Analgesic Efficacy of Inhaled Morphine in Patients after Bunionectomy Surgery


Background: The AERx® Pain Management System (Aradigm Corporation, Hayward, CA) is a novel pulmonary delivery system for the systemic administration of morphine. The authors compared the relative analgesic efficacy and safety of the AERx® Pain Management System with those of placebo and intravenous morphine in an orthopedic postsurgical pain model.

Methods: Eighty-nine male and female PS-1 to PS-3 patients underwent standardized bunionectomy surgery and received multiple doses of inhaled or intravenous placebo, inhaled morphine (one inhalation [2.2 mg] or three inhalations [6.6 mg]), or intravenous morphine (4 mg) in a blinded fashion. Open-label rescue morphine (2 mg) was also available as needed. Pain intensity, pain relief, and time to pain relief were measured after the first dose. Global evaluation, morphine consumption, vital signs, and adverse events were monitored for 8 h after treatment. Blinded study personnel performed all treatment administrations and pain assessments.

Results: Three inhalations of morphine and 4 mg intravenous morphine provided comparable single- and multiple-dose analgesia. One inhalation of morphine was statistically indistinguishable from placebo. Three inhalations of morphine and 4 mg intravenous morphine both consistently demonstrated significantly greater analgesic efficacy than did placebo and one inhalation of morphine.

Conclusions: Comparable analgesic efficacy was demonstrated between a carefully matched dose of inhaled and intravenous morphine in a postsurgical pain model.

MORPHINE and other μ-receptor agonists provide effective analgesia in patients with moderate-to-severe acute pain. In the acute postsurgical pain setting, intravenous patient-controlled analgesia (PCA) has become the standard of care for the early inpatient management of patients.1 PCA is invasive and requires dedicated equipment, trained staff, and sterile compounding. Most patients are switched from PCA to oral opioids within 24 to 48 h after surgery, provided that the postsurgical pain is under control, bowel function has been restored, and there is an absence of significant postsurgical nausea and vomiting. Unfortunately, oral therapy is not an optimal method for delivering opioid analgesics to patients with acute pain, because of the delay in achieving onset of meaningful pain relief. Over the past decade, there has been a growing trend toward outpatient surgery, requiring discharge within hours after completion of surgery. In such patients, oral therapy is currently the only practical option for the management of acute pain. Significant progress has been made with alternative methods of administering opioids, including the transmucosal2 and transdermal3 routes of delivery. We describe an alternative method of delivering morphine via the inhalation route.

Although drugs have frequently been administered in the past by the inhalation route, with the exception of volatile anesthetics, this method of delivery has largely been confined to drugs with local lung effects for diseases, such as asthma or chronic obstructive pulmonary disease. Over the past decade, there has been a growing interest in the inhalation route as a means for administering drugs intended for systemic effects. Among the potential advantages of this route of administration are rapid onset of effect, bypass of hepatic first pass metabolism, and a noninvasive method of delivery for drugs that cannot be given orally.

The physiology of the lung is ideal for the rapid, systemic delivery of drugs. Its large surface area, high permeability, and extensive vascularization facilitate rapid absorption of drugs into the bloodstream. Efficient systemic delivery via the lung requires that the drug be deposited in the distal lung, particularly in the alveolar region. A combination of optimal aerosol particle size (1–3 μm) and breath control to regulate delivery velocity and timing is required for efficient and consistent deposition in the distal lung.4

The AERx® Pain Management System (AERx® PMS) (Aradigm Corporation, Hayward, CA) (fig. 1) is a novel drug–device combination under development for the pulmonary delivery, via oral inhalation, of aerosolized liquid drug formulations. In contrast to nebulizers or metered dose inhalers, the AERx® PMS provides an efficient method for drug delivery into the distal lung.

The objective of this study was to compare the analgesic efficacy of single- and multiple-dose inhaled morphine delivered via the AERx® PMS with that of intra-
venous morphine and placebo in patients with moderate-to-severe pain after bunionectomy surgery.

**Materials and Methods**

We performed a third-party, blinded, randomized, placebo- and active-controlled study of two dose levels of inhaled morphine delivered using the AERx® PMS. The study was conducted from June to August 2001 in the outpatient surgical clinics of Dr. K. R. Reber (St. George, Utah) and Dr. G. J. Millward (Boise, Idaho). The protocol was approved before study initiation by a central human institutional review board.

