Effect of Fluticasone Propionate Nasal Spray on Bioavailability of Intranasal Hydromorphone Hydrochloride in Patients with Allergic Rhinitis

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Study Objective. To investigate the effect of the nasal corticosteroid fluticasone propionate on the bioavailability and pharmacokinetics of single-dose intranasal hydromorphone hydrochloride in patients with allergic rhinitis.

Design. Randomized, three-way, crossover pharmacokinetic study.

Setting. University clinical research unit.

Patients. Twelve patients with allergic rhinitis.

Intervention. Hydromorphone hydrochloride 2.0 mg was administered by intravenous infusion (treatment A), intranasal spray without allergic rhinitis treatment (treatment B), and intranasal spray after 6 days of fluticasone propionate (treatment C). Blood samples were collected serially from 0–16 hours.

Measurements and Main Results. Pharmacokinetic parameters were determined by noncompartmental methods. An analysis of variance (ANOVA) model was used for statistical analysis. Mean (% coefficient of variation) absolute bioavailability of intranasal hydromorphone was 51.9% (28.2) and 46.9% (30.3) in patients with allergic rhinitis with and without treatment with fluticasone propionate, respectively. Mean maximum concentration (C_{max}) values were 3.02 and 3.56 ng/ml, respectively. No statistical differences in C_{max} and area under the concentration versus time curve were detected between intranasal treatments. Bioavailability values for both intranasal treatments were lower than those in healthy volunteers (57%). Median time to C_{max} (T_{max}) values were significantly different ($p=0.02$) for treatments B and C (15 and 30 min, respectively) using rank-transformed T_{max} for ANOVA. Adverse effects were consistent with known effects of hydromorphone administered by other routes, with the exception of bad taste after intranasal administration.

Conclusion. Hydromorphone was rapidly absorbed after nasal administration, with maximum concentrations occurring for most subjects within 30 minutes. Allergic rhinitis may affect pain management strategies for intranasal hydromorphone, with a delay in onset of action for patients treated with fluticasone propionate.

Key Words: intranasal hydromorphone, allergic rhinitis, fluticasone propionate, bioavailability.

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Methods to improve routes of delivery of opioid analgesics, including the intranasal route, are receiving growing interest.[1] Most patients with moderate-to-severe pain from cancer can be

managed with oral opioids, but 33–70% require alternative routes of administration.[2–4] For ambulatory postoperative patients, oral opioids are the mainstay of pain control, but other routes are recommended for treatment of acute pain.[5] Nasal administration may have advantages over more invasive routes, including ease of administration, rapid onset, and patient control. Several opioids have been studied for intranasal administration, including alfentanil,[6] fentanyl,[7] sufentanil,[8] oxycodone,[9] buprenorphine,[10] butorphanol,[11] methadone,[12] and, most recently, hydromorphone.[13, 14]

Hydromorphone, a μ-selective opioid agonist 5–8 times more potent than morphine, is effective in managing postoperative and moderate-to-severe chronic pain.[15–17] Similar to morphine, orally administered hydromorphone undergoes extensive first-pass effect resulting in a low and variable systemic bioavailability ranging from 10–65%.[18–21] Intranasal administration has been investigated because it bypasses gut metabolism and first-pass effect. A study of hydromorphone pharmacokinetics in healthy volunteers reported mean bioavailabilities of 52% and 57% after single intranasal doses of 1.0 and 2.0 mg, respectively.[14] In patients with nonallergic rhinitis, bioavailabilities were 54.4% and 59.8%, respectively, with and without rhinitis treatment (oral pseudoephedrine hydrochloride or intranasal oxymetazoline hydrochloride) (Davis et al, unpublished data, 2001). In both studies, intranasal hydromorphone was well tolerated, with bad taste being the most common adverse event.

