Pharmacokinetics and Bioavailability of Single-Dose Intranasal Hydromorphone Hydrochloride in Healthy Volunteers

Barbara A. Coda, MD*†, Anita C. Rudy, PhD‡, Sanford M. Archer, MD§, and Daniel P. Wermeling, PharmD‡‖

*Department of Anesthesiology, University of Washington, Seattle; †McKenzie Anesthesia Group, Springfield, Oregon; ‡Intranasal Technology, Inc; §Division of Otolaryngology-Head & Neck Surgery, University of Kentucky, A.B. Chandler Medical Center; and ‖University of Kentucky College of Pharmacy, Lexington, Kentucky

We evaluated pharmacokinetics and absolute bioavailability of single doses of hydromorphone hydrochloride after administration of 1.0 and 2.0 mg of intranasal (IN) and 2.0 mg of IV hydromorphone hydrochloride. An open-label, randomized, three-way crossover study was conducted in 24 healthy volunteers (13 men and 11 women). IN doses were delivered as 0.1-mL metered-dose sprays into one or both nostrils for 1.0- and 2.0-mg doses, respectively. Blood samples were taken serially from 0 to 16 h after each dose. Plasma hydromorphone concentrations were determined by liquid chromatography-mass spectrometry-mass spectrometry. Noncompartmental analysis was used to estimate pharmacokinetic variables. Mean hydromorphone bioavailabilities and percent coefficient of variation of 52.4% (22.7) and 57.5% (18.6) were seen after the 1.0- and 2.0-mg IN doses, respectively. Median times to maximum concentration were 20 and 25 min for IN doses. Adverse events included somnolence and dizziness with all routes of administration and a bad taste after IN doses. Dose proportionality for the 1.0- and 2.0-mg IN doses was observed. IN hydromorphone hydrochloride met the minimum requirements for safety and demonstrated rapid nasal drug absorption and clinically relevant bioavailability. Results support further development of this novel hydromorphone hydrochloride nasal spray.

(Anesth Analg 2003;97:117–23)

Over the past several decades, major efforts have been made to improve methods and delivery routes of opioid analgesics. Goals of these efforts include minimizing differences in opioid pharmacokinetics and pharmacodynamics and maximizing patient convenience, comfort, and safety. The transmucosal route seems promising as a useful method of delivering opioid analgesics. Its potential advantages include increased safety and convenience compared with IV and IM administration, more rapid onset of action compared with oral and IM dosing, and reliable analgesia without an increase in side effects. The transmucosal route has been effective for delivery of a variety of opioid analgesics, including sufentanil (1), fentanyl (2–6), alfentanil (7), diamorphine (8), morphine (9), hydromorphone (10), meperidine (11), and butorphanol (12–16). Bioavailability with nasal administration is approximately 71% for fentanyl (5), 65% for alfentanil (7), 78% for sufentanil (17), and 70% for butorphanol (18).

Hydromorphone, a semisynthetic derivative of morphine, has been used in clinical practice for over 70 yr and is a reasonable alternative to morphine for the treatment of moderate to severe pain. It is used in a variety of settings, most frequently for surgical and cancer-related pain. Hydromorphone has a reported potency of 3–7.5 times that of morphine (19–23) and a similar side-effect profile to that of morphine (24,25). Lipid solubility is also similar to that of morphine (octanol:water partition coefficient 0.3 and 1.0, respectively) (26,27). Hydromorphone is currently marketed in IV, suppository, oral solution, and tablet formulations. Hydromorphone's moderate μ-opioid agonist potency, medium (3–4 h) duration of clinical activity, and high water solubility make it an excellent candidate for nasal transmucosal delivery. Chang et al. (28) reported 103.6% bioavailability in an *in situ* recirculation study in rabbits,

Supported, in part, by Inhalation Technology, Inc, now Intranasal Technology, Inc, Lexington, Kentucky.

Accepted for publication February 25, 2003.

Address correspondence and reprint requests to Daniel P. Wermeling, PharmD, Intranasal Technology, Inc, Coldstream Research Campus, 1513 Bull Lea Blvd., Lexington, KY 40511-1200. Address e-mail to info@intranasal.com.