Male and female subjects (age range, 18–70 yr) who were PS-1 to PS-3 in the American Society of Anesthesiologists Physical Status Classification System were recruited from the two outpatient orthopedic centers.

Prospective patients were excluded if they had a history of severe asthma or chronic obstructive pulmonary disease, were unable to use the AERx® PMS after training, had a history of substance abuse or depression, had significant renal or hepatic abnormalities demonstrated by laboratory testing, or were breast-feeding a child.

All patients underwent a primary unilateral first metatarsal bunionectomy with or without ipsilateral hammer-toe repair during standardized local anesthesia with intravenous sedation. Briefly, after intravenous sedation with propofol and/or midazolam, a Mayo block of the first metatarsal was induced using lidocaine, 2%, without epinephrine. Lidocaine without epinephrine was used instead of bupivacaine to ensure that pain could be assessed soon after surgery. A pneumatic ankle tourniquet was inflated to between 150 and 250 mmHg and was applied for up to 110 min. The surgical procedure was limited to a maximum of 110 min. After completion of surgery, a postsurgical support shoe was applied to the operated foot and was held in place for the duration of the study. Thereafter, patients were transported to postsurgical observation rooms, where trained study personnel managed the patients.

No analgesic use was permitted before the start of the study. Patients who developed moderate-to-severe pain (≥ 50 mm on a 100-mm visual analog scale) within 6 h after surgery were randomized to one of six treatments (fig. 2): intravenous morphine, three inhalations of morphine, one inhalation of morphine, intravenous saline, three inhalations of water, or one inhalation of water. A block randomization procedure was used, with a 3-to-1 ratio of active morphine to placebo treatments, so that overall each patient had a 25% chance of receiving intravenous morphine, a 25% chance of receiving three inhalations of morphine, a 25% chance of receiving one inhalation of morphine, and a 25% chance of receiving a placebo treatment (equally distributed as intravenous saline, three inhalations of water, or one inhalation of water). For analysis purposes, the three placebo treatments were combined and compared with the active morphine treatments.

Patients were informed during the consent process that they would receive their primary pain medication via either the intravenous or the inhaled route. They were also told that regardless of the route of administration, there was a one-in-four chance that the medication they received would be placebo and that neither they nor their healthcare provider would know which treatment was being administered. Finally, patients were informed that in all circumstances, open-label intravenous morphine was available as rescue medication. All patients received treatment and were assessed in private observation rooms to prevent interaction with other patients. To ensure that all treatment assignments and study assessments were double-blinded, nurses involved in the preparation of study drug were not involved with the administration or subsequent assessment of patients. Study coordinators who administered study drug and assessed patients for efficacy and safety were blinded to the treatment assignment.

All intravenous medications were given as a continuous 2-min infusion. Inhaled medications took from 30 s...
to 2 min to deliver. Measurement of study time was initiated on completion of the intravenous or inhaled dosing.

Inhaled study drug was delivered with the AERx® PMS (fig. 1). The AERx® PMS consists of a portable, battery-powered, hand-held, microprocessor-controlled device. The AERx® PMS is breath actuated, and patients are guided by visual cues (light-emitting diodes of different color) to inhale deeply in the optimal range of inspiratory flow rates. The AERx® PMS aerosolizes a liquid formulation of drug filled into a disposable unit-dose dosage form. Each AERx® PMS dosage form contained 2.2 mg of aqueous morphine sulfate with an estimated systemic bioavailability of 1.4 mg of morphine per inhalation.

Trained study nurses collected study data using standardized methods and questionnaires. Patients were observed for at least 8 h after receiving the first dose of study drug. Vital signs (heart rate, respiratory rate, blood pressure, and level of consciousness) were monitored at regular intervals, and all adverse events were recorded during the 8-h posttreatment observation period. Patients provided single-dose pain scores at selected time points (0, 5, 10, 15, 30, 45, 60, 90, and 120 min) after the first dose of study drug. Pain intensity was measured using a visual analog scale (from 0 [no pain] to 100 [extreme pain]). Pain relief was measured using a 5-point categorical scale (0 [none] to 4 [complete]). Time to onset of perceptible and meaningful pain relief was measured by the two-stopwatch method.

