Sufentanil Sublingual Tablet 30 mcg for the Management of Pain Following Abdominal Surgery: A Randomized, Placebo-Controlled, Phase-3 Study

Harold S. Minkowitz, MD*; David Leiman, MD†; Timothy Melson, MD‡; Neil Singla, MD§; Karen P. DiDonato, RN, MSN‖; Pamela P. Palmer, MD, PhD‖

*Department of Anesthesiology, Memorial Hermann Memorial City Medical Center, Houston, Texas; †Research Department, Hermann Drive Surgical Hospital, Houston, Texas; ‡Department of Anesthesiology, Shoals Medical Trials, Inc, Sheffield, Alabama; §Lotus Clinical Research, Pasadena, California; ‖Medical and Clinical Affairs, AcelRx Pharmaceuticals, Redwood City, California U.S.A

Abstract

Background: Results from a phase-3, prospective, randomized, double-blind, placebo-controlled trial evaluating sufentanil sublingual tablet 30 mcg (SST) for the management of pain after ambulatory abdominal surgery are presented.

Methods: Adults with American Society of Anesthesiologists status 1 to 3 scheduled to undergo abdominoplasty, open tension-free inguinal hernioplasty, or laparoscopic abdominal surgery under general or spinal anesthesia that did not include intrathecal opioids during the operation were eligible. Opioid-tolerant patients were excluded. The primary endpoint was the time-weighted summed pain intensity difference to baseline (SPID) over 12 hours. Secondary endpoints included SPID over 24 and 48 hours, total pain relief, and patient and healthcare professional (HCP) global assessments.

Results: Overall, 161 patients were randomized to SST (N = 107) or placebo (N = 54); pain scores were recorded for up to 48 hours. SPID 12 was higher (greater pain intensity reduction from baseline) in the SST group compared with placebo (25.8 vs. 13.1; P < 0.001, with a difference of 12.7 [95% confidence interval 7.16, 18.23]). In the SST group, a greater proportion of patients and HCPs responded “good” or “excellent” on the global assessments compared with placebo (P < 0.001 for both). There was a numerically, but not statistically, higher incidence of nausea and headache in the SST group.

Conclusions: In patients following abdominal surgery in an ambulatory care setting, SST was an effective opioid analgesic in postoperative pain management. In addition, SST was well tolerated with mild-to-moderate side effects, similar to those found in placebo-treated patients.

Key Words: opioid analgesics, postoperative pain, pain assessment, oral, safety, phase-3 study, abdominal surgery, ambulatory surgery
INTRODUCTION

The quality of postoperative analgesia following surgery in ambulatory surgery centers (ASCs) has a significant impact on patient satisfaction, timeliness of discharge, readmission rates, and patient care costs.1–4 A number of studies have demonstrated the advantages of multimodal analgesia in the ASC setting, such as lower adverse events (AEs) and lower pain intensity scores both upon admission to the phase-1 unit as well as in the phase-2 unit and at discharge.5–7 A growing number of major surgical procedures are being performed in ASCs, and while effective employment of multimodal analgesia regimens can decrease the use of opioids, significant quantities of opioids are still utilized to provide adequate analgesia following these larger, more invasive surgeries.8–11 However, new advances in postoperative opioids have been lacking over the past 3 decades and current opioid analgesics (eg, intravenous [IV] morphine) have limitations.12–18

Disadvantages of IV morphine include a delayed plasma:central nervous system (CNS) equilibration half-life ($t_{1/2}k_{e0}$) of 2.8 hours, delayed effects of the active metabolite morphine-6-glucuronide (M6G), which has an even slower $t_{1/2}k_{e0}$ of 6.4 hours, and possibly a higher postoperative nausea and vomiting rate compared with fentanyl in ASCs.19,20 Intravenous hydro-morphine has a relatively shorter $t_{1/2}k_{e0}$ of 46 minutes, but results in a similar side effect profile as IV morphine,21 with some studies suggesting a higher rate of postoperative sedation/CNS side effects with hydro-morphine.22 Intravenous fentanyl, while resulting in a quick onset of action due to its lipophilic nature ($t_{1/2}k_{e0} = 6.6$ minutes), has demonstrated a limited duration of analgesia following ambulatory surgery, resulting in frequent use of supplemental opioids and increasing pain scores after only 30 minutes.19,23,24 This prompt offset of analgesia is most likely due to fentanyl’s rapid alpha distribution half-life of 0.8 to 2 minutes following IV administration.25 The lipophilic opioids, sufentanil, alfentanil, and remifentanil, can have an even more abrupt offset of analgesia due to brief initial distribution phases and/or rapid metabolism following IV bolus administration, and are therefore rarely used for postoperative analgesia.26–29

