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Sublingual sufentanil tablet for analgesia in emergency medical services and search and rescue agencies

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ABSTRACT

OBJECTIVES: Pain management in the potentially austere search and rescue (SAR) and emergency medical services (EMS) environments can be challenging. Intravenous (IV) and intramuscular (IM) routes of administration may be less practical. This study assesses the efficacy and safety of the sublingual sufentanil tablet (SST) in prehospital settings and hypothesizes that its use will reduce pain while maintaining a reasonable safety profile.

METHODS: This was a retrospective case analysis examining patient records from Teton County Search and Rescue, Grand Teton National Park EMS, and Jackson Hole Fire/EMS from 2021-2023, based on the criteria that they were administered SST in a prehospital setting. Cases in which SST was used were examined to assess patient characteristics, injury classification, patient reported pain scale before and after SST, other medications administered, and vital signs.

RESULTS: Seventy patients met the inclusion criteria. Six individuals were excluded due to missing one or more of the key variables, and the analysis was carried out with the remaining (N=64 cases). The mean pain score decreased from 8.0 ± 1.9 before medication administration to 5.5 ± 2.5 after administration, reflecting a statistically significant difference of 2.6 ± 2.1 ($p < 0.001$). The results also revealed statistically significant reductions in heart rate (HR) and systolic blood pressure (SBP) following SST administration (mean HR dropped by 4.2 ± 9.1 beats/min, $p = 0.004$, and mean SBP dropped by 11.1 ± 21.8 mmHg, $p = 0.01$). Changes in vital signs, although statistically significant, were not clinically significant and did not necessitate additional monitoring or intervention in any patients.

CONCLUSIONS: Our study demonstrated that SST administration led to a significant reduction in pain scores and exhibited a favorable safety profile regarding vital signs, including SBP, HR, respiratory rate

(RR), and O_2 saturation. These findings support the utilization of SST for pain management in the prehospital setting, particularly in austere environments where traditional routes of administration may be impractical.

Keywords: *Prehospital, pain management, Search and Rescue, Emergency Medical Services, sufentanil, sublingual*

INTRODUCTION

Sufentanil is a synthetic, highly potent opioid that is highly selective to the μ-opioid receptors. With a potency 5-10x that of fentanyl, a rapid plasma-to-CNS equilibration time ($t_{½}k_{e0}$ = 6 minutes compared to 2.8 hours for morphine) (1), and through its highly lipophilic nature, sufentanil is capable of achieving effective bioavailability through the sublingual route. Sublingual sufentanil tablet (SST), known by the trade name Dsuvia, is a dissolving sublingual tablet form of sufentanil. Sublingual sufentanil tablet was approved by the FDA in 2018 with a Risk Evaluation and Management Strategy (REMS) for use in certified medically supervised health care settings for the management of acute pain (2). This sublingual form allows for a non-invasive route of opioid administration. The well-documented adverse effects of both oral (PO), intravenous (IV), and intravenous patient-controlled analgesia (IV-PCA) of opiates (3-7) include respiratory depression, excessive sedation, delirium, catheter infiltration, IV tubing obstructions, and pump-programming errors. The above side effects and challenges have led to an interest in an alternative such as SST. Unlike other opiates, sufentanil lacks active metabolites which leads to a wide therapeutic index, decreasing the chance for drug accumulation in the body, particularly in those with hepatic or renal impairment.

Limited studies have demonstrated effectiveness of SST in the hospital environment. A study investigating the administration of SST 30 mcg versus placebo after outpatient abdominal surgery demonstrated that SST was well-tolerated and provided reduction in pain intensity in as early as 15 minutes following medication administration (1). When compared to the synthetic opioid analgesic piritramide administered via IV-PCA following spinal fusion surgery, 15 mcg SST was found to be more effective on postoperative day 0 and demonstrated increased patient mobility. In a separate study, when 15mcg SST following major open abdominal or orthopedic surgery was compared with morphine sulfate via IV-PCA (ms), results demonstrated more rapid onset of analgesia and increased nurse and

patient satisfaction secondary to ease of administration. This study also demonstrated fewer desaturation events than when compared to IV-PCA-ms (3). In another study when SST was compared with IV-PCA using fentanyl (IV-PCA-f), SST demonstrated comparable analgesic efficacy and decreased rates of nausea and vomiting (4). A further study which investigated the use of SST in patients with a higher burden of medical comorbidities with moderate-severe post-operative pain demonstrated adequate analgesia achievement in 15-30 minutes with no desaturations or other meaningful vital sign changes (5).

