailability via the SL route.

METHODS
After receiving Ethics Committee approval, the trial was registered with the Australian Therapeutic Goods Administration under the Clinical Trial Notification scheme and with the Australian and New Zealand Clinical Trials Registry (number 2010/0606).

This study was performed at Linear Clinical Research Ltd., Perth, Western Australia, in accordance with the principles of the Declaration of Helsinki\(^4\) and Good Clinical Practice Guidelines.\(^5\)

Study Subjects
Healthy volunteers gave written informed consent on an approved subject consent form, before undergoing trial procedures. Subjects between 19 and 32 years of age who had a body mass index between 18 and 30 kg/m\(^2\), had no history or evidence of drug or alcohol dependence or abuse, had normal findings after a clinical history and laboratory testing, were free of SL or buccal ulceration or disease, and had negative findings for human immunodeficiency virus, hepatitis B, and hepatitis C viral testing were included in the study.

Twenty-four volunteers who met the study inclusion and exclusion criteria were enrolled in this study. On the basis of an SD of the area under the curve (AUC), values of 35% and a 20% difference being significant gives a power of 84% (\(\alpha = 0.05\)).

Study Design
This was a single-center (Linear Clinical Research Ltd., Perth, Australia), randomized, open-label, single-dose, 2-treatment, 2-period, 2-way crossover study. According to the randomization plan, subjects were divided into 2 groups, in a 1:1 ratio using a computer-generated table of random numbers. The volunteers were given either IV fentanyl citrate or an SL fentanyl citrate wafer (equivalent to 100 \(\mu\)g of fentanyl). Each volunteer subsequently received the alternative route after a 7-day washout period.

The wafer was administered by placing it under the tongue. The volunteer was requested to avoid swallowing for as long as possible, at least for 10 minutes.

A naltrexone tablet (50 mg) was administered orally every 12 hours from before day 1 to the evening of day 2 (12 hours after the last fentanyl dose), so as to block any systemic effects of fentanyl.

Before commencement of the study, a dedicated IV cannula was placed in the forearm for subsequent venous blood sampling. Blood samples (7 mL) were taken predose before the commencement of wafer administration and then at 2, 5, 10, 15, 20, 30, 45, 60, 120, 180, 360, 460, 600, 720, 960, and 1440 minutes after administration commencement. For IV infusion, blood samples were taken at predose, at 2 and 3 minutes after commencement, and at 5 minutes (end infusion), then at 7, 10, 15, 20, 25, 30, 45, 60, 120, 180, 360, 460, 600, 720, 840, 960, and 1440 minutes from infusion commencement.

After collection, the blood samples were immediately centrifuged at 4°C, 2000 to 2500 g for 15 minutes and the plasma extracted and placed into polypropylene storage tubes. The plasma was stored at \(-80°C \pm 10°C\) until transfer to the bioanalytical laboratory. Sample extracts were analyzed on an API 4000 LC-MS/MS system (Applied Biosystems, Foster City, CA), preceded by a Shimadzu Prominence high-performance liquid chromatography system with d5-fentanyl as the internal standard. The assay had a limit of detection of 10 pg/mL. Precision was determined by duplicate analyses of plasma containing 10, 40, and 400 pg/mL fentanyl. The results were precise to within \(\pm 6.2\%\), \(\pm 3.3\%\), and \(\pm 1.7\%\) of the mean measured concentration values of 10, 40, and 400 pg/mL, respectively, and accurate to within 102%, 99.9%, and 101.4% of the nominal concentrations of 10, 40, and 400 pg/mL, respectively. At each concentration the number of replicates was 6.

Pharmacokinetics
The pharmacokinetic parameters were determined using Phoenix WinNonlin version 6.1 (Pharsight, A Certara\(^\text{TM}\) Company, St. Louis, MO). The pharmacokinetic data were \(C_{\text{max}}, t_{\text{max}}, \text{AUC}_{0\text{ to }\text{t}}^\text{t}, \text{AUC}_{0\text{ to }\infty}^\text{t}, k_{\text{el}}, \text{and } t_{1/2}\). First detectable fentanyl plasma concentration after SL administration (\(C_{\text{t1/2}}\)) and the time to \(C_{\text{t1/2}}\) (\(t_{\text{t1/2}}\)) were read directly from the plasma fentanyl concentration–time curves.