Ideally, a postoperative opioid analgesic would blend the rapid onset and tolerability of IV lipophilic opioids with a duration of action that is better suited to ASC patients (eg, 2 to 3 hours, facilitating pain management both through recovery period and the transition to the home setting). A lack of active metabolites and non-invasive route of administration would confer additional advantages by reducing the potential for delayed side effects and allowing adequate analgesia while discontinuing IV lines in preparation for discharge. With these goals in mind, a sufentanil sublingual tablet 30 mcg (SST), prepackaged in a single-dose applicator, has been developed and the results of a phase-3 efficacy and safety study in patients following ambulatory abdominal surgery are reported herein. Previous studies evaluating a patient-controlled analgesia (PCA) device containing SST 15 mcg tablets have demonstrated suitable pharmacokinetics, rapid onset of action compared with IV morphine PCA, and an average inter-dosing interval of 80 to 100 minutes,17,30–32 suggesting a higher dosage strength administered by a healthcare professional (HCP) could potentially provide the desired onset of action and duration of analgesia for an ASC setting.

METHOD

This phase-3, prospective, randomized, double-blind, placebo-controlled trial was conducted at 4 hospitals in the United States. The study was registered with clinicaltrials.gov on February 2, 2015 (Clinicaltrials.gov Identifier: NCT02356588). The protocol was approved by the Institutional Review Board for each study site, and written informed consent was obtained from all patients. The study was conducted under the International Conference on Harmonisation, Harmonised Tri-partite Guideline for Good Clinical Practice, and the Guidelines of the Declaration of Helsinki.

Primary Inclusion and Exclusion Criteria

Male and nonpregnant female patients aged ≥18 years scheduled to undergo abdominoplasty, open tension-free inguinal hernioplasty (Lichtenstein repair with mesh), or laparoscopic abdominal surgery (under general or spinal anesthesia that did not include intrathecal opioids during the operation), and who were classified as American Society of Anesthesiologists physical class 1 to 3,33 were eligible for inclusion.

All patients were expected, by virtue of the type of surgery performed, to have ≥24 hours of moderate-to-severe postoperative pain. Patients were excluded if they had previously taken an opioid for >30 consecutive days, at a daily dose of >15 mcg of oral morphine (or equivalent), ≤3 months prior to surgery.
Randomization

Using an Interactive Web Response System, patients meeting eligibility criteria at screening and following surgery (stable vital signs and arterial oxygen saturation by pulse oximetry maintained at ≥ 95% with or without supplemental oxygen) were randomized 2:1 to the SST or an identical-appearing placebo tablet (placebo) group, and then stratified by sex. The study period began once the first SST or placebo was administered into the patient’s sublingual space by a HCP via the single-dose applicator, which was packaged in a numbered pouch to maintain the double-blind. There was no restriction on the type of surgical anesthesia or analgesia allowed with the exception of long-acting regional anesthesia, as the initial dosing of study drug required the patient to report a pain intensity score of ≥ 4 on an 11-point numerical rating scale (NRS; 0 = no pain; 10 = worst possible pain). Patients could request additional doses over the 24-hour study period, with a minimum 60-minute redosing interval. Patients were considered Completers if they completed 24 hours in the study. An extension redosing interval. Patients were considered Completers 24-hour study period, with a minimum 60-minute

Efficacy and Safety Assessments Included in this Analysis

Efficacy was assessed by patient reports of pain intensity on the 11-point NRS, a 5-point pain relief scale (0 = no relief; 1 = a little relief; 2 = moderate relief; 3 = a lot of relief; 4 = complete relief), percentage of patients dropping out of the study due to inadequate analgesia, and patient and HCP global assessments (PGA and HPGA, respectively). In addition, all HCPs who administered study drug to ≥ 3 patients answered a Study Drug Administration Questionnaire at the end of the study.

Pain intensity was initially recorded at baseline prior to dosing. Pain intensity and pain relief scores were then obtained at 15 minutes and 30 minutes, followed by every hour (from 1 to 12 hours) and every 2 hours (from 12 to 24 hours) following first dose of study drug, as well as prior to rescue analgesia administration. PGA and HPGA were completed at 24 hours or at study termination.

The primary efficacy endpoint was the time-weighted summed pain intensity difference to baseline (SPID) over the 12-hour study period (SPID12). Secondary efficacy endpoints included SPID over 1 hour (SPID1) and 24 hours (SPID24), time-weighted total pain relief (TOTPAR) over 12 (TOTPAR12) and 24 (TOTPAR24) hours, and summed pain relief intensity difference (SPRID) over 12 (SPRID12) and 24 (SPRID24) hours. Other secondary endpoints included the proportion of patients terminating the study and/or requiring rescue medication due to inadequate analgesia, the proportion of patients and HCPs who responded “excellent” or “good” to the global assessments, pain intensity, pain intensity difference (PID) to baseline, pain relief, pain relief intensity difference at each evaluation time point, proportion of patients not requiring study drug after 24 hours, and time to first use of rescue medication.

