# Pharmacokinetic Properties of Single- and Repeated-dose Sufentanil Sublingual Tablets in Healthy Volunteers

Sandra K. Willsie, DO, MA[1]; Mark A. Evashenk, BS[2]; Lawrence G. Hamel, BS[2]; Stephen S. Hwang, PhD*; Yu-Kun Chiang, PhD[3]; and Pamela P. Palmer, MD, PhD[2]

*[1]PRA Health Sciences, Lenexa, Kansas; [2]AcelRx Pharmaceuticals, Inc, Redwood City, California; and [3]Essence Sciences, San Jose, California*

## ABSTRACT

**Purpose:** Sufentanil is a μ-opioid agonist with a high therapeutic index in preclinical studies and no active metabolites, and it is highly lipophilic, thereby enabling a transmucosal route of administration. Rapid distribution from the plasma after IV sufentanil administration results in a short duration of action requiring excessive repeated dosing if used for postoperative analgesia. The sufentanil sublingual tablet system (SSTS) is a handheld, preprogrammed, patient-controlled analgesia system designed to allow patients to self-administer sufentanil 15-μg tablets under their tongue with a 20-minute lockout. The pharmacokinetic (PK) characteristics of sufentanil, administered by different routes of delivery and after single and repeated sublingual (SL) administration, were examined in 2 studies.

**Methods:** A randomized, open-label, crossover study in healthy subjects evaluated the PK profile of sufentanil 15 μg administered by different routes: IV, SL, buccal (BU), and PO. A second open-label, crossover study in healthy subjects evaluated the PK parameters after single and repeated doses (full SSTS drug cartridge of 40 consecutive SL doses administered every 20 minutes) of a sufentanil 15-μg SL tablet. Doses were self-administered using the SSTS.

**Findings:** In the route of administration study (n = 25), mean $C_{max}$ values were highest with IV administration, and bioavailability values were: SL, 59%; BU, 78%; and PO, 9%. The absorption across the oral mucosa was associated with a median plasma half-time (time from $C_{max}$ to 50% of $C_{max}$) that was 25-fold longer (2.5 hours) with SL versus IV administration (0.1 hours). In the single- and repeated-dose study (n = 38), mean $AUC_{0-\infty}$ was 125.5 h · pg/mL, and $C_{max}$ was 35.0 pg/mL, with a median $T_{max}$ of 0.8 hours after the administration of a single sufentanil SL tablet. With 40 consecutive doses, $C_{max}$ was 8-fold higher compared with that of a single dose, and steady state was achieved after the 13th dose. Median plasma half-time after the 40th dose was not statistically longer than that after a single dose (2.7 vs 2.2 hours, respectively), and the median $T_{max}$ was 0.3 hours after the last repeated dose.

**Implications:** These study results support the viability of the SSTS for use in patient-controlled analgesia. The wide range of mean drug concentrations achieved after repeated dosing at 20-minute intervals compared with those with a single dose suggests the flexibility of patient-controlled dosing to meet individual analgesic requirements. The prolonged plasma half-time with SL administration is expected to provide a more appropriate duration of analgesia compared with that of IV administration, and the PK properties of repeated-dose administration support a 20-minute lockout interval. (*Clin Ther*. 2015;37:145–155) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

**Key words:** context-sensitive half-time, patient-controlled analgesia, sublingual, sufentanil.

## INTRODUCTION

Despite increased awareness and the availability of guidelines and quality standards encouraging or mandating improvements in acute pain management,[1–3] the majority of surgical patients receive inadequate postoperative pain relief.[4–7] Although results have

*Accepted for publication November 3, 2014.*
http://dx.doi.org/10.1016/j.clinthera.2014.11.001
0149-2918/$ - see front matter



*Consultant, AcelRx Pharmaceuticals.

differed slightly between studies, a significant proportion of hospitalized patients experience moderate to severe pain after surgery. In a survey of 250 surgical patients, 80% experienced acute postoperative pain, and of these, the pain was moderate or severe in 86%.[4] Another study among surgical inpatients reported that 41% experienced moderate to severe pain on the 1st postoperative day, and that 15% continued to experience this level of pain on the 4th postoperative day.[7] Poor postoperative pain control may delay recovery and negatively affect morbidity and mortality.[8,9] These findings suggest a crucial need for innovative approaches to acute pain management that will result in improved analgesic efficacy with a lower risk for adverse events (AEs) and complications from therapy.

IV patient-controlled analgesia (PCA) provides an effective method for postoperative pain control.[10,11] However, despite its benefits, IV PCA has drawbacks, such as the risks for device-programming errors, medication-prescribing errors, pump malfunction, limitations on patient mobility, poor IV access, infection at the venipuncture site, and challenges with setting up and maintaining a functioning infusion pump.[12–14] Furthermore, morphine and hydromorphone, which are the opioids most commonly used for IV PCA, are associated with a potential risk for delayed AEs because both drugs have less-than-ideal pharmacokinetic (PK)/pharmacodynamic properties for use in IV PCA.[15–17] Opioids function at CNS receptors and not in the plasma; thus, conventional venous PK parameters can be misleading in determining opioid effects. Thus, the plasma/CNS equilibration half-life ($t_{1/2}k_{e0}$) is more accurate than is $T_{max}$ in predicting onset of action.[14,18,19] Morphine, its active metabolite morphine-6-glucuronide, and hydromorphone exhibit prolonged plasma:CNS equilibration times ($t_{1/2}k_{e0}$, approximately 3 hours, 6 hours, and 46 minutes, respectively) compared with more lipophilic μ-opioid agonists, such as sufentanil and fentanyl ($t_{1/2}k_{e0}$, 6 minutes).[16,17,20]

