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Bioavailability and Pharmacokinetics of Intranasal Hydromorphone in Patients Experiencing Vasomotor Rhinitis

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Abstract

Background and objective: Narcotic analgesics such as hydromorphone undergo an extensive first-pass effect resulting in a low systemic bioavailability following oral administration. Alternative dosing routes, such as rectal and intranasal (IN) routes, have been suggested as options for oral or intravenous administration. Rhinitis and pharmacological agents used for treatment are considered factors that could alter the rate and extent of absorption of drugs administered by the nasal route. The purpose of this study was to evaluate the pharmacokinetics of intranasal hydromorphone hydrochloride (HCl) in patients with vasomotor rhinitis.

Methods: Ten patients completed the randomised, three-way crossover study. During the three treatment periods, a single dose of hydromorphone HCl 2.0mg was administered via intravenous infusion (treatment A) and the intranasal route without (treatment B) or with (treatment C) vasoconstrictor pretreatment for rhinitis. Blood samples were collected serially from 0 to 16 hours. Noncompartmental methods were used to determine pharmacokinetic parameters.

Results: Maximum plasma concentrations were 3.69 and 3.38 μg/L for treatments B and C, respectively. Mean (% coefficient of variation) bioavailability of intranasal hydromorphone was 54.4% (34.8) and 59.8% (22.1) with and without pretreatment, respectively. Pretreatment of rhinitis did not significantly affect the rate or extent of absorption of hydromorphone in this study. There was not a significant difference in bioavailability between treated and untreated rhinitis.

Conclusions: This study found intranasal administration of hydromorphone in patients experiencing vasomotor rhinitis had acceptable bioavailability and a pharmacokinetic profile comparable to previous studies. These data support further investigation of this single-dose delivery system for clinical use.

Hydromorphone, a μ-selective opioid agonist, is a semisynthetic derivative of morphine used for the management of postoperative pain and moderate-to-severe chronic pain associated with terminal illnesses, such as cancer.[1-3] On a milligram basis, hydromorphone is 5–8.5 times as potent as morphine when given by the oral route, and 5–7.5 times as potent as morphine when given intravenously.[4]

Narcotic analgesics such as hydromorphone and morphine have been suggested to undergo an extensive first-pass effect resulting in a low systemic bioavailability following oral administration. Similar to morphine, hydromorphone has been reported to have wide interindividual variation of oral bioavailability ranging from 10% to 65%.[5-9]

Alternative dosing routes, such as rectal and intranasal (IN), have been suggested as options for oral or intravenous administration of opioids.[10] Rectal administration of hydromorphone has been evaluated in healthy adults and found to have low bioavailability (33%) with wide interindividual variation (10–65%).[6,7] Factors potentially influencing rectal bioavailability include poor absorption from the rectal mucosa because of high ionisation, small rectal surface area, slow release from the suppository, reduced contact with the rectal epithelial tissue, and first-pass elimination.[6]

The IN route potentially improves systemic bioavailability of drugs since it bypasses gastrointestinal degradation and the hepatic first-pass effect. Potential advantages of IN administration include ease of administration, rapid onset and patient control. There are also potential benefits in safety with the avoidance of needles associated with intravenous (IV) or intramuscular (IM) administration. An alternative dosing route may also be valuable in patients experiencing nausea and vomiting or in the paediatric setting. Other narcotics, such as alfentanil, butorphanol, buprenorphine, fentanyl, oxycodone and sufentanil, have been evaluated in humans following intranasal administration with favourable results.[9]

Rhinitis, inflammation of the nasal mucosa, is a common condition in which the permeability of the nasal mucosa increases, nasal blood flow increases, and secretions permeate out of the nasal glands.[10] Chronic rhinitis is classified by aetiology as allergic or nonallergic. Allergic rhinitis is the most prevalent type of chronic rhinitis, but 30–50% of patients diagnosed with rhinitis may have nonallergic causes.[11] Vasomotor rhinitis is a subtype of nonallergic rhinitis and described as chronic, noninfectious rhinitis usually without nasal eosinophilia. Vasomotor rhinitis manifests as nasal symptoms (rhinorrhoea, nasal congestion, sneezing and postnasal drip) that occur in response to environmental conditions such as cold air, high humidity, strong odours and inhaled irritants. Rhinitis, regardless of aetiology, is considered a factor that could alter the rate and extent of absorption of drugs administered by the nasal route. Moreover, it is also common for patients with rhinitis to use nasal vasoconstrictors or oral decongestants as treatment. Treatment with these agents could theoretically alter the extent and rate of nasal absorption of other medications.