DOI: 10.1213/01.ANE.0000066311.40978.4F

0003-2999/03

demonstrating a great potential for hydromorphone absorption from the nasal mucosa.

This study evaluated the pharmacokinetics and absolute bioavailability of intranasal (IN) and IV hydromorphone hydrochloride (HCl) in healthy volunteers. Objectives of the study were to determine the bioavailability of 2.0 mg of hydromorphone HCl after IN administration compared with a 2.0-mg hydromorphone HCl dose administered IV and to determine dose proportionality between 1.0 and 2.0 mg of IN hydromorphone.

Methods

Twenty-four, nonsmoking, healthy subjects (13 men and 11 women) between the ages of 18 and 36 yr (25.3 ± 5.3 yr; mean ± SD) and weighing 51 to 94 kg (men, 76.3 ± 9.1; women, 66.9 ± 9.3; mean ± SD) participated in this inpatient study. All subjects gave written informed consent for this study as approved by the Medical IRB of the University of Kentucky. Three volunteers were African-American, and 21 were white. All were within ±20% of ideal body weight in relation to height and body frame (per Metropolitan Life Insurance Tables). The volunteers had no history of allergies, acute or chronic nasal symptoms, clinically significant previous nasal surgery, trauma or polyps, or any systemic medical illness. Subjects were asked to abstain from prescription and nonprescription drugs from the date of screening until the end of the study. Subjects abstained from alcohol and caffeine-containing beverages and any medications 48 h before the dosing period and during the study. For all treatments, the subjects fasted for 8 h (except for water *ad libitum* and a caffeine-free soft drink at least 1 h before dosing) before receiving the study drug and continued to fast for 4 h after the drug administration. Subjects were admitted to the Clinical Research Center at University of Kentucky at approximately 6:00 PM on the evening before each study day. Standardized, xanthine-free meals were provided to all subjects at 12:00 PM and 6:00 PM, and a snack was provided at 4:00 PM and 8:00 PM on each study day.

A randomized, open-label, three-way crossover design was used. On three different occasions, the subjects received a single dose of each of the following three treatments in random order, counterbalanced so that an equal number of subjects received each treatment first, second, or third:

- Treatment A: 2.0 mg IV of hydromorphone HCl
- Treatment B: 2.0 mg IN of hydromorphone HCl
- Treatment C: 1.0 mg IN of hydromorphone HCl

All subjects received all three treatments, each separated by a 1-wk washout period.

The hydromorphone HCl IN formulation was prepared in the University of Kentucky College of Pharmacy Center for Pharmaceutical Science and Technology. The composition of the IN solution was identical to the Dilaudid-HP® product (Knoll Pharmaceutical Co, Mount Olive, NJ; 10 mg/mL of hydromorphone HCl) and prepared under Good Manufacturing Practice conditions. The IN formulation, an aqueous solution buffered to a pH value of 4.0 with 0.2% sodium citrate and 0.2% citric acid, provided 1.0 mg of hydromorphone HCl in a 0.1-mL spray from a commercially available, single-dose metered sprayer. Commercially available hydromorphone HCl (Dilaudid® 1.0 mg/mL; Knoll Pharmaceutical) was purchased for comparative IV administration.

Before study drug administration, the subject gently blew his or her nose. A physician administered the nasal spray and attempted to concentrate the application on the lateral nasal wall, particularly the inferior and middle turbinate mucosa. After study drug administration, subjects remained in a semirecumbent position with the head of the bed elevated at a 30- to 45-degree angle for 10 min and refrained from blowing his or her nose for at least 60 min. For IN administration, each subject received a single spray in one nostril for the 1.0-mg dose or a single spray in each nostril for a total of 2.0 mg. IV doses were given through an IV catheter in an antecubital vein in the arm opposite the one from which blood samples were taken. The IV dose (2.0 mg of hydromorphone HCl in 10.0 mL of sterile solution) was administered by infusion over a period of 10 min. All study drugs were administered at approximately 8:00 AM on the study day.