An ideal PCA opioid would provide a rapid and consistent onset of action afforded by fast equilibration within the CNS and would have limited efflux transporter effects, no active metabolites, limited effect of hepatic or renal impairment on clearance, and an acceptable tolerability profile. An ideal PCA delivery system would provide noninvasive drug delivery without restricting mobility and would eliminate errors in medication prescribing and device programming.[14] Sufentanil is a μ-opioid agonist that is rapidly equilibrating with the CNS, has a high therapeutic index and no active metabolites, and thus has the potential to reduce the risks and enhance the pain control associated with PCA.[14,21] However, the use of sufentanil for IV PCA is limited by a very short initial distribution half-life (1.4 minutes) when administered by the IV route.[22] Pilot studies suggest that a sufentanil sublingual tablet system (SSTS) provides a highly consistent PK profile with a rapid uptake and onset of action while minimizing the high peak levels and short duration associated with IV administration, and also avoids the first-pass metabolism associated with the PO route of administration.[23] Results from 2 PK studies in healthy volunteers are presented here, including: (1) the favorable PK profile of sublingual (SL) administration relative to IV and PO administration; and (2) the PK profile of sufentanil SL tablets after single- and repeated-dose administration.

## SUBJECTS AND METHODS

For each study, the study protocol, amendments, and informed-consent form were approved by MidLands Independent Institutional Review Board (Overland Park, Kansas). All subjects provided written informed consent before study participation, and each subject was free to withdraw from the study for any reason at any time. Both studies were conducted in compliance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. The studies were conducted during July 2012 and February 2013.

### Subject Selection

For each study, nonsmoking, healthy men and women aged 18 to 45 years with a body mass index between 18 and 30 kg/m$^2$ were eligible if they had no clinically significant medical conditions as determined by the investigator and had a negative urine test for drugs of abuse, cotinine, and alcohol at screening. Women were required to agree to use a medically acceptable form of contraception during the study.

Subjects were excluded if they had a resting heart rate of $<40$ or $>100$ beats/min; a corrected (Fridericia) QT interval $\geq 450$ msec and/or a history of risk factors for torsades de pointes; systolic blood pressure outside of the range of 90 to 139 mm Hg and/or diastolic blood pressure outside of the range of 60 to

89 mm Hg; orthostatic hypotension or symptoms of lightheadedness, dizziness, or fainting on standing; hemoglobin <13.5 g/dL (in men) or <11.5 g/dL (in women); positive blood test for HIV antibody, hepatitis B surface antigen, and/or hepatitis C antibody; allergy or hypersensitivity to opioids and/or naltrexone; recent (within 3 to 14 days of dosing) use of prescription or over-the-counter medications; and/or consumption of caffeine >450 mg/d.

## Study Design

### *Route of Administration Study*

In this single-center, randomized, open-label, 4-treatment, 4-period, 6-sequence crossover study, each subject received a single IV dose of sufentanil,* followed by 3 different routes of administration of sufentanil sublingual tablets dosed by a health care professional using forceps and according to 1 of 6 randomly assigned sequences. The 4 routes of administration were slow IV push over 1 minute, SL administration, buccal (BU) administration (in front of lower front teeth to avoid accidental swallowing), and PO. The following sequences of treatment were used: sequence 1: IV, SL, BU, PO; sequence 2: IV, SL, PO, BU; sequence 3: IV, BU, SL, PO; sequence 4: IV, BU, PO, SL; sequence 5: IV, PO, SL, BU; and sequence 6: IV, PO, BU, SL.

### *Single- and Repeated-Dose Study*

This single-center, open-label, fixed-sequence crossover study was conducted in healthy subjects. Each subject received a single sufentanil 15-μg SL tablet, followed later by 40 consecutive doses administered every 20 minutes. Doses were self-administered by each subject under the direction of the site staff using the SSTS, a handheld, preprogrammed, patient-administered analgesia device with a 20-minute lockout interval that is under review by the US Food and Drug Administration for the treatment of moderate to severe acute pain in the hospital setting.

In both studies, subjects remained in the facility during all treatments. A 48-hour washout period separated each treatment period. The washout period began with the start of dosing. Subjects received naltrexone 50 mg PO both before and after dosing with sufentanil tablets to block the μ-opioid effects of sufentanil. Aside from naltrexone, the only concurrent medications allowed during the study were oral contraceptives, acetaminophen (<2 g/d), and multivitamins. Subjects were asked to discontinue the intake of caffeine, alcohol, xanthines, grapefruits (or juice), Seville oranges (orange marmalade), and quinine 4 days before study drug administration.

*Trademark: Sufenta® (Taylor Pharmaceuticals, Decatur, Illinois [now defunct]).

## Study Assessments

For both studies, a complete medical history, physical examination, clinical laboratory tests (blood chemistry, complete blood count, urinalysis, and serology), 12-lead ECG, pregnancy test, and alcohol, cotinine, and drug screen were performed at screening. The physical examination, clinical laboratory tests, and ECG were repeated at the end of the study. Blood pressure, heart rate, respiratory rate, and oxygen saturation were determined at screening and on each study day. Tolerability monitoring included periodic measurement of vital signs and other assessments of AEs.