The terminal elimination rate constant (\(k_{\text{el}}\)) was determined as the slope of the regression line of best fit to the approximately log-linear terminal elimination phase. All fitting was performed with unity weighting of the data. The terminal elimination half-life (\(t_{1/2}\)) was obtained from \(k_{\text{el}}\) and equaled \(\ln 2/k_{\text{el}}\). The \(\text{AUC}_{0\text{ to }\text{t}}^\text{t}\) and \(\text{AUC}_{0\text{ to }\infty}^\text{t}\) values were obtained using the trapezoidal rule. The extrapolation to \(\text{AUC}_{0\text{ to }\infty}^\text{t}\) was calculated from \(\text{AUC}_{0\text{ to }\text{t}}^\text{t} + C_{\text{t2}}/k_{\text{el}}\).

Safety and Tolerability
Safety and tolerability were assessed by monitoring vital signs (arterial blood pressure and heart rate) after fentanyl administration. A full physical examination was performed before and 48 hours after drug administration. Laboratory tests and a 12-lead electrocardiogram were performed at baseline and completion of the study. Adverse events were assessed using direct observation, spontaneous reporting, and nonspecific questioning.

Statistical Analysis
Summary statistics were computed by treatment of each pharmacokinetic parameter. Bioavailability of SL fentanyl was determined separately for each subject as the ratio of \(C_{\text{max}}, \text{AUC}_{0\text{ to }\text{t}}^\text{t}, \text{AUC}_{0\text{ to }\infty}^\text{t}, k_{\text{el}}, \text{and } t_{1/2}\) for SL administration in comparison with IV administration. Overall bioavailability was estimated as the back-transform of the


difference between treatments for log-transformed $C_{\text{max}}$, $AUC_{0\to t}$, $AUC_{0\to t}$, and $AUC_{0\to t}$ values using a linear model with terms for treatment, period, sequence, and subject within sequence. The 90% confidence interval (CI) was also calculated, and $P$ values $<0.05$ were considered statistically significant. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., 2008). Differences in formulations were evaluated using Student $t$ tests.

**RESULTS**

Twenty-four patients were randomized, 12 to the SL:IV sequence and 12 to the IV:SL sequence. Two volunteers did not complete the SL or the IV administration arm of the study and were eliminated from all analyses. The volunteer characteristics are reported in Table 1.

**Pharmacokinetic Results**

Mean plasma ($\pm$SEM) fentanyl concentration versus time curves for the IV and SL routes are shown in Fig. 1. Individual subject plasma concentration profiles are shown for the SL route in Figure 2. The mean values ($\pm$1 SD) for the plasma pharmacokinetic parameters $C_{\text{max}}$, $t_{\text{max}}$, $AUC_{0\to t}$, $AUC_{0\to t}$, and $AUC_{0\to t}$ for fentanyl are shown in Table 2.

The first detectable plasma fentanyl concentration ($C_{\text{first}}$), after SL administration, was observed between 2 and 10 minutes after administration. The cumulative percentage of the 22 volunteers with $t_{\text{first}}$ at 2, 5, and 10 minutes and their mean plasma fentanyl concentration ($C_{\text{first}}$) were 12.5% (32.4 pg/mL), 62.5% (30.7 pg/mL), and 100.0% (49.0 pg/mL), respectively.

The mean time to peak plasma concentrations ($t_{\text{max}}$) after commencing IV and SL administration was 0.12 hour and 0.92 hour, respectively ($P < 0.0001$) (Table 2).

The mean ($\pm$SD) terminal half-life ($t_{1/2}$) for IV and SL administration was $13.07 \pm 3.00$ hours and $12.49 \pm 5.24$ hours, respectively ($P = 0.889$).

The mean ($\pm$SD) terminal elimination rate constant ($k_{\text{el}}$) for IV and SL administration was $0.055 \pm 0.012$ h$^{-1}$ and $0.064 \pm 0.025$ h$^{-1}$, respectively ($P = 0.317$).

Bioavailability was assessed by the percentage ratios of SL/IV for $AUC_{0\to t}$, $AUC_{0\to t}$, and $AUC_{0\to t}$ values. The mean bioavailability of SL fentanyl was estimated to be 72.1% (CI, 65.3% to 79.6%) from $AUC_{0\to t}$, 73.2% (CI, 66.3% to 80.9%) from $AUC_{0\to t}$, and 78.9% (CI, 51.1% to 121.7%) on the basis of the $AUC_{0\to t}$ values.

