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# Efficacy and Safety of Sublingual Sufentanil for the Management of Acute Pain

**Authors :** Neil Singla, Derek Muse, Karen DiDonato, Pamela Palmer

**Abstract :** Introduction: Pain is the most common reason people visit emergency rooms. Studies indicate however, that Emergency Department (ED) physicians often do not provide adequate analgesia to their patients as a result of gender and age bias, opiophobia and insufficient knowledge of and formal training in acute pain management. Novel classes of analgesics have recently been introduced, but many patients suffer from acute pain in settings where the availability of intravenous (IV) access may be limited, so there remains a clinical need for rapid-acting, potent analgesics that do not require an invasive route of delivery. A sublingual sufentanil tablet (SST), dispensed using a single-dose applicator, is in development for treatment of moderate-to-severe acute pain in a medically-supervised setting. Objective: The primary objective of this study was to demonstrate the repeat-dose efficacy, safety and tolerability of sufentanil 20 mcg and 30 mcg sublingual tablets compared to placebo for the management of acute pain as determined by the time-weighted sum of pain intensity differences (SPID) to baseline over the 12-hour study period (SPID12). Key secondary efficacy variables included SPID over the first hour (SPID1), Total pain relief over the 12-hour study period (TOTPAR12), time to perceived pain relief (PR) and time to meaningful PR. Safety variables consisted of adverse events (AE), vital signs, oxygen saturation and early termination. Methods: In this Phase 2, double-blind, dose-finding study, an equal number of male and female patients were randomly assigned in a 2:2:1 ratio to SST 20 mcg, SS 30 mcg or placebo, respectively, following bunionectomy. Study drug was dosed as needed, but not more frequently than hourly. Rescue medication was available as needed. The primary endpoint was the Summed Pain Intensity Difference to baseline over 12h (SPIDI2). Safety was assessed by continuous oxygen saturation monitoring and adverse event reporting. Results: 101 patients (51 Male/50 Female) were randomized, 100 received study treatment (intent-to-treat [ITT] population), and 91 completed the study. Reasons for early discontinuation were lack of efficacy (6), adverse events (2) and drug-dosing error (1). Mean age was 42.5 years. For the ITT population, SST 30 mcg was superior to placebo (p=0.003) for the SPID12. SPID12 scores in the active groups were superior for both male (ANOVA overall p-value =0.038) and female (ANOVA overall p-value=0.005) patients. Statistically significant differences in favour of sublingual sufentanil were also observed between the SST 30mcg and placebo group for SPID1(p<0.001), TOTPAR12(p=0.002), time to perceived PR (p=0.023) and time to meaningful PR (p=0.010). Nausea, vomiting and somnolence were more frequent in the sufentanil groups but there were no significant differences between treatment arms for the proportion of patients who prematurely terminated due to AE or inadequate analgesia. Conclusions: Sufentanil tablets dispensed sublingually using a single-dose applicator is in development for treatment of patients with moderate-to-severe acute pain in a medically-supervised setting where immediate IV access is limited. When administered sublingually, sufentanil's pharmacokinetic profile and non-invasive delivery makes it a useful alternative to IM or IV dosing.

**Keywords :** acute pain, pain management, sublingual, sufentanil
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