## Pharmacokinetic Assessments

Standard PK parameters were calculated, and results across routes of administration were compared. The PK parameters determined from plasma sufentanil concentrations were $C_{max}$ and $T_{max}$, both of which were determined directly from observations. AUC was calculated using the linear trapezoidal method for $AUC_{0-t}$ and $AUC_{0-\infty}$. $AUC_{0-\infty}$ was calculated as the sum of $AUC_{0-t}$ and $C_{last}/k_e$, where $C_{last}$ was the last measurable concentration and $k_e$ was the apparent terminal elimination rate constant (estimated from the slope of the elimination phase of the concentration–time curve). The geometric mean of $AUC_{0-\tau}$ (based on the redosing interval [τ] of 20 minutes) after the last (40th) repeated dose was calculated and divided by the geometric mean $AUC_{0-20}$ for the single dose to determine the accumulation ratio. The $t_{1/2}$ value was calculated as $\ln 2/k_e$. The clearance (CL) in each subject was calculated as dose/$AUC_{0-\infty}$ for IV sufentanil only. In each subject, estimates of the absolute amount of sufentanil absorbed were calculated by multiplying each treatment's $AUC_{0-\infty}$ and CL derived from IV sufentanil. The bioavailability of each treatment was calculated as the ratio of the amount of sufentanil absorbed divided by the nominal dose administered. Plasma half-time (HT) was measured as the time from $T_{max}$ to

time at which plasma concentration reached half of $C_{max}$ after discontinuation of drug administration.

In the route of administration study, blood samples from IV treatment for PK analysis were obtained predose and at 1, 4, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 600, 720, and 840 minutes and at 24 hours after dosing. For the SL, BU, and PO routes, blood samples for PK analysis were obtained predose and at 10, 20, 30, 40, 50, 60, 70, 80, 90, 120, 180, 240, 360, 480, 600, 720, and 840 minutes and at 24 hours after dosing.

For the PK analysis of single-dose sufentanil, blood samples were obtained predose and at 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 120, 180, 240, 360, 480, 600, 720, 800, and 840 minutes and at 24 hours after dosing. For the PK analysis of repeated-dose sufentanil, blood samples were obtained pre-dose and at 20, 120, 240, 360, 480, 600, 720, 760, 780, 785, 790, 795, 800, 810, 820, 830, 840, 850, 860, 870, 900, 960, 1020, 1140, 1260, 1380, 1500, 1580, and 1620 minutes and at 37 hours after the administration of the first dose on day 3.

## Analytical Methods

Plasma concentrations of sufentanil were determined by PRA Health Sciences (Lenexa, Kansas) using a validated HPLC-MS/MS method. The HPLC system (Acquity; Waters Corporation, Milford, Massachusetts) was coupled to an API 5500 MS/MS detector (AB Sciex, Farmington, Massachusetts). Chromatographic separation was achieved on a Zorbax 300-SCX HPLC column (50 × 3.0 mm; internal diameter, 5 μm; Agilent Technologies, Inc, Santa Clara, California). The mobile phase consisted of 80% acetonitrile/20% ammonium formate buffer (vol/vol) that was delivered at a flow rate of 1.0 mL/min. Briefly, sufentanil standard solutions were diluted in methanol and diluted in blank plasma to provide concentrations of 1.00, 2.00, 5.00, 20.0, 50.0, 200, 500, 800, and 1000 pg/mL. Subsequently, 50.0 μL of internal standard solution was added to the mixture, and liquid–liquid extraction was performed. The supernatants were evaporated at 45°C and reconstituted in 150 μL of the mobile phase solution. This was followed by a 10-μL injection of the sample into the HPLC-MS/MS system. The calibration standards were prepared in bulk in plasma and were extracted along with blanks, plasma, and quality-control samples. Calibration curves were linear over the range of 1.00 to 1000 pg/mL, and the $R^2$ values were always $>0.99$. The lower limit of quantification (LLOQ) was 1.00 pg/mL. At each concentration, the overall bias was within ±15.0% of the nominal value (±20.0% at the LLOQ) and the within-run, between-run, and total %CVs were all $\leq$15.0% (±20.0% at the LLOQ).

## Data Analysis

Descriptive statistics (eg, mean [SD], least squares [LS] geometric mean [for natural logarithm (nl)-transformed ANOVA model analysis], LS means [for non-transformed ANOVA model analysis], geometric means for nl-transformed paired *t* test analysis, and 90% CI) of the PK parameters were calculated. All statistical tests were 2-sided and a significance level of 0.05 was used. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

### *Route of Administration Study*

An ANOVA model for crossover design was performed on nl-transformed $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ values. This ANOVA model included sequence, subject within sequence, period, treatment, and period by treatment interaction factors. This same ANOVA model for crossover design was used to analyze $T_{max}$, $k_e$, $t_{1/2}$, and plasma HT without log-transformation. The CL and absolute amount of sufentanil absorbed are summarized descriptively.

### *Single- and Repeated-Dose Study*

Individual subject treatment-specific PK parameters ($AUC_{0-\infty}$, $AUC_{0-20}$, and $C_{max}$) were nl-transformed first. The $T_{max}$, $k_e$, $t_{1/2}$, and plasma HT were not log-transformed. A paired *t* test was used to test the significance of the mean difference in these PK parameters against 0. Assessment of steady state for the sufentanil 15-μg SL tablet after multiple dosing was performed using the Helmert method.[24] This method of determining steady state evaluates the ratio of the LS geometric mean of the drug concentration at each corresponding time point, divided by the LS geometric mean of the pooled concentrations of all remaining time points. The assessment time with a calculated ratio that does not statistically differentiate from a value of 1 is considered the time to steady state.

## RESULTS

### Subject Disposition and Baseline Demographic Characteristics

#### *Route of Administration Study*

In the route of administration study, 25 subjects were enrolled and included in the tolerability analysis, and 22 were included in PK analysis. Three subjects withdrew consent during the study. Baseline demographic characteristics were comparable among groups according to treatment sequence (Table I).

#### *Single- and Repeated-Dose Study*

For the single- and repeated-dose study, 40 subjects were enrolled and included in the tolerability analysis, and 38 were included in the PK analysis. One subject was discontinued due to noncompliance, and 1 was discontinued due to an AE of mild nausea. At baseline, the mean (SD) age was 28.0 (6.0) years, 21 (52.5%) were male, mean (SD) weight was 75.0 (11.4) kg, and mean (SD) body mass index was 25.9 (3.1) kg/m$^2$. Twenty-two (55.0%) were black or African American, 17 (42.5%) were white, and 1 (2.5%) was of "other" race (data not shown).

