A Medication Use Evaluation of Sufentanil Sublingual Tablet 30 mcg for the Perioperative Management of Surgical Pain

Abstract

Background: Our institution conducted a medication use evaluation of a novel sublingual opioid for use as an analgesic in the perioperative setting for a wide variety of surgical procedures to compare perioperative opioid utilization and recovery times between two different opioid dosing protocols.

Method and Materials: Patients undergoing a surgical procedure requiring opioid-level analgesia were dosed sublingually with a sufentanil sublingual tablet 30 mcg in place of a standard dose of intravenous opioid (fentanyl, hydromorphone, or morphine) typically used for the procedure. The total dose of intraoperative and postoperative morphine milligram equivalents was calculated as well as the time in the recovery unit.

Results: Overall, 140 patients were dosed perioperatively with the sublingual sufentanil tablet from June 2019 to March 2020 and compared to 158 matched control patients undergoing similar surgeries with the same surgeons over a similar time period. Dosing of the tablet was either just prior to induction or intraoperatively in 137/140 of the patients, whereas 3 patients received a dose only in the recovery unit. The majority (90%) of patients required only a single tablet, while 14 patients required an additional dose in the recovery unit. The sufentanil sublingual tablet reduced opioid dosing requirements in the recovery unit by greater than 50% (p<0.001) compared to traditional intraoperative intravenous opioid dosing and resulted in an overall decrease in recovery discharge time by 14 min (p<0.001).

Conclusion: Perioperative sufentanil sublingual tablet administration can provide enhanced recovery compared to standard intravenous opioid administration.

Keywords: Postoperative; Acute pain; Opioid analgesic

Introduction

Providing optimal pain management in the immediate postoperative period is critical to maintain patient satisfaction as well as post-anesthesia care unit (PACU) efficiency. Uncontrolled pain is one of the top three medical reasons for delayed PACU discharge, along with drowsiness and nausea/vomiting [1]. Repeated dosing of intravenous (IV) opioids in the PACU period may effectively treat postoperative pain, but will likely exacerbate the cognitive and gastrointestinal side effects that delay discharge [2,3]. Repeated requirements for IV opioid administration in the PACU also requires time-consuming medication retrieval and witnessed-waste documentation. The tasks involved in medication administration in postsurgical patients accounts for approximately 30% of nursing time [4]. PACUs also typically have mandatory observation periods following administration of IV opioids, such that patients must be kept in the PACU following dosing, which further delays discharge. While this inefficiency in PACU patient recovery can result in staff overtime costs, the more costly expense is the lost surgical opportunity. The lost indirect overhead per minute in an operating room averages $14-$16 [5]. Taking into account surgical throughput inefficiency that...
congestion in the PACU creates, even a 15-minute decrease in discharge time per patient can have a substantial financial impact when multiplied over thousands of patients yearly.

IV fentanyl is commonly utilized both intraoperatively and in the PACU due to its rapid onset of action and lack of active metabolites [6,7]. While its lipophilic nature allows for a fast onset of analgesia due to rapid blood: brain equilibration [8], this property is also why it has a rapid decline following peak plasma concentrations, with pain scores returning to baseline within 30 minutes [9]. A recently FDA-approved sublingual opioid, sufentanil sublingual tablet (SST) 30 mcg (DSUVIA®, AcelRx Pharmaceuticals, Redwood City, CA) has been shown in clinical trials to have an onset of analgesia in approximately 15 minutes and a duration of action of 3-4 hours, based on redosing times in the postoperative setting [10]. Sufentanil is even more lipophilic than fentanyl [11]; however, the sublingual tissues release the drug over time such that the pharmacokinetic profile is dramatically altered from IV administration. Peak plasma concentrations with sublingual delivery are decreased 17-fold compared to IV administration and the time from Cmax to 50% of Cmax (plasma half-time) is extended to 2.5 hours [12]. Similar to fentanyl, sufentanil lacks active metabolites, therefore mild to moderate renal impairment, which often occurs after surgery especially in the elderly, does not affect SST dosing or clearance [12,13].

We conducted a medication use evaluation of SST dosed just prior to, or during, surgery to determine if its extended duration of action reduces the need for IV opioid dosing in the PACU and enhances overall PACU efficiency.

Methodology

As SST is approved for the management of acute pain severe enough to require an opioid (Figure 1), the hospital deemed that this medication use evaluation of two opioids was a quality improvement study and was therefore exempt from human subjects research requirements. SST-treated patients were analyzed from June 2019 to March 2020. The medical records of control subjects were analyzed if they underwent similar types of surgery over approximately the same timeframe, April 2019 to February 2020.

