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Initial pharmacokinetic, safety and efficacy evaluation of nasal morphine gluconate for breakthrough pain in cancer patients

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Abstract

Patients with controlled background pain associated with cancer frequently also experience episodes of moderate to severe intensity breakthrough pain. Opioid pharmacotherapy, particularly with oral morphine, remains the cornerstone for the management of cancer pain. Nasal administration of opioids provides a mechanism for more rapid drug absorption and more rapid onset of pain relief compared with oral dosing. This non-randomized, open-label, uncontrolled investigation evaluated the pharmacokinetics, safety and efficacy of a single 40 mg dose of nasal morphine gluconate, administered to cancer patients in response to an episode of breakthrough pain. Single dose nasal morphine gluconate administered to 11 patients was associated with effective plasma morphine concentrations (mean C_{max} 64 ng/ml; range 33.8–121 ng/ml) and low plasma morphine metabolites (morphine-6-glucuronide mean C_{max} 114 ng/ml; range 46–189 ng/ml; morphine-3-glucuronide mean C_{max} 572 ng/ml; range 257–990 ng/ml). Side effects were minor and limited to nasal irritation. Patients reported rapid onset of pain relief (perceptible pain relief achieved in 10/11 patients, time to onset 2.4 ± 2.1 min; and meaningful pain relief, achieved in five patients, 6.8 ± 7.3 min to onset, mean t_{max} 0.36 h). Pain intensity scores were significantly reduced at all times after dosing; pain relief scores were unchanged. Patient satisfaction ratings were high. These results show that nasal morphine has rapid absorption and apparent onset of effect. Additional multi-dose, dose-ranging and placebo-controlled studies of nasal morphine for cancer pain are warranted.

Keywords: Morphine; Breakthrough pain; Nasal mucosa; Pharmacokinetics; Analgesia

1. Introduction

Opioid pharmacotherapy is the mainstay for cancer-related pain that is moderate to severe in intensity (World Health Organization, 1996). In addition to constant background pain, many cancer patients frequently experience breakthrough pain superimposed on a background of otherwise stable persistent pain in patients receiving around-the-clock opioid therapy (Caraceni and Portenoy, 1999). Breakthrough pain is a commonly encountered pain problem in cancer patients with an incidence rate of 50–89% (Portenoy and Hagen, 1990; Zeppetella et al., 2000). Breakthrough pain typically is frequent (median six episodes per day), moderate to severe in intensity, rapid in onset and escalates rapidly (3 min interval from onset to peak intensity), and is relatively brief in duration (Portenoy et al., 1999).

Traditionally, breakthrough pain is controlled with oral opioids. Oral morphine is considered the standard opioid for moderate to severe intensity cancer pain (World Health Organization, 1996). Adequate treatment of breakthrough pain requires opioids that are rapid in onset. The oral route may not be optimal for treatment for breakthrough pain as conventional oral morphine preparations are not rapidly absorbed and also have a significant first-pass effect (Hasselstrom and Sawe, 1993; Hoskin et al., 1989) resulting in a relatively low bioavailablity of 20 (Bourget et al., 1995) to 32% (Westerling et al., 1995). Further issues with oral morphine include a slow onset of pain relief of 45–120 min (Sawe et al., 1983).

The nasal route has shown increasing promise as a route of opioid administration that achieves rapid absorption and onset of effect (Dale et al., 2002). Previous studies with nasal administration of opioids such as alfentanil, fentanyl,

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sufentanil, oxycodone, buprenorphine, and butorphanol have shown that mean maximum serum concentrations were achieved between 5 and 49 min, although significant inter-individual variation was observed (Eriksen et al., 1989; Helmers et al., 1989; Schwagmeier et al., 1995; Shyu et al., 1993; Takala et al., 1997). A nasal formulation of morphine may provide a mechanism for more rapid drug absorption and possibly more rapid onset of pain relief compared with oral dosing.

The objective of this study was to evaluate the pharmacokinetics, efficacy, and safety of a single dose of a nasally administered formulation of morphine gluconate in patients with breakthrough cancer pain.