### Pharmacokinetic Properties

#### *Route of Administration Study*

For the comparison of routes of administration, relative to IV administration, the bioavailability values of SL, BU, and PO sufentanil treatments were 59%, 78%, and 9%, respectively, and IV sufentanil CL was 57.6 (14.0) L/h. The other PK parameters are shown in Table II. Compared with IV administration, SL and BU administration was associated with lower exposure (AUC) and lower $C_{max}$ (Figure 1). The mean $AUC_{0-\infty}$ and $C_{max}$ values with PO administration were lower by 85% and 89%, respectively, compared with those with SL administration. The median plasma HT values were 2.5, 2.3, and 2.0 hours, respectively, with SL, BU, and PO administration, which were significantly longer than that with IV administration (0.1 hours).

#### *Single- and Repeated-Dose Study*

In the single- and repeated-dose study, after a single dose of sufentanil 15-μg SL tablet, mean $C_{max}$ was 35.0 pg/mL, and median $T_{max}$ was 0.8 hours (Table III). Repeated administration of sufentanil 15-μg SL tablet every 20 minutes for 40 consecutive doses was associated with greater overall systemic exposure ($C_{max}$ and $AUC_{0-\infty}$) versus that of a single dose. The mean $C_{max}$ with repeated dosing was 8-fold higher than after a single dose (276.0 vs 35.0 pg/mL, respectively), and median $T_{max}$ was 12.0 hours (Table III and Figure 2). $C_{ss}$ after repeated dosing of sufentanil 15-μg SL tablets was achieved by dose number 13 (ie, by 4 hours).

After the last (40th) repeated dose, $C_{max}$ was 7-fold greater compared with that after single-dose administration ($P < 0.001$) (Table III and Figure 3). The accumulation ratio (ratio of geometric means of $AUC_{0-20,\text{last dose}}$ over $AUC_{0-20,\text{single dose}}$) was 26.6. After the last repeated dose, median $T_{max,\text{last dose}}$ was 0.3 hours, consistent with having obtained steady

Table I. Baseline demographic characteristics of the subjects in the study of the pharmacokinetic properties of sufentanil 15 μg administered by different routes.

| | Treatment Sequence | | | | | | All Subjects |
|---|---|---|---|---|---|---|---|
| Characteristic | 1 (n = 4) | 2 (n = 4) | 3 (n = 4) | 4 (n = 5) | 5 (n = 4) | 6 (n = 4) | (n = 25) |
| Age, mean (SD), y | 27.0 (5.7) | 29.0 (6.6) | 21.0 (1.8) | 36.6 (7.3) | 29.5 (4.1) | 33.8 (9.4) | 29.8 (7.7) |
| Male, no. (%) | 2 (50) | 1 (25) | 1 (25) | 4 (80) | 3 (75) | 2 (50) | 13 (52) |
| Race, no. (%) | | | | | | | |
| Black/African American | 3 (75) | 2 (50) | 2 (50) | 0 | 1 (25) | 4 (100) | 12 (48) |
| White | 1 (25) | 1 (25) | 1 (25) | 5 (100) | 3 (75) | 0 | 11 (44) |
| Other/Asian | 0 | 1 (25) | 1 (25) | 0 | 0 | 0 | 2 (8) |
| BMI, kg/m$^2$ | 22.9 (2.6) | 24.8 (3.3) | 21.1 (3.6) | 26.7 (2.1) | 24.9 (3.0) | 25.5 (2.7) | 24.4 (3.2) |

BMI = body mass index.

Table II. Pharmacokinetic properties of single-dose administration of sufentanil 15 μg, by route of administration.

| Parameter | SL (n = 22) | IV (n = 22) | BU (n = 22) | PO (n = 22)* | P† |
|---|---|---|---|---|---|
| $AUC_{0-\infty}$, h · pg/mL | | | | | <0.001 |
| Mean (SD) | 163.4 (52.5) | 273.8 (61.1) | 212.5 (57.0) | 24.9 (14.1) | |
| LSGM (90% CI) | 156.0 (138.4–175.9) | 270.4 (239.8–304.9) | 206.4 (183.1–232.8) | 22.4 (19.7–25.5) | |
| $C_{max}$, pg/mL | | | | | <0.001 |
| Mean (SD) | 40.6 (14.8) | 445.1 (312.0) | 58.9 (25.7) | 4.3 (3.8) | |
| LSGM (90% CI) | 38.5 (30.9–47.9) | 365.0 (292.9–454.9) | 53.5 (43.4–66.7) | 3.3 (2.6–4.1) | |
| $T_{max}$, h | | | | | 0.010 |
| Mean (SD) | 0.9 (0.3) | 0.1 (0.0) | 1.1 (0.5) | 1.2 (0.5) | |
| Median | 0.8 | 0.1 | 0.9 | 1.1 | |
| LSM (90% CI) | 0.9 (0.8–1.0) | 0.1 (–0.1–0.2) | 1.1 (0.9–1.2) | 1.2 (1.1–1.3) | |
| $t_{1/2}$, h | | | | | NS |
| Mean (SD) | 9.7 (7.3) | 11.3 (7.6) | 9.4 (7.7) | 6.2 (6.6) | |
| Median | 7.2 | 10.5 | 5.3 | 4.4 | |
| LSM (90% CI) | 9.6 (6.9–12.4) | 11.4 (8.6–14.1) | 9.4 (6.7–12.2) | 6.6 (3.5–9.7) | |
| Plasma HT, h | | | | | NS |
| Mean (SD) | 2.6 (0.9) | 0.2 (0.1) | 2.1 (1.1) | 2.2 (1.0) | |
| Median | 2.5 | 0.1 | 2.3 | 2.0 | |
| LSM (90% CI) | 2.6 (2.3–2.9) | 0.2 (-0.1–0.5) | 2.1 (1.8–2.4) | 2.3 (1.9–2.7) | |

BU = buccal; HT = half-time; time from $C_{max}$ to 50% $C_{max}$; LSGM = least squares geometric mean; LSM = least squares mean; SL = sublingual.