Safety assessments included AEs and use of concomitant medications, periodic monitoring of vital signs (blood pressure, heart rate [HR], and respiratory rate [RR]), and continuous monitoring of oxygen saturation.

Statistical Analysis

Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all patients who were randomized and received ≥ 1 dose of the study drug. A sample size of 159 patients (106 SST and 53 placebo) was based on an effect size of 0.55 for SPID12 and was sufficient to provide 90% power to demonstrate statistical difference at 0.05 between the 2 treatment groups. This calculation was based on a 2-sided 2-sample t-test with a 2-to-1 sample size allocation ratio, and a significance level of α = 0.05. Assuming a 10% nonevaluable rate for both treatment groups, a randomized sample size of 180 patients (120 in the SST group and 60 in the placebo group) was planned. A modified Brown’s analysis was used to impute any remaining missing data points up through the end of the study period for all early dropouts in either treatment group. Briefly, pain intensity data from the placebo group were used to derive a time-specific “imputing value k” for each time point. This k value included a combination of pain intensity values from placebo patients remaining in the study at that time point and the worst pain intensity values of placebo group dropouts who terminated prior to the time point. To minimize the impact of rescue
medication on primary and secondary endpoint analysis, pain intensity and pain relief scores obtained just prior to rescue opioid administration were imputed for 1 hour following the use of rescue, after which time the regularly scheduled assessments were then analyzed.

Data pooled from all study sites were examined using an F-test before applying the 2-sample t-test. Fisher’s exact test was used to analyze categorical data. Least-squares (LS) means and 95% confidence intervals (CIs) for SPID12 and continuous secondary efficacy variables were constructed using an ANCOVA model, which included treatment, treatment center, sex, and baseline pain intensity as covariates. Cochran–Mantel–Haenszel test stratified by sex with modified ridit scores was used for categorical data. A 2-sample Z-test was used to analyze dichotomous outcome data on 2 proportions, difference between proportions, and 95% CI between SST and placebo.

Survival analysis methods were used for time to event data. Kaplan–Meier product limit estimators were used to measure the cumulative rates of patients that reach the termination event (ie, termination due to inadequate analgesia and time to take first rescue medication). A log-rank test was used to compare the 2 groups. The Fisher’s exact test was used to compare the 2 groups for incidence of most frequent or severe AEs for patients during the study and for 12 hours following discontinuation of study drug dosing.

RESULTS

The first patient enrolled March 2015, and the final patient completed the study June 2015. A total of 163 patients were randomized and 161 of these patients received study drug and were included in the ITT and safety populations (Figure 1 and Table S1). A total of 143 patients completed the 24-hour study period (89%) and were included in the efficacy analysis for Completers. Overall, 53 of 131 (33%) patients entered the extension period (beyond 24 hours) and were included in the safety population (Table S1). The mean age of patients in the ITT population was 40.9 years with 1.2% aged ≥ 65 years. There were no statistically significant differences in baseline demographics and characteristics between treatment groups (Table 1).

Efficacy

The primary endpoint, the LS mean SPID12 score, was significantly higher (greater reduction in pain intensity from baseline) in the SST than in the placebo group (25.8 vs. 13.1; P < 0.001), with a difference of 12.7 (95% CI: [7.16, 18.23]) between groups (Table 2). For the secondary endpoints, mean SPID, TOTPAR, and SPRID scores were also significantly higher (greater reduction in pain intensity and/or greater pain relief) in the SST group at the 1- (SPID), 12- (TOTPAR, SPRID), and 24-hour (SPID, TOTPAR, SPRID) time points (Table 2). Among those patients completing 24 hours (Completers), the LS mean SPID12 score remained significantly higher in the SST compared with the placebo group (26.07 vs. 16.09; P < 0.001), with a difference of 9.98 (3.00; 95% CI: [4.05, 15.90]) between groups.

When evaluated at different time points over 24 hours, SPID, TOTPAR, and SPRID scores at each time point were significantly better in the SST compared with the placebo group (P < 0.05 for each). When SPID12 data were analyzed by age, sex, race, body mass index (BMI), and type of surgery, scores were higher with SST than placebo for all subgroups. However, the total number of patients per subgroup, particularly in the placebo arm (range: SST = 23 to 106; placebo = 10 to 53), was relatively small compared with the full study cohort (Table S2). These differences were significant for age < 65 years (P < 0.001), female sex (P < 0.001), Caucasian race (P = 0.001), non-Caucasian race (P = 0.003), BMI < 30 kg/m², abdominoplasty (P = 0.001), and laparoscopic abdominal surgery (P = 0.019), but not for male sex, BMI ≥ 30 kg/m², and hernioplasty.

