Sublingual Sufentanil, an "Ideal" Opioid for Acute and Breakthrough Pain: The Clinical Importance of $CST_{½}$ and $t_{½ke0}$

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Introduction

- Opioids function at CNS receptor sites so traditional venous PK parameters, such as C_{max} and elimination $t_{1/2}$, are less meaningful in determining true therapeutic effect, especially for non-lipophilic opioids such as morphine which have a slow transfer into the CNS.
- $t_{½ke0}$ (plasma-CNS equilibration half-life) is preferred over plasma T_{max} values for predicting analgesic onset of action, given the widely varying lipid solubility of opioids.
- $CST_{1/2}$ ("context sensitive half-time" or time duration from C_{max} to 50% of C_{max}) is a better reflection of duration/offset than traditional elimination $t_{1/2}$.
- Sufentanil is a synthetic opioid analgesic approximately 5 to 10 times more potent than its parent drug, fentanyl, and 500 times as potent as morphine. The drug possesses a high therapeutic index (26,000 compared to 70 for morphine)[1] in animal models and rapid equilibration between plasma and CNS ($t_{½ke0}$ = 6 min compared to 2.8 hrs for morphine)[2,3] **(Table 1).**
- AcelRx Pharmaceuticals (Redwood City, CA) is developing the following four product candidates to optimize drug delivery of sufentanil for acute and breakthrough pain:
  - 15 mcg tablets, patient-administered via a pre-programmed, non-invasive device for the management of acute pain in the hospital setting **(Figure 1)**;
    - The Zalviso™ sufentanil sublingual microtablet system (SSMS) is currently under FDA review;
  - 30 mcg tablets, healthcare professional-administered via a single-dose, sublingual applicator for the management of acute pain in a medically supervised setting (ARX-04)
  - 20 to 80 mcg tablets for control of breakthrough cancer pain (ARX-02);
  - 15 mcg sufentanil/200mcg triazolam combination product to address post-procedural pain and sedation (ARX-03).
- A clinical pharmacology study was performed to evaluate the PK characteristics of sufentanil following four different routes of delivery (intravenous, oral, sublingual and buccal).

Table 1. Comparison of the Therapeutic Index and $t_{½ke0}$ of Common Opioids

	Therapeutic Index	$t_{½ke0}$ (min)
Morphine*	71[1]	168[2]
Hydromorphone	232[4]	46[5]
Meperidine	5[1]	10[5]
Fentanyl	277[1]	6.6[3]
Sufentanil	26,716[1]	6.2[3]

*M6G (morphine-6-glucuronide), an active morphine metabolite has a $t_{½ke0}$ of 384 minutes (6.4 h)[2]

Figure 1. Sufentanil Sublingual Microtablet System (SSMS)

Methods

- This was a randomized, open-label, 4-treatment, 4-period, crossover study in healthy male/female subjects aged 18 to 45 years and body mass index 18 to 30 kg/m^2.
- The study objective was to determine the safety and tolerability of tablet formulation sufentanil and to assess pharmacokinetics (PK) of the various administration routes compared to intravenous (IV) sufentanil (Sufenta® 50 mcg/mL; Akorn).
- Each subject received a single IV dose of sufentanil followed by three sufentanil tablet treatments in random order and administered by a healthcare professional using forceps.
  - IV = Single 15 mcg dose slow IV push over 1 minute
  - SL = Single 15 mcg tablet placed under the tongue (sublingual)
  - PO = Single 15 mcg tablet swallowed (oral)
  - BU = Single 15 mcg tablet held between the front teeth and lower lip (buccal)
- Subjects received concomitant dosing of naltrexone 50 mg the evening before Period 1 and twice each dosing day in order to block any mu opioid-related effects.
  - The only other concomitant medications allowed during the study were contraceptives, acetaminophen (less 2 g daily) and multivitamins.
- A 48-hour washout period separated each treatment period and subjects remained in the facility during all treatments.
- PK sampling occurred prior to T0 and at 1, 4, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 600, 720, and 840 minutes, and 24 hours after dosing.
- Standard PK parameters were calculated (**Table 2**) and results across routes of administration were compared.
- Safety monitoring included pre- and post-study physical examination, laboratory assessments (blood chemistry, complete blood count [CBC], urinalysis, and serology) and ECGs as well as periodic measurement of vital signs, observation of the oral mucosal for irritation, and assessment of adverse events (AEs).

Table 2. PK Parameters and Definitions

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AUC_{0-x}	Area under the plasma concentration-time curve from time 0 to x where x = t (time to last quantifiable concentration) or ∞ (infinity) [h•pg/mL]
C_{max}	Maximum plasma concentration over the sampling period [pg/mL]
CL	Elimination clearance [mL/h]
$CST_{½}$	Context sensitive half-time (time from C_{max} to ½ C_{max}) [h]
F	Bioavailability value compared to IV administration [%]
K_{el}	Apparent terminal elimination rate constant [L/h]
$t_{½}$	Apparent elimination half-life [h]
T_{max}	Time to reach C_{max} [h]

Results

Patient Disposition and Baseline Demographics

- Twenty-five subjects (13 male and 12 female) were enrolled in the study, including 12 black, 11 white, 1 Asian subject, and 1 subject categorized as "Other."
  - Mean age was 29.8 years (range 19-45 years).
  - Mean body mass index (BMI) was 24.4 kg/m^2 (range: 18.2-29.3 kg/m^2).
- 22 subjects completed the study and were included in the PK analysis
  - PK analyses were performed by PRA Bioanalytical Services in Lenexa, KS

Results (cont.)