Serial blood samples were obtained through an indwelling venous catheter according to the following schedule: 0 (predose), 5, 10, 15, 20, 30, and 45 min, and 1, 2, 3, 4, 6, 8, 12, and 16 h after drug administration. The beginning of the IV administration was considered time zero. Blood samples were collected in 10-mL heparinized Vacutainer® tubes. After collection, the blood was centrifuged at 4°C, and the plasma was transferred to polypropylene tubes. The plasma was stored at approximately −70°C at the study site until shipped to Kansas City Analytical Services, Inc (Shawnee, KS; now AAI, Kansas City Facility) for hydromorphone assay.

Plasma samples were analyzed for hydromorphone using a validated liquid chromatography-mass spectrometry-mass spectrometry assay by Kansas City Analytical Services, Inc (29). Concentrations <20 pg/mL were reported as less than quantitation limit. The method is linear over the range of 20 to 2000 pg/mL. Between-day and within-day accuracy and precision were <12% relative SD.

A physician was in attendance for at least 4 h after each dose, and subjects were observed throughout the

study session by a research nurse. Vital signs (blood pressure, pulse, and respiratory rate) were measured before and at 0.5, 1, 2, 4, 8, 12, and 16 h after each dose. In addition to spontaneously reported subjective symptoms that were allowed at any time, subjects were also questioned as to their adverse event experience each time vital signs were recorded. Adverse event severity was classified as mild, moderate, or severe using the following definitions: mild = subjective awareness of the symptom but easily tolerated, moderate = symptom produces enough discomfort to interfere with usual activity, and severe = symptom results in incapacity to work or to perform usual activity.

An otolaryngologist examined the nasal passages to evaluate development of local mucosal irritation, inflammation, bleeding, and excoriation or ulceration. Nasal examination was performed at screening, before dosing on each study day, at 2–4 h after each dose, and within 72 h after the subject had received all three treatments.

It should be noted that adverse events were monitored primarily for safety reasons and not to fully characterize the adverse or side effect profile of IN hydromorphone alone or compared with other routes of administration. Full characterization of side effects will require formal quantification using subjective and objective methodologies in laboratory and clinical settings.

Pharmacokinetic variables were determined using standard noncompartmental methods (30) with log-linear least square regression analysis (weighting factor 1/Y) to determine the elimination rate constants (λ_Z) (WinNonlin version 3.2, Pharsight Corp, Palo Alto, CA). Time to and maximum plasma concentration (T_{max} and C_{max}), elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), and volume of distribution at steady state (V_{ss}) (for IV dose only, calculated by V_{ss} = MRT × clearance, where MRT = mean residence time) were also calculated by WinNonlin. The absolute bioavailability (F) for the IN dosage forms, corrected for dose, was determined by the formula $F = Dose_{IV} \times AUC_{IN,0-\infty}/Dose_{IN} \times AUC_{IV,0-\infty}$. Mean plasma concentrations were calculated for graphical evaluation only. Data included in the calculation were for samples with measurable concentrations drawn within 5% of the expected sampling time points.

The syringes and nasal spray pumps were weighed before and after dosing. These weights were used to confirm each subject's dose and to evaluate the accuracy of dose delivery but were not used to calculate individual subject's doses for pharmacokinetic analysis.

Descriptive statistics such as mean and coefficient of variation (%CV) were calculated for the pharmacokinetic variables. Statistical analyses were performed with PC-SAS (version 6.12, SAS Institute, Cary, NC). The statistical tests were two-sided with a critical level of 0.05. The analysis of variance (ANOVA) model included factors sequence, subject (sequence), treatment, and period unless otherwise noted. The carryover effect for the three treatments was analyzed using an ANOVA of log-transformed $AUC_{0-\infty}$, C_{max}, $t_{1/2}$, and F. The carryover effect was not statistically significant ($P > 0.1$). These analyses were performed on the pharmacokinetic variables; ANOVA was performed on log-transformed variables to compare IN treatments. ANOVA of log-transformed dose-normalized variables $AUC_{0-\infty}$ and C_{max} with factors treatment and period was performed to assess dose proportionality of the variables after IN treatments. *P* values are from the ANOVA. Note that an ANOVA comparison of all three treatments showed that $AUC_{0-\infty}$, C_{max}, and F were statistically significantly different ($P < 0.0001$), but this was expected because they are dose- and route-dependent variables. The difference in T_{max} and $t_{1/2}$ values between IN treatments was compared using an ANOVA of rank-transformed T_{max} and $t_{1/2}$. *P* values for comparison of adverse events were calculated using the McNemar test, which takes into account the crossover design.