2. Methods

2.1. Study subjects and drug administration

The study was approved by the University of Washington Institutional Review Board, and written informed consent was obtained from each subject prior to participation. The design was a single center, single dose, open label, uncontrolled study. Eligible subjects included male and female patients 18–80 yr with chronic background pain due to hematological malignancy or solid tumor that was controlled with opioid with or without non-opioid medications. Patients were opioid-tolerant (using oral opioids on a regular basis for at least 1 week) and had controlled levels of background pain (defined as either pain which was experienced for more than half the waking time during the previous week, or the use of a fixed schedule opioid on more than half the days during the previous week). If patients described their background pain as being mild, moderate or absent due to effective pain relief more than half the time, then patients were considered to have controlled background pain. Patients with uncontrolled background pain were not eligible. Patients were required to experience at least two episodes daily of breakthrough pain while awake, in spite of chronic pain medication(s), including opioids. Hence eligibility required controlled background pain with breakthrough pain. Exclusion criteria included females of childbearing potential who were not actively using a method of effective birth control or who were currently pregnant or lactating, a history of hypersensitivity or idiosyncratic event to morphine, history of nosebleeds, allergic rhinitis, alcoholism or drug abuse; and allergy to sulfites.

Patients were instructed not to take any nasal medications starting 3 days before the treatment visit. Patients were asked to maintain a normal opioid and non-opioid pain medication schedule, even if dosing occurred during the treatment visit, except that they took no medication for breakthrough pain on the treatment day prior to study drug administration. Each patient was treated with intranasal morphine (a single 0.1 ml = 20 mg spray in each nostril for a total dose of 40 mg). Morphine was delivered using a metered dose inhaler while subjects tilted their head slightly backward for dosing, and then returned their head to an upright position while sniffing gently after dosing. The nasal morphine spray was a morphine alkaloid base that was converted into a more soluble morphine gluconate salt. A morphine gluconate solubility of 200 mg/g could easily be achieved. The formulation also contained citrate buffer, an antioxidant (sodium metabisulfite), humectant (glycerin), a preservative (benzalkonium chloride), permeation enhancer (oleic acid), and polysorbate 20 as a solubilizing agent for the oleic acid. Patients received no other medication for 30 min after nasal morphine. If after 30 min patients did not report at least 'moderate' pain relief (pain relief ≥ 2, where 0 = none and 4 = complete), they were then instructed to take their regular breakthrough pain medicine for rescue. Patients who did not report breakthrough pain at the time of presentation to the clinic were encouraged to ambulate for up to 30 min until they experienced breakthrough pain.

2.2. Pharmacokinetic measures

Venous blood samples were obtained before and 5, 10, 15, 30, 60, 90, 120, 180, and 240 min after dosing. Morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) together with their internal standards (morphine-d3, d3-M3G and d3-M6G) were extracted from plasma by solid phase extraction. The eluent was evaporated to dryness under nitrogen and the residue was reconstituted in mobile phase. A small amount of the reconstituted sample was injected into a PE SCIEX API 3000 HPLC/MS/MS system equipped with a PE Series 200 pump and autosampler for separation and quantitation. The transition ions at *m/z* 286.1 → 165.2, 462.2 → 286.1, 289.1 → 165.2 and 465.2 → 289.1 were monitored for morphine, M3G/M6G, morphine-d3 and M3G-d3/M6G-d3, respectively. Calibration curves (ng/ml) were used for 0.5–100 morphine, 10–2000 M3G and 2–400 M6G. The limits of quantitation were the lowest calibration standards. For morphine, the intrabatch precision (%CV) was 2.9 (1.5 ng/ml) and 9.7% (70 ng/ml). For M3G, it was 1.4 (30 ng/ml) and 3.1% (1400 ng/ml), and 2.5 (6 ng/ml) and 4.6% (280 ng/ml) for M6G. For morphine, M3G and M6G the interbatch precision (%CV) was 0.9–5.7, 0.5–1.9, and 1.6–5.0%, respectively. Noncompartmental methods (WinNonlin Version 4.0, Pharsight Corp., Mountain View, CA) were used to determine $C_{\max}$, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, k_e, and $t_{1/2}$.