The objectives of this study were to assess the absolute bioavailability and single-dose tolerance of intranasal hydromorphone hydrochloride (HCl), and the effect of an oral decongestant (pseudoephedrine) or nasal vasoconstrictor (oxymetazoline) on the rate or extent of absorption of IN hydromorphone in patients experiencing vasomotor rhinitis.

Patients and Methods

Subjects

Twelve nonsmoking patients with vasomotor rhinitis (five males, seven females) between the ages of 28 and 55 years participated in this inpatient study after providing written informed consent. The Medical Institutional Review Board of the University of Kentucky approved the study.

Study participants were selected based on medical history, physical and nasal examinations, vital signs, clinical laboratory tests and their history of nonallergic rhinitis. An allergy questionnaire was used by an otolaryngologist to screen patients to distinguish between allergic and nonallergic rhinitis. Patients had no acute or chronic nasal symptoms other than the nonallergic rhinitis, and no clinically significant previous nasal surgery or polyps or other physical abnormalities of the nose, cardiovascular, gastrointestinal, renal, hepatic, pulmonary or haematological disease. Patients abstained from alcohol and caffeine-containing beverages 48 hours before the dosing period and during the study. Patients were asked to abstain from prescription and nonprescription drugs that might interact with hydromorphone metabolism or nasal physiology, with the exception of pseudoephedrine and oxymetazoline provided for this study. Patients receiving the IV dose were allowed to take their usual

rhinitis medications as approved by the medical supervisor.

Study Procedures

This was a randomised, three-way crossover, single-dose study with each treatment separated by a washout period of at least 2 days. Twelve patients were enrolled and randomised to one of six sequence groups (ABC, ACB, BCA, BAC, CAB or CBA) to receive each of the following treatments:

Treatment A: IV hydromorphone HCl 2.0mg

Treatment B: IN hydromorphone HCl 2.0mg

Treatment C: IN hydromorphone HCl 2.0mg with pretreatment for rhinitis.

In a random manner, half of the subjects received vasoconstrictor pretreatment consisting of a 60mg oral dose of pseudoephedrine hydrochloride (Sudafed®, Pfizer Inc., New York, NY, USA)[1] administered 1 hour before or two nasal sprays per nostril of 0.05% oxymetazoline (Afrin®, Schering-Plough, Kenilworth, NJ, USA) administered immediately prior to dosing.

Eleven patients reported to the research centre the night prior to treatment and one patient was admitted the morning of the treatment, 2 hours prior to dosing. Study patients remained in the centre approximately 16 hours after dosing. Drug administration occurred at approximately 8am on each study day. Except for water *ad libitum*, the study patients underwent an overnight fast of ≥8 hours. Blood pressure, respiration and pulse rate were measured at predetermined times throughout the study. Adverse events were monitored by study personnel. Nasal examinations were completed by an otolaryngologist prior to study drug administration, 2–4 hours after administration, and at the post-study evaluation. Any significant change in nasal physiology was documented as an adverse effect and relationship to study drug was determined.

Venous blood samples (10mL) were obtained from an indwelling catheter at 0 (predose), 5, 10, 15, 20, 30 and 45 minutes, and 1, 2, 3, 4, 6, 8, 12 and 16 hours after hydromorphone administration. The samples were collected in Vacutainer® tubes containing the anticoagulant sodium heparin, centrifuged at 4°C to separate the plasma and the cells, and the plasma was transferred to polypropylene tubes and stored at approximately –20°C.

Dose Administration

For treatment A, hydromorphone HCl 2.0mg (Dilaudid® Injection, 1 mg/mL) was diluted to 10mL and infused over 10 minutes. IN doses (treatments B and C) of hydromorphone HCl were administered using a single-dose spray pump (Pfeiffer of America, Princeton, NJ, USA). Patients were asked to gently blow their nose immediately prior to intranasal administration and were then not allowed to blow their nose again until 60 minutes following drug administration. A single spray of hydromorphone HCl (1.0mg/100μL) was administered to the lateral nasal wall of each nostril. Patients remained in bed at a 30- to 45-degree angle prior to and for 2 hours following drug administration.