Results

All subjects completed the study. Mean plasma hydromorphone versus time curve profiles ($n = 24$) after IV and IN administration are shown in Figure 1. Plasma concentrations were still detectable 16 h after administration. Mean concentration versus time curves suggest the multiexponential behavior of hydromorphone (Fig. 1). Mean pharmacokinetic variables from the noncompartmental analysis of measured plasma concentrations for the three doses are presented in Table 1. Absorption of hydromorphone HCl after IN administration was rapid, as indicated by the fact that concentrations were detected in all subjects within 5 min after the IN administration. No significant difference was found between T_{max} values for IN doses. The median T_{max} values were 20 and 25 min for the 1.0- and 2.0-mg IN doses, respectively. Comparison of dose-normalized pharmacokinetic variables demonstrated no significant differences in C_{max} or $AUC_{0-\infty}$ ($P > 0.2$). These findings suggest dose-proportional pharmacokinetics for 1.0- and 2.0-mg doses given IN. As expected, the $t_{1/2}$ values were independent of route of administration and treatment ($P > 0.05$ for comparison of all three treatments). The mean V_{ss} for the IV dose was 384 L (CV 44.2%).

The actual doses administered that were determined by weighing the spray pumps were very close to the planned doses. On average, 1.046 mg (CV 4.3%) and 2.069 mg (CV 4.3%) were dispensed from the spray pumps for the 1.0- and 2.0-mg doses, respectively.

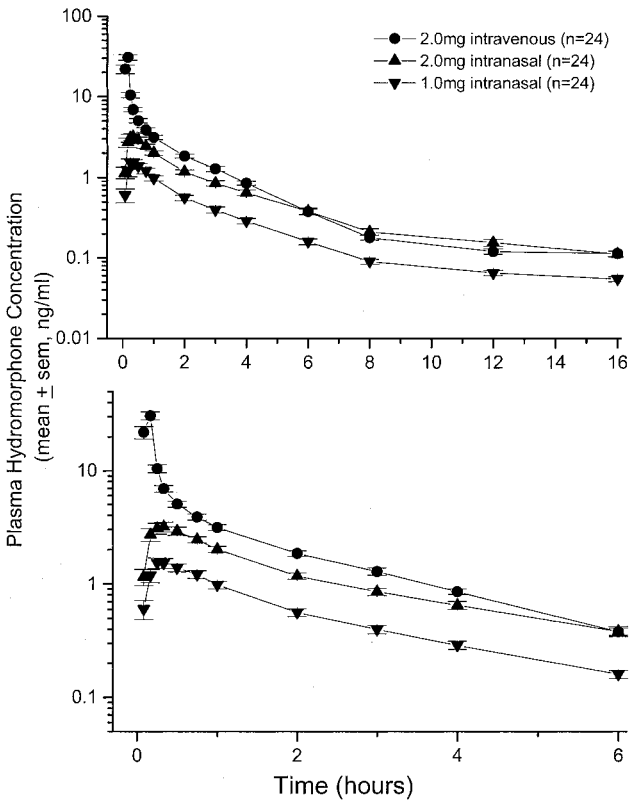

Figure 1. Plasma concentrations of hydromorphone after 1.0- and 2.0-mg intranasal (IN) and 2.0-mg IV hydromorphone hydrochloride (HCl) administration. Values are mean (± SEM) for 24 subjects at each dose. The upper panel includes all measurements over each 16-h study period. The bottom panel displays the same data during the first 6 h for better illustration of absorption and redistribution phases.

There was a statistically significant difference between bioavailabilities for the IN doses. The range of bioavailability was 26%–71% for the 1.0-mg dose and 36%–78% for the 2.0-mg dose. Overall, bioavailability was approximately 55%.