Onset of Analgesia. The drop in pain intensity from baseline (PID) was greater for the SST group compared with the placebo group at the first evaluation time point (15 minutes; P = 0.002) (Figure 2). The remaining time points remained numerically greater for the SST group, with 3 time points (4, 20, and 22 hours) falling just short of statistical significance (P = 0.051 to 0.082).

Termination Due to Inadequate Analgesia. Before the end of the 24-hour study period, a significantly higher proportion of patients in the placebo group (18.5%; 10/54) compared with the SST group (3.7%; 4/107) discontinued treatment (P = 0.002) or terminated the study early (P = 0.001) due to inadequate analgesia (Figure 3A).

Rescue Medication. A significantly higher proportion of patients in the placebo group (64.8%; 35/54)
compared with the SST (27.1%; 29/107) group required rescue medication due to inadequate analgesia ($P < 0.001$). Additionally, significantly more patients in the placebo group compared with the SST group took their first rescue medication earlier ($P < 0.001$; Figure 3B). The mean (standard deviation [SD]) cumulative number of rescue morphine doses during the 24-hour study period was significantly higher in the placebo group (2.1 [2.9] compared with the SST group (0.5 [1.4]; $P < 0.001$).

**PGA and HPGA.** A significantly higher proportion of patients and HCPs in the SST compared with the placebo group reported success (“good” or “excellent”) on the PGA (80.4% [N = 86] vs. 51.9% [N = 28]) with a difference of 28.5% (95% CI: [13.20, 43.80]; $P < 0.001$) between groups at 24 hours and on the HPGA (80.4% [N = 86] vs. 53.7% [N = 29]) with a difference of 26.7% (95% CI: [11.42, 41.98]; $P < 0.001$) between groups at 24 hours.

Overall, a higher proportion of patients and HCPs responded “excellent” and a smaller proportion of patients responded “poor”, “fair”, or “good” in the SST compared with the placebo group for PGA ($P = 0.004$ overall) and HPGA ($P = 0.022$ overall) at 24 hours (Table S3).

**Study Drug Dosing.** Over the 24-hour study period, the total mean (SD) number of study drug doses used was not statistically significantly different between the SST (7.0 [3.6]) and placebo (6.4 [3.8]) groups.

The LS mean (SEM) interdosing interval was significantly longer in the SST group compared with the placebo group for the 12-hour study period (185.41 [8.80] vs. 146.55 [11.97] minutes; $P = 0.008$), but not for the 24-hour period (220.81 [10.87] vs. 189.82 [14.78] minutes; $P = 0.083$).

**Sufentanil Plasma Concentrations.** For patients in the SST group, mean (SD) sufentanil plasma concentrations

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**Figure 1.** Patient disposition. Placebo, sublingual placebo tablet; SST, sufentanil sublingual tablet 30 mcg.
were 40.8 (25.0), 39.1 (30.0), and 43.7 (37.2) pg/mL at 1, 12, and 24 hours, respectively. At the same time points, there were no differences in sufentanil concentrations when analyzed by sex or BMI (< 30 vs. ≥ 30 kg/m²).

Safety

Seventy (43.5%) patients had ≥ 1 AE considered possibly or probably related to study drug (Table 3). The most frequently (in ≥ 2% of patients) reported AEs were nausea (26.7%) and headache (11.8%). There were no significant differences between treatment groups for the incidence of any type of AE.

The majority of AEs were mild to moderate in severity. Two patients in the placebo group discontinued the study due to a treatment-emergent serious AE (SAE; moderate syncope and severe hemiparesis, resolved by the end of study), whereas no patients in the SST group experienced an SAE (Table 3). Severe AEs that were considered related to study drug were reported for 5 patients in the SST group (nausea, vomiting, and headache) and 1 patient in the placebo group (hemiparesis) (Table 3).

There were clinically small, but statistically significant (P < 0.05) differences within treatment groups for mean changes from baseline for all vital signs in both treatment groups, including systolic (SBP) and diastolic blood pressure (DBP), HR, RR, and oxygen saturation (SPO₂) at ≥ 1 time point during the 24-hour study period. The largest mean changes from baseline for the SST group were as follows: SBP/C0 13 mmHg at 16 hours; DBP/C0 10 mmHg at 16 hours; HR + 7 beats per minute at 24 hours; RR +1 breaths per minute at 24 hours; SPO₂ –1% at 20 hours. The largest mean changes from baseline for the placebo group were as follows: SBP/C0 10 mmHg at 16 hours; DBP/C0 7 mmHg at 16 hours; HR +8 beats per minute at 24 hours; RR +1 breaths per minute at 6 hours; SPO₂ –1% at 24 hours.