Assay of Samples

The sample analysis was conducted using a liquid chromatography/mass spectrometry/mass spectroscopy assay method by AAI International, Inc. – Kansas City (Shawnee, KS, USA). Concentrations <20 ng/L were reported as below the quantitation limit. Samples with concentrations >2000 ng/L were reanalysed using a dilution so that the assayed concentration was within the range of 20–2000 ng/L. Between-day and within-day accuracy and precision were <12% relative standard deviation.

Pharmacokinetic Analysis

Pharmacokinetic parameters were determined using standard noncompartmental methods with log-linear least square regression analysis to determine the elimination rate constants using WinNonlin (version 3.2, Pharsight Corp., Palo Alto, CA, USA). The areas under the concentration versus time curves from time zero to infinity (AUC_∞) were calculated using a combination of the linear and logarithmic trapezoidal rules, with extrapolation to infinity by dividing the last measurable serum concentration by the elimination rate constant (λ_z).[12] Values for maximum concentration (C_{max}) and time to C_{max} (t_{max}) were determined by WinNonlin. The

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Mean (coefficient of variation [CV] %) single-dose hydromorphone pharmacokinetic parameters following administration of intravenous (IV; treatment A) and intranasal (IN) hydromorphone HCl 2.0mg in patients with untreated (treatment B) or treated (treatment C) rhinitis (n = 10; except n = 9 in treatment A due to inadequate characterisation of the elimination rate constant for one of the subjects)

Pharmacokinetic parameter	Treatment A (2.0mg IV)	Treatment B (2.0mg IN)	Treatment C (2.0mg IN pretreated)
t_{max} (h)	0.167 (0.133–0.167)	0.333 (0.250–0.750)	0.358 (0.167–0.767)
C_{max} (μg/L)	32.48 (29.0)	3.69 (46.1)	3.38 (63.3)
$t_{1/2}$ (h)	4.77 (42.5)	6.13 (55.5)	6.32 (63.4)
AUC_t (μg • h/L)	13.7 (18.3)	8.41 (35.3)	7.61 (48.9)
AUC_∞ (μg • h/L)	14.1 (20.7)	9.19 (37.2)	8.43 (47.0)
MRT (h)	2.90 (31.8)	5.47 (34.7)	6.13 (47.4)
CL or CL/F (L/h)	131 (24.0)	212 (28.3)	252 (40.1)
V_{ss} (L)	367 (24.7)		
F (%)	Assume 100	59.8 (22.1)	54.4 (34.8)

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; **AUC_t** = area under the plasma concentration-time curve from time zero to last time point; **CL** = clearance; **CL/F** = clearance/bioavailability; **C_{max}** = maximum plasma concentration; **F** = bioavailability; **MRT** = mean residence time; **t_{max}** = time to maximum plasma concentration; **$t_{1/2}$** = elimination half-life; **V_{ss}** = steady-state volume of distribution.

elimination half-life ($t_{1/2}$) was determined from $0.693/\lambda_z$. Clearance/bioavailability (CL/F) was calculated by dividing the dose by AUC_∞. Volume of distribution at steady state (V_{ss}) was determined by moment curves. V_{ss} was calculated as CL • MRT for IV data with the correction for the infusion time, where MRT is mean residence time.[13]

Statistical Considerations

Statistical analyses were performed with PC-SAS (version 6.12, SAS Institute, Cary, NC, USA). The statistical tests were 2-sided with a critical level of 0.05. An analysis of variance (ANOVA) with factors and subject sequence, treatment and period was performed for log-transformed AUC and C_{max}. The least-square geometric means from the ANOVA were used to calculate the ratios and their 90% confidence intervals (CIs) between treatment groups for AUC and C_{max}. The carryover effect for the two intranasal treatments was analysed using an ANOVA of log-transformed AUC and C_{max}. Rank-transformed PK parameters (F and t_{max}) were analysed using an ANOVA with effects for sequence, subject (sequence), treatment and period.

Results

Safety Assessment

All 12 patients who enrolled in the study were Caucasian. Ten patients completed the study without clinically significant or serious adverse events. Two subjects dropped out for reasons unrelated to the study drug. There were no clinically relevant changes in physical examination, nasal evaluations or laboratory tests. The adverse effects, as reflected by number and intensity of adverse response, were greater for the IV treatment compared with the two intranasal treatments. The most common side effects were associated with known hydromorphone effects (i.e. dizziness, sedation, nausea, etc.). A frequently reported adverse effect for the IN formulation was a "bad (or bitter) taste in the back of the throat", but it resolved in 20–60 minutes.