All 24 subjects completed the study without serious adverse events. The most common drug-related adverse events are summarized in Table 2. A drug-related adverse event was an event with relationship to the study drug recorded as possible, probable, or highly probable. A subject was counted at most once for multiple occurrences of an adverse event. If a subject experienced more than one adverse event, only the occurrence with maximum severity was counted.

Adverse events were generally mild to moderate in severity. Most subjects (88% of IN doses) reported feeling a bad taste immediately after the IN doses, but it resolved in approximately 30 min on average. Two (8.3%) subjects reported a mild bad taste after the IV dose. Whereas 21%–25% reported symptoms consistent with nasopharyngeal irritation for a short time after nasal administration, no inflammation was seen on early or follow-up nasal evaluations. The most common adverse events seen with nasal administration were those frequently associated with hydromorphone, e.g., somnolence (38% and 63% for 1.0- and 2.0-mg doses, respectively), dizziness (33% and 58% for 1.0- and 2.0-mg doses, respectively), warm sensation (8% and 29% for 1.0- and 2.0-mg doses, respectively), relaxed feeling (17% for each IN dose), and nausea (4% and 25% for 1.0- and 2.0-mg doses, respectively). Somnolence and dizziness occurred with similar frequency after the 2.0-mg IN and IV doses. Otherwise, these adverse events seemed to be dose-related (assuming the IV dose is larger than the IN dose because of increased bioavailability) and generally mild. There were no clinically relevant changes in vital signs. Importantly, no respiratory depression (decreased rate, decrease in oxygen saturation, or reports of respiratory symptoms) occurred after IN hydromorphone administration in any subject.

Discussion

This article is the first report of the pharmacokinetics of IN hydromorphone HCl in humans. Previous reports establish that orally administered hydromorphone HCl undergoes extensive first-pass metabolism, resulting in a bioavailability of approximately 51% with large interindividual variability (CV 59%) (26). Previous studies have also reported the times to peak plasma concentration as 1 h after oral administration and 1.5 h after rectal administration (26,31). The results of the present study in 24 healthy volunteers show that the IN formulation of hydromorphone HCL achieved comparable plasma levels with a more rapid absorption (peak times of 20–25 min) and reasonable bioavailability with less variability (approximately 55% ± 20%) compared with an oral tablet.

Many factors can influence the variability that would be seen within dosing of hydromorphone in practice. Thus, further investigation is required to demonstrate whether our laboratory findings will translate to more consistency in clinical results with IN administration compared with oral dosing. For example, in the current study, IN doses were administered by a physician who attempted to concentrate application to the lateral nasal wall, particularly the inferior and middle turbinate mucosa. In clinical practice settings, trained personnel would be most likely to administer IN hydromorphone, but in some settings, patients might self-administer doses, and this could increase variability in bioavailability and observed effects. However, a previous study has shown that dose delivery using this unit dose spray pump is accurate and relatively operator-independent (32). Another potential source of increased variability is the presence of

Table 1. Bioavailability and Pharmacokinetics of Hydromorphone (mean and CV as a %) After Administration of 2.0 mg by IV Infusion over 10 min and 1.0 or 2.0 mg of IN Hydromorphone HCl in Healthy Volunteers ($n = 24$)

Formulation	T_{max} (h)[a]	C_{max} (pg/mL)	$AUC_{0-\infty}$ (pg · h/mL)	$t_{1/2}$ (h)	F (%)
2.0 mg IV	0.167 (0.083–0.25)	33207 (35.2)	17222 (23.5)[b]	5.9 (53.2)[b]	assume 100%
1.0 mg IN	0.333 (0.083–1.0)	1743 (41.2)	4420 (28.2)[b]	6.1 (31.3)[b]	52.4 (22.7)[c]
2.0 mg IN	0.417 (0.167–1.0)	3543 (42.3)	9582 (24.8)	6.2 (32.4)	57.5 (18.6)[c]
ANOVA[d]	NS	$P < 0.0001$	$P < 0.0001$	NS	$P < 0.05$
ANOVA on dose normalized variables[e]	NA	NS	NS	NA	NA

T_{max} = time to maximum plasma concentration; C_{max} = maximum plasma concentration; $t_{1/2}$ = elimination half-life; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; F = bioavailability; IV = intravenous; IN = intranasal; NS = not significant ($P > 0.05$), NA = not applicable; ANOVA = analysis of variance.