Almost all (96.9%) patients took ≥ 1 concomitant medication during the study. The most common, with a similar proportion used between treatment groups, were medical gases (55.9%), serotonin (5-HT₃) antagonists (41.6%), natural opium alkaloids (39.8%), and solution affecting electrolyte balance (38.5%).

Table 1. Patient Demographics and Baseline Characteristics (ITT Population)

| Characteristic          | Patients, N (%) | Placebo, N (N = 54) | Total, N (N = 161) |
|-------------------------|-----------------|---------------------|--------------------|
| Age, years              |                 |                     |                    |
| < 65                    | 106 (99.1)      | 53 (98.1)           | 159 (98.8)         |
| ≥ 65                    | 1 (0.9)         | 1 (1.9)             | 2 (1.2)            |
| Mean (SD)               | 41.2 (10.6)     | 40.4 (12.1)         | 40.9 (11.1)        |
| Sex                     |                 |                     |                    |
| Male                    | 34 (31.8)       | 18 (33.3)           | 52 (32.3)          |
| Female                  | 73 (68.2)       | 36 (66.7)           | 109 (67.7)         |
| Race                    |                 |                     |                    |
| White                   | 76 (71.0)       | 37 (68.5)           | 113 (70.2)         |
| Black or African American | 21 (19.6)   | 10 (18.3)           | 31 (19.3)          |
| Asian                   | 3 (2.8)         | 1 (1.9)             | 4 (2.5)            |
| Other                   | 7 (6.5)         | 6 (11.1)            | 13 (8.1)           |
| Ethnicity               |                 |                     |                    |
| Hispanic or Latino      | 42 (39.3)       | 19 (35.2)           | 61 (37.9)          |
| Not Hispanic or Latino  | 65 (60.7)       | 35 (64.8)           | 100 (62.1)         |
| BMI, kg/m²              |                 |                     |                    |
| < 30                    | 77 (72.0)       | 35 (64.8)           | 112 (69.6)         |
| ≥ 30                    | 30 (28.0)       | 19 (35.2)           | 49 (30.4)          |
| Mean (SD)               | 27.5 (4.8)      | 27.6 (4.9)          | 27.5 (4.8)         |
| Surgery                 |                 |                     |                    |
| Abdominoplasty          | 52 (48.6)       | 28 (51.9)           | 80 (49.7)          |
| Hernioplasty            | 23 (21.5)       | 10 (18.5)           | 33 (20.5)          |
| Abdominal laparoscopy   | 32 (29.9)       | 16 (29.6)           | 48 (29.8)          |

Table 2. SPID over 1, 12, and 24 Hours, and TOTPAR and SPRID over 12 and 24 Hours (ITT Population). Higher Values (LS Means) Indicate Better Efficacy

| SPID          | LS Mean (SEM) | Placebo (N = 54) | Effect Size* (SST-Placebo) | 95% CI of Effect Size | P  |
|---------------|---------------|-----------------|----------------------------|-----------------------|----|
| SPID1         | 1.09 (0.15)   | -0.37 (0.21)    | 1.46 (0.25)                | 0.97, 1.95            | < 0.001 |
| SPID12†       | 25.84 (1.71)  | 13.14 (2.35)    | 12.70 (2.80)               | 7.16, 18.23           | < 0.001 |
| SPID 24       | 57.96 (3.45)  | 37.28 (4.75)    | 20.68 (5.65)               | 9.51, 31.85           | < 0.001 |
| TOTPAR12      | 21.18 (0.87)  | 15.36 (1.19)    | 5.83 (1.42)                | 3.03, 8.63            | < 0.001 |
| TOTPAR24      | 45.80 (1.81)  | 35.45 (2.49)    | 10.36 (2.97)               | 4.50, 16.22           | 0.001  |
| SPRID12       | 47.03 (2.35)  | 28.62 (3.24)    | 18.41 (3.86)               | 10.79, 26.02          | < 0.001 |
| SPRID24       | 103.88 (4.81) | 73.05 (6.62)    | 30.83 (7.89)               | 15.24, 46.42          | < 0.001 |

BMI, body mass index; ITT, intent to treat; LS, least squares; placebo, sublingual placebo tablet; SD, standard deviation; SST, sufentanil sublingual tablet 30 mcg.

