Original Article

Evolution of Patient-Controlled Analgesia: From Intravenous to Sublingual Treatment

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ABSTRACT

Opioid administration delivered intravenously (IV) by patient-controlled analgesia (PCA) devices has been an important development in addressing insufficient management of acute pain in the postsurgical setting. However, IV PCA has several disadvantages, including operator error, risk of patient exposure to analgesic gaps, IV line patency issues, and risk of catheter-related infection, all of which contribute to the total cost of care. Morphine, the most commonly used opioid in IV PCA, has a relatively slow onset of analgesia, which may leave patients with inadequate initial pain control and at risk of opioid dose-stacking.

Sufentanil is an opioid with no major active metabolites and a rapid onset of analgesia. The sufentanil sublingual tablet system (SSTS) with a 20-minute lockout and other safety features is a novel noninvasive PCA system in development for on-demand relief of moderate to severe acute pain in the hospital setting. Data from phase 3 trials of the use of SSTS after elective major open abdominal and orthopedic surgery show that analgesia is rapidly achieved, with a longer mean interdosing interval compared with IV PCA morphine (81 vs 47 minutes) and a high level of patient and nurse satisfaction. These data suggest that SSTS may also aid in the avoidance of some of the pitfalls inherent with IV PCA, which may help reduce hospital costs associated with IV PCA–related issues. This article describes the evolution, benefits, issues, and costs associated with IV PCA and reviews data from preclinical studies of sufentanil through SSTS phase 3 trials.

Key Words—opioid analgesics, patient-controlled analgesia, postoperative pain, safety, sublingual administration, sufentanil, treatment efficacy

Management of acute pain in the hospital setting continues to be a challenge for health care professionals. Novel analgesics, advances in drug administration systems, and an emphasis on regional anesthesia techniques and multimodal analgesia have all been a focus of in-hospital pain management over the last half century. Opioid-sparing techniques, including recently approved dosage forms of nonopioid analgesics, are appropriately gaining more widespread use as clinical and economic effects of opioid-related adverse events are becoming better understood. However, opioids remain an important part of the multimodal management of moderate to severe pain. This article will discuss the evolution of a commonly used method of administering opioids to hospitalized patients – intravenous patient-controlled analgesia (IV PCA) systems – and the choice of opioid, risks, and costs associated with IV PCA usage. Data from preclinical through phase 3 trials of a novel noninvasive approach to PCA will also be presented.

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INTRAVENOUS PCA

The development of PCA was initially prompted by reports of insufficient pain relief from conventional intramuscular delivery of opioids. Introduced almost 5 decades ago, PCA has become widely prescribed for pain management. The method of IV PCA for the delivery of opioids, which is now commonly used to treat acute pain in the postsurgical setting (approximately 20% of orthopedic and 29% of major abdominal surgeries), offers greater analgesic efficacy and potentially fewer adverse events than intermittent administration because of the ability of patients to titrate generally smaller on-demand doses according to their own needs compared with those administered by a nurse. Furthermore, studies have shown that patients given this degree of autonomy cited better pain relief and control of medication and expressed greater satisfaction with their hospital stay than with conventional treatment with nurse-administered drugs. PCA also benefits patients indirectly by alleviating the time demand on nurses, so they may focus on addressing the other needs of their patients.

Since the inception and initial use of PCA by Sechzer in 1968, devices for IV PCA have evolved to include greater ease in programming, more sophisticated programming (eg, the use of smart pump technology), data recording, security features, and better portability. Despite these advances, the use of IV PCA is associated with a number of challenges. The devices in current use have safeguards and the risk for errors is low (7% of all IV PCA–related events), but patients are still vulnerable to device and operator errors. Of the operator errors, 81% resulted from programming errors, almost half of which were associated with patient harm.

IV PCA is also associated with a risk of patient exposure to analgesic gaps from the malfunction or failure of the device, as well as IV line connection or patency issues. These problems deprive patients of opioids and leave them vulnerable to pain. Furthermore, the requirement of venous access increases the risk of catheter-related infection (eg, 7%-9% for phlebitis and 0.2%-0.4% for bacteremia) and imposes mobility constraints on patients.

IV PCA devices are associated with factors that put patients at an increased risk for errors. An analysis of US databases found that the annual overall cost of errors attributable to both IV PCA medications and the device itself is approximately $388 million in 2006 US dollars. Furthermore, data from the US Food and Drug Administration (FDA) indicated that various types of external programmable infusion pump technology, including pumps for IV PCA, were a growing concern. Between 2005 and 2009, approximately 56,000 adverse events related to all types of infusion pumps, not just PCA devices, were reported to the FDA. This prompted 87 pump model recalls, 70 of which were designated as class II and 17 as class I (class I is defined as having reasonable probability that the device will cause serious adverse health consequences or death). This led the FDA to issue an initiative for improving infusion pumps that deliver liquids (eg, nutrients or medications such as insulin, antibiotics, chemotherapeutic agents, and analgesics) to spur the development of safer devices.

Smart pumps have therefore been designed with additional safety features, such as a barcode scanner, a drug library, and a memory log. Since the implementation of these pumps, a study suggested that smart pump technology with IV PCA is associated with a reduction in some types of errors and associated costs, while another study reported a reduction in adverse events associated with PCA use when smart pumps were combined with the clinical decision support via computerized prescriber order entry technology. However, comparative studies are lacking; whereas smart pumps may mitigate some programming risks, outstanding safety issues associated with IV PCA include analgesic gaps due to tubing/catheter patency, infection, wrong drug or concentration, inadequate patient monitoring, and prescribing and programming (dose/concentration) errors related to dosing interval, rate, and limit.