Search and rescue (SAR) and emergency medical services (EMS) agencies have the challenging task of providing pain management in remote and/or austere settings. In these environments, intravenous (IV) administration of analgesics may be less practical because of the need to establish and maintain IV access. Administration of intranasal (IN) and intramuscular (IM) medications is also challenging as these routes require keeping vials from freezing, as well as the need for syringes and needles to administer. The sublingual route of SST administration overcomes many of these obstacles and thus seems particularly suited to the challenges of the prehospital, remote, or austere environments. Because of its efficacy, wide therapeutic index, quick onset of action, and ability to be administered without intravenous access, SST is an attractive candidate for pain management in prehospital settings.

Jackson Hole Fire/EMS (JHFEMS) gained REMS approval to begin use of SST in October 2020, Grand Teton National Park (GTNP) in September 2021, and Teton County Search and Rescue (TCSAR) in September 2021. JHFEMS and GTNP implemented protocols allowing use of SST in situations where rapid analgesia was needed but IV access was not possible or would be delayed. TCSAR implemented a protocol allowing use in similar situations given the difficulty of IV access in the SAR environment. Ultimately the choice to use SST was left to the responder on scene if allowed by protocol. Prior to

implementing SST as an option these agencies had IN Fentanyl and Ketamine available as their primary means of administering analgesia prior to IV access. As one of the first places to implement SST in the prehospital environment, we aimed to evaluate the safety and efficacy of this medication in this setting and examine the population in which it was used. We hypothesized that SST would provide effective analgesia with a safe profile in prehospital scenarios.

METHODS

Design and setting

This was a retrospective chart review analysis of all prehospital cases that were administered SST by TCSAR, GTNP, and JHFEMS from implementation to July 25, 2023. All cases of SST use were identified through EMR search. We identified all patients from each agency that received SST from its implementation until the end of the study date. Jackson Hole Fire/EMS first administered on 7/29/21, GTNP on 10/2/21 and TCSAR on 2/7/22. A patient/case list was generated and each chart was independently reviewed and data points were extracted for analysis. The study was reviewed by the University of Utah IRB and deemed exempt.

Study population

Emergency responders identified patients requiring pain management per their protocol and administered SST when deemed appropriate by the responder on scene. Additional analgesics or other pain control adjuncts were allowed at the discretion of the treating responder. This includes IV analgesics once IV access was obtained. Patients under 18 years of age, those with major crush traumas, thermal or chemical injuries, or life-threatening traumas were excluded.

Variables of Interest

The primary outcome of interest was the efficacy of SST use in prehospital settings which was assessed through patient self-reporting of pain intensity on an 11-point rating scale, where 0 indicates no pain, and 10 represents the highest level of pain. Baseline pain scores reported 1-10 minutes before SST administration were considered for analysis. Post-med pain scores were reported 20-38 minutes after SST administration. The secondary outcome was safety measured by vital signs before and after SST administration. These included respiratory rate (RR), O_2 saturation,

heart rate (HR), and systolic blood pressure (SBP), and diastolic blood pressure (DBP). Vital signs reported within 20-38 minutes after the sublingual medication administration were analyzed. Data was also collected on other covariates, including age, sex, race/ethnicity, pre-existing medical conditions, home analgesic medication use (including opioids), mechanism of injury, injury classification, and other medications administered prior to SST.

Data analysis

Descriptive statistics were run for baseline characteristics in the full cohort. Mean pain scores were calculated for pre and post meds, and paired sample t-tests were applied to examine the statistical significance and magnitude of the difference in mean pain scores. Similarly, the mean RR, mean O_2 saturation, mean HR, mean SBP, and mean DBP were computed before and after medication administration, and paired sample t-tests were utilized to assess potential statistically significant differences in these means before and after medication.