Table 3. SPID over 1, 12, and 24 Hours, and TOTPAR and SPRID over 12 and 24 Hours (ITT Population). Higher Values (LS Means) Indicate Better Efficacy

CL: confidence interval; ITT, intent to treat; LS, least squares; placebo, sublingual placebo tablet; SEM, standard error of the LS mean; SPID, summed pain intensity difference over 1 hour (SPID1), 12 hours (SPID12), and 24 hours (SPID24); SPRID, summed pain relief intensity difference.

*Effect size is difference in LS means between treatment groups.

†Primary efficacy endpoint (SPID12).
Figure 2. LS mean of PID over 24 hours (ITT population). ITT, intent to treat; LS, least squares; PID, pain intensity difference; placebo, sublingual placebo tablet; SST, sufentanil sublingual tablet 30 mcg.

Figure 3. Kaplan–Meier cumulative event rates for time to study discontinuation (A) and time to take first rescue medication (B) due to inadequate analgesia, over the 24-hour study period (ITT population). ITT, intent to treat; placebo, placebo sublingual tablet; SST, sufentanil sublingual tablet 30 mcg.
DISCUSSION

In this phase-3 study in patients treated for acute postoperative pain following typical outpatient abdominal surgical procedures, SST 30 mcg showed significantly superior pain control compared with placebo for the primary efficacy endpoint (SPID12) and for secondary endpoints related to pain intensity and pain relief. Rapid onset of analgesia was observed in the SST group, with statistically significant improvements in pain intensity compared with the placebo group as early as 15 minutes after the start of study drug dosing. SPID12 ratings remained numerically superior in the SST group across age, race, female sex, and BMI < 30 kg/m² compared with placebo. However, these results did not reach statistical significance due to the small number of patients included in each subgroup. Additionally, fewer patients in the SST compared with the placebo group discontinued because of inadequate analgesia or required rescue morphine. The types of AEs reported in this study were generally as expected in this patient population following outpatient abdominal surgery, and there were no clinically meaningful differences between treatment groups in AEs or vital signs.

As more invasive and painful procedures are performed in ASCs, emphasis on multimodal analgesia including opioids will be necessary to efficiently manage postoperative pain in these patients. While IV morphine is still commonly used in this setting, it poses several complications, as do similar opioids, such as hydromorphone. These opioids are hydrophilic and cannot easily pass through the blood–brain barrier to target the CNS. In particular, IV morphine has a delayed plasma: CNS equilibration $t_{1/2}$ of 2.8 hours. Conversely, the highly lipophilic opioid sufentanil passes more rapidly through the blood–brain barrier, with a 6.2 minute $t_{1/2}$. This lipophilic nature of sufentanil (1,300 and 1,700 times higher octanol:water partition coefficient than hydromorphone and morphine, respectively) also allows for prompt uptake from the sublingual tissues following drug administration. This rapid transition from sublingual tissue to mu-opioid receptor activation was evident in this study by the greater decrease in pain intensity from baseline at the first time point measured (15 minutes).

The average interdosing interval of SST in this study was 185 minutes over 12 hours, suggesting that the sublingual route of administration results in an extended duration of analgesia compared with the IV bolus administration of lipophilic opioids, such as fentanyl or sufentanil. The time from peak plasma concentration ($C_{max}$) to 50% of $C_{max}$ for sublingual sufentanil (2.5 hours) is extended 25-fold compared with bolus IV sufentanil administration of the same dose. SST may afford the ability to obtain rapid analgesia via a noninvasive route of administration while avoiding the frequent redosing often required for IV fentanyl.

Sufentanil, unlike morphine and hydromorphone, also avoids the issue of active metabolites that can lead to prolonged, untoward effects, which can complicate postoperative care and affect patient discharge. As patients are often discharged within a few hours following outpatient surgery, delayed untoward effects of opioids due to both the delayed accumulation of active metabolites and the slower CNS penetration of these water-soluble glucuronide moieties becomes more of a concern than following inpatient surgery where patients are more closely monitored.
Limitations

This study had several limitations that require careful interpretation of results. As this study was meant to reflect the typical surgical population, patient enrollment was not limited by age. Yet, the elderly were still under-represented in this study (1.2% of patients were age > 65 years). Additional evaluation of SST 30 mcg in the elderly is currently ongoing in phase-3 clinical trials.

A 12-hour evaluation period was chosen as the primary endpoint as ambulatory care surgery typically results in same-day discharge. This study, therefore, cannot fully interpret the longer term effects of SST in this population. However, the majority of patients in this study were followed for 24 hours. Lastly, our limited sample size (< 500) may also affect the generalizability of these results.