All patients were classified as American Society of Anesthesiologists (ASA) physical class I–III and underwent surgical procedures requiring opioid-level analgesia. A multimodal approach to analgesia is used in all patients in the perioperative setting and, therefore, was used in both the SST and control groups. Dosing of opioids was on an “as needed” basis. Patients were dosed intraoperatively with IV opioids based on their hemodynamic response to surgical stimuli. Administration of opioids in the PACU was in response to moderate-to-severe pain (i.e., a verbal report of pain intensity of 4 or greater on an 11-point [0-10] numeric rating scale). Intraoperative and postoperative opioid utilization was assessed by converting all opioids to IV morphine milligram equivalents (MME) using the online Practical Pain Management Opioid Calculator [14]. PACU discharge time was recorded at the time patients were discharged from the Phase 1 unit either to Phase 2 for a transition to home for same-day surgery or to the surgical floor for inpatient stays. Adverse events in the PACU were compared by assessing dosing of antiemetic agents for nausea and naloxone for respiratory events. Two-tailed t-tests were used to compare intraoperative and postoperative opioid MME and PACU discharge times between the groups and Chi-square tests were used to compare whether patients required opioids or antiemetics in the PACU.

Results

A total of 140 patients who were dosed with SST are included in this medication use evaluation study. These patients spanned across sixteen different surgeons and 6 different surgical specialties within the hospital. The largest subspecialty utilizing SST was general (abdominal) surgery (n = 52 patients), which included a large number of bariatric surgical patients, followed by orthopedic (n = 48), gynecologic (n = 19), urologic (n = 15), otolaryngologic (ENT) (n = 4), and spine surgery (n = 2) (Figure 2A). A total of 158 patients for the matching control group were analyzed from a similar distribution of surgical subspecialties (Figure 2B). The patient demographics were similar between the two groups. SST-treated patients had of mean (SD) age of 49.6 (16.5) years, 68% were female, and mean (SD) weight of 93.3 (27.7) kg. The control group patients had a mean (SD) age of 52.0 (18.4), 70% were female, and mean (SD) weight of 93.4 (24.1).

Dosing

The 140 SST-treated patients received a total of 154 doses of SST. Fourteen patients required a second dose of SST in the PACU (these doses were included in the total MME for each patient). The vast majority (137/140) of SST dosing was preoperatively, approximately 15 min prior to intubation, or intraoperatively 30 min prior to extubation for longer duration surgeries. Three patients received a single dose of SST only in the PACU.

Intra-operative IV opioid use

Patients in the control group overall received 66% higher mean (SE) dosing of intraoperative IV opioids compared to patients receiving SST (15.7 ± 0.7 mg vs 9.6 ± 0.5 mg; p<0.001) (Figure 3).
This was consistent across the different surgical subspecialties. When adding the MME for SST (approximately 5 mg IV morphine; Miner 2019), the overall pre- and intraoperative MME dose was similar between the control and SST groups (15.7 mg vs 14.6 mg).

**Post-operative opioid use**

The mean (SE) opioid requirement of the SST group was less than half of the control group (3.6 ± 0.4 mg vs 8.1 ± 0.5 mg; p<0.001) (Figure 4). The largest percent reduction in PACU opioid use occurred in the orthopedic surgery group (69% reduction), whereas the ENT patients had the shortest Phase 1 recovery time and no decrease from the control group.

**PACU time to discharge**

The Phase 1 recovery time in the PACU was reduced by an average of 14 min across the patients in the SST group compared to the control group (66 ± 2 [SE] vs 80 ± 2 [SE] min; p<0.001) (Figure 5). The largest decrease in Phase 1 recovery time was observed for the abdominal surgery patients (23 min; 25% reduction), whereas the ENT patients had the shortest Phase 1 recovery time and no decrease from the control group.

**Adverse events**

Dosing of the antiemetics promethazine or ondansetron for nausea in the PACU occurred in 14 patients out of 140 (10% incidence) in the SST group, with 2 of these patients receiving both medications. The control group had a greater incidence of antiemetic use (16.5%; 26 of 158 patients), with 6 of these patients receiving both medications, however this increase did not reach statistical significance (p = 0.10).

There was no naloxone use required in the SST group. A total of 3...
Reduced PACU opioid administration is likely a key contributor to patients (51.4%) requiring PACU opioid analgesics. Requirements in the PACU, and a lower percentage of SST-treated period, resulting in a greater than 50% decrease in total opioid SST provided analgesia that extended into the postoperative quite differentiated from IV fentanyl. The duration of action of depot of the drug produces a pharmacokinetic profile that is sufentanil, like fentanyl, is a lipophilic opioid, the sublingual requiring additional opioid administration in the PACU. Although historically, intraoperative dosing of opioids in this study intraoperatively is consistent with similar levels of pain stimuli matched for type of surgery, the overall equivalent opioid dose prior to admission to the PACU. Since the control group was matched for type of surgery, the overall equivalent opioid dose intraoperatively is consistent with similar levels of pain stimuli from these matched surgical procedures between groups.

Historically, intraoperative dosing of opioids in this study consisted mainly of IV fentanyl and, given its short duration of action, resulted in a high percentage of control patients (83.5%) requiring additional opioid administration in the PACU. Although sufentanil, like fentanyl, is a lipophilic opioid, the sublingual depot of the drug produces a pharmacokinetic profile that is quite differentiated from IV fentanyl. The duration of action of SST provided analgesia that extended into the postoperative period, resulting in a greater than 50% decrease in total opioid requirements in the PACU, and a lower percentage of SST-treated patients (51.4%) requiring PACU opioid analgesics.