2.3. Side effect measures

Side effects were determined by subjective self-assessment and quantified by visual analog scales (VAS) for sedation, energy level, confusion, calmness, clumsiness, and nausea. Nasal exams were performed before and 10, 30, 60, 90, 120, 180, and 240 min after dosing. Study drug tolerability was rated by the subjects addressing nasal

itching, nasal burning or stinging, nasal pain, nasal bleeding, nasal discharge, sneezing, tearing, headache, unusual taste, and sore throat, using a 5 point severity score. Safety was assessed throughout the study day and all adverse events were recorded.

2.4. Efficacy measures

Pain intensity was determined before study drug administration using an 11 point (0–10) pain intensity scale: 0 = none, 5 = moderate, and 10 = intolerable. Pain relief was determined using a 5 point (0–4) pain relief scale: 0 = none, 1 = slight, 2 = moderate, 3 = a lot, 4 = complete. Pain intensity and pain relief scores were determined before and 5, 10, 15, 30, 60, 90, 120, 180, and 240 min after study drug administration. Time to improvement in pain was determined using the 2-stopwatch technique. Patients started both stopwatches upon nasal morphine administration, and were instructed to stop them when they experienced 'perceptible improvement in pain' and 'meaningful improvement in pain'. Onset of pain relief was defined by the time to perceptible improvement in pain relief, time to meaningful improvement in pain relief, and the number of patients experiencing each measure. Adequate pain relief was defined as a patient's decision not to use rescue medication, and the number of patients requiring rescue medication was quantified. Patients' global evaluation of study medication at 60 and 240 min after dosing was based on the following scale: 0 = pain, 1 = fair, 2 = good, 3 = very good, 4 = excellent.

Standard measures for analysis of efficacy were used (Farrar et al., 2000). Time-specific pain intensity and pain relief scores were compared with baseline values by repeated measures ANOVA. Additional measures included the absolute difference in pain intensity (PID, 0–10), the relative percent difference in pain intensity (PID%, 0–100%), peak PID, peak pain relief, time to peak PID, time to peak pain relief, sum of the absolute difference in pain intensity (SPID, determined for 0–15 min after the dose, the 0–60 min interval, and the 0–240 min interval), and the summed pain relief scores (TOTPAR) over the 0–60 min and 0–240 min intervals. If patients required rescue medication at the 60 min time, data (SPID, TOTPAR) was analyzed by the last observation carried forward (LOCF).

2.5. Statistical analysis

All data manipulations, tabulations of descriptive statistics, and parameter estimation and testing were performed using PC-SAS for Windows (Version 6.12, SAS Institute, Cary, NC). Pain intensity and pain relief were analyzed using a repeated measures ANOVA. Patients' global assessment 60 and 240 min post-dosing was compared with the Wilcoxon signed-Rank test. Unless otherwise indicated, all statistical tests of significance were performed as two-sided tests, and a difference resulting in $p < 0.05$ was considered statistically significant.

3. Results

Eleven subjects (six males, five females; mean age 47 yr, range 35–54) received nasal morphine. Each subject had a different type of tumor; there was no preponderance of tumor type (Table 1).

Individual and mean plasma concentrations of morphine and morphine glucuronide metabolites are shown in Fig. 1, and pharmacokinetic parameters are summarized in Table 2. The mean t_{max} for morphine was 0.36 h after intranasal dosing, and the longest t_{max} was 0.5 h, indicating rapid and reproducible absorption. Mean elimination $t_{1/2}$ for morphine was 2.0 h suggesting a short half-life. The metabolite/parent AUC_{0-t} ratios for M6G and M3G were 2.1 ± 1.2 (range 0.7–3.8) and 10.2 ± 4.8 (range 3.7–16.2), respectively.

Side effects, determined by subjective self-assessment and quantified by VAS scores, are shown in Fig. 2. There were small but statistically significant changes for confusion, but none for sedation, energy level, calmness, clumsiness, or nausea. All adverse events were considered related to treatment. There were no serious adverse events. Adverse events were mild and resolved without medical intervention and without lasting effects. The most frequent adverse event was rhinitis (nasal congestion, burning, stinging, discharge, and sneezing, as described by patients), which occurred in 82% of patients (Table 3). All nasal symptoms were considered mild and resolved without medical intervention and with no lasting effects. There were no clinically significant vital sign changes from baseline to post-treatment for systolic and diastolic blood pressure, heart rate, respiratory rate and oxygen saturation, based on adverse events reported.