Drugs typically used with IV PCA may not be ideally suited for patients who require quick relief from moderate to severe pain in the postsurgical setting. The most studied and commonly used drug with IV PCA in the United States is morphine; however, other drugs, such as hydromorphone and, to a lesser extent, fentanyl, are gaining in popularity. However, because a loading dose (an IV bolus of 2 to 4 times the typical on-demand PCA dose) is not always administered and the onset of analgesia with nonlipophilic opioids can be relatively slow, patients in pain who receive IV PCA opioids may not be adequately managed and may repeatedly dose with on-demand doses as well as request rescue analgesia. When the delayed summation of these peak central nervous system (CNS) opioid concentrations finally occurs (ie, dose-stacking), the pharmacodynamic effects can be deleterious. Issues surrounding operator error may be effectively addressed with additional training, but improvements regarding drug choice and the design...
of the PCA device are needed to circumvent problems related to opioid delivery and achievement of adequate analgesia.

CURRENT COSTS ASSOCIATED WITH IV PCA

The selection of an appropriate pain management regimen in the postsurgical hospital setting is driven primarily by the safety and efficacy of the agents and modalities. However, an important factor that clinicians and administrators must consider is the cost of these choices. Estimating the total cost of PCA is more complex than the pricing of an individual drug. Direct costs may include the cost of medication used in the device and for rescue analgesia, as well as the costs of equipment and ancillary supplies (ie, syringes, tubing, pumps, and saline). Indirect costs may include the costs of treating IV-related complications, IV PCA pump–related dosing errors, catheter-related infections, adverse events, and needle-stick injuries, as well as the labor associated with nursing care.\(^5,32\)

Hospital costs related to IV PCA following major surgery are thought to be substantial, but little information has been available to date. Results from a recent hospital database analysis and literature search estimated that patients using IV PCA incur an average of $196 to $243 in direct costs. In addition, up to $146 in indirect costs, averaged over all the patients treated, are related to IV PCA delivery of opioids for pain management 48 hours after major surgeries, such as total knee and total hip arthroplasty and open abdominal surgery.\(^5\) Indirect costs arising from complications and equipment errors are, therefore, approximately 38% to 43% of the total cost associated with IV PCA. For example, the overall average hospital cost per patient for bacteremia/phlebitis from an indwelling peripheral vascular catheter is $108.94.\(^5\) IV PCA dosing errors (device-related and medication) led to an additional overall cost of $35 on average per treated patient.\(^5,16,17,19\) In addition, adverse events resulting from the reduced ambulation associated with IV PCA contributed an average of $18.17 (deep vein thrombosis), $43.19 (pulmonary embolism), and $265.02 (postsurgical pneumonia) in costs.\(^5,32\) These indirect costs are harder to estimate, and it can be difficult to assign causality.

Overall, these data suggest that using IV PCA following major surgery may add substantial direct and indirect patient costs. With the development of preprogrammed, noninvasive PCA systems, the subset of costs that are directly related to programming errors and IV administration (including catheter-related infections) can be avoided.

NOVEL APPROACHES TO PCA

Given the advantages of patient-controlled delivery of analgesics, the development of PCA systems that can avoid some of the complicating factors associated with IV PCA would be an advantage in the treatment of moderate to severe acute pain in hospitalized patients. Several non-IV methods of opioid administration are under development.\(^23,33\) Oral PCA (eg, on-demand bedside dispensing of opioid tablets, such as hydromorphone or oxycodone) lacks rapid titratability due to slow and erratic gastrointestinal drug absorption.\(^23,33\) Other on-demand methods either currently approved, investigated in the past, or in development include electrical current-driven (ie, iontophoretic) transdermal delivery of fentanyl, intranasal delivery of morphine and sufentanil, and delivery of morphine and fentanyl by inhalation.\(^23,33\)

The focus of the remainder of this article is on the development of a novel sublingual PCA system, as a considerable amount of recent clinical data exists on this product. The use of an optimized opioid analgesic together with a delivery system and a route of administration that overcome the disadvantages of IV PCA have led to the development of the sufentanil sublingual tablet system (SSTS; AcelRx Pharmaceuticals, Redwood City, CA), currently under review by the FDA. This system pairs a hand-held PCA device with very small sufentanil tablets that were designed to maximize sublingual transmucosal drug uptake by minimizing the natural salivary response to larger tablets. This serves to reduce the amount of drug that is solubilized in saliva and inadvertently swallowed, providing greater bioavailability and more consistent pharmacokinetics by diminishing the first-pass effect. The device, which is assembled at the patient’s bedside, is preprogrammed with a 20-minute lockout interval and is designed to allow single-patient access via a radio-frequency identification (RFID) adhesive tag on the thumb of the patient. The opioid, dose, and lockout interval are all preprogrammed (ie, fixed) and unalterable by health care professionals and patients so as to avoid medication prescribing, programming, and dosing errors.