Rhinitis (inflammation of the nasal mucosa) is classified by etiology as allergic or nonallergic. Allergic rhinitis is the most prevalent, affecting 20–40 million people in the United States annually.[22, 23] Rhinitis is a hypersensitivity reaction manifested by increased cholinergic and sensory nerve activity in the nasal mucosa, resulting in one or more of the following symptoms: nasal itching, rhinorrhea, nasal congestion, and sneezing.[23] Parasympathetic nerve stimulation dilates arterioles, which causes increased permeability and congestion of the nasal mucosa and promotes nasal airway glands to increase secretion. Sensory nerve stimulation leads to perception of nasal itch and congestion that causes sneezing. The early inflammatory response of allergic rhinitis is mediated primarily by immunoglobulin E causing release of inflammatory mediators (e.g., histamine, leukotrienes, prostaglandins).[24–26] Late-phase response is characterized by T lymphocyte activation, production of TH_2-type cytokines, and tissue eosinophilia.[25] Intranasal corticosteroids are the most effective agents for managing allergic rhinitis.[26–29] Corticosteroids potently inhibit T lymphocyte responses, and in clinical studies in subjects with allergic rhinitis, they were extremely effective in blocking both early- and late-phase allergic reactions.[27]

Because of the highly vascular nature of nasal tissues, inflammation from rhinitis results in increased nasal blood flow and permeability of the nasal mucosa.[30, 31] It follows that inflammation and treatment with a nasally inhaled corticosteroid could alter the extent and rate of nasal absorption of other drugs. The objectives of our study were to assess the bioavailability and tolerance of a single dose of intranasal hydromorphone, and the effect of nasal corticosteroid fluticasone propionate on the rate and extent of absorption of intranasal hydromorphone in patients with allergic rhinitis.

Methods

Twelve nonsmoking subjects with perennial or seasonal allergic rhinitis (5 men, 7 women; 10 Caucasian, 2 African-American; age range 21–45 yrs, mean 29.4 yrs) participated in this open-label, randomized, three-way crossover inpatient study after giving informed consent. The study was conducted according to principles of the Helsinki Declaration and was approved by the medical institutional review board of the University of Kentucky.

Participants were selected based on medical history, physical and nasal examinations, vital signs, and clinical laboratory tests. They were required to have a history of seasonal or perennial allergies, and were screened by an allergy questionnaire to distinguish between allergic and nonallergic rhinitis. Participants had no acute or

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chronic nasal symptoms other than allergic rhinitis; no clinically significant nasal surgery, polyps, or other physical abnormalities of the nose; and no cardiovascular, gastrointestinal, renal, hepatic, pulmonary, or hematologic disease. They abstained from alcohol and beverages containing caffeine for 48 hours before the dosing period and during the study.

Hydromorphone Hydrochloride and Fluticasone Propionate Administration

Subjects were randomized to receive single doses of hydromorphone hydrochloride 2.0 mg administered intravenously (treatment A), intranasally with no pretreatment (treatment B), or intranasally after 6 days of pretreatment with fluticasone propionate 200 µg (treatment C). The three treatment periods were separated by a 6-day washout period. For intravenous administration, hydromorphone hydrochloride 2.0 mg (Dilaudid Injection, 1 mg/1 ml; Knoll Pharmaceutical, Whippany, NJ) was diluted to 10 ml and infused over 10 minutes. Intranasal doses of hydromorphone hydrochloride (1.0 mg/100 µl) were administered by a single-dose spray pump (Pfeiffer of America, Princeton, NJ) to the lateral wall of each nostril. Subjects were asked to blow their noses gently immediately before and not again until 60 minutes after intranasal administration.

Subjects were instructed not to take any new systemic or additional nasal drugs, prescription or nonprescription, during the study that might interact with hydromorphone metabolism or nasal physiology, with the exception of fluticasone propionate provided for the study. Allergy shots were not allowed for 1 week before any treatment. Subjects receiving treatment A were allowed to take their usual rhinitis drugs as approved by the medical supervisor. Six days before treatment B, subjects were asked to stop taking nasal and systemic treatment for rhinitis. Six days before treatment C, subjects were allowed to take only fluticasone propionate 4 sprays (50 µg/spray) every evening until the day they received treatment C.