Pharmacokinetic Results

- Sublingual, buccal, and swallowed routes of administration resulted in significantly lower C_{max}, AUC_{0-t}, and AUC_{0-inf} values and longer T_{max} compared to IV sufentanil **(Figure 2 and Figure 3).**
- Relative to IV administration, the bioavailability of sublingual, buccal, and swallowed sufentanil treatments was 59%, 78%, and 9%, respectively, indicating that the bioavailability from sublingual and buccal routes were similar while that from swallowed sufentanil was poor.
- The buccal route of administration resulted in higher C_{max} (31%) and systemic exposure (24%) compared to sublingual administration, however, statistical analysis of the data showed that the lower bounds of the 90% CI for the geometric mean ratios of AUC_{0-t} and C_{max} were still within the standard equivalence range (**Table 3**).
- Median $t_{½}$ values ranged from 4.4 to 10.5 hours across the 4 treatments (1.5 to 3.8 hours for 2 pg/mL LLOQ).
- Median $CST_{½}$ values were 2.50, 2.28, and 2.00 hours, respectively, for sublingual, buccal, and swallowed sufentanil, all of which were significantly longer than seen with IV sufentanil (8 minutes).
- Complete sufentanil PK analysis is summarized in **Table 3.**

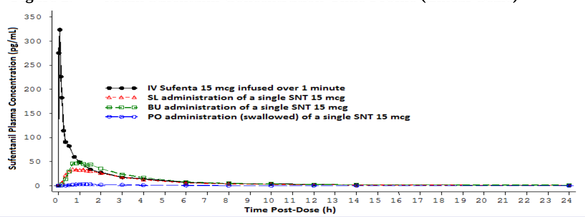
Table 3. Summary of Sufentanil PK (analysis using 1 pg/mL LLOQ)

PK Parameter		IV	SL	BU	PO	p-value*
AUC_{0-t} h•pg/mL	Mean (SD) GeoMean (CV)	250.42 (59.95) 242.3 (23.94)	145.63 (45.42) 138.4 (31.18)	191.92 (55.17) 183.1 (28.75)	12.90 (11.04) 8.1 (85.58)	< 0.001
$AUC_{0-\infty}$ h•pg/mL	Mean (SD) GeoMean (CV)	273.84 (61.09) 267.7 (22.31)	163.39 (52.54) 154.5 (32.16)	212.47 (56.97) 204.4 (26.81)	24.87 (14.08) 21.3 (56.62)	< 0.001
F %	Mean (SD) Median	100.0 (0.0) 100.0	59.2 (12.9) 60.9	78.1 (16.1) 82.5	8.9 (4.7) 7.4	< 0.001
C_{max} pg/mL	Mean (SD) GeoMean (CV)	445.05 (312.02) 361.4 (70.11)	40.59 (14.81) 37.7 (36.48)	58.87 (25.68) 53.0 (43.63)	4.33 (3.78) 3.3 (87.43)	< 0.001
T_{max} h	Mean (SD) Median	0.05 (0.03) 0.07	0.89 (0.34) 0.83	1.05 (0.45) 0.85	1.22 (0.47) 1.11	0.010
$CST_{½}$ h	Mean (SD) Median	0.18 (0.14) 0.14	2.61 (0.86) 2.50	2.08 (1.07) 2.28	2.15 (1.04) 2.00	0.103
$t_{½}$ h	Mean (SD) Median	11.34 (7.62) 10.54	9.65 (7.25) 7.21	9.40 (7.70) 5.28	6.18 (6.60) 4.43	0.405
CL mL/h	Mean (SD) Median	57619 (14047) 52883	NA	NA	NA	NA

Note that CV = coefficient of variability; GeoMean = geometric mean, SD = standard deviation. The number of subjects (n) receiving PO was less than 17 subjects for the following PK parameters: AUC_{0-inf} (n=12); $t_{½}$ (n=12); CL (n=12); and $CST_{½}$ (n=6).

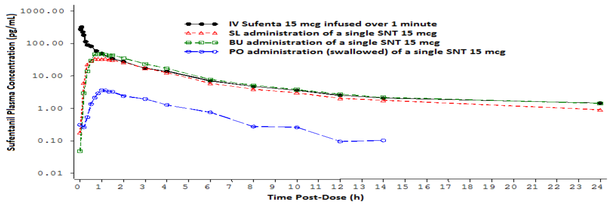
*The p-value for the overall comparison among all treatments was based on Type III analysis from the ANOVA model that included sequence, period, treatment, and period by treatment fixed factors, and subject within sequence random factor.

Figure 2. Mean Sufentanil Concentration-Time Profile (Linear Scale)



Results (cont.)

Figure 3. Mean Sufentanil Concentration-Time Profile (Semi-log Scale)



Safety Results

- There were no deaths or serious AEs (SAEs) during the study, and no subject discontinued the study due to an AE.
  - Two subjects had 4 AEs that were possibly related to study drug (1 AE of dizziness, 1 AE of diarrhea, 1 AE of nausea, and 1 AE of vomiting).
  - All AEs were mild in severity.
- There were no reports of nausea or vomiting events with the sublingual route of administration. IV sufentanil generated numerically more nausea reports (4 events) than seen with buccal (1 event) or swallowed (2 events) administration.

Conclusions

- Sublingual, buccal, and swallowed routes of administration resulted in significantly lower C_{max}, AUC_{0-t}, and AUC_{0-inf}, and longer T_{max} compared to sufentanil IV.
- $CST_{½}$, a more relevant predictor of duration of effect than $t_{½}$, was 18-fold longer for the sufentanil SL tablet compared to IV (when given as a 1 minute slow IV push), suggesting this formulation may be an attractive option for PRN dosing of acute and breakthrough pain as the rapid redistribution following IV sufentanil does not occur with SL administration.
- The sufentanil 15 mcg tablet administered in this study was generally safe and well tolerated regardless of route of administration, although subjects were naltrexone-blocked.

References

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