[a] Data are mean (%CV) except median and range are given for T_{max}.

[b] $n = 23$ because elimination rate constants could not be determined for one subject in each treatment.

[c] $n = 23$ for F for both IN treatments because AUC could not be extrapolated to infinity for one subject's IV treatment.

[d] P values are from an ANOVA with factors sequence, subject (sequence), treatment and period; comparisons made of only the two nasal treatments.

[e] P values are from an ANOVA with factors treatment and period; comparisons made of the dose-normalized variables for only the two nasal treatments.

Table 2. Summary of the Most Common Drug-Related Adverse Events After 2.0 mg of IV and 1.0 mg of IN and 2.0 mg of IN Hydromorphone HCl

Adverse Event (descriptors)	Treatment A 2.0 mg IV ($n = 24$) total (mod–severe)	Treatment B 2.0 mg IN ($n = 24$) total (mod–severe)	Treatment C 1.0 mg IN ($n = 24$) total (mod–severe)	Test[a]
Nasal, oral, pharyngeal				
Bad taste in mouth	2 (1)	21 (6)	21 (5)	b,c
Rhinitis/pharyngitis (burning, stinging, runny, or congested nose; sore throat)	1 (1)	6 (1)	5 (1)	NS
Dry mouth	11 (5)	4 (3)	1 (1)	c
Gastrointestinal				
Nausea	13 (7)	6 (3)	1 (1)	b,c
Vomiting	9 (4)	2 (2)	0	b,c
Psychomotor				
Dizziness (dizzy, lightheaded, and woozy)	16 (11)	14 (7)	8 (1)	c
Somnolence (sleepy, drowsy, and groggy)	14 (11)	15 (9)	9 (3)	NS
Relaxed	2 (1)	4 (2)	4 (1)	NS
Euphoria (high, feel good, and floating)	5 (3)	1 (0)	1 (0)	NS
Asthenia (tired and weak heavy feeling)	10 (6)	2 (1)	5 (2)	b
Other				
Headache	4 (2)	6 (1)	5 (0)	NS
Warm sensation (warm, hot, flushed, and sweaty)	13 (5)	7 (1)	2 (0)	c
Pruritus (itchy nose, face, and all over)	11 (3)	2 (0)	0	b,c

Values indicate the number of subjects reporting the event after each treatment and those in parentheses are the number of adverse events that were rated moderate or severe.

IN = intranasal; NS = not significant, $P > 0.05$.

[a] P values were calculated using the McNemar test.

[b] Treatment A compared to B, $P < 0.05$.

[c] Treatment A compared to C, $P < 0.05$.

[d] Treatment B compared to C, $P < 0.05$.

nasal mucosal pathology. For example, hyperemia associated with nasal mucosal inflammation would be expected to influence drug absorption after IN application. A recent crossover study evaluated hydromorphone pharmacokinetics and bioavailability in 12 pretreated (with IN fluticasone allergy treatment) and untreated allergic rhinitis patients. There was no difference in hydromorphone bioavailability between untreated and pretreated patients, but the rate of absorption of hydromorphone was significantly slower in allergic rhinitis patients after fluticasone pretreatment compared with those who were untreated (median peak times were 30 and 15 minutes, respectively) (33).

The decreased bioavailability of nasal hydromorphone in the present study compared with the animal study (103.6% bioavailability in rabbits) reported by Chang et al. (28) can be attributed to the method used. In that study, a recirculation technique was used in which the nasopalatine tract was surgically closed and drug solution was recirculated through the nasal cavity for several hours, creating an artificially increased

opportunity for absorption. Less than complete bioavailability after IN administration may be explained by metabolism during absorption across the nasal mucosa similar to first pass elimination in the case of oral administration or simply incomplete absorption and swallowing. There was no evidence of swallowing in this study. Although hydromorphone's high aqueous solubility is an advantage for developing nasal formulations, it hinders absorption through biological membranes. There is evidence of the influence of solubility in studies of the IN administration of more lipophilic opioids such as alfentanil (7) and sufentanil (17). Their greater lipophilicity is probably responsible for their larger bioavailabilities (65% and 78%, respectively) and earlier peak plasma concentrations (9 and 10 minutes, respectively).