Patients were encouraged to avoid remedication for at least 60 min after the first dose of study drug. After 60 min, patients were allowed to remedicate with the same study medication used for the first dose, as frequently as every 15 min, according to analgesic need. At any time in the study, patients were allowed to receive open-label rescue (2 mg intravenous morphine) up to three times an hour. Patients were required to request remedication or rescue medication directly from study nurses to allow assessment of their level of consciousness. All interventions, however, were self-administered without nursing assistance. Once a patient remedicated or received rescue medication, collection of the single-dose pain scores was stopped, and the patient was asked to rate his or her pain medication using a 5-point global evaluation questionnaire (1 = poor to 5 = excellent). The global evaluation questionnaire was repeated at 8 h. Patients could discontinue use of study medications at any time but were required to stay the full 8 h after the first dose. Patients returned to the clinic at 6–10 days for safety follow-up.

**Statistical Methods**

A sample size of 20 patients per treatment group was intended to provide preliminary information on the efficacy and safety of two dose levels of the study drug when administered by using AERx® PMS. To our knowledge, this is the first reported study describing the use of inhaled morphine for postsurgical analgesia. Statistical testing of treatment differences was performed by means of a priori ordered hypotheses, thus not requiring α adjustments for multiple comparisons. Using a variance estimate of 0.58 (SD) from a study involving oral and parenteral ketorolac, a sample size of 20 patients per treatment group was expected to provide 80% power to detect a mean categorical pain intensity difference of 0.51 at 45 min after dosing at a significance level of 0.05 (two-sided test).

The intent-to-treat population was defined as all patients who received study medication. The efficacy evaluable population was defined as all patients who received study medication, had efficacy information recorded at baseline, and completed efficacy assessments for at least up to the 60-min observation period after dosing. Efficacy analysis was to be performed for both the intent-to-treat and efficacy evaluable populations. Allocation of the intent-to-treat and efficacy evaluable populations was performed before unblinding of the study. The primary analysis of efficacy was based on data for the intent-to-treat population. Isolated missing data were imputed on a patient-by-patient basis using linear interpolation between observed pain scale values. Linear interpolation was used for up to three consecutive missing assessments. If more than three consecutive observations were missing, the missing values were imputed using the last observation carried forward method. If two consecutive observations were missed in the first 2 h after initiation of treatment, the patient was excluded from analysis.

For each efficacy endpoint, all treatment groups were compared using one-way ANOVA for continuous variables or the Kruskal–Wallis test for categorical data. If results of the four-way ANOVA or Kruskal–Wallis test were significant ($P < 0.05$), pairwise $t$ tests or chi-square tests were also conducted between pairs of treatments in an a priori sequence. For survival endpoints, comparisons between study groups were made using the non-parametric log-rank test.

The primary measure of efficacy was the sum of pain intensity difference from 0 to 60 min. Secondary measures of efficacy included total pain relief at multiple times, sum of pain intensity difference at other time points, time from study medication administration to onset of pain relief and first remedication, peak pain intensity difference, peak pain relief, patient global evaluation (single-dose), patient global evaluation (multiple-dose), and frequency and quantity of rescue medication used. All measures of efficacy represent standard measures employed in studies of analgesic agents.

The primary endpoint of this study, the sum of pain intensity difference over 60 min, was calculated by summing the differences in pain intensity observed just be-
fore treatment (0 time) with the pain intensities recorded at 5, 10, 15, 30, 45, and 60 min. The sum of pain intensity difference over 60 min is the sum of the products of the pain intensity difference from baseline and the elapsed time since the previous observation. The total pain relief over 60 min was calculated in the same way but using pain relief scores. Peak pain intensity difference and peak pain relief were calculated by averaging the maximum change in pain intensity difference or pain relief after the first dose of study drug.

Results

No patients were excluded from the study because of inability to use the AERx® PMS. Ninety-three patients met the inclusion criteria and underwent surgery (fig. 2). Four patients did not achieve the required 50-mm pain threshold by the 6-h postsurgery deadline and were not randomized to receive study drug. Eighty-nine subjects were randomized and received the study drug. All 89 randomized patients waited at least 60 min after the first dose before remedicating or receiving open-label rescue morphine. Data for the intent-to-treat and efficacy evaluable populations and analysis were therefore the same. All 89 randomized patients also completed the 8-h postsurgery observation period and returned for the 1-week follow-up visit.