Prevention of Drug Abuse and Diversion

Drug abuse and diversion are major concerns with opioids.\(^34\) The SSTS (Figures 1 and 2) was therefore designed with a number of security features. The prefilled drug cartridge, which contains 40 sufentanil tablets at a dose of 15 µg, should be accessed from locked storage; upon setup, it is
Locking to the hand-held controller. The SSTS system is then locked via a security tether to the bed rail or other secure location; an alarm on the device sounds if tampering occurs with either of these locking mechanisms. The controller and cartridge both contain RFID technology to track tablet count, aid in drug usage accountability, and allow reconciliation by pharmacy staff. The cartridge also contains a tamper-evident priming cap as a means to minimize drug diversion prior to system setup and to allow the system to detect the unauthorized re-use of a used cartridge. A unique patient RFID thumb tag minimizes proxy dosing or other means of misuse and/or abuse. The drug cartridge is packaged separately and should be in locked medication storage prior to system setup. Individuals disposing of the drug cartridge should follow standard hospital guidelines regarding drug wastage of controlled substances. Monitoring to ensure compliance with dispensing, as well as administration and waste documentation, will be needed to establish the effectiveness of these safety measures in the real-world setting.

**Opioid Preclinical Data**

Preclinical studies examining the potential toxicity of commonly used opioids for pain management have included evaluation of the therapeutic index, a parameter that may be reflective of the margin of safety of a drug. The term therapeutic index is defined as the ratio of 50% of the lethal dose to 50% of the effective dose. Sufentanil, for example, has a substantially wider therapeutic index than other opioids that may be prescribed for acute pain in the postsurgical setting (ie, 26,716 for sufentanil vs 71 for morphine) (Table 1). Small clinical studies have provided evidence that sufentanil may have less respiratory depressive effects compared with other opioids; however, no data exist from large-scale studies that demonstrate that differences in the therapeutic index between these opioids clinically impact human safety.39
Figure 2. Sufentanil sublingual tablet system (SSTS) components. Disposable components include: (1) Dispenser: inserted into the Controller and locked into place; (2) Cap: protects the Dispenser tip between dosing and must be removed prior to any administration attempt; (3) Drug Cartridge: inserted into the SSTS dispenser at point-of-use; contains a green tamper-evident priming cap and 40 sufentanil 15-μg tablets and radio-frequency identification (RFID); tracks utilization. [Not shown] Patient ID Thumb Tag: contains the RFID; co-located to the Controller during set-up; limits use to intended patient. Reusable components include: (4) Controller: handheld, rechargeable; contains all electronics and software (includes dose history; indicator lights for dosing, errors, and lockout audio tones, etc); (5) Authorized Access Card (AAC): contains an RFID tag allowing the health care professional to securely interact with SSTS; activate and set up SSTS by touching the AAC to the blue Dose Button on the Controller; (6) Security Tether: secures SSTS to an appropriate fixed fixture (such as the bedrail) to prevent unauthorized removal. [Not shown] Holster: clamps to patient bedside rail or wheelchair to hold SSTS when not in use. Reprinted with permission from Minkowitz HS. A review of sufentanil and the sufentanil sublingual tablet system for acute moderate to severe pain. Pain Manag. 2015;5(4):237-250. Copyright © Future Medicine Ltd.
Table 1. Therapeutic index and clinical pharmacological parameters of commonly used parenteral opioids for postsurgical pain management

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Therapeutic index&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Plasma:CNS equilibrium half-life&lt;sup&gt;b&lt;/sup&gt; (&lt;i&gt;t&lt;sub&gt;1/2&lt;/sub&gt;k&lt;sub&gt;e0&lt;/sub&gt;&lt;/i&gt;)&lt;sup&gt;b&lt;/sup&gt;, min</th>
<th>Active metabolite&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Metabolic pathway</th>
<th>Analgesic activity&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>277&lt;sup&gt;39&lt;/sup&gt;</td>
<td>6.6&lt;sup&gt;54&lt;/sup&gt;</td>
<td>None</td>
<td>CYP 3A4</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>232&lt;sup&gt;70,71&lt;/sup&gt;</td>
<td>46&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Hydromorphone-3-glucuronide</td>
<td>UGTB27</td>
<td>No</td>
<td>Nausea&lt;sup&gt;72,73&lt;/sup&gt;; neuroexcitation&lt;sup&gt;43,44,73&lt;/sup&gt;; cognitive impairment&lt;sup&gt;53&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hydromorphone-6-glucuronide</td>
<td>UGT1A3</td>
<td>Yes</td>
<td>Prolonged duration of analgesic effects&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Morphine</td>
<td>71&lt;sup&gt;39&lt;/sup&gt;</td>
<td>168&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Morphine-3-glucuronide</td>
<td>UGTB27</td>
<td>No</td>
<td>Nausea&lt;sup&gt;52&lt;/sup&gt;; cognitive impairment&lt;sup&gt;52&lt;/sup&gt;; neuroexcitation&lt;sup&gt;43,44&lt;/sup&gt;; dysphoria&lt;sup&gt;42,45,46&lt;/sup&gt;; agitation&lt;sup&gt;42,45,46&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Morphine-6-glucuronide</td>
<td></td>
<td>Yes</td>
<td>Cognitive impairment&lt;sup&gt;52&lt;/sup&gt;; prolonged duration of analgesic effects&lt;sup&gt;43,44,46&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>26,716&lt;sup&gt;179&lt;/sup&gt;</td>
<td>6.2&lt;sup&gt;54&lt;/sup&gt;</td>
<td>None</td>
<td>CYP 3A4</td>
<td>No</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note: CNS = central nervous system; CYP = cytochrome P450; NA = not applicable; <i>t<sub>1/2</sub>k<sub>e0</sub></i> = plasma:CNS equilibration half-life.

<sup>a</sup>The therapeutic index is calculated as the lethal dose [LD<sub>50</sub>] / effective dose [ED<sub>50</sub>]).