The unit dose spray pump accurately and easily delivered the aqueous solution of hydromorphone HCl. All the inactive ingredients used were generally recognized as safe materials. Whereas nasal stuffiness or rhinitis occurred in a few subjects, and bad taste was common, the administration of hydromorphone nasal solution did not cause any local irritation in this single-dose study. Future investigations to evaluate effects of multiple doses on nasal mucosal are warranted. The systemic adverse event profile was similar to that observed after IM administration of similar doses of hydromorphone (22,34). Observed differences in occurrence of adverse events across study days is most likely because of differences in plasma concentrations achieved with the different administration routes and IN doses of hydromorphone. It is important to note that this study was not designed to measure analgesic effects of IN hydromorphone compared with other routes of administration. Such investigations of pharmacodynamic effects, either in the laboratory or clinical setting, are required to characterize the magnitude and time course of analgesic effects and to compare analgesia to the side-effect load.

IN hydromorphone is a promising alternative to injectable (IV and IM) hydromorphone. Health care professionals have an abundance of experience with hydromorphone, and this noninvasive method of administration offers a more convenient and palatable alternative to injection for many patients with severe pain.

In conclusion, this study clearly demonstrates that for the doses tested, IN hydromorphone HCl is rapidly and reliably absorbed. On the basis of this study in healthy volunteers, this aqueous formulation of IN hydromorphone HCL is worthy of further investigation as a therapeutic alternative for a convenient, noninvasive, and rapidly acting opiate analgesic for treating acute pain.

The authors acknowledge the skillful assistance of Mrs. Debbie Browne in data verification and summarization.

References

1. Henderson JM, Brodsky DA, Fisher DM, et al. Preinduction of anesthesia in pediatric patients with nasally-administered sufentanil. Anesthesiology 1988;68:671–5.
2. Streisand JB, Stanley TH, Hague B, et al. Oral transmucosal fentanyl citrate premedication in children. Anesth Analg 1989; 69:28–34.
3. Striebel HW, Koenigs D, Kramer J. Postoperative pain management by intranasal demand-adapted fentanyl titration. Anesthesiology 1992;77:281–5.
4. Striebel HW, Pommerening J, Rieger A. Intranasal fentanyl titration for postoperative pain management in an unselected population. Anaesthesia 1993;48:753–7.
5. Striebel HW, Oelmann T, Spies C, et al. Patient-controlled intranasal analgesia: a method for noninvasive postoperative pain management. Anesth Analg 1996;83:548–51.
6. Sharar SR, Bratton SL, Carrougher GJ, et al. A comparison of oral transmucosal fentanyl citrate and oral hydromorphone for inpatient pediatric burn wound care analgesia. J Burn Care Rehabil 1998;19:516–21.
7. Schwagmeier R, Boerger N, Meissner W, Striebel HW. Pharmacokinetics of intranasal alfentanil. J Clin Anesth 1995;7:109–13.
8. Hallett A, O'Higgins F, Francis V, Cook TM. Patient-controlled intranasal diamorphine for postoperative pain: an acceptability study. Anaesthesia 2000;55:532–9.
9. Chrubasik J, Friedrich G, Geller E. Absorption and bioavailability of morphine offered via inhalation. Reg Anesth 1988;13:27 (suppl 25).
10. Rudy A, Wermeling D, Coda BA, et al. Pharmacokinetics and bioavailability of hydromorphone HCl after intranasal and intravenous administration. AAPS Pharm Sci Suppl 2001;3.
11. Striebel WH, Malewicz J, Hermanns K, Castello R. Intranasal meperidine titration for postoperative pain relief. Anesth Analg 1993;76:1047–51.
12. Elenbaas RM, Iacono CU, Koellner KJ, et al. Dose effectiveness and safety of butorphanol in acute migraine headache. Pharmacotherapy 1991;11:56–63.
13. Joyce TH 3rd, Kubicek MF, Skjonsby BS, Jones MM. Efficacy of transnasal butorphanol tartrate in postepisiotomy pain: a model to assess analgesia. Clin Ther 1993;15:160–7.
14. Scott JL, Smith MS, Sanford SM, et al. Effectiveness of transnasal butorphanol for the treatment of musculoskeletal pain. Am J Emerg Med 1994;12:467–71.
15. Abboud TK, Zhu J, Gangolly J, et al. Transnasal butorphanol: a new method for pain relief in post-cesarean section pain. Acta Anaesthesiol Scand 1991;35:14–8.
16. Gillis JC, Benfield P, Goa KL. Transnasal butorphanol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute pain management. Drugs 1995;50: 157–75.
17. Helmers JH, Noorduin H, Van Peer A, et al. Comparison of intravenous and intranasal sufentanil absorption and sedation. Can J Anaesth 1989;36:494–7.
18. Shyu WC, Pittman KA, Robinson D, Barbhaiya RH. The absolute bioavailability of transnasal butorphanol in patients experiencing rhinitis. Eur J Clin Pharmacol 1993;45:559–62.
19. Hill JL, Zacny JP. Comparing the subjective, psychomotor, and physiological effects of intravenous hydromorphone and morphine in healthy volunteers. Psychopharmacology (Berl) 2000; 152:31–9.
20. Coda B, Tanaka A, Jacobson RC, et al. Hydromorphone analgesia after intravenous bolus administration. Pain 1997;71:41–8.
21. Dunbar PJ, Chapman CR, Buckley FP, Gavrin JR. Clinical analgesic equivalence for morphine and hydromorphone with prolonged PCA. Pain 1996;68:265–70.
22. Mahler DL, Forrest WH Jr. Relative analgesic potencies of morphine and hydromorphone in postoperative pain. Anesthesiology 1975;42:602–7.
23. Hanna C, Mazuzan JE Jr, Abajian J Jr. An evaluation of dihydromorphinone in treating postoperative pain. Anesth Analg 1962;41:755–61.