Blood Samples

Blood samples (10 ml) were collected in glass tubes containing heparin and centrifuged, and plasma was separated and stored at -20°C at the study site until analyzed for hydromorphone concentration. Serial blood samples were obtained by venipuncture according to the following schedule: 0 (predose), 5, 10, 15, 20, 30, and 45 minutes, and 1, 2, 3, 4, 6, 8, 12, and 16 hours after drug administration.

Hydromorphone Assay

The sample analysis was conducted using a validated liquid chromatography–mass spectrometry–mass spectroscopy assay method (AAI Development Services, Inc.–Kansas City, Shawnee, KS). Concentrations less than 20 pg/ml were reported as below quantification limit. Samples with concentrations greater than 2000 pg/ml were reanalyzed using a dilution so that the assayed concentration was within the range of 20–2000 pg/ml. Between-day and within-day accuracy and precision were below 12% relative standard deviation.

Pharmacokinetic Analyses

Pharmacokinetic parameters were determined by standard noncompartmental methods with log-linear least square regression analysis to determine elimination rate constants using WinNonlin Standard, version 3.2 (Pharsight Corp., Palo Alto, CA). Areas under the concentration versus time curves from time zero to infinity ($AUC_{0-\infty}$) were calculated using a combination of linear and logarithmic trapezoidal rules, with extrapolation to infinity by dividing the last measurable serum concentration by the elimination rate constant (λ_z).[32] Values for maximum concentration (C_{max}) and time to C_{max} (T_{max}) were determined by WinNonlin. The elimination half-life was determined from $0.693/\lambda_z$. Clearance/bioavailability was calculated by dividing the dose by $AUC_{0-\infty}$. Volume of distribution at steady state was calculated as clearance x mean residence time for intravenous data with correction for the infusion time.[32]

Statistical Analyses

Statistical analyses were performed with PC-SAS, version 6.12 (SAS Institute, Cary, NC). Statistical tests were two-sided with a critical level of 0.05. Analysis of variance (ANOVA) with factors for sequence, subject (sequence), treatment, and period was performed for log-transformed AUC and C_{max}. Least squares geometric means from ANOVA were used to calculate ratios and their 90% confidence intervals (CIs) among treatment groups for AUC and C_{max}. The carryover effect for the two intranasal treatments was analyzed using an

Table 1. Pharmacokinetic Parameters After Single-Dose Hydromorphone Hydrochloride 2.0 mg Administration in Each Treatment Group

Parameter	Treatment A	Treatment B	Treatment C
T_{max} (hrs)	0.167 (0.083–0.167)	0.250 (0.167–0.5)	0.500 (0.167–1.967)
C_{max} (ng/ml)	34.76 (47.0)	3.56 (36.3)	3.02 (57.3)
Half-life (hrs)	5.61 (56.3)	6.44 (48.8)	4.85 (31.7)
AUC_{0-t} (ng•hr/ml)	15.54 (20.7)	6.70 (28.9)	7.76 (29.6)
$AUC_{0-\infty}$ (ng•hr/ml)	16.29 (21.3)	7.44 (26.0)	8.31(26.7)
MRT (hrs)	3.28 (26.4)	6.05 (33.4)	5.27 (25.8)
Clearance (L/hr)	113 (19.7)	—	—
V_{ss} (L)	370 (31.3)	—	—
Bioavailability	Assume 100	46.9 (30.3)	51.9 (28.2)

Treatment A = intravenous hydromorphone HCl 2.0 mg; treatment B = intranasal hydromorphone HCl 2.0 mg without pretreatment with fluticasone propionate; treatment C = intranasal hydromorphone HCl 2.0 mg with pretreatment with fluticasone propionate; AUC_{0-t} = area under the concentration-time curve from time zero to time t; $AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; MRT = mean residence time; V_{ss} = volume of distribution at steady state.
Data are mean (% coefficient of variation), except for T_{max} values which are median (range).