*For the PO treatment, $AUC_{0-\infty}$, n = 18; $t_{1/2}$, n = 18; and plasma HT, n = 16.

†*P* for the overall comparison among all treatments was based on type III analysis from the ANOVA model that included sequence, period, treatment, and period by treatment fixed factors, and subject within sequence random factor.

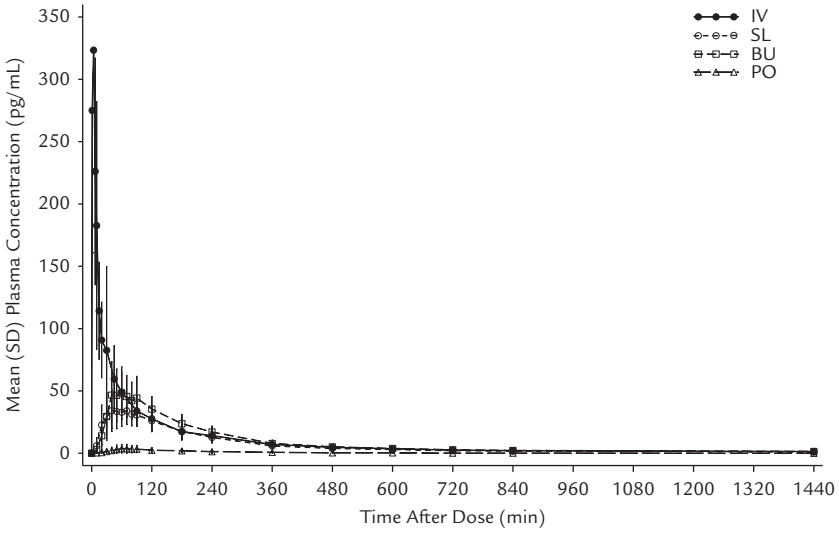


Figure 1. Plasma concentrations over time after a single 15-μg dose of sufentanil via the IV, sublingual (SL), buccal (BU), and PO routes.

Table III. Pharmacokinetic properties of single- and repeated-dose sufentanil 15-µg sublingual tablets.

| Parameter | Single Dose (n = 38) | Repeated Dose (n = 38) | $P^*$ |
|---|---|---|---|
| $AUC_{0-\infty}$, h · pg/mL | | | <0.001 |
| Mean (SD) | 125.5 (47.7) | 4216.6 (1225.5) | |
| GM (90% CI) | 117.9 (106.7–130.3) | 4064.3 (3751.8–4402.8) | |
| $C_{max}$, pg/mL | | | <0.001 |
| Mean (SD) | 35.0 (12.2) | 276.0 (77.3) | |
| GM (90% CI) | 33.1 (30.0–36.2) | 265.1 (247.2–287.2) | |
| $T_{max}$, h | | | <0.001 |
| Mean (SD) | 0.9 (0.1) | 10.9 (0.5) | |
| Median (90% CI) | 0.8 (0.76–0.94) | 12.0 (10.1–11.7) | |

GM = geometric mean.
These repeated-dose data are from the entire dosing period in contrast to the data in Table IV which is all from after the last of the repeated doses.
*$P$ for the test of the mean change between treatments was based on the paired $t$ test.

state by 4 hours with a 20-minute redosing interval (Table IV). Mean $t_{1/2}$ was increased after the last dose of repeated administration compared with that of a single dose. Median plasma HT was not significantly different after a single dose versus the 40th dose, suggesting a predictable and consistent offset after maximal repeated dosing of sufentanil 15-µg SL tablet over 13 hours.

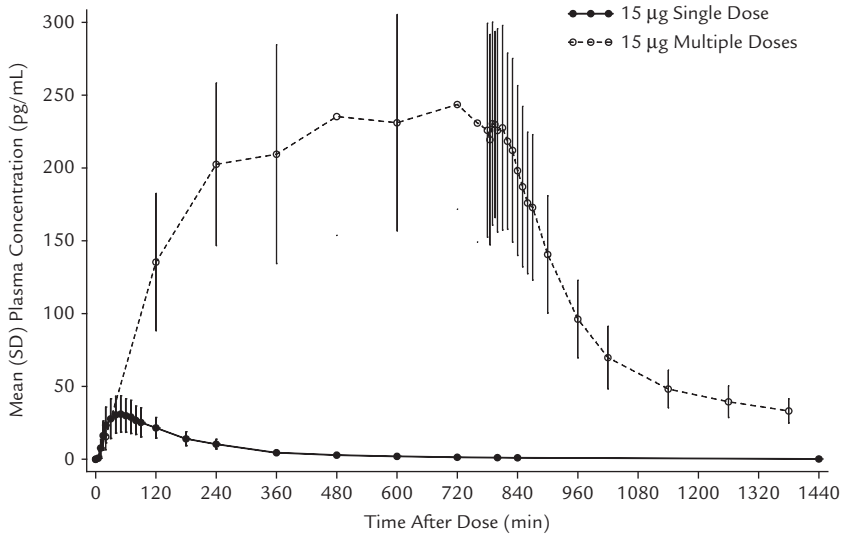


Figure 2. Plasma concentrations over time with the administration of single- and repeated-dose sufentanil 15-µg sublingual tablets. Repeated doses were self-administered by patients every 20 minutes for 13 hours.