<sup>b</sup>Prolonged duration of analgesic effects, particularly in patients with renal insufficiency.

<sup>c</sup>The active metabolite is determined by the metabolic pathway indicated.

<sup>d</sup>Cognitive impairment: confusion, disorientation, memory loss, forgetfulness, hallucinations, and disorientation.
**OPIOID CLINICAL PHARMACOLOGY DATA**

**Active Metabolites**

Opioids are biotransformed by various mechanisms into molecules that are ultimately renally excreted. Opioids that undergo hepatic metabolism are modified by enzymes catalyzing phase 1 cytochrome P450–mediated and/or phase 2 conjugation reactions to produce active and inactive metabolites (see Table 1). The rate at which opioids are metabolized and eliminated impacts the duration of action and the adverse event profile of the drug. Disruption of these processes leads to variability in the pharmacokinetics and pharmacodynamics of opioids and/or their metabolites. Specifically, organ impairment has important implications for the selection of opioids, particularly for opioids that produce active metabolites, which can elicit prolonged analgesic effects and adverse events, such as confusion, respiratory depression, dysphoria, and neuroexcitation (see Table 1). Glucuronide metabolites from morphine (morphine-6-glucuronide [M6G] and morphine-3-glucuronide [M3G]) and hydromorphone (hydromorphone-3-glucuronide [H3G]), for example, may accumulate to a greater degree than the parent drug in patients with renal impairment and induce adverse events. M6G, a μ-opioid agonist with different pharmacokinetic properties than morphine, has been implicated in causing cognitive impairment and prolonged sedation, particularly in patients with renal insufficiency. Although M3G and H3G do not have μ-opioid receptor activity, accumulation is thought to cause hyperexcitability. Sufentanil and fentanyl are not known to have any major active metabolites.

**Pharmacodynamics**

An important parameter in opioid PCA use is the time of analgesic onset, which occurs when the drug reaches the CNS. Given the typical short lockout times (6-10 minutes) for IV PCA, the slow onset of action of some opioids can easily result in the patient dosing excessively in an attempt to remedy the initial lack of analgesia. For opioids, the measurement of the equilibration half-life between the plasma and the CNS (referred to as the $t_{1/2 \cdot k_{eq}}$) is most reflective of the pharmacodynamics of analgesic onset (see Table 1). The long $t_{1/2 \cdot k_{eq}}$ associated with some hydrophilic opioids (ie, 3 hours for morphine and 46 minutes for hydromorphone) may leave patients with insufficient initial analgesia, which can lead to dose-stacking and a concomitant increase in the risk of late-occurring adverse events, such as respiratory depression. Furthermore, some adverse events may also be the result of the active metabolite of opioids, such as M6G, which is a major active metabolite of morphine with a $t_{1/2 \cdot k_{eq}}$ of 384 minutes. Comparatively, fentanyl and sufentanil, which are highly lipophilic opioids, have a short $t_{1/2 \cdot k_{eq}}$ of 6.6 and 6.2 minutes, respectively, which allows patients to achieve effective analgesia in a much shorter time.

In addition to onset, the titratability of a PCA opioid requires the consistent and predictable offset of effect. While the elimination half-life of a drug can be used as a rough measure of drug offset, this parameter is actually a measure of the time for 50% of the drug to be eliminated from the body. For lipophilic drugs, plasma concentrations can be rapidly reduced owing not to elimination but rather to distribution into lipid depots. Therefore, a parameter that is more reflective of opioid offset than the elimination half-life and thus a more appropriate measurement is the plasma half-time, which is the time required for the drug plasma concentration to drop from the maximum concentration ($C_{max}$) to 50% of $C_{max}$. This measurement is valid for the period up to the next dose, since new drug administration will affect the plasma concentration decay curve. A long plasma half-time can expose patients to prolonged drug effects and reduce the titratable nature of the PCA system, which is ultimately an issue of safety. As an example, in multicompartment modeling, when an infusion of fentanyl is administered for durations longer than 4 hours, large increases in its plasma half-time (from approximately 180 minutes following termination of a 4-hour infusion to 290 minutes following termination of an 8-hour infusion) may occur; in contrast, the plasma half-time of sufentanil is minimally prolonged even during infusion durations of 8 hours (plasma half-time of 30 minutes at 4 hours and 45 minutes at 8 hours).

As discussed, the lipophilic characteristics of fentanyl and sufentanil result not only in the rapid onset of action but also, unfortunately, in its rapid distribution (ie, short alpha half-life) following IV administration. While the achievement of adequate analgesia can occur rapidly, the distribution out of the plasma is also rapid and the plasma half-time following IV administration is short, thereby resulting in a short duration of drug action when administered IV. Patients, therefore, may need to dose themselves very frequently to maintain analgesia. To circumvent this for sufentanil, an alternative mode of administration (sublingual)
has been developed to strike a balance between the excessively short plasma half-time of IV sufentanil and the prolonged plasma half-time of other opioids. The sublingual tablet formulation of sufentanil optimally modifies the pharmacokinetic properties of sufentanil for the use of PCA and allows for a noninvasive route of delivery.\textsuperscript{56,57}

**Sufentanil Plasma Half-time: IV vs Sublingual Administration**

Data from a phase 1 study in healthy subjects showed that the plasma half-time of sufentanil was extended from a median of 6 minutes with IV administration to a median of 150 minutes with sublingual administration.\textsuperscript{57} This 25-fold extension of plasma half-time should overcome the short duration of action observed with IV sufentanil administration. Data from phase 1 studies on repeat dosing, in which healthy subjects were dosed every 20 minutes, also showed that the peak plasma level was achieved at a mean time of 25 minutes\textsuperscript{(56)} (median time of 20 minutes)\textsuperscript{57} after the previous dose. This suggests the potential for safe and reliable redosing with a 20-minute lockout interval, which was the minimal redosing frequency allowed in the phase 2 dose-finding studies that will be discussed in the following paragraphs, as well as the phase 3 pivotal efficacy and safety studies.