There was a significant difference in the time-specific measure of pain intensity compared with baseline (Fig. 3). There was no significant difference in the time specific pain relief scores after drug administration. The mean total pain relief scores (TOTPAR) for 0–60 and 0–240 min were

Table 1
Cancer diagnosis by patient

Patient number	Diagnosis
1	Stage IIIB inflammatory cancer of the right breast
2	Squamous cell cancer, floor of mouth
3	Neurofibromatosis
4	Left ear, parotid squamous cell cancer
5	Waldenstrom's macroglobulinemia
6	Right optic nerve glioma
7	Right lower extremity sarcoma
8	Mediastinal lymphoma
9	Chondrosarcoma
10	Gastric adenocarcinoma
11	Retroperitoneal hemangioma

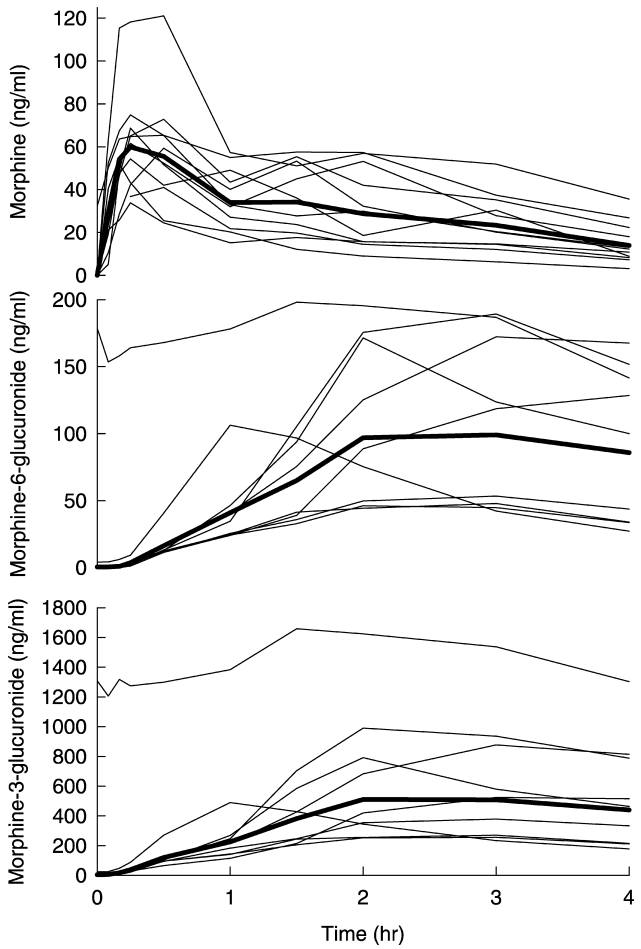

Fig. 1. Plasma concentrations of morphine and glucuronide metabolites. Results are shown for individual subjects and for mean values (heavy line). One subject had high baseline morphine glucuronide concentrations, and these were omitted from the calculated means.

91 ± 72 (range 15–220) and 413 ± 228 (range 195–940), respectively. The time to perceptible pain improvement was 2.2 ± 2.1 min ($n = 10$, one subject did not achieve perceptible pain improvement) and 91% of patients experienced perceptible pain improvement before taking additional rescue medication. Five patients experienced meaningful pain relief (time to meaningful pain relief 9.1 ± 8.6 min in these patients) before taking additional rescue medication. Overall, 72% of patients required rescue medication during the study. Thirty-six and 55% of patients required rescue medication between 30–60 min and within 120 min after dosing, respectively. Seventy-three percent of patients' global assessment at 60 min was fair to very good. There was no significant difference in patients' global assessment comparing the results from 60 and 240 min post-dosing.