The overall mean age was 47 yr (range, 18–70 yr). Most (89%) of the patients were female. There were no significant differences in demographic characteristics between treatment groups, nor were there any significant differences in efficacy between the three placebo groups (table 1). Therefore, all placebo groups were combined and compared with the three morphine treatment groups.

Three inhalations of morphine and intravenous morphine (4 mg) both consistently demonstrated greater analgesic efficacy than placebo or a single inhalation of morphine. Similar analgesic efficacy was seen for a single inhalation of morphine and placebo.

Because patients were discouraged from remedicating for 60 min and most patients remedicating very soon after 60 min had elapsed, the median time to first remedication and time to rescue morphine did not seem to differ clinically between study groups, although the difference in median remedication time between three inhalations of morphine (66 min) and one inhalation of morphine and placebo (both 64 min) did reach statistical significance (P = 0.038, log-rank test).

The median time to onset of perceptible pain relief was significantly faster (P = 0.008, log-rank test) for both intravenous morphine (2.4 min) and three inhalations of morphine (2.5 min) than for both placebo (6.4 min) and one inhalation of morphine (6.7 min). No differences were observed between treatments in median time to receipt of open-label rescue morphine or to receipt of nonstudy rescue medication (usually ketorolac).

Multiple-dose efficacy results were consistent with the single-dose efficacy results. A trend was observed for a greater proportion of patients receiving intravenous morphine (47%) and three inhalations of morphine (47.8%) to rate their status at the 8-h global evaluation as good-to-excellent compared with patients receiving one inhalation of morphine (20.5%) or placebo (21.7%). This difference, however, did not reach statistical significance (chi-square = 6.93; 3 degrees of freedom; P ≥ 0.07). Hourly rescue morphine consumption was similar between the three inhalations of morphine group and the intravenous morphine group and less than that required by the placebo and one inhalation of morphine groups (table 2, fig. 4). Patients receiving three inhalations of

Table 1. Comparison of Three Placebo Groups

<table>
<thead>
<tr>
<th></th>
<th>1 Inhalation of Placebo (n = 9)</th>
<th>3 Inhalations of Placebo (n = 7)</th>
<th>IV Placebo (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean/Median SD</td>
<td>Mean/Median SD</td>
<td>Mean/Median SD</td>
</tr>
<tr>
<td>SPID 60</td>
<td>−194</td>
<td>−278</td>
<td>−214</td>
</tr>
<tr>
<td>TOTPAR 60</td>
<td>37</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>PPID</td>
<td>18</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>PPR</td>
<td>0.44</td>
<td>0.43</td>
<td>0.43</td>
</tr>
<tr>
<td>Time to perceptible pain relief (min)</td>
<td>221</td>
<td>213</td>
<td>213</td>
</tr>
<tr>
<td>Global, single dose</td>
<td>1.63</td>
<td>1.43</td>
<td>1.43</td>
</tr>
<tr>
<td>Global, 8 h</td>
<td>1.78</td>
<td>1.71</td>
<td>1.57</td>
</tr>
<tr>
<td>Hourly rescue morphine</td>
<td>1.19</td>
<td>1.17</td>
<td>1.30</td>
</tr>
</tbody>
</table>

Data are mean or median time and SD.

IV = intravenous; PPID = peak pain intensity difference; PPR = peak pain relief; SPID 60 = summary of pain intensity difference from 0 to 60 min; TOTPAR 60 = total pain relief from 0 to 60 min.
morphine (43.5%) or intravenous morphine (36.8%) were less likely to request nonstudy rescue medication by the end of the 8-h observation period than were patients receiving placebo (78.3%) or one inhalation of morphine (70.8%) (chi-square = 11.01; 3 degrees of freedom; P = 0.01).

No significant alterations in vital signs were observed during the 8-h observation period. Intravenous morphine had the highest rate of adverse events, and placebo had the lowest rate; however, except for infection, none of the differences reached statistical significance (table 3). Four patients in the placebo group and one patient in the three inhalations of morphine group had wound infections at the site of surgery, none of which were considered related to treatment.