ANOVA of log-transformed AUC and C_{max}. The difference in T_{max} between intranasal treatments was compared by ANOVA of rank-transformed T_{max}.

Results

Safety Assessment

Twelve subjects completed the study without clinically significant or serious adverse events. The most common adverse effects were those generally associated with hydromorphone, sedation and nausea. Their intensity tended to be greater for the intravenous treatment than for the two intranasal treatments. One frequently reported adverse event for the intranasal formulation was a bad taste in the back of the throat. No clinically relevant changes were seen in physical examinations, nasal evaluations, or laboratory tests.

Pharmacokinetic and Statistical Analyses

Table 1 summarizes pharmacokinetic data for the three treatments. The mean plasma concentration versus time profiles over the first 3 hours for intranasal doses and 12 hours for all doses are shown in Figure 1. Hydromorphone appears to have a biphasic concentration versus time profile after intravenous administration. The graphs show that hydromorphone's absorption after intranasal administration was rapid. Median T_{max} values were 15 and 30 minutes for the intranasal doses after treatments B and C, respectively. The range of T_{max} values after treatment C from 10–120 minutes suggested delayed absorption, but only three subjects had values greater than 30 minutes and one reached 95% of peak by 30 minutes. No significant sex differences were found for AUC_{0-t} and $AUC_{0-\infty}$ ($p>0.1$). A significant difference was found for C_{max} values between men and women ($p<0.02$, men < women). Table 2 summarizes ratios and 90% CIs of C_{max} and AUC values after the three treatments. The AUC_{0-t} and $AUC_{0-\infty}$ were comparable between intranasal treatments.

Discussion

To our knowledge, this is the first study to evaluate effects of allergic rhinitis and pretreatment with an intranasal corticosteroid on the

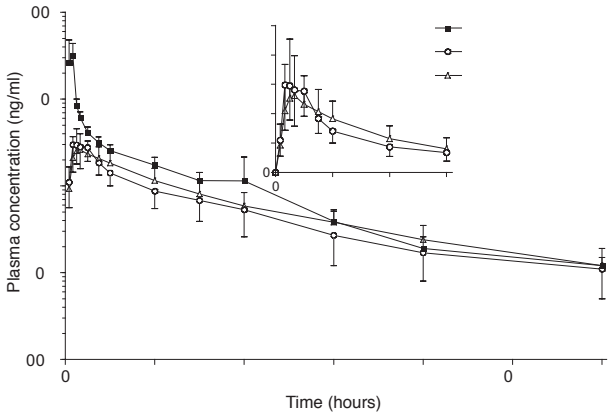

Figure 1. Mean ± SD plasma hydromorphone concentration versus time profiles after single doses of hydromorphone HCl 2.0 mg by intravenous (IV) infusion (treatment A), and intranasal (IN) administration without (treatment B) and with (treatment C) pretreatment with fluticasone propionate. The inset is comparison of treatments B and C during the first 3 hours.

Table 2. Summary of Ratios of Least Squares Geometric Means and 90% Confidence Intervals

	Geometric Means[a]			Ratios (90% confidence intervals)		
Parameter	A	B	C	B:A	C:A	C:B
$AUC_{0-\infty}$ (ng•hr/ml)	15.98	7.20	7.99	0.45 (0.39–0.52)	0.50 (0.43–0.58)	1.11 (0.96–1.28)
AUC_{0-t} (ng•hr/ml)	15.25	6.43	7.39	0.42 (0.36–0.49)	0.48 (0.42–0.57)	1.15 (0.99–1.34)
C_{max} (ng/ml)	31.57	3.38	2.60	0.11 (0.08–0.14)	0.08 (0.06–0.11)	0.77 (0.58–1.03)

A = treatment with intravenous hydromorphone HCl 2.0 mg; B = intranasal hydromorphone HCl 2.0 mg without pretreatment with fluticasone propionate; C = intranasal hydromorphone HCl 2.0 mg with pretreatment with fluticasone propionate; $AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; AUC_{0-t} = area under the concentration-time curve from time zero to time t; C_{max} = maximum concentration.