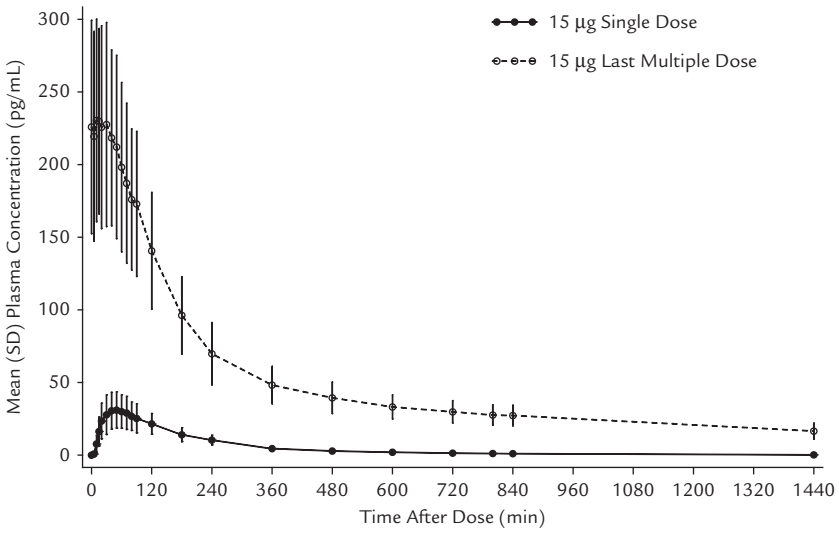


Figure 3. Plasma concentrations over time for single versus last (40th) dose of sufentanil 15-µg sublingual tablets.

## Tolerability Analysis

### *Route of Administration Study*

The subjects' concurrently receiving naltrexone during both studies was a confounding factor for assessing the tolerability of sufentanil. In the route of administration study, 8 subjects reported 12 AEs during treatment with IV sufentanil (4 reports of nausea [2 related to study drug], 2 of headache

Table IV. Pharmacokinetic properties of single- and repeated-dose (after the last dose) administration of sufentanil 15-µg sublingual tablets.

| Parameter | Single Dose (n = 38) | Last Repeated Dose (n = 38) | *P** |
|---|---|---|---|
| $AUC_{0-\infty}$, h · pg/mL | | | <0.001 |
| Mean (SD) | 3.2 (1.8) | 75.1 (22.4) | |
| GM (90% CI) | 2.7 (2.3–3.2) | 71.5 (66.0–78.3) | |
| $C_{max}$, pg/mL | | | <0.001 |
| Mean (SD) | 35.0 (12.2) | 249.6 (72.1) | |
| GM (90% CI) | 33.1 (30.0–36.2) | 239.9 (219.2–259.8) | |
| $T_{max}$, h | | | <0.001 |
| Mean (SD) | 0.9 (0.3) | 0.4 (0.2) | |
| Median (90% CI) | 0.8 (0.8–0.9) | 0.3 (0.3–0.4) | |
| $t_{1/2}$, h | | | <0.001 |
| Mean (SD) | 6.6 (6.7) | 17.6 (18.9) | |
| Median (90% CI) | 4.2 (4.7–8.4) | 12.7 (12.4–22.8) | |
| Plasma HT, h | | | NS |
| Mean (SD) | 2.2 (0.9) | 2.5 (0.6) | |
| Median (90% CI) | 2.2 (1.9–2.4) | 2.7 (2.3–2.7) | |

GM = geometric mean; HT = (half-time), the time from $C_{max}$ to 50% $C_{max}$.
*$P$ for the test of the mean change between treatments was based on the paired $t$ test.

[1 related], and 1 each of photophobia, abdominal pain [related], infusion-site pain, decreased appetite, flat affect [related], and hyperhidrosis); 4 subjects reported 5 AEs during treatment with SL administration (1 report for each of oral paresthesia [related], fatigue [related], headache [related], paresthesia, and flat affect [related]); 5 subjects reported 5 AEs during treatment with BU administration (2 reports of headache and 1 each of nausea, hypoesthesia oral [related], and flat affect [related]); and 3 subjects reported 5 AEs during treatment with PO administration (2 reports of nausea [both related] and 1 each of diarrhea, vomiting, and dizziness). All AEs were considered by the investigators as mild in intensity, 1 AE required treatment, and all events resolved by the end of the study. No clinically significant findings on clinical laboratory testing, physical examination including vital sign measurements, or ECG were observed.

### *Single- and Repeated-Dose Study*

In the single- and repeated-dosing study, 5 subjects (12.5%) reported 7 AEs with single-dose administration and 18 subjects (46.2%) reported 37 AEs with repeated-dose administration. One AE occurred in >5% of subjects with single-dose sufentanil: headache (4 [10.0%; 2 related]). The AEs occurring in >5% of subjects with repeated-dose sufentanil were nausea (6 [15.4%; all related]), headache (6 [15.4%; 5 related]), somnolence (4 [10.3%; all related]), dizziness (3 [7.7%; all related]), hot flush (3 [7.7%; all related]), and photophobia (2 [5.1%; both related]). All AEs were rated as mild by the investigators with the exception of one related AE of somnolence, which was rated as moderate in severity. No clinically significant findings on clinical laboratory testing, physical examination including vital sign measurements, or ECG were observed.

## DISCUSSION

In a comparison of routes of administration of sufentanil, the systemic exposure, as measured by $C_{max}$ and $AUC_{0-\infty}$, was significantly less and $T_{max}$ was longer with SL administration compared with IV administration. The plasma HT of SL administration was 25-fold longer than that of IV administration, and this is consistent with the dosing observed in patients using SSTS in the Phase III clinical trials. In a study in patients treated for up to 72 hours after major abdominal surgery and major joint replacement surgery, patients received treatment with SSTS approximately every 80 minutes, on average and demonstrated significantly greater analgesia.[14] Patients and healthcare providers rated SSTS as superior to IV PCA with morphine for the global assessment of method of pain control. Sufentanil has not been utilized clinically for IV PCA due to its short plasma HT; the SL route of administration of sufentanil ameliorates this issue.