**Discussion**

The primary objective of this study was to evaluate the relative analgesic efficacy of inhaled morphine compared with that of placebo and bolus intravenous morphine. Both single- and multiple-dose efficacy endpoints demonstrated that three inhalations of morphine and 4 mg of intravenous morphine provided comparable analgesic efficacy in this pain model. These results are consistent with earlier pharmacokinetic predictions of bioavailability with the AERx PMS. Three inhalations of morphine and intravenous morphine both were consistently more efficacious than single inhalation of morphine or placebo.

**Table 2. Summary of Efficacy Results**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 23)</th>
<th>1 Inhalation of Morphine (n = 24)</th>
<th>3 Inhalations of Morphine (n = 23)</th>
<th>IV Morphine (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPID 60</td>
<td>−194 (−484–203)</td>
<td>−140 (−582–195)</td>
<td>977 (340–1,614)</td>
<td>1,023 (381–1,664)</td>
</tr>
<tr>
<td>TOTPAR 60</td>
<td>28.5 (10.1–46.9)</td>
<td>27.1 (13.6–40.6)</td>
<td>66.3 (37.8–94.7)</td>
<td>73.2 (46.5–99.8)</td>
</tr>
<tr>
<td>PPR</td>
<td>1.1 (0.60–1.57)</td>
<td>1.2 (0.82–1.51)</td>
<td>1.7 (1.12–2.35)</td>
<td>2.3 (1.79–2.74)</td>
</tr>
<tr>
<td>PPID</td>
<td>17 (8.4–26.1)</td>
<td>14 (6.0–20.9)</td>
<td>37 (24.4–48.8)</td>
<td>39 (27.8–50.7)</td>
</tr>
<tr>
<td>Global, single dose</td>
<td>1.5 (1.15–1.89)</td>
<td>1.4 (1.11–1.69)</td>
<td>2.3 (1.74–2.86)</td>
<td>2.3 (1.60–2.92)</td>
</tr>
<tr>
<td>Global, 8 h</td>
<td>1.7 (1.25–2.14)</td>
<td>2.0 (1.58–2.50)</td>
<td>2.3 (1.78–2.83)</td>
<td>2.7 (2.0–3.37)</td>
</tr>
<tr>
<td>Morphine consumption (mg/h)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.21 (0.91–1.51)</td>
<td>2.59 (2.26–2.92)</td>
<td>4.48 (3.73–5.23)</td>
<td>3.98 (3.33–4.63)</td>
</tr>
<tr>
<td>Remedication</td>
<td>0</td>
<td>1.62 (1.38–186)</td>
<td>3.88 (3.22–4.54)</td>
<td>3.39 (2.83–3.95)</td>
</tr>
<tr>
<td>Rescue</td>
<td>1.21 (0.91–1.51)</td>
<td>0.97 (0.72–1.22)</td>
<td>0.61 (0.31–0.91)</td>
<td>0.59 (0.21–0.97)</td>
</tr>
</tbody>
</table>

Data are mean (95% confidence interval).

* Estimated using 1.4 mg morphine for each inhalation of morphine.

IV = intravenous; PPID = peak pain intensity differences; PPR = peak pain relief; SPID 60 = summary of pain intensity difference from 0 to 60 min; TOTPAR 60 = total pain relief from 0 to 60 min.
Inhalation of morphine via commercially available jet nebulizers has been studied primarily for the treatment of dyspnea. Much less has been reported on the ef

ficiency of inhaled morphine as an analgesic, although data suggest that postsurgical pain control may be achieved with fentanyl, a potent opioid, when delivered by inhalation. The efficacy of inhaled opioids for pain control may be directly related to the potency of the opioid and to the dose delivered. The dose delivered, in turn, is affected by the efficiency of the delivery system. Although standard nebulizers achieve some degree of systemic delivery, their poor delivery efficiency seems to limit their effectiveness. Indeed, using a conventional nebulizer, Masood and Thomas demonstrated only a 5% bioavailability for inhaled morphine, and Chrubasik et al. demonstrated a 17% bioavailability for inhaled morphine with a nebulizer in intubated patients.