**PHASE 2 STUDIES: SUBLINGUAL SUFENTANIL TABLETS FOR POSTSURGICAL PAIN**

The efficacy and safety of sublingual sufentanil tablets (5-15 µg) for the management of moderate to severe postsurgical pain following elective knee replacement ($N = 101$) or open abdominal surgery ($N = 94$) was evaluated in two phase 2, double-blind, randomized, placebo-controlled, studies.\textsuperscript{56} These early phase 2 studies on dose finding did not employ the SSTSs system, but sufentanil tablets were administered with forceps by research staff directly onto patients’ sublingual space with a minimum of 20 minutes between doses. The 5-µg dose was not evaluated in the study of open abdominal surgery because of the relatively high rate of dropout due to inadequate analgesia (54%) found at this dose in the knee replacement study (Table 2). Placebo tablets were nonactive, but supplemental analgesia (IV morphine) was allowed within 30 minutes following administration of the first dose of the study drug. Patients requiring additional rescue analgesia were discontinued from the study and administered standard postoperative analgesics.

Efficacy evaluations included measurements of pain intensity (primary efficacy variable) and pain relief. Pain intensity was expressed as the summed pain intensity difference (SPID) compared with baseline over the 12-hour treatment period (SPID-12).

### Table 2. Phase 2 studies: Efficacy of sublingual sufentanil tablets for postsurgical pain following elective knee replacement or open abdominal surgery

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Knee replacement surgery</th>
<th>Open abdominal surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sufentanil dose</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>5 µg ($n=24$)</td>
<td>10 µg ($n=25$)</td>
</tr>
<tr>
<td>Pain intensity (ITT), LS mean (SEM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6 (0.3)</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>SPID-12, LOCF</td>
<td>3 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Pain relief</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to inadequate analgesia, $n$ (%)</td>
<td>13 (54)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Total pain relief over 12 hours, LS mean (SEM)</td>
<td>17 (2)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>“Poor” pain relief, $d, n$ (%)</td>
<td>8 (33)</td>
<td>10 (40)</td>
</tr>
</tbody>
</table>

*Note: Shaded areas represent significance compared with placebo.\textsuperscript{b} ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SEM = standard error of the LS mean; SPID-12 = summed pain intensity difference compared with baseline over the 12-hour treatment period.\textsuperscript{d} $P < .05$ compared with placebo.\textsuperscript{e} $P < .001$ compared with placebo. In an open-label study of sublingual sufentanil 15 µg (delivered using a handheld dispensing device) following total knee replacement surgery ($N = 30$), 7% of patients discontinued due to inadequate analgesia.\textsuperscript{51} Patients responded “poor” in an evaluation of pain relief (global score).\textsuperscript{f} $P = .05$ compared with placebo.\textsuperscript{g} $P < .01$ compared with placebo.
Higher SPID-12 scores indicate lower pain intensity (ie, larger decreases from baseline). Patients graded the intensity of their pain on a scale of 0 to 10, with 0 indicating “no pain” and 10 indicating “the worst possible pain.” Discontinuation as a result of inadequate analgesia, total pain relief over 12 hours, and global evaluation of pain relief (measured at the end of the study) were also assessed.

**Efficacy**

For the primary efficacy measure (SPID-12), sublingual sufentanil 15 µg for knee replacement surgery ($P < .05$) and sublingual sufentanil 10 µg and 15 µg for open-abdominal surgery ($P < .001$) were superior to placebo in reducing pain intensity in patients over a 12-hour period (see Table 2).

In both studies, discontinuation due to inadequate analgesia was dose-related (see Table 2). Compared with placebo, there were significantly fewer discontinuations in the 15-µg group following knee replacement and in the 10-µg and 15-µg groups following open abdominal surgery ($P < .001$, for each). Total pain relief scores over 12 hours were numerically higher (ie, greater pain relief) with all active doses compared with placebo; however, these differences were only significant for patients in the open abdominal surgery study ($P < .001$) (see Table 2). “Poor” pain relief (a global evaluation) was reported by significantly more patients treated with placebo than with the 15 µg (knee replacement, $P < .05$; open abdominal surgery, $P < .001$) and 10 µg (open abdominal surgery, $P < .01$) doses of sublingual sufentanil (see Table 2).

**Safety**

All doses of sufentanil across both phase 2 studies were well tolerated. The incidence of adverse events was similar between active and placebo groups, with the exception of pruritus, which was higher with all doses of sufentanil. Across all sufentanil doses, the most frequently reported adverse events considered related to study drug (events occurring in ≥5% of patients in any treatment arm) compared with placebo, respectively, were nausea (37% vs 32%), pruritus (9% vs 0%), vomiting (9% vs 6%), and dizziness (5% vs 2%).