4. Discussion

Because breakthrough pain is typically moderate to severe in intensity and rapid in onset (within 3 min), it is important to use a drug and a route of administration that will provide a time-action profile characterized by rapid onset and early peak effect with a relatively short duration.

Nasal administration is an alternative route that may achieve a rapid onset of opioid effect. The nasal mucosa has characteristics that favor rapid drug uptake (Dale et al., 2002). In addition, nasal morphine may be absorbed directly from the nasal cavity into the systemic circulation thus bypassing the gastrointestinal tract, the liver and consequently first pass metabolism. Pharmacokinetic studies of nasal administration with various opioids have shown bioavailabilities of 50–70%, which are generally higher than for oral or rectal administration. Maximum serum concentrations (C_{max}) have been reached 10–50 min after administration of a variety of opioids including buprenorphine, alfentanil, and oxycodone (Eriksen et al., 1989; Schwagmeier et al., 1995; Takala et al., 1997; Dale et al., 2002;).

In this study, the mean t_{max} for nasal morphine was 0.36 h (range 10–30 min) after intranasal dosing, indicating rapid and reproducible absorption. This is substantially faster than the time (approximately 1.1 h) to C_{max} for oral morphine (Collins et al., 1998). The mean elimination $t_{1/2}$ (2 h) of nasal morphine was comparable to that previously reported for intravenous morphine (Ward et al., 1997). Absolute and relative (to oral) bioavailability of nasal morphine gluconate in this investigation was estimated using previous $AUC_{0-\infty}$ data for intravenous (91.2 ng h/ml for 5 mg) and oral (18.17 ng h/ml for 10 mg) dosing (Nastech data on file). Computations indicate that nasal

Table 2
Morphine pharmacokinetic parameters

Parameter	Morphine ($n = 10$)	Morphine-6-glucuronide ($n = 7$)	Morphine-3-glucuronide ($n = 7$)
C_{max} (ng/ml)	64.0 ± 22.8 (33.8–121)	114 ± 60 (46–189)	572 ± 281 (257–990)
t_{max} (h)	0.36 ± 0.14 (0.17–0.50)	2.5 ± 0.8 (1–4)	2.3 ± 0.6 (1–2.7)
AUC_{0-t} (ng h/ml)	127 ± 57 (53–243)	273 ± 135 (127–468)	1460 ± 666 (760–2560)
$AUC_{0-\infty}$ (ng h/ml)	174 ± 94 (59–390)		
K_e (1/h)	0.38 ± 0.11 (0.19–0.53)		
$t_{1/2}$ (h)	2.0 ± 0.7 (1.3–3.6)		

Results are shown as mean ± SD (range). One subject, receiving high doses of morphine for background pain control, was omitted from the pharmacokinetic analysis. Glucuronide data were not available for all subjects.