The $C_{\text{max}}$ of SL fentanyl was 18.8% (CI, 14.4% to 24.6%) of the IV administration value, with the average time to maximum concentration being 0.9 hour. For IV administration, $C_{\text{max}}$ generally occurred at the end of the infusion, with a rapid reduction over the half hour immediately postdose. From approximately 2 hours postdose, the mean

### Table 1. Demographic Characteristics of the Study Volunteers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>24</td>
</tr>
<tr>
<td>Mean age years (range)</td>
<td>23.2 (19–32)</td>
</tr>
<tr>
<td>Sex</td>
<td>14 female; 10 male</td>
</tr>
<tr>
<td>Mean weight in kg (range)</td>
<td>67.1 (51.4–100.7)</td>
</tr>
<tr>
<td>Study dose of fentanyl (µg)</td>
<td>100</td>
</tr>
</tbody>
</table>

![Figure 1](https://example.com/image1.png)  
**Figure 1.** Mean ($\pm$SEM) plasma concentration (pg/mL) over time profiles for sublingual fentanyl wafer and IV fentanyl. Inset figure is an expanded profile for the initial 2-hour period.
concentration–time profiles were similar for the 2 modes of administration.

Tolerability
All reported adverse events were mild to moderate. The mean (±SD) time for the wafer to dissolve in the SL pouch was 73 ± 76 seconds.

There was only 1 (4%) of 24 volunteers who reported nausea, commencing 5 minutes after administration of the wafer and increasing in severity to a maximum rating of 2 (of 10) at 30 to 60 minutes after administration. This volunteer nevertheless rated the wafer as acceptable. Three volunteers reported sedation in the first 5 minutes after administration, the reported number increasing to 4 at 10 and 15 minutes, and 5 at 30 minutes, then reducing to 1 volunteer only at 60 minutes. One (4%) volunteer experienced a burning (tingling) sensation within 5 minutes of administration, which then resolved. All μ receptor effects would have been moderated by concomitant naltrexone administration.

DISCUSSION
This study was designed as a phase I study to determine the basic pharmacokinetic parameters of a recently developed rapidly dissolving fentanyl wafer. It also collected some data on subject acceptance of the product.

It was found that the Cmax and tmax values for the SL fentanyl (100 μg) wafer were comparable (Table 3) to data reported from a previously studied SL fentanyl (100 μg) tablet.30 The Cmax and tmax values provide an indication of the rate of absorption of drugs. The wafer has similar Cmax, tmax, and AUC values, in comparison with the SL tablet (P = 0.573, 0.331, and 0.103, respectively); no absolute bioavailability data were available for the SL tablet. It was

Figure 2. Plasma concentration data (pg/mL) over time profiles for sublingual fentanyl wafer for each volunteer (n = 22).

Table 2. Mean Values (±1 SD) of Fentanyl Plasma Pharmacokinetic Parametersa

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tmax (hours)</th>
<th>Cmax (pg/mL)</th>
<th>AUC0–12 (h*pg/mL)</th>
<th>AUC0–t (h*pg/mL)</th>
<th>AUC0–∞ (h*pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV fentanyl90 (100 μg) (n = 22)</td>
<td>0.12 (±0.05)</td>
<td>1451.0 (±970.1)</td>
<td>1404.8 (±285.5)</td>
<td>1703.7 (±375.9)</td>
<td>1952.9 (±378.8)</td>
</tr>
<tr>
<td>Sublingual fentanyl wafer (100 μg) (n = 22)</td>
<td>0.91 (±0.73)</td>
<td>219.3 (±70.5)</td>
<td>1046.1 (±388.4)</td>
<td>1299.8 (±517.1)</td>
<td>1739.9 (±815.2)</td>
</tr>
</tbody>
</table>

AUC = area under curve.

a Two volunteers were excluded. They did not complete IV administration.

b Given as a 5-minute infusion.