Sufentanil is metabolized by hepatic cytochrome P-450 3A4 when administered IV[25]; however, this enzyme is also present in the small intestine and can substantially reduce bioavailability after PO (swallowed) administration of drugs that are cytochrome P-450 3A4 substrates.[26] Therefore, very low (<10%) bioavailability of a swallowed sufentanil tablet is expected. BU administration of the tablet was associated with a slightly greater bioavailability, most likely due to the placement in front of the lower front teeth, which is a protected location that minimizes the swallowing of saliva containing solubilized sufentanil. Clinically, this oral location is not convenient for patients to dose using the device, but it was chosen to avoid accidental swallowing of the very small tablet for this PK study.

The PK results with single and repeated administration of sufentanil 15-μg SL tablets were consistent with those from previous studies of sufentanil SL tablets.[23] As expected, both $C_{max}$ and AUC were greater after repeated administrations compared with those after single-dose administration of sufentanil. However, $C_{max}$ with repeated SL administration of the 15-μg sufentanil tablet at maximal frequency of dosing (every 20 minutes) was lower than that after a single IV dose of sufentanil 15 μg. This finding suggests a greater margin of tolerability with the sufentanil SL tablet compared with IV sufentanil dosing with respect to avoiding rapid high plasma concentrations that may produce undesirable AEs, such as chest rigidity (3% - 9% occurrence rate) and postoperative respiratory depression (less than 1% occurrence rate).[27] Even with repeated dosing at the maximum frequency of administration, the full SSTS drug cartridge of 40 doses of sufentanil SL tablets was associated with mean plasma concentrations that remained approximately at or below the median plasma sufentanil concentration (250 pg/mL) required for patients to breathe on their own after anesthesia with sufentanil.[28] Studies of the clinical use of the SSTS in postoperative patients have reported dosing frequencies and plasma sufentanil

concentrations much lower than the maximal utilization evaluated in this Phase I study.[14,29,30]

The $T_{max}$ of 20 minutes after repeated SL doses of sufentanil supports the results of an earlier, shorter-duration study that reported a median $T_{max}$ of 20 minutes (mean, 24 minutes) after the last (4th) repeated dose of SL sufentanil.[23] In addition, the rapid $t_{1/2}k_{e0}$ of 6 minutes for sufentanil suggests that the plasma $T_{max}$ is a relevant indicator of peak CNS drug effect.[20] The rapid equilibration of sufentanil is likely due to its high lipophilicity (octanol:buffer partition coefficient, 1757:1) as well as a 20% non-ionized fraction (at pH 7.4).[31] Morphine is not lipophilic (octanol:buffer partition coefficient, 1:1) and, therefore, even when delivered intravenously, has a $t_{1/2}k_{e0}$ of 2.8 hours and the active metabolite, morphine-6-glucuronide, has an even more delayed equilibration ($t_{1/2}k_{e0}$, 6.4 hours), in which case the CNS opioid effects of morphine significantly lag behind the plasma concentrations.[16,18,19]

Despite an increase in the elimination half-life with repeated SL dosing, no significant prolongation in plasma HT was observed, suggesting that redosing every 20 minutes allows for a predictable and consistent offset of analgesic effect with sufentanil SL tablets even with a maximal dosing frequency of over 13 hours. The high accumulation ratio may be expected given that the lockout interval of 20 minutes is much shorter than the elimination half-life of sufentanil (164 minutes).[22] Clinically, patients utilizing PCA modalities dose to effect, and the interdosing interval is longer than the lockout interval, as reported in the Phase III SSTS studies.[14,29,30] Achievement of steady state at as early as 4 hours with maximal repeated dosing also may be expected given the highly lipophilic nature of sufentanil, in which case the AUC associated with the terminal log-linear portion is small relative to the total area under the entire plasma drug–concentration profile. Therefore, the achievement of the steady-state trough concentration is minimally affected by the terminal half-life. A limitation of the study relates to the assessment of AEs, since naltrexone was administered orally to block the pharmacodynamic effects of sufentanil.

## CONCLUSIONS

The findings from these 2 studies support the viability of the 15-μg SSTS for use in PCA with a 20-minute lockout period. The sufentanil SL tablet dispensed from a handheld system potentially offers the attributes of an ideal PCA system, that is, it provides for a rapid and consistent onset of action, allows patients to self-dose with a 20-minute lockout, and provides a noninvasive drug-delivery method without restricting mobility. These findings, together with those from previously published clinical studies of the SSTS, support its efficacy and tolerability in treating patients with acute postoperative pain.

## ACKNOWLEDGMENTS

Editorial assistance for the preparation of this manuscript was provided by Richard Perry, PharmD. All of the authors were involved in design of the studies, data analysis, and article preparation. Dr. Willsie was involved in the conduct of the studies. All of the authors approved the submission of the manuscript.

## CONFLICTS OF INTEREST

Research funding and editorial assistance was supported by AcelRx Pharmaceuticals, Inc, the makers of SSTS. Mr. Evashenk, Mr. Hamel, and Dr. Palmer are employees of, and hold stock options in AcelRx Pharmaceuticals. Dr. Willsie is an employee of PRA Health Sciences, which received support from AcelRx Pharmaceuticals for the conduct of the study. Drs. Hwang and Chiang have received consulting fees from AcelRx Pharmaceuticals. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

## REFERENCES

1. Rosenquist RW, Rosenberg J. Postoperative pain guidelines. *Reg Anesth Pain Med*. 2003;28:279–288.
2. Gordon DB, Dahl JL, Miaskowski C, et al. American Pain Society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. *Arch Intern Med*. 2005;165:1574–1580.
3. American Society of Anesthesiologists Task Force on Acute Pain Management: Perioperative guidelines for acute pain management in the perioperative setting. *Anesthesiology*. 2012;116:248–273.
4. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*. 2003;97:534–540.
5. Lorentzen V, Hermansen IL, Botti M. A prospective analysis of pain experience, beliefs and attitudes, and pain management of a cohort of Danish surgical patients. *Eur J Pain*. 2012;16:278–288.