Overall, data from the phase 2 dose-finding studies demonstrated that 15 µg of sufentanil, administered as a sublingual tablet for the management of postsurgical pain, was the optimal dose and resulted in effective analgesia and an adverse event profile similar to lower dose strengths. These results suggest that sublingual sufentanil might be a useful alternative to IV-administered opioids if they are dispensed from a secure, handheld PCA device at the bedside of patients. Therefore, phase 3 studies were initiated to further assess the safety and efficacy of the 15-µg dose administered by patients using the SSTS device with a 20-minute lockout interval.

**PHASE 3 STUDIES: SSTS FOR THE TREATMENT OF POSTSURGICAL PAIN**

Three phase 3 studies were conducted to evaluate the efficacy, safety, and ease of care (EOC) of SSTS compared with either IV PCA morphine sulfate or placebo for moderate to severe pain following elective open abdominal or orthopedic (knee or hip replacement) surgery (Table 3).

**SSTS vs IV PCA Morphine Sulfate**

An open-label, 48-hour (with optional extension to 72 hours) noninferiority study compared SSTS with IV PCA morphine sulfate (1 mg with a 6-minute lockout interval) in patients following elective major open abdominal or orthopedic (hip or knee replacement) surgery. The primary outcome measure was the patient global assessment (PGA) of the method of pain control at the 48-hour time point (PGA-48; 1 = poor, 2 = fair, 3 = good, and 4 = excellent); success was defined as patients responding “good” or “excellent.” Secondary endpoints included PGA at 24 and 72 hours, as well as health care professional global assessment of method of pain control (HPGA) at these time points. Validated patient and nurse EOC questionnaires were completed to assess the ease of use of both PCA systems.$^{59,60}$

**Efficacy**

For the primary efficacy endpoint, noninferiority was demonstrated: more patients achieved PGA-48 “success” with SSTS compared with IV PCA morphine (79% vs 66%; $P < .001$). A secondary analysis of the primary endpoint demonstrated statistical superiority for treatment effect ($P = .007$). Onset of analgesia was faster and interdosing intervals were longer with SSTS compared with IV PCA morphine. Patients in the SSTS group had faster onset of pain reduction based on significantly greater pain intensity differences compared with baseline at 1, 2, and 4 hours ($P < .01$) (Figure 3). On average, patients in the IV PCA morphine and SSTS groups required 7 hours and 1.3 hours (5.4-fold difference), respectively, to obtain a mean pain...
Table 3. Design of phase 3 studies: Efficacy of sufentanil sublingual tablet system (SSTS) versus intravenous patient-controlled analgesia (IV PCA) morphine sulfate or placebo for postsurgical pain following elective major open abdominal or orthopedic surgery

<table>
<thead>
<tr>
<th>Study parameter</th>
<th>Study 1&lt;sup&gt;st&lt;/sup&gt;  (N=359)</th>
<th>Study 2&lt;sup&gt;nd&lt;/sup&gt;  (N=178)</th>
<th>Study 3&lt;sup&gt;rd&lt;/sup&gt;  (N=426)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active and comparator arm</td>
<td>SSTS (n=178)</td>
<td>SSTS (n=119)</td>
<td>SSTS (n=321)</td>
</tr>
<tr>
<td></td>
<td>IV PCA MS&lt;sup&gt;a&lt;/sup&gt; (n=181)</td>
<td>Placebo&lt;sup&gt;b&lt;/sup&gt; (n=59)</td>
<td>Placebo&lt;sup&gt;b&lt;/sup&gt; (n=105)</td>
</tr>
<tr>
<td>Elective major surgery type</td>
<td>Open abdominal or knee replacement or hip replacement</td>
<td>Open abdominal</td>
<td>Knee replacement or hip replacement</td>
</tr>
<tr>
<td>Study type</td>
<td>Prospective, randomized, open-label, noninferiority</td>
<td>Prospective, randomized, double-blind</td>
<td>Prospective, randomized, double-blind</td>
</tr>
<tr>
<td>Primary efficacy endpoint</td>
<td>PGA-48 (success defined as patients responding “good” or “excellent”)</td>
<td>SPID-48</td>
<td>SPID-48</td>
</tr>
<tr>
<td>Key secondary efficacy endpoints</td>
<td>PGA and HPGA at 24 and 72 hours; patient/nurse ease of care</td>
<td>SPID-24 and -72; total pain relief; PGA and HPGA at 24, 48, and 72 hours; patient/nurse ease of care</td>
<td>SPID-24 and -72; total pain relief; PGA and HPGA at 24, 48, and 72 hours; patient/nurse ease of care; nurse ease of care by IV PCA experience</td>
</tr>
<tr>
<td>Safety variables (monitoring)</td>
<td>Spontaneously reported AEs; vital signs; oxygen saturation; sedation (RASS); concomitant medications</td>
<td>AEs; vital signs; oxygen saturation (continuous monitoring); vital signs; concomitant medications</td>
<td>AEs; vital signs; oxygen saturation (continuous monitoring); vital signs; concomitant medications</td>
</tr>
<tr>
<td><strong>Clinicaltrials.gov identifier</strong></td>
<td>NCT01539538</td>
<td>NCT01539642</td>
<td>NCT01660763</td>
</tr>
</tbody>
</table>

Note: AE = adverse event; HPGA = health care professional global assessment of method of pain control at 24 hours (HPGA-24), 48 hours (HPGA-48), and 72 hours (HPGA-72); IV = intravenous; MS = morphine sulfate; PGA = patient global assessment of the method of pain control at 24 hours (PGA-24), 48 hours (PGA-48), and 72 hours (PGA-72); RASS = Richmond Agitation-Sedation Scale; SPID = summed pain intensity difference between each evaluation time point and baseline over 24 hours (SPID-24), 48 hours (SPID-48), and 72 hours (SPID-72).<sup>a</sup>IV PCA MS 1 mg with a 6-minute lockout interval = IV PCA MS.<sup>b</sup>Placebo = rescue morphine.