24. Rapp SE, Egan KJ, Ross BK, et al. A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 1996;82:1043–8.
25. Coda BA, O'Sullivan B, Donaldson G, et al. Comparative efficacy of patient-controlled administration of morphine, hydromorphone, or sufentanil for the treatment of oral mucositis pain following bone marrow transplant. Pain 1997;72:333–46.
26. Parab PV, Ritschel WA, Coyle DE, et al. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. Biopharm Drug Dispos 1988;9: 187–99.
27. Roy SD, Flynn GL. Solubility and related physiochemical properties of narcotic analgesics. Pharm Res 1988;5:580–6.
28. Chang S-F, Moore L, Chien YW. Pharmacokinetics and bioavailability of hydromorphone: effect of various routes of administration. Pharm Res 1988;5:718–21.
29. Liu Y, Schorno KS, Mason WD, Fu CHJ. Determination of hydromorphone in human plasma by liquid chromatography coupled with tandem mass spectrometry. Presented at 16th Montreux Liquid Chromatography Mass Spectrometry Symposium, Hilton Head Island, SC, November 1999.
30. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Marcel Dekker, 1982:409–17.
31. Vallner JJ, Stewart JT, Kotzan JA, et al. Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. J Clin Pharmacol 1981; 21:152–6.
32. Rudy AC, Wermeling DPH, Archer SM, Jay M. Accuracy of intranasal (IN) butorphanol tartrate (BT) delivery in 2 nasal spray pumps used in clinical study. AAPS Pharm Sci Suppl 2000;2.
33. McNamara P, Davis G, Miller J, et al. Bioavailability and pharmacokinetics of intranasal hydromorphone in treated and untreated allergic rhinitis patients: Presented at the American College of Clinical Pharmacy Annual Meeting, Tampa, FL, October 2001. Pharmacotherapy 2001;21:1265.
34. Wallenstein SL, Houde RW, Portenoy R, et al. Clinical analgesic assay of repeated and single doses of heroin and hydromorphone. Pain 1990;41:5–13.