6. Phillip DM. JCAHO Pain management standards are unveiled. *JAMA*. 2000;284:428–429.
7. Sommer M, de Rijke JM, van Kleef M, et al. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur J Anaesthesiol*. 2008;25:267–274.
8. Werner MU, Søholm L, Rotbøll-Nielsen P, Kehlet H. Does an acute pain service improve postoperative outcome? *Anesth Analg*. 2002;95:1361–1372.
9. White PF, Kehlet H. Improving postoperative pain management: what are the unresolved issues? *Anesthesiology*. 2010;112:220–225.
10. Viscusi ER. Patient-controlled drug delivery for acute postoperative pain management: a review of current and emerging technologies. *Reg Anesth Pain Med*. 2008;33:146–158.
11. Momeni M, Crucitti M, De KM. Patient-controlled analgesia in the management of postoperative pain. *Drugs*. 2006;66:2321–2337.
12. Meissner B, Nelson W, Hicks R, et al. The rate and costs attributable to intravenous patient-controlled analgesia errors. *Hosp Pharm*. 2009;44:312–324.
13. Panchal SJ, Damaraju CV, Nelson WW, et al. System-related events and analgesic gaps during postoperative pain management with the fentanyl iontophoretic transdermal system and morphine intravenous patient-controlled analgesia. *Anesth Analg*. 2007;105:1437–1441.
14. Melson TI, Boyer DL, Minkowitz HS, Turan A, Chiang Y, Evashenk MA, Palmer PP. Sufentanil sublingual tablet system vs. intravenous patient-controlled analgesia with morphine for postoperative pain control: a randomized, active-comparator trial. *Pain Practice*. 2014;14:679–688.
15. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain*. 2002;3:159–180.
16. Lotsch J. Pharmacokinetic-pharmacodynamic modeling of opioids. *J Pain Symptom Manage*. 2005;29. (S90–103).
17. Shafer SL, Flood PD. The pharmacology of opioids in geriatric patients. In: Silverstein JH, Rooke GE, Reves JG, McLeskey CH, eds. *Geriatric Anesthesiology*. New York: Springer Science; 2007 p. 209.
18. Romberg R, Olofsen E, Sarton E, et al. Pharmacokinetic-pharmacodynamic modeling of morphine-6-glucuronide-induced analgesia in healthy volunteers: absence of sex differences. *Anesthesiology*. 2004;100:120–133.
19. Skarke C, Darimont J, Schmidt H, et al. Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. *Clin Pharmacol Ther*. 2003;73:107–121.
20. Scott JC, Cooke JE, Stanski DR. Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil. *Anesthesiology*. 1991;74:34–42.
21. Monk JP, Beresford R, Ward A, Sufentanil A. A review of its pharmacological properties and therapeutic use. *Drugs*. 1988;36:286–313.
22. Bovill JG, Sebel PS, Blackburn CL, et al. The pharmacokinetics of sufentanil in surgical patients. *Anesthesiology*. 1984;61:502–506.
23. Minkowitz HS, Singla NK, Evashenk MA, et al. Pharmacokinetics of sublingual sufentanil tablets and efficacy and safety in the management of postoperative pain. *Reg Anesth Pain Med*. 2013;38:131–139.
24. Maganti L, Panebianco DL, Maes AL. Evaluation of methods for estimating time to steady state with examples from phase 1 studies. *AAPS J*. 2008;10:141–147.
25. Tateishi T, Krivoruk Y, Ueng YF, et al. Identification of human liver cytochrome P-450 3A4 as the enzyme responsible for fentanyl and sufentanil N-dealkylation. *Anesth Analg*. 1996;82:167–172.
26. Kato M. Intestinal first-pass metabolism of CYP3A4 substrates. *Drug Metab Pharmacokinet*. 2008;23:87–94.
27. http://www.akorn.com/documents/catalog/package_inserts/17478-050-01.pdf.
28. Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology*. 1991;74:53–63.
29. Ringold FG, Minkowitz H, Gan TJ, et al. A randomized, double-blind trial to evaluate the efficacy and safety of the Sufentanil NanoTab PCA System/15 mcg plus rescue morphine versus placebo plus rescue morphine in patients with moderate-to-severe pain after open abdominal surgery. Poster presented at the Annual Meeting of the American Society of Anesthesiologists, October 15, 2013, San Francisco, CA.
30. Royal MA, Minkowitz H, Jove M, et al. A randomized, double-blind, placebo-controlled trial of the sufentanil sublingual microtablet system after major orthopedic surgery. Poster presented at the 67th Annual Postgraduate Assembly in Anesthesiology, December 15 2013c, New York, NY. http://www.call4abstracts.com/handouts/nyssa/view.php?nu=NYSSA13L1_1069 (accessed July 30, 2014).
31. Bernards CM. Clinical implications of physicochemical properties of opioids. In: Stein C, ed. *Opioids in Pain Control: Basic and Clinical Aspects*. Cambridge, UK: Cambridge University Press; 1999.


**Address correspondence to:** Pamela P. Palmer, MD, PhD, AcelRx Pharmaceuticals, Inc, 351 Galveston Drive, Redwood City, CA 94063. E-mail: ppalmer@acelrx.com