Intensity difference of 1.3 points (validated as the minimum clinically significant difference in acute pain, on a scale of 1 to 10).<sup>61,62</sup> Patients in the SSTS group also had longer time periods before needing to re-dose; the mean interdosing intervals throughout the study were 81 minutes for SSTS and 47 minutes for IV PCA morphine, a 58% difference ($P < .001$). A single SSTS cartridge provided a median of 48 hours of use. Overall, pain intensity scores were not significantly different between SSTS and IV PCA morphine at 24 hours (SPID-24), 48 hours (SPID-48), and 72 hours (SPID-72); however, total pain relief (TOTPAR) was significantly better at 24 hours (TOTPAR-24; $P = .031$) and 72 hours (TOTPAR-72; $P = .024$), but not at 48 hours (TOTPAR-48; $P = .055$), for patients treated with SSTS compared with IV PCA morphine.

Data from the EOC questionnaires show that EOC and overall satisfaction (rated on a scale from 0 to 5) were significantly higher (better) with SSTS than with IV PCA morphine for both patients and nurses (Table 4). The patient EOC total score consisted of 6 subscales: confidence with device, comfort with device, ease of movement, dosing confidence, pain control, and knowledge and understanding of device. The nurse EOC total score consisted of 2 subscales: a “bothersome” scale and a “time-consuming” scale.

**Safety**

Over the course of the study, adverse events were typical to what is observed when opioids are administered following surgery and were similar between the 2 groups. However, significantly fewer patients in the group receiving SSTS compared with those receiving IV PCA morphine experienced oxygen desaturation less than 95% ($P = .028$) (Figure 4).

Overall, results from this phase 3 study demonstrate that patients using SSTS achieved faster onset of analgesia and took a longer time to re-dose compared with patients using IV PCA morphine. Furthermore, both patients and nurses indicated better satisfaction with SSTS on most measures of the EOC questionnaires.
Sublingual Patient-Controlled Analgesia


Table 4. Phase 3 study: Patient and nurse ease of care and satisfaction with sufentanil sublingual tablet system (SSTS) or intravenous patient-controlled analgesia morphine sulfate (IV PCA MS) for postsurgical pain following elective major open abdominal or orthopedic surgery.

<table>
<thead>
<tr>
<th>Score, mean (SD)</th>
<th>SSTS</th>
<th>IV PCA MS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient EOC questionnaire</td>
<td>n=177</td>
<td>n=180</td>
<td></td>
</tr>
<tr>
<td>EOC total</td>
<td>4.45 (0.51)</td>
<td>4.07 (0.66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Overall satisfaction</td>
<td>4.15 (0.99)</td>
<td>3.84 (1.01)</td>
<td>.004</td>
</tr>
<tr>
<td>Nurse EOC questionnaire</td>
<td>n=44</td>
<td>n=43</td>
<td></td>
</tr>
<tr>
<td>EOC total</td>
<td>4.27 (0.58)</td>
<td>3.82 (0.84)</td>
<td>.017</td>
</tr>
<tr>
<td>Overall satisfaction</td>
<td>3.92 (0.65)</td>
<td>3.35 (0.57)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: EOC = ease of care.


SSTS vs placebo (with rescue morphine)63,64

Two phase 3 pivotal studies compared SSTS with placebo in patients after either elective open abdominal or orthopedic (knee or hip replacement) surgery (see Table 3). For blinding purposes, placebo was administered in the same SSTS device that was used to deliver sufentanil tablets. In both studies, a nurse-administered 2 mg IV morphine bolus, no more frequently than once an hour, was allowed to manage pain not adequately treated by study drug. For each dose of rescue morphine, pre-rescue pain scores were imputed for the next hour to avoid

the analgesic effect of the rescue IV morphine from affecting primary and secondary endpoints.

Efficacy

Following either open abdominal or major orthopedic surgery, respectively, pain intensity scores were significantly improved with SSTS versus placebo at the 48-hour primary endpoint (SPID-48; P = .001 and P < .001) and also at 24 hours (SPID-24; P < .001 and P < .001) and 72 hours (SPID-72; P = .004 and P < .001) [data on file, AcelRx]. A subgroup analysis of SPID-48 in patients in the orthopedic study significantly favored SSTS compared with placebo for all subgroups (by sex, age, body mass index, and type of surgery) (P < .001). Furthermore, the least-squares mean interdosing interval was also significantly longer with SSTS than with placebo for patients in both studies (open abdominal surgery: 100 vs 79 minutes, P < .05; orthopedic surgery: 84 minutes vs 58 minutes, P < .001) [data on file, AcelRx].