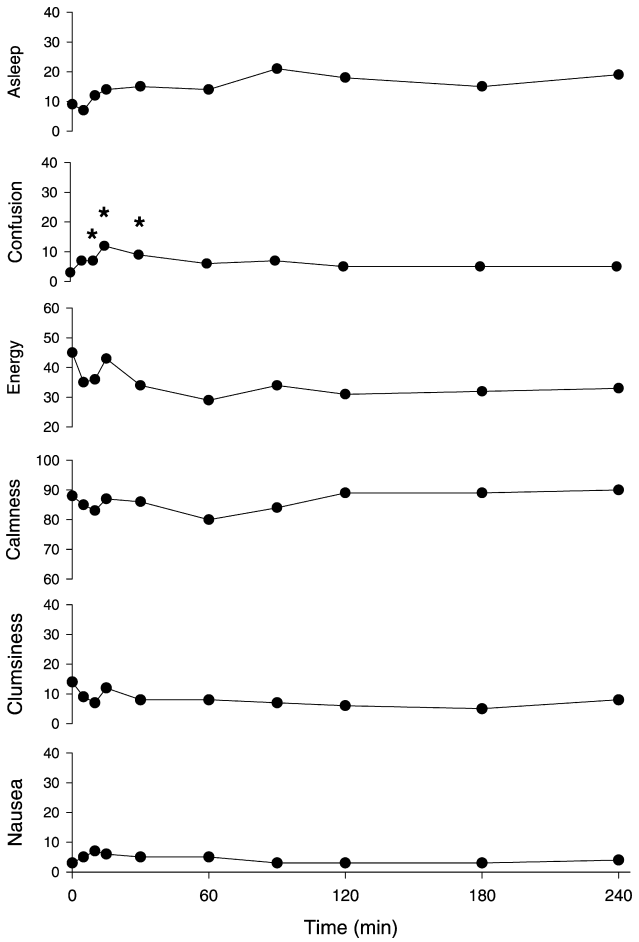

Fig. 2. VAS scores for opioid side effects. Results are the mean values for all subjects. *Significantly different from baseline ($p < 0.05$).

morphine gluconate had an absolute bioavailability of approximately 22% and a relative (to oral) bioavailability of approximately 226%. This compares favorably with an absolute oral morphine bioavailability of 20 (Bourget et al., 1995) to 32% (Westerling et al., 1995). The high bioavailability of nasal morphine in this investigation is due, in part, to the small volume and high concentration administered. The morphine gluconate solubility of 200 mg/ml allowed 40 mg to be administered with two sprays, which would have been precluded by the use of morphine sulfate, which has a lower aqueous solubility.

The most common adverse event in this study was nasal burning and stinging. All nasal symptoms were considered mild and resolved without medical intervention and with no lasting effects. Furthermore, the absence of serious adverse effects and global medication performance indices used in this study indicate a high level of patient acceptability for this format of morphine administration.

The relationship between plasma concentrations of morphine and analgesic effect is complex, especially in patients who are opioid-tolerant. In a study of pain after major abdominal surgery, the calculated minimum effective concentration of morphine was 54 nmol/l (Dahlstrom et al., 1982). Klepstad et al. (2000) suggested that a mean serum trough morphine concentration of 66 nmol/l was sufficient to relieve moderate to severe cancer pain, although it should be noted that the morphine dose adequate to relieve pain varies between the individual cancer patients and the correct dose in each patient is not predictable before the start of treatment (Klepstad et al., 2003). In our study, the average C_{max} value observed was 64 ng/ml (range 33.8–121 ng/ml) reflecting at least adequate absorption of the drug by the nasal route.

Table 3
Adverse event rates

Body system	Number (%) of patients
Respiratory system	11 (100%)
Epistaxis	1 (9.1%)
Erythema	1 (9.1%)
Hyperventilation	1 (9.1%)
Hypoventilation	1 (9.1%)
Pain/discomfort in nasal cavity	1 (9.1%)
Rhinitis	9 (81.8%)
Special senses	6 (54.4%)
Lacrimation discrimination	1 (9.1%)
Taste perversion	6 (54.4%)
Nervous system	1 (9.1%)
Dizziness	1 (9.1%)
Digestive system	4 (36.4%)
Pharyngitis	4 (36.4%)

The overall number (%) of any adverse event was 11 (100%). There were no serious adverse events.

Morphine is eliminated largely by hepatic metabolism and its principal metabolites (M6G, M3G) by renal excretion. The metabolism of morphine occurs not only in the liver, but may also take place in the brain and the kidneys (Christrup, 1997). Measurement of M6G and M3G

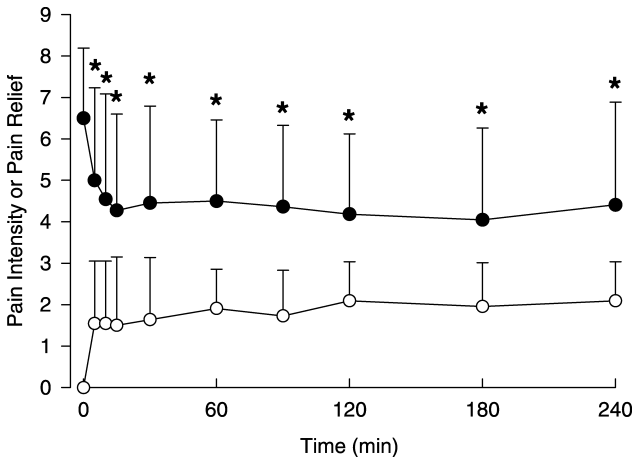

Fig. 3. Pain intensity (●) and pain relief (○) for all patients after nasal morphine administration (time = 0). Results are the mean ± SD. Pain intensity was measured on an 11 point scale (0 = no pain, 10 = intolerable pain), and pain relief was measured on a 5 point scale (0 = no relief, 4 = complete relief). *Significantly different from baseline ($p < 0.05$).