Reduced PACU opioid administration is likely a key contributor to the reduced Phase 1 discharge time observed in the SST-treated patients. The nursing time to retrieve, administer, document and monitor patients following IV opioid administration in the PACU is time-consuming and contributes to delays in transitioning patients out of the Phase 1 unit. It is also possible that the high therapeutic index of sufentanil compared to fentanyl and other commonly used opioids, contributes to a more awake and alert patient in the PACU [16]. A cognitive impairment study has previously shown SST to have no impact on cognition following dosing in the emergency department [17].

While direct comparison of opioid-induced side effects between SST and control patients receiving only IV opioid administration was not possible given the nature of this study, the reduced PACU time essentially acts as a composite measure of efficacy and tolerability of SST. A combination of adequate pain control and lack of side effects allows a patient to be discharged from the Phase 1 unit. Given that SST reduced Phase 1 recovery by an average of 14 min among all patients, and an average of 23 min in the general (abdominal) surgery population, this demonstrates both the effectiveness and tolerable safety profile of SST. Furthermore, the trend towards reduced use of antiemetics and the lack of respiratory depression requiring naloxone in the SST group, compared to 3 patients requiring naloxone in the control group, additionally adds supportive evidence as to the safety of SST. The shortest PACU time in the control group was ENT procedures, and SST did not shorten this further. The sample size was small (total of 4 SST and 5 control patients,) but it is possible that rapid-recovery procedures may not be amenable to additional time efficiencies with SST.

These data include patients undergoing bariatric surgery which often require higher doses of PACU opioids as well as careful monitoring in the PACU. These patients were included in the abdominal surgery population for this study and contributed to the higher PACU opioid requirements and longer Phase 1 recovery time observed in this control group (10.3 mg MME and 92 min Phase 1 recovery time). The fact that SST was able to reduce PACU opioid dosing and recovery time by 54% and 25%, respectively, in this abdominal surgery patient population compared to intraoperative IV opioids alone, not only indicates better patient care but also reduced hospital PACU costs and enhanced surgical throughput for settings where PACU recovery is a limiting factor.

A recently published study evaluating a single preoperative SST dose in outpatient general surgery patients showed similar results regarding decreased PACU recovery time and decreased opioid requirements postoperatively compared to a historical control group [18]. The current study included patients undergoing both inpatient and outpatient surgeries across a broad range of surgical subspecialties and therefore broaden the findings of the earlier study.

**Limitations**

This was a single-center, retrospective study of SST dosing in a surgical patient population and physicians were allowed to dose the medication when they thought it was appropriate so there was not a consistent timing of SST administration in all patients.

**Discussion**

Based on the pharmacokinetics of sublingual sufentanil, a medication use evaluation was performed to determine if a single dose of SST administered just prior to induction or intraoperatively could reduce PACU opioid use and therefore decrease the discharge time from the Phase 1 unit in the PACU. Compared to matched controls, SST reduced intraoperative IV opioid dosing, reduced PACU opioid dosing and reduced the Phase 1 unit recovery time.

The decrease in intraoperative IV opioid use by 6.1 mg IV MME in the SST group compared to the control group is not surprising given that SST is approximately equivalent to IV morphine 5 mg [15]. Patients therefore received similar MME dosing of opioids prior to admission to the PACU. Since the control group was matched for type of surgery, the overall equivalent opioid dose intraoperatively is consistent with similar levels of pain stimuli from these matched surgical procedures between groups.

Historically, intraoperative dosing of opioids in this study consisted mainly of IV fentanyl and, given its short duration of action, resulted in a high percentage of control patients (83.5%) requiring additional opioid administration in the PACU. Although sufentanil, like fentanyl, is a lipophilic opioid, the sublingual depot of the drug produces a pharmacokinetic profile that is quite differentiated from IV fentanyl. The duration of action of SST provided analgesia that extended into the postoperative period, resulting in a greater than 50% decrease in total opioid requirements in the PACU, and a lower percentage of SST-treated patients (51.4%) requiring PACU opioid analgesics.

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Both inpatient and outpatient surgeries were included; however, Phase 1 unit discharge time was consistently used instead of overall PACU time which might differ between these two populations. The study did not control for whether patients were opiate naïve or opiate tolerant in either the SST group nor the control group, so while this could have resulted in longer PACU stays and higher postoperative opioid dosing requirements for the opioid-tolerant patient, there is no reason for these patients to be present at a substantially higher frequency in the control group.

**Conclusion**

Overall, SST dosed preoperatively or intraoperatively, significantly reduced both PACU opioid dosing requirements and Phase 1 discharge time compared to matched control patients who received standard IV opioids intraoperatively. SST was well tolerated, with no significant adverse events, such as respiratory depression.

**References**