[a]Least squares geometric means are from an analysis of variance with factors sequence, subject (sequence), treatment, and period for log-transformed AUCs and C_{max}.

pharmacokinetics of intranasal hydromorphone. It was conducted because physiologic changes associated with rhinitis and treatment theoretically could affect drug absorption through the nasal mucosa. Clinicians should understand the potential effects of this common ailment on bioavailability and plasma concentrations of this potent opiate.

Intranasal hydromorphone in our untreated patients with allergic rhinitis had rapid absorption, similar to studies in healthy volunteers,[14] lactating women,[13] and those with nonallergic rhinitis (Davis et al, unpublished data, 2001). However, absorption in patients with rhinitis pretreated with fluticasone propionate was delayed, with a median T_{max} of 30 minutes. The range of bioavailabilities (32–73%) in our subjects was similar to that in other studies. In healthy volunteers, mean absolute bioavailability after intranasal hydromorphone hydrochloride use was 57% (range 36–78%).[14] After pretreatment with either an oral decongestant (pseudoephedrine hydrochloride) or nasal vasoconstrictor (oxymetazoline hydrochloride) in patients with nonallergic rhinitis, mean absolute bioavailability of intranasal hydromorphone was 54% (range 33–96%), but it was not significantly different from 60% in untreated patients (range 50–89%) (Davis et al, unpublished data, 2001). In our study, absorption of intranasal hydromorphone in patients with (46.9%) and without (51.9%) fluticasone propionate pretreatment was somewhat lower than previously reported. However, fluticasone propionate did not affect systemic bioavailability of intranasal hydromorphone significantly compared with the untreated group.

Our results suggest that the fraction of the intranasal dose of hydromorphone absorbed by inflamed nasal mucosa is similar in subjects treated and not treated with a nasal corticosteroid. The lack of effect of nasal mucosa inflammation on drug absorption is consistent with studies with butorphanol,[33] buserelin,[34] and triamcinolone acetonide,[35] but not desmopressin.[36] The absolute bioavailability of intranasal butorphanol was around 70% when administered with and without the topical nasal decongestant oxymetazoline in patients with acute or allergic rhinitis.[33] This was similar to the bioavailability of intranasal butorphanol in healthy volunteers.[11, 37, 38] However, pretreatment with the topical decongestant significantly slowed the rate of absorption and lowered the C_{max} of intranasal butorphanol.[33] Vasoconstriction and reduced blood flow were suggested to affect the rate but not extent of intranasal absorption of butorphanol. Absorption of intranasal buserelin, measured as the serum luteinizing hormone response, was not affected in volunteer men after experimental induction of rhinitis with histamine.[34] Short- and long-term intranasal administration of triamcinolone acetonide to patients with inflamed nasal mucosa did not result in enhanced systemic drug absorption or accumulation.[35] However, the antidiuretic activity and, presumably, absorption of intranasal desmopressin were enhanced in healthy men after experimental induction of rhinitis with intranasal histamine.[36] Increased intranasal absorption of desmopressin was attributed to the apparent increase in nasal blood flow.

Our study was not designed to measure analgesic effects of intranasal hydromorphone when administered concomitantly with fluticasone propionate. However, plasma concentrations were consistent with the therapeutic range reported in pharmacokinetic studies.[39, 40] When hydromorphone concentrations were measured in patients treated for chronic severe pain, the minimum effective plasma concentration was approximately 4 ng/ml.[39] For patients with

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