Potential confounders, including within-patient correlation, were addressed using linear mixed-effects analysis. A random intercept was introduced to capture individual-level variability. We first constructed an intercept-only model (null model) to estimate the intercept and variance. A forward variable selection technique was then used and developed a series of multivariable mixed models. Patient-level variables with potential effects on the outcome were modelled as fixed effects. Covariates were incorporated in the model if they were of statistical significance or improved the model fit. We used the Akaike information criterion (AIC) guided model selection for overall fit assessment. Significance was assessed at the 0.05 level. All analyses were performed using R version 4.3.1, Vienna, Austria. The study was reviewed and considered Exempt by the University of Utah Institutional Review Board.

RESULTS

Seventy patients met the inclusion criteria. Six individuals were excluded due to missing one or more of the key variables, and the analysis was carried out with the remaining (N=64 cases). The mean age for the cohort was 51.5 ± 18.5. Among them, 33 (52.4%) were females, 32 (50.0%) had no preexisting medical conditions, and 10 (15.6%) had a history of cardiac disease. The general injury classification was musculoskeletal injuries in 55 cases (85.9%), and others in 9 cases (14.1%). Table 1 presents descriptive statistics of the patient population, including demographics and medication history. Table 2 describes pre-existing medical conditions of the patient population, and Table 3 lists the various activities during which injury occurred for patients given SST.

The paired sample t-test results indicated a significant reduction in pain scores following SST administration. The mean pain score decreased from 8.0 ± 1.9 before medication administration to 5.5 ± 2.5 after administration, reflecting a statistically significant difference of 2.6 ± 2.1 ($p < 0.001$). The results also revealed statistically significant reductions in HR, SBP, and DBP following sufentanil administration (mean HR dropped by 4.2 ± 9.1 beats/min, $p = 0.004$, mean SBP dropped by 11.1 ± 21.8 mmHg, $p = 0.01$), and mean DBP dropped by 7.1 mmHg, ($p = 0.001$) (Table 4).

Multivariable linear mixed model analysis

Multivariable linear mixed model analysis revealed a statistically significant 2.6-point decrease in the mean pain intensity when post sufentanil time was the only variable in the model (crude b coefficient = -2.59, 95% CI -3.09 to -1.95, $p < 0.001$). Upon sequentially incorporating additional variables associated with the pain score, the final model demonstrated that sufentanil administration was associated to a 2.45-point reduction in the mean pain score, with all other variables held constant (adjusted b coefficient = -2.45, 95% CI -3.01 to -1.90, $p < 0.001$) (Table 5). This final model exhibited a lower AIC

value of 473.34, indicating a strong fit of the model to the data. For the secondary outcome, mixed-effects analysis indicated no significant change in O_2 saturation following sufentanil administration. However, there were notable reductions in SBP by 11mmHg, DBP by 6 mmHg, and HR by 5 beats/min with all other variables held constant (Table 6).

DISCUSSION

We found that SST was an effective analgesic in the out-of-hospital environment as shown by the statistically significant reduction in the pain score in the paired sample t-test. The subsequent linear mixed model analysis, beginning with the crude model that focused on post-sufentanil time alone, confirmed a significant 2.6-point reduction, consistent with the paired sample t-test findings. Changes in vital signs shown above suggest that the medication was well tolerated and did not result in unsafe conditions. Changes in pain scale (decrease 2.6 ± 2.1), RR (decrease 1 ± 3), HR (decrease 4.2 ± 9.1), and SBP (decrease 11.1 ± 21.8), and DBP (decrease 6.1 ± 8.0) post-SST administration were all statistically significant, however only the changes in pain, HR, and SBP held clinical significance. These reductions in HR and SBP, although statistically significant and clinically relevant, were not significant enough to warrant increased monitoring or medical intervention from responders. The decrease in SBP and HR can be attributed to the physiological response to pain (8), as evidenced by the slightly elevated mean SBP (141.9 ± 26.8) and HR (85.0 ± 14.2) before SST administration, which normalized post-treatment. From statistical and clinical viewpoints, these reductions may further highlight the efficacy of SST as an analgesic. The decrease in SBP and HR can be attributed to the physiological response to pain, as indicated by the slightly elevated mean SBP (141.9 ± 26.8) and HR (85.0 ± 14.2) before SST administration, which normalized post-treatment. The reduction in DBP was only 6 mmHg, further supporting the assertion that the decreases in SBP and heart rate were likely physiological responses to pain reduction. From both statistical and clinical perspectives, these reductions underscore the efficacy of SST as an analgesic.

