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

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## 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

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

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