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A Multicenter, Open-Label, Exploratory Dose-Ranging Trial of Intranasal Hydromorphone for Managing Acute Pain from Traumatic Injury

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Abstract: We conducted a prospective multicenter, open-label, escalating dose-range trial to compare, across patients, single intranasal doses (2, 4, 6, 8, and 10 mg) of hydromorphone HCl in the treatment of acute trauma pain The main outcome measure of pain-intensity reduction was derived from serial Numerical Pain-Rating Scores and calculated as the summed pain-intensity difference over 3 hours (SPID 3). Nasal examinations, vital signs, and adverse events were reported as safety outcomes. The mean decrease in pain intensity from baseline to 30 minutes was 39 to 44% for the 4-, 6-, 8- and 10-mg doses (n = 19, 33, 28, and 19 per group) and only 24% reduction for the 2-mg dose (n = 14). SPID 3 for the 2-mg dose was 40 to 50% below all other doses. There were no clinically meaningful changes in vital signs or nasal examinations. Adverse events (nausea, vomiting, pruritis, oxygen desaturation, bad taste, dizziness) were of mild to moderate intensity, increased with dose, and expected, based on route of administration and opioid pharmacology. Intranasal hydromorphone provides a component of rapid pain relief in the care of emergency department patients suffering from acute trauma pain.

***Perspective:** This article presents a pilot dose-ranging study of intranasally administered hydromorphone, administered in the emergency department to patients suffering from acute trauma pain. This study demonstrates research success in this setting and noninjection-based delivery and certain doses of intranasal hydromorphone may be effective in treating acute trauma pain.*

***Key words:** Hydromorphone, intranasal delivery, trauma pain, acute pain.*

Pain management practices in emergency departments have advanced. However, there is much room for improvement according to historical and recent studies.[1-3,6,13] Ritsema et al[11] recently reported a study of national scope examining the quality of emergency department pain management for long-bone fractures. According to the study, only 50% of patients received a dose of an opiate analgesic for pain relief. Similarly, Todd et al[14] reported a multicenter emergency department study in which median pain intensity upon arrival was rated as severe, or 8 out of 10, on a 10-point scale. Only 60% of patients received any analgesic, with half of those treated receiving an opiate or opiate/NSAID after a median delay of 90 minutes for

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administration. These results were attributed to overcrowded facilities and physicians focusing more on the cause of the symptoms than treating the pain.[8,14] The sum of experience from these papers is that there remains a significant unmet medical need to provide prompt, effective analgesia in emergency departments.[8]

While morphine and fentanyl are frequently used for the treatment of pain in emergency settings, other opioid agents are available. Hydromorphone is 1 such opioid that was first synthesized in 1921 as a semisynthetic morphine analog and its therapeutic utility has been well-documented.[10] A recent study comparing hydromorphone with morphine concludes that "…for the treatment of acute, severe pain in the emergency department, intravenous hydromorphone at .015 mg/kg represents a feasible alternative to intravenous morphine at .1 mg/kg".[4]

Missing from the aforementioned papers is the consideration that drug-delivery procedures required for intravenous administration consume time and delay prompt treatment. Kendall et al[7] addressed this problem by conducting a study of intranasal diamorphine (an opiate chemically similar to hydromorphone) compared to intramuscular morphine in children and teenagers with long-bone fractures. The study demonstrated rapid onset of pain relief that was superior to intramuscular morphine and that the patients much preferred the nasal spray to an injection.

Hydromorphone hydrochloride (HCl) nasal spray has been administered to healthy volunteers to obtain pharmacokinetic and tolerability data.[5,12] These data demonstrated rapid nasal absorption of hydromorphone. However, the intranasal delivery doses that might be useful to treat acute posttraumatic pain have not been determined. The goal of this trial was to explore the tolerability and efficacy of an escalating dose-range of intranasal hydromorphone HCl in moderate to severe acute pain from traumatic injury. Clinically relevant efficacy was considered as a 30% or greater reduction in pain intensity by 30 minutes and 50% or greater reduction by 60 minutes postdose. A secondary goal was to assess plasma levels of hydromorphone at select time points.

Methods

Study Design

This was a prospective, multicenter, open-label, escalating dose-range trial designed to compare, across patients, single intranasal doses of hydromorphone HCl in the treatment of acute pain following traumatic injury presenting to the emergency department. Data from a minimum of 6 patients per Dose Level were assessed for tolerance and efficacy and to determine the dose for subsequent patients enrolled. The rationale for the study approach was driven by several considerations including: 1) no direct information for dose selection to use in a randomized, double-blind trial design; 2) placebo arms were considered unethical by a prestudy survey of emergency department physicians and institutional review board (IRB) chairs; 3) little publication or regulatory experience with emergency department studies for drug registration; and 4) desire for efficiency in eliminating ineffective doses from further study. As this was an exploratory study, no sample size calculations were performed.

The protocol and consent form were approved by the IRB of each hospital and written informed consent was obtained from each subject. The study was conducted in emergency departments of 5 acute-care hospitals and trauma centers. Four hospitals were from a large urban setting and affiliated with universities and 1 hospital was in a rural community setting. The 4 larger centers generally enrolled patients from 8 am to 5 pm, while the rural center enrolled patients 24 hours a day. The rural center enrolled 46% of the patients, 1 academic center 35% of the patients, and the 3 remaining centers enrolled 9, 6, and 4% respectively. The study was conducted from February through August, 2007.

Selection of Patients

The study population consisted of a convenience sample of adult male and female patients between the ages of 18 to 65 years with acute pain following traumatic injury. Included patients met the following criteria: ability to provide informed consent; in general good health; suffered acute trauma resulting in fracture, sprains, or strains; burns; traumatic amputations; penetrating wounds, etc. that are appropriate for treatment with opioid analgesics; having a baseline pain-intensity score of at least 5 on the 0 to 10 Numerical Pain Rating Scale (NPRS) (0 = no pain; 10 = pain as bad as can be imagined); participate for at least 3 hours; and able to submit to venipuncture for pharmacokinetic samples. Patients were excluded for: a known allergy or significant reaction to hydromorphone or the components of the intranasal formulation; uncontrolled bleeding; head trauma or impaired mental status; a need of benzodiazepines or other sedating medications; surgery or significant emergency department procedures within 3 hours of admission to the study; history of any condition that may interfere with the absorption, distribution, metabolism, or excretion of hydromorphone; any condition that in the opinion of the investigator would place the patient at increased risk or may confound the study results; second- or third-degree burns of over 20% of their body surface area or burns with pulmonary involvement; having taken a short-acting opioid within 3 days or had taken a long-acting opioid within 7 days prior to dosing or had a history of regular/chronic opioid use; a role of alcohol or drug abuse in presenting condition; participation in a study of an investigational drug, biologic, or device within 30 days prior to dosing; and pregnancy or breast-feeding.

Interventions

Initial evaluation of patients by a treating physician or investigator included medical history, physical and nasal-cavity examinations, vital signs including oxygen saturation, medication history and pain assessment and NPRS score. Qualified patients received a single dose of 2, 4, 6, 8, or 10 mg of intranasal hydromorphone HCl. Doses