Contrary to the limitations of this study, over 600 patients exposed to SST 15 mcg in the 3 phase-3 clinical trials—which evaluated the sublingual sufentanil tablet system (containing SST 15 mcg doses in a bedside patient-controlled dispenser [Zalviso; Grünenthal GmbH, Aachen, Germany; authorized for use in Europe September 2015]) for moderate-to-severe postoperative pain following open-abdominal and/or major orthopedic surgery—have shown a similar safety profile to this study.17,31,32 These SST 15 mcg-treated patients included a significant elderly population (approximately 50% were age > 65 and 20% were age > 75 years) and were followed for up to 72 hours. SST 15 mcg could be dosed as frequently as every 20 minutes, and therefore, the exposure to sufentanil was similar, or higher, than in the current study.

All patients, including those in the SST group, were permitted to receive IV opioids in the operating room as well as IV morphine for rescue analgesia. However, SST demonstrated superior pain relief compared with placebo despite this potential confound.31,32 One of these phase-3 studies evaluated SST 15 mcg PCA vs. IV morphine PCA for moderate-to-severe pain following major orthopedic or open-abdominal surgery, and patients treated with SST 15 mcg (pro re nata [prn] every 20 minutes) had a significantly greater mean pain intensity reduction from baseline at 1, 2, and 4 hours compared with IV morphine (1 mg prn with a 6-minute lockout), further supporting the rapid onset of action of sublingual sufentanil.17 Future studies comparing SST 30 mcg with IV morphine or other opioids may further elucidate this issue.

CONCLUSIONS

Overall, SST 30 mcg was well tolerated, with no unexpected AEs, no clinically meaningful vital sign changes, and a safety profile that was as expected for this postoperative patient population.

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DISCLOSURES

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Patient disposition over the 24-hour study period and extension period.

Table S2. SPID12, by subgroup variable (ITT population).

Table S3. Response to the PGA (patient) and HPGA (HCP) at 24 hours (ITT population).

REFERENCES

1. Gold MI, Sacks DJ, Grosnoff DB, Herrington C, Skillman CA. Use of esmolol during anesthesia to treat tachycardia and hypertension. Anesth Analg. 1989;68:101–104.

2. Rawal N, Hylander J, Nydahl RA, Olofsson I, Gupta A. Survey of postoperative analgesia following ambulatory surgery. Acta Anaesthesiol Scand. 1997;41:1017–1022.

3. Fortier J, Chung F, Su J. Unanticipated admission after ambulatory surgery—a prospective study. Can J Anaesth. 1998;45:612–619.

4. Pavlin DJ, Rapp SE, Polissar NL, Malmgren JA, Koerschgen M, Keyes H. Factors affecting discharge time in adult outpatients. Anesth Analg. 1998;87:816–826.

5. White PF, Sacan O, Tufanogullari B, Eng M, Nuangchamnong N, Ogunnaike B. Effect of short-term...
postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. Can J Anaesth. 2007;54:342–348.

6. Cho CH, Song KS, Min BW, et al. Multimodal approach to postoperative pain control in patients undergoing rotator cuff repair. Knee Surg Sports Traumatol Arthrosc. 2011;19:1744–1748.

7. van der Worp F, Stapel JT, Lako S, Hendriks J, Vissers KC, Steegers MA. The comparison of two analgesic regimes after ambulatory surgery: an observational study. Pain Pract. 2014;14:260–270.

8. Cook TM, Eaton JM, Goodwin AP. Epidural analgesia following upper abdominal surgery: United Kingdom practice. Acta Anaesthesiol Scand. 1997;41:18–24.

9. Fotiadis RJ, Badvie S, Weston MD, Allen-Mersh TG. Epidural analgesia in gastrointestinal surgery. Br J Surg. 2004;91:828–841.

10. Moss E, Taverner T, Norton P, Lesser P, Cole P. A survey of postoperative pain management in fourteen hospitals in the UK. Acute Pain. 2005;7:13–20.

11. Armaghani SJ, Lee DS, Bible JE, et al. Preoperative opioid use and its association with perioperative opioid demand and postoperative opioid independence in patients undergoing spine surgery. Spine. 2014;39:1524–1530.

12. Simopoulos TT, Smith HS, Peeters-Asdourian C, Stevens DS. Use of meperidine in patient-controlled analgesia and the development of a normeperidine toxic reaction. Arch Surg. 2002;137:84–88.