The administration of intravenous analgesia, such as morphine or fentanyl, requires obtaining intravenous access which can be difficult in any environment, let alone in the often cold and austere environments encountered by prehospital responders. Previous attempts to mitigate

prehospital analgesic delays have included the use of intranasal medication administration which, although efficient and effective (9), have been shown to result in inconsistent and unpredictable pharmacokinetics and dosing, with one study citing a 30% of between-subject variability (10). Inconsistent and unpredictable pharmacokinetics likely increase the potential for the well-known adverse effects of opiates, including respiratory depression, altered mental status, dizziness, nausea, and vomiting.

Opioids administered in IV boluses, while effective, come with various side effects including nausea, vomiting, gastrointestinal upset, and altered mental status. While the side effects of increased nausea and vomiting are certainly unpleasant in any situation, emesis in an austere environment could exacerbate an already dehydrated or hypothermic individual. While no studies to our knowledge have directly compared these side effects in a prehospital environment, inpatient postoperative studies have demonstrated a decreased rate of administration of antiemetic pharmacotherapy to curb GI side effects when SST is used compared with bolus IV opioid medication (11). If a patient in a remote environment becomes more altered, they cannot assist in their rescue could become a liability for SAR team safety. When compared to bolus IV opioids, the more steady, gradual onset and duration of action (12) of SST likely makes its administration preferable in prehospital environments where the monitoring capabilities are more limited and the complications of respiratory depression are more pronounced.

\Additionally, when compared to IV bolus administration, the longer duration of action of SST potentially allows for a decreased need to re-dose, aiding in the facilitation of the challenging technical rescues required by EMS and SAR responders over constant medication vigilance. The

ease of access, analgesic effectiveness, dosing predictability, and prolonged duration of action of SST have the potential to serve as beneficial attributes for prehospital medical responders.

While this study did not include the aforementioned adverse side effects as primary or secondary outcomes, no events of apnea were observed in the recorded respiratory rates, and vital signs were overall observed to statistically improve with no evidence of decompensation. Given this demonstrated safety with consideration for the benefits of SST as described above, based upon our retrospective chart review analysis that SST would serve a safe and beneficial role for prehospital analgesia.

Despite our determination of its safety and efficacy, certain considerations must be taken into account. First, the cost of SST may be up to or above $60 per dose (11) making it greater than that of IV morphine/dilaudid (13). However, the added cost of materials needed to start and maintain IV access for other analgesics may decrease this difference resulting in less of a barrier for use. SST may be unable to be administered due to facial trauma, so other analgesics must be available for these patients. Because sufentanil is more potent than fentanyl, responders should be educated on the expected time of onset, bioavailability, duration, side effects, and safety profile.

Other studies have examined the use of various opioid analgesics in the prehospital setting and have shown their efficacy (14). However, they do not address the challenges of dosing and administration in unconventional environments which is where we believe SST may have an advantage over other methods. Our study is different from other studies in that, to our knowledge, it is the first to assess the impact of SST on pain severity and vital signs in out-of-hospital clinical environments and targets a unique population contacted by SAR and EMS agencies.

LIMITATIONS

Study limitations include its retrospective design, which may have introduced selection bias or missing data. Additionally, because sublingual sufentanil is a relatively new drug and our study analyzed its use in a nonclassical environment, the study had a relatively small sample size and excluded patients under 18 years of age. Therefore, the study findings may not be generalizable to these populations. Furthermore, there may be other confounders not accounted for in the analysis such as inconsistencies in documentation. Analgesia administered in conjunction with SST was also a confounder. A prospective study with a larger sample size may be required to validate the results more robustly.

CONCLUSIONS

Our study demonstrated that SST administration led to a significant reduction in pain scores and exhibited a favorable safety profile regarding vital signs, including SBP, DBP, HR, RR, and O_2 saturation. These findings support the utilization of SST for pain management in the prehospital setting, particularly in austere environments where traditional routes of administration may be impractical.