levels may indirectly reflect the degree of first pass metabolism of morphine (Faura et al., 1998) and opioid-related side effects profile (Ashby et al., 1997; Lotsch et al., 1999). Faura et al (1998) found that routes of morphine administration which avoided first pass metabolism (intravenous, transdermal, rectal, intramuscular, epidural and intrathecal) resulted in lower metabolite production (M6G and M3G) than oral, buccal or sublingual. In addition, Faura et al. hypothesized that extensive first pass metabolism was the presumed basis of this difference between routes in metabolite to morphine ratios. Ashby et al. (1997) found that that accumulation of M3G and M6G may be a causal or aggravating factor in the nausea and vomiting and cognitive function profile of palliative and terminal care patients with significant renal function impairment. Thus, lower serum concentrations of morphine metabolites such as M6G may be associated with less opioid-related side effects, particularly for long-term oral dosing of morphine (Lotsch et al., 1999). In a study investigating the relationships between serum concentrations and clinical effects of morphine and its metabolites associated with start of oral morphine treatment in cancer patients, Klepstad et al. (2000) found the mean trough serum morphine concentration associated with pain relief was 66 nmol/l and the corresponding mean concentrations of M6G and M3G were 257 and 1943 nmol/l, respectively. In this study, C_{max} for M6G was 114 ng/ml (range 46–189) and C_{max} for M3G was 572 ng/ml (range 257–990). The observed lower values in part may reflect nasal administration of morphine gluconate and less first pass metabolism. Further studies are needed to evaluate morphine glucuronide metabolites after nasal administration at higher or multiple doses.

In this study, all patients demonstrated a significant difference in the time-specific measure of pain intensity compared with baseline (Fig. 3). Nasal morphine gluconate achieved perceptible pain relief in a mean of 2 min and meaningful pain relief in a mean of 9 min in those subjects achieving relief. The TOTPAR score range from 0–60 min was 15 to 220 and 0–240 min was 195 to 940. These results compare favorably to other studies in postoperative patients with nasal opioids which demonstrated mean times of pain relief onset from 12 to 16 min (Dale et al., 2002; Schwagmeier et al., 1995; Striebel et al., 1993a,b). For example, Striebel et al. (1993a) administered a mean dose of 104 mg intranasal meperidine to patients undergoing hysterectomy and noted a mean onset time of 12 min and a peak effect at 33 min. Abboud et al. (1991) noted that intranasal butorphanol in doses varying from 1 to 2 mg in caesarean section patients had an onset time of approximately 15 min.

Although pain relief scores did not differ significantly after nasal morphine administration, this may reflect a protocol design and dosing issue. Specifically, only one dose (40 mg) was used in this study. A higher single dose or a multidose regimen might be expected to achieve better pain relief, and such protocols are warranted based on the results shown here.

Conversely, a significant limitation in interpreting the efficacy data in this study was the measurement of subjective pain responses without the use of blinding, randomization and placebo controls. Nonetheless, this was a pilot study, and the pharmacokinetic, concentration and initial efficacy data do, however, indicate rapid absorption and achievement of therapeutic concentrations, and suggest that further, randomized, double-blind, and placebo-controlled studies are warranted.

In conclusion, this study has demonstrated that morphine gluconate is rapidly absorbed and reaches an early peak plasma concentration after nasal administration. The metabolites (M3G, M6G) of morphine were also relatively low. In addition, nasal morphine was well-tolerated and is potentially an effective treatment for breakthrough pain in cancer patients. Reduction in nasal side effects would be ideal. Additional, multiple dose and placebo-controlled studies are needed to further characterize the safety and efficacy of nasal morphine gluconate for breakthrough pain in cancer patients.

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