The AERx® PMS has been used in human clinical trials for the pulmonary delivery of systemic proteins such as insulin, topical proteins such as rhDNase, and small molecules such as fentanyl. In previous pharmacokinetic studies, the AERx® PMS demonstrated a morphine concentration–time curve very similar in profile to an intravenous morphine bolus, with a maximum concentration observed at 2 min after dosing. Absolute systemic bioavailability in these studies ranged from 59% to 100% of the dosage form content. In the current study, each AERx® PMS dosage form contained 2.2 mg morphine. In vitro testing for the prototype used in this study predicted an emitted dose of 65%. Each inhalation was therefore expected to deliver up to 1.4 mg morphine to the lung with 100% absorption, approximately the same amount to the systemic circulation. The intravenous morphine control dose, 4 mg, was therefore chosen to provide a dose similar to the highest dose of inhaled morphine.

Using the formula of Lehmann to compute an equipotent dose for three inhalations of morphine relative to intravenous morphine, an equipotent dose for drug A = (pain score for drug A × consumption for drug A)/(pain score for morphine × consumption for morphine). Using visual analog scale pain intensity scores, we estimate that each inhalation of AERx® PMS delivered 1.34 mg morphine, which agrees closely with the in vitro bioavailability estimate.

Although a double dummy design would have been optimal, a limited supply of placebo dosage forms for this prototype prevented the use of this design. No differences were seen between the three placebo groups, suggesting that the nested placebo design and the blinding procedures used for both patients and nurses were effective.

The group receiving one inhalation of morphine was not distinguishable from the placebo group. This may be partially explained by a strong placebo effect or the possibility that one inhalation of morphine did not achieve a minimum effective plasma morphine concentration in this model. A mean reduction in pain intensity of 10 mm was seen in the first 5 min after placebo therapy (fig. 3). Placebo therapy, when combined with an active treatment maneuver and reinforced by a healthcare professional, may result in analgesia. This “placebo” effect may be partly attributable to the release of endogenous opioids.

In PCA studies, small changes in plasma concentrations of opioids such as meperidine and fentanyl are associated with a transition from pain to analgesia. The minimum effective plasma morphine concentration for analgesia in postoperative studies ranged from 15 to 65 ng/ml. For a mixed abdominal and gynecologic postoperative patient population using PCA morphine, Graves et al. demonstrated a minimum effective concentration ranging from 20 to 40 ng/ml. Dahlstrom et al. demonstrated a minimum effective concentration ranging from 6 to 33 ng/ml for patients using PCA morphine after abdominal surgery.

In a previous pharmacokinetic study, four inhalations of morphine with the AERx® PMS resulted in a peak plasma morphine concentration of 80 ng/ml 2 min after dosing. However, the plasma morphine concentration returned to less than 20 ng/ml within 30 min. In the current study, patients receiving placebo or a single inhalation of morphine had similar analgesic responses immediately after treatment, but these responses returned to the pretreatment baseline pain intensity levels within 20 min (fig. 3). This finding suggests that a single inhalation of morphine delivering 1.4 mg morphine at

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 23)</th>
<th>One Inhalation of Morphine (n = 24)</th>
<th>Three Inhalations of Morphine (n = 23)</th>
<th>Intravenous Morphine (n = 19)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>15 / 65</td>
<td>16 / 67</td>
<td>18 / 78</td>
<td>16 / 84</td>
<td>0.4</td>
</tr>
<tr>
<td>Dizzy/lightheaded</td>
<td>0 / 0</td>
<td>3 / 13</td>
<td>3 / 13</td>
<td>4 / 21</td>
<td>0.19</td>
</tr>
<tr>
<td>Emesis</td>
<td>8 / 35</td>
<td>12 / 50</td>
<td>10 / 44</td>
<td>11 / 58</td>
<td>0.35</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 / 39</td>
<td>11 / 46</td>
<td>15 / 65</td>
<td>14 / 74</td>
<td>0.09</td>
</tr>
<tr>
<td>Infection</td>
<td>4 / 17</td>
<td>0 / 0</td>
<td>1 / 4</td>
<td>0 / 0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are number/and percentage of patients.

<table>
<thead>
<tr>
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<td>1 / 4</td>
<td>0 / 0</td>
</tr>
</tbody>
</table>

P Value
intervals of greater than 15 min does not produce an adequate plasma morphine concentration to achieve and maintain analgesia in this model. Plasma morphine concentrations were not measured in this study. Monitoring of plasma morphine concentrations in future efficacy studies may allow better characterization of the pharmacokinetic-pharmacodynamic relationship with this route of administration.