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and agreement to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1: *Demographics (N=64)*

Variable	***Frequency (%)***
Age (mean ± SD)	*51.5 ± 18.5*
Gender	
Male	*30 (46.9%)*
Female	*33 (52.4%)*
Unknown	*01(1.6%%)*
Ethnicity	
White	*37 (57.8%)*
Hispanic/Latino	*07 (10.9%)*
Black American	*06 (09.4%)*
Unknown	*14 (21.9%)*
On home meds with analgesic effect	
No	*51 (79.7%)*
Yes	*13 (20.3%)*
Injury classification	
Musculoskeletal	*55 (85.9%)*
*Other**	*09 (14.1%)*
Meds given prior to sufentanil	
No medication	*44 (68.8%)*
Ondansetron	*13 (20.3%)*
Opioids/Analgesia	*07 (10.9%)*

**Others: Non-life-threatening injury including nervous system, internal organ, and genital injuries.*

Table 2: *Pre-existing medical conditions*

Pre-existing condition	***Frequency (%)***
None	*32 (50.0%)*
Orthopedic	*09 (14.1%)*
Cardiac	*10 (15.6%)*
Endocrine	*06 (09.4%)*
Other(s)	*07 (10.9%)*

Table 3: *Activities during which injury occurred*

Activity	***Frequency (%)***
Winter sports (skiing, snowboarding/snowmobiling)	*17 (26.6%)*
Walking or work injury	*16 (25.0%)*
Mountain biking	*8 (12.5%)*
Horseback riding	*11 (17.2%)*
Rafting/ATV	*06 (9.4%)*
Others	*06 (9.4%)*

Table 4: *Effect of sufentanil on pain scores and vital signs: paired sample t test*

Variable	***Pre-sufentanil Mean ± SD***	***Post-sufentanil Mean ± SD***	***Difference***	***P-value***
Pain Score	*8.0 ± 1.9*	*5.5 ± 2.5*	*2.6 ± 2.1*	*<0.001*
RR	*19 ± 5*	*18 ± 4*	*1 ± 3*	*0.006*
O_2 Saturation	*95.4 ± 3.0*	*95.9 ± 3.0*	*0.6 ± 2.4*	*0.063*
HR	*85.0± 14.2*	*79.8 ± 15.4*	*4.2 ± 9.1*	*0.004*
SBP	*141.9 ± 26.8*	*130.7 ± 28.5*	*11.1 ± 21.8*	*0.010*
DBP	*80.0 ±15.4*	*73.9 ± 14.7*	*6.1 ± 8.0*	*0.001*

Table 5: *Multivariable linear mixed model results for repeated pain score over time*

Variable	*beta coefficient*	*(95% C I)*	*P-value*
Post meds time (crude)	*-2.59*	*-3.09 – -1.95*	*<0.001*
Post meds time (adjusted)	*-2.45*	*-3.01 – -1.90*	*<0.001*
Age	*-0.02*	*-1.19 – 1.99*	*0.18*
Female sex	*1.06*	*-0.02 – 2.11*	*0.04*
Caucasian race/ethnicity	*1.308*	*0.25 – 2.37*	*0.02*
Home pain meds	*0.40*	*-1.19 – 1.99*	*0.61*
Injury classification deep	*0.46*	*-0.90 – 1.83*	*0.49*
Received analgesia prior to sufentanil	*0.65*	*-0.94 – 2.25*	*0.41*
Preexisting Orthopedic condition	*0.89*	*-1.32 – 3.09*	*0.42*
Preexisting cardiac disease	*-0.05*	*-2.41 – 2.32*	*0.97*

Table 6: *Multivariable linear mixed model results for repeated vital signs over time*

Variable	***beta coefficient***	***(95% C I)***	***P value***
Post-meds RR	*-1.00*	*-1.74 – -0.25*	*0.009*
Post-meds O2 Sat	*-0.59*	*-1.22 – 0.04*	*0.07*
Post-meds HR	*-5.02*	*-7.89 – -1.87*	*0.005*
Post-meds SBP	*-10.75*	*-16.90 – -4.60*	*0.001*
Post meds DBP	*-5.98*	*-8.1 – -3.97*	*0.001*

Adjusted for age, sex, ethnicity, home pain meds, analgesia prior to sufentanil, and preexisting condition.