In both phase 3 studies, a higher proportion of patients in the placebo group compared with the SSTS group discontinued the study before 48 hours owing to inadequate analgesia (open abdominal surgery: 32% vs 17%, P = .035; orthopedic surgery: 48% vs 14%; P < .001). In addition, following open abdominal surgery, IV morphine for inadequate analgesia was requested by a significantly higher proportion of patients in the placebo group than in the SSTS group (67% vs 33%; P < .001). Similarly, after orthopedic surgery, a higher proportion of patients in the placebo group (73%) than in the SSTS group (51%) required at least 1 dose of IV morphine within 48 hours (P < .001). In both studies, later use of the first IV morphine dose was observed with SSTS compared with placebo (P < .001). Furthermore, patients in the SSTS group used significantly fewer mean rescue IV morphine doses of 2 mg each than did those in the placebo group at 24 hours (open abdominal surgery: 0.7 vs 2.0 doses, P < .001; orthopedic surgery: 1.1 vs 2.4 doses, P < .001) and 48 hours (open abdominal surgery: 1.0 vs 2.6 doses, P = .001; orthopedic surgery: 1.5 vs 3.0 doses, P < .001) [data on file, AcelRx].
For the patient and nurse EOC questionnaires, scores in both studies showed similar high marks (>4 of 5) for the total EOC score in both treatment groups; this was not unexpected since most questions related to ease of use of the device and the system was the same for both treatment groups.

**Safety**

The incidence of treatment-emergent adverse events in the open abdominal surgery study was not significantly different between study groups (64% with SSTS vs 67% with placebo), with the exception of pruritus (9% with SSTS vs 0% with placebo; \( P = .017 \), all considered to be mild) [data on file, AcelRx], which is a frequently observed opioid-related adverse event.\(^4\) In the orthopedic surgery study, a higher proportion of patients in the SSTS than in the placebo group had at least 1 adverse event related to study drug (54% vs 34%; \( P < .001 \)); however, all events were considered to be mild or moderate in severity. In both of these studies, there were no statistically significant differences between treatment groups for mean oxygen saturation values throughout the study.

Overall results from these phase 3 studies suggest that SSTS is effective for the management of postsurgical pain in patients who are undergoing open abdominal or orthopedic surgery. Favorable results from the EOC questionnaires further suggest that SSTS is user-friendly for both patients and nurses. No unexpected safety signals were observed in either of these placebo-controlled studies.

**DISCUSSION**

Opioids continue to be the most commonly used drug class for managing pain in postsurgical patients. While their analgesic effects are well known, information is becoming available on the clinical and economic impact of adverse events associated with commonly used opioids. In fact, a recent study revealed that gastrointestinal surgical patients (eg, laparoscopic cholecystectomy, laparoscopic gastric bypass, and open colectomy) receiving currently prescribed opioids who have multiple risk factors for opioid-related respiratory, gastrointestinal, or genitourinary adverse events have increases in total hospital costs, length of hospital stays, and 30-day readmission rates relative to those with fewer risk factors.\(^6\) Strategies are needed to reduce the development of adverse events from opioids, particularly in patients at high risk.

Moreover, the 2014 report of the most recent results of a survey conducted by the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) showed that patients rated US hospitals an average score of 71 out of 100 in the category of pain management, indicating that there is room for improvement.\(^5\) Although analgesic efficacy is not the sole indicator of satisfaction with pain management HCAHPS scores, there are cost implications associated with lower scores whereby institutions receive a lower reimbursement.\(^6\) There is, therefore, a clear need for an alternative analgesic system in the hospital setting that can provide effective analgesia while minimizing errors and adverse effects and that is also relatively easy to use and provides a high degree of satisfaction to both the patient and the health care provider.

The wide therapeutic index, lack of active metabolites, optimal route of administration, and rapid onset of analgesia that characterize sublingual sufentanil make it an attractive candidate as an alternative to IV PCA morphine or hydromorphone. In the phase 3 studies of SSTS, significantly fewer patients experienced oxygen desaturation less than 95% compared with IV PCA morphine.\(^58\) Sufentanil also has no active major metabolites. In comparison, major metabolites of morphine (morphine-6-glucuronide, in particular) can accumulate in patients with renal impairment, with an increased risk of prolonged duration of action and possible concomitant adverse events.\(^67-69\)

Limitations to the use of SSTS include the requirement that patients should be assessed for impaired cognitive ability or manual dexterity as they may not be able to understand or manage the device properly. Further, SSTS should be used with caution in patients with severe impaired hepatic or renal function, due to the importance of these organs in the metabolism and excretion of sufentanil. SSTS should also be used in caution in patients with bradyarrhythmias or hypovolemia and in patients who may be particularly susceptible to the intracranial effects of \( CO_2 \) retention. Concomitant use of other CNS depressants may produce additive depressant effects.

However, in the phase 2 and phase 3 trials of sublingual sufentanil, delivered with or without the handheld PCA device, there were no unexpected safety signals with sufentanil 15 µg.\(^56,58,63,64\) Further, in the phase 3 study that compared SSTS with IV PCA morphine, onset of analgesia was faster, and interdosing intervals were longer, with SSTS.\(^58\) This earlier onset of analgesia may be related to the faster entry of sufentanil into the CNS effect site.
In the phase 3 SSTS studies, the patient and nurse satisfaction ratings, as well as the EOC assessments for SSTS setup and use, indicated a high level of patient and nurse satisfaction with SSTS, suggesting that there are greater benefits with SSTS over IV PCA morphine.

CONCLUSIONS

The methods of providing PCA, with the goal of improving the management of postsurgical pain, continue to evolve. Although a multimodal approach to pain management relies on nonopioid analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs, local anesthetic, gabapentinoids), opioid rescue for breakthrough pain following surgery is usually necessary (at least for the first 24 to 72 hours). Data from clinical studies indicate that SSTS is an effective, noninvasive, patient-controlled system for the management of moderate to severe acute pain in the hospital setting. SSTS provides rapid onset of analgesia and a high level of patient and nurse satisfaction, and its use may also help avoid some of the pitfalls inherent with current IV PCA systems.

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