13. High alert medication feature: reducing patient harm from opiates [newsletter]. Horsham, PA: Institute for Safe Medication Practices. Published February 2007. http://www.ismp.org/Newsletters/acute-care/articles/20070222.asp (accessed February 8, 2016)

14. American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 6th ed. Glenview, IL: American Pain Society; 2008.

15. Centers for Medicare & Medicaid Services. Hospital quality initiative program. CMS.gov Web site. Updated April 10, 2013. http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/index.html?redirect=/hospitalqualityinits/30_hospitalhcahps.aspx (accessed February 8, 2016)

16. Hospital Consumer Assessment of Healthcare Providers and Systems. Summary of HCAHPS Survey Results, October 2012–September 2013 discharges. Hospital Consumer Assessment of Healthcare Providers and Systems Web site, published July 2014. http://www.hcahpsonline.org/SummaryAnalyses.aspx#summary (accessed February 8, 2016)

17. Melson TI, Boyer DL, Minkowitz HS, et al. Sufentanil sublingual tablet system vs. intravenous patient-controlled analgesia with morphine for postoperative pain control: a randomized, active-comparator trial. Pain Pract. 2014;14:679–688.

18. Minkowitz HS, Scranton R, Gruschkus SK, Nipper-Johnson K, Menditto L, Dandapanavar A. Development and validation of a risk score to identify patients at high risk for opioid-related adverse drug events. J Manag Care Spec Pharm. 2014;20:948–958.

19. Claxton AR, McGuire G, Chung F, Cruise C. Evaluation of morphine versus fentanyl for postoperative analgesia after ambulatory surgical procedures. Anesth Analg. 1997;84:509–514.

20. Lötsch J, Geisslinger G. Morphine-6-glucuronide. Clin Pharmacokinet. 2001;40:485–499.

21. Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. Br J Anaesth. 2011;107:319–328.

22. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain. 2002;3:159–180.

23. Iwata Y, Mizota Y, Mizota T, Koyama T, Shichino T. Postoperative continuous intravenous infusion of fentanyl is associated with the development of orthostatic intolerance and delayed ambulation in patients after gynecologic laparoscopic surgery. J Anesth. 2012;26:503–508.

24. White PF, Elvir-Lazlo OL, Zaentz AS, et al. Does small-dose fentanyl improve perioperative outcomes in the ambulatory setting? A randomized, double-blind, placebo-controlled study. Acta Anaesthesiol Scand. 2015;59:56–64.

25. Shafer SL, Varvel JR, Aziz N, Scott JC. Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. Anesthesiology. 1990;73:1091–1102.

26. Gepts E, Shafer S, Camu F, et al. Linearity of pharmacokinetics and model estimation of sufentanil. Anesthesiology. 1995;83:1194–1204.

27. Bounes V, Barthélyem R, Diez O, Charpentier S, Montastruc JL, Ducassé JL. Sufentanil is not superior to morphine for the treatment of acute traumatic pain in an emergency setting: a randomized, double-blind, out-of-hospital trial. Ann Emerg Med. 2010;56:509–516.

28. Bujedo BM. Spinal opioid bioavailability in postoperative pain. Pain Pract. 2014;14:350–364.

29. Hwang W, Lee J, Park J, Joo J. Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study. BMC Anesthesiol. 2015;15:21.

30. Willisce SK, Evashenk MA, Hamel LG, Hwang SS, Chiang YK, Palmer PP. Pharmacokinetic properties of single-and repeated-dose sufentanil sublingual tablets in healthy volunteers. Clin Ther. 2015;37:145–155.

31. Jove M, Griffin DW, Minkowitz HS, Ben-David B, Evashenk MA, Palmer PP. Sufentanil sublingual tablet system for the management of postoperative pain after knee or hip arthroplasty: a randomized, placebo-controlled study. Anesthesiology. 2015;123:434–443.

32. Ringold FG, Minkowitz HS, Gan TJ, et al. Sufentanil sublingual tablet system for the management of postoperative pain following open abdominal surgery: a randomized, placebo-controlled study. Reg Anesth Pain Med. 2015;40:22–30.

33. American Society of Anesthesiologists. ASA Physician Status Classification System. October 15, 2014.
34. Brown MB. A test for the difference between two treatments in a continuous measure of outcome when there are dropouts. Control Clin Trials. 1992;13:213–225.

35. 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; 1999:166–187.

36. Momeni M, Crucitti M, De Kock M. Patient-controlled analgesia in the management of postoperative pain. Drugs. 2006;66:2321–2337.

37. Wright AW, Mather LE, Smith MT. Hydromorphone-3-glucuronide: a more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. Life Sci. 2001;69:409–420.

38. Cann C, Curran J, Milner T, Ho B. Unwanted effects of morphine-6-glucuronide and morphine. Anaesthesia. 2002;57:1200–1203.

39. Paramanandam G, Prommer E, Schwenke DC. Adverse effects in hospice patients with chronic kidney disease receiving hydromorphone. J Palliat Med. 2011;14:1029–1033.

40. Juba KM, Wahler RG, Daron SM. Morphine and hydromorphone-induced hyperalgesia in a hospice patient. J Palliat Med. 2013;16:809–812.