Table 3. Comparative Literature Pharmacokinetic Data (Mean ± 1 SD) for Buccal and Sublingual (SL) Fentanyl Dosage Formsa

<table>
<thead>
<tr>
<th>Data</th>
<th>Buccal soluble film</th>
<th>Buccal tablet</th>
<th>SL tablet</th>
<th>SL wafer (this study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (μg)</td>
<td>800</td>
<td>400</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Study period (hours)</td>
<td>48</td>
<td>72</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>AUC0–∞, h/ng/mL</td>
<td>13.03 ± 3.45</td>
<td>6.48 ± 2.98</td>
<td>1.24 ± 0.52</td>
<td>1.74 ± 0.82</td>
</tr>
<tr>
<td>t1/2, hours</td>
<td>19.03 ± 8.31</td>
<td>11.6 ± 7.8</td>
<td>6.1 ± 2.0</td>
<td>12.5 ± 5.2</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>1.33 ± 0.31</td>
<td>1.02 ± 0.42</td>
<td>0.24 ± 0.14</td>
<td>0.22 ± 0.07</td>
</tr>
<tr>
<td>tmax, hours (range)</td>
<td>1.5 (0.75–4.00)</td>
<td>0.78 (0.33–4.0)</td>
<td>0.66 ± 0.29</td>
<td>0.91 ± 0.73</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>71</td>
<td>65</td>
<td>Not available</td>
<td>78.9</td>
</tr>
</tbody>
</table>

AUC = area under curve; Cmax = peak plasma concentration; tmax = time to peak plasma concentration.

a The t1/2 terminal elimination half-life.
noted that the SL tablet was evaluated in cancer patients over a 10-hour collection period, which causes different t1/2 values of 6.1 and 12.5 hours for the tablet and wafer, respectively (P = 0.0013).

After SL administration, rapid absorption of fentanyl was evidenced by detectable plasma concentrations within 2 to 10 minutes (tmax), occurring in most cases within 5 minutes. The wafer formulation had a Cfirst similar to that of the SL tablet. This reflects fentanyl’s high permeability into the rich bloodflow (and good venous outflow) of the SL mucosa, which bypasses the hepatic “first-pass” effect. The SL mucosa (100 to 200 µm) is thicker than the nasal mucosa (40 to 80 µm); hence a slower absorption rate was expected in comparison with that reported after IN administration (tmax for IN fentanyl 4.2 to 11.4 minutes versus 54.6 minutes for SL fentanyl in this study). Furthermore, IN fentanyl is delivered in solution, allowing immediate absorption, whereas the SL wafer is in a solid dosage form that needs saliva for dissolution, thus creating a lag period before absorption. On the other hand, the thicker SL mucosa may provide a “reservoir” effect, whereby the lipophilic fentanyl molecules are sequestered and then released into the circulation.

The buccal mucosa is thicker (500 to 800 µm) than the SL mucosa (100 to 200 µm), which may also explain more prolonged absorption after buccal administration. The thicker buccal layer, plus underlying smooth muscle in the buccal area of the oral cavity, may provide a more retentive system, possibly also accounting for the slower drug absorption rate. It is notable that the plasma SL fentanyl concentrations were indistinguishable from the IV data 2 hours after administration, indicating similar therapeutic effects. The initial high peak of the IV profile could potentially produce more side effects.

The bioavailability of this SL fentanyl wafer was 78.9%, which was similar to the bioavailability of IN fentanyl 71% and fentanyl buccal soluble film (71%).

The high bioavailability of fentanyl from the wafer suggests that wafer fentanyl is reliably absorbed sublingually and less likely to be partially swallowed, hence avoiding first-pass metabolism. No attempt was made to apportion bioavailability to these routes of absorption in this study. The analgesic efficacy of the wafer formulation appears satisfactory, on the basis of an earlier pilot study conducted among postoperative surgical patients.

CONCLUSION

This SL fentanyl wafer resulted in rapidly detectable plasma fentanyl concentrations in healthy volunteers, within 10 minutes of administration, indicating potential for the treatment of breakthrough pain. The bioavailability was 78.9% in relation to IV administration.

DISCLOSURES

Name: Chin Beng Stephen Lim, PhD.
Contribution: This author helped design the study and prepare the manuscript.
Conflict of Interest: Funding from iX BioPharma, Pty Ltd., Singapore, for this phase 1 study.

Name: Michael James Paech, DM.
Contribution: This author helped prepare the manuscript.
Conflict of Interest: The author has no conflict of interest to declare.

Name: Yandi Liu, PhD.
Contribution: This author helped design the study and prepare the manuscript.
Conflict of Interest: The author has no conflict of interest to declare.

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REFERENCES