The demand dose and dosing interval (lockout) have been shown to affect analgesic efficacy. \(^1\) Recommended morphine demand doses typically range from 0.5 to 4 mg with lockout periods of 5–10 min. Owen \textit{et al}.\(^2\) demonstrated that a PCA bolus dose of 1 mg as often as every 5 min was optimal in a mixed abdominal surgery model. However, patients in these studies were titrated to “no pain” before PCA use. Because the patients in our study were effectively limited to boluses of 1.4–4 mg with a greater than 15-min lockout period and were also required to have moderate-to-severe pain before dosing, they effectively spent the 8-h treatment period “catching” up. The 15-min lockout period was chosen to ensure that patients had any analgesic effect from the study treatment before requesting any further medication. Overall pain control in this study was not optimal in any of the study groups, including the 4-mg intravenous morphine group. This is demonstrated by the failure of at least 50% of patients in any of the four treatment groups to achieve meaningful pain relief. A 4-mg morphine bolus would normally be considered a high-demand dose in patients using PCA. The current study design, including the 4-mg intravenous morphine control group, did allow for the separation of effective \textit{versus} suboptimal treatments. Future studies in this and other more severe postoperative pain models may require a shorter lockout period and/or stabilization of pain control before initiation of the study drug.

The adverse events observed in this study (table 3) are common side effects of morphine administered to opioid-naïve individuals. The presence of nausea and vomiting in the placebo group reflected the use of open-label rescue morphine.

For almost a decade, guidelines have been available for the evaluation of analgesics after single-dose administration to patients with acute pain.\(^2\) Although these guidelines have demonstrated their utility, drug developers and regulators are increasingly being challenged by surgical and pharmacologic “standard of care” issues that make it difficult to measure the response of putative analgesics in a broad range of pain models. There is a need for robust, alternative models for the evaluation of analgesic drug response in acute pain after single- and multiple-dose treatment. Although postsurgical pain after third molar extraction is a mainstay of analgesic drug evaluation for regulatory approval, we elected to use an alternative pain model for several reasons. These included the relative lack of assay sensitivity of this model for opioid analgesics and the possibility of oral and glossopharyngeal deposition of a portion of the dose in view of the excessive postsurgical sialorrhea.

Postsurgical pain after orthopedic surgery is a sensitive model for evaluation of analgesic effects of putative analgesics. Evaluation of single-dose analgesic response after bunionectomy surgery has been used to characterize the efficacy of cyclooxygenase-2 inhibitors\(^2\) and opioids.\(^2\) In addition to single-dose efficacy, this study demonstrated multiple-dose analgesic efficacy in the bunionectomy model. The bunionectomy model offers certain advantages: patients are generally conscious during the procedure, so that dosing may begin soon after the procedure is completed, and the procedure is elective and done in an outpatient or ambulatory care setting, thereby allowing rapid patient recruitment. The trauma associated with bunionectomy surgery also provides a very predictable level of pain. Bunion surgery involves bony and capsular tissue repair around the first metatarsal-phalangeal joint of the foot. Considerable edema follows these surgical procedures because of disruption of fascial tissue, external or internal fixation, slow healing of capsular tissue, and newly aligned bone fragments. The result is substantial postoperative inflammation consistent with other orthopedic surgical procedures, except that the swelling is confined to a smaller area of the lower extremity. Patients typically have moderate or severe pain for weeks after surgery.\(^2\)–\(^2\) For these reasons, bunionectomy surgery may prove to be a useful model for assessing the efficacy of analgesics. In view of the growing trend toward ambulatory surgery, bunionectomy also represented an appropriate model for evaluation of inhaled morphine.

In conclusion, this study demonstrated analgesic comparability between carefully matched doses of intravenous and inhaled morphine, dose response, and superiority to placebo in a new short-term single- and multiple-dose pain model. The AERx\textsuperscript{®} PMS, like PCA morphine, may allow better pain control while reducing the adverse effects of opioids by allowing patients to self-titrate their pain medications. Inhaled morphine given \textit{via} the AERx\textsuperscript{®} PMS may provide a viable noninvasive method of delivering systemic opioids in the outpatient management of postsurgical pain.

References