Pharmacokinetics and Statistical Analyses

Table I summarises pharmacokinetic data for the three treatments. Median t_{max} values were 20 and 21.5 minutes for the intranasal doses after treatment B (no pretreatment) and treatment C (decongestant pretreatment), respectively, suggesting similar absorption rates in the two treatment groups. The differences in t_{max} and F between treatments B and C were not statistically significant ($p > 0.8$ and > 0.4, respectively). The area under the plasma con-

centration-time curve from time zero to the last time point (AUC_t) and AUC_∞ were comparable between the two IN treatments as shown by treatments C/B ratios (90% CIs) of 0.89 (0.75, 1.04) and 0.90 (0.77, 1.04), respectively. Treatments C/B ratios (90% CI) for C_{max} were 0.83 (0.61, 1.14).

Of the ten subjects who completed the study, four received nasal oxymetolazone and six received oral pseudoephedrine as pretreatment for rhinitis. However, the data obtained in treatment C were limited by sample size and did not allow for a statistical comparison between pretreatments.

Statistical analysis of carryover effect on log transformed AUC_∞, AUC_t and C_{max} for the two IN treatments was performed. p-Values from an ANOVA with factors sequence, subject (sequence), treatment and period for sequence BC and CB were >0.13, so the carryover effects were not significant.

Discussion

Plasma concentrations and pharmacokinetic parameters of hydromorphone in patients with rhinitis were found to be very similar to healthy volunteers.[14] The IN formulation of hydromorphone had rapid absorption (median peak times of 20 and 21.5 minutes after treatments B and C, respectively). However, one subject (who received oral pseudoephedrine in treatment C) had much higher concentrations than average after each treatment that significantly contributed to the reported t_{max} and C_{max} values. The data from this subject also contributed to a noticeable difference following treatment B between median t_{max} (21.5 minutes) and the time to reach the average peak concentration (10 minutes) as shown in the concentration-time plot (figure 1 inset). C_{max}, AUC, CL, V_{ss} and $t_{1/2}$ and MRT values after the IV dose were very similar to other studies.[5,7,8] Mean absolute bioavailability for the 2.0mg IN dose in healthy volunteers was 57% (range 36–78%). The range of bioavailability values in this

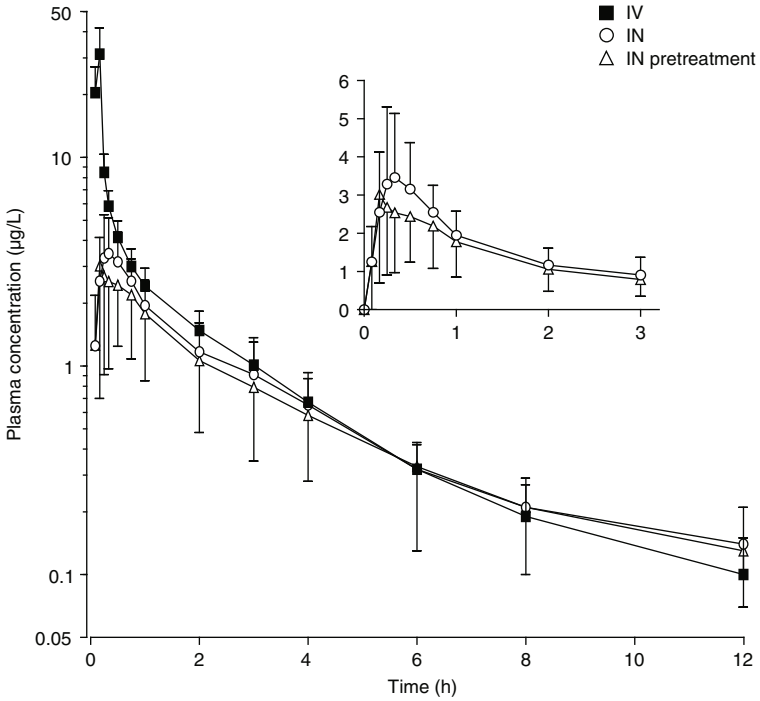

Fig. 1. Mean (n = 10) plasma hydromorphone concentration vs time profiles following a single dose of hydromorphone hydrochloride (HCl) 2.0mg by intravenous (IV) infusion (treatment A) and intranasal (IN) hydromorphone HCl 2.0mg without (treatment B) and with (treatment C) pretreatment with decongestants. The inset figure shows a comparison of treatments B and C during the first 3 hours.

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