Intranasal Hydromorphone for the Treatment of Acute Pain in Children: A Pilot Study

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Study Purpose and Rationale:

Hydromorphone is a commonly prescribed opioid analgesic that is used in both adults and children. It can be administered by the oral (PO) route, but is associated with poor bioavailability and slow time to onset of action. It can also be administered by the intramuscular (IM) or intravenous (IV) routes, but both require needle sticks, which children report to be their most feared medical procedure, and that which they find highly distressing. The intranasal (IN) route is a safe and effective way of administering opioid analgesics (e.g. fentanyl, sufentanil) in both adults and children. Although there have been studies evaluating the bioavailability, pharmacokinetics, clinical efficacy, and adverse events of IN hydromorphone in adults, IN hydromorphone has not been yet been studied in children. Given the safe and efficacious reports of IN hydromorphone in adults, and the potential benefits of administering hydromorphone by the IN route for children, we aim to conduct a pilot study to evaluate the efficacy of IN hydromorphone in reducing pain in children with acute pain who present to the pediatric emergency department.

Study Design:

This will be a pilot study, in which we will prospectively enroll a convenience sample of children who present with moderate to severe acute pain to the pediatric emergency department of a single institution.

Study Procedures:

The treating physician will determine if their patient fulfills inclusion criteria. If they do, the physician will approach the patient and family to see if they are willing to discuss the study with a member of the study team. If they agree, a member of the study team will determine if the patient is eligible for the study, and if they are, they will then approach the patient and family to discuss the study and obtain consent. The consent and assent process will be conducted in the patients primary language (English or Spanish only). Patients who are eligible for the study and have provided consent/assent will first have their pain intensity measured within 15 minutes prior to receiving the IN hydromorphone (baseline assessment). They will be monitored as per standard practice by the health care providers in the emergency department for patients receiving an opioid analgesic (i.e. pulse oximetry, interval vital signs including blood pressure). All pain assessments will be performed using the Faces Pain Scale – Revised (FPS-R) and verbal Numeric Rating Scale (vNRS) by a research assistant, coordinator or study team physician. A nurse will administer the IN hydromorphone using a mucosal atomization device: this is Time 0. Immediately after the medication is administered, the patient will be asked to report how much pain or discomfort they experienced with the administration (also using the FPS-R and vNRS). The patient will have their pain assessed at the following time points: 5 minutes, 15 minutes, 30 minutes, 45 minutes, 60 minutes, and then every 30 minutes thereafter until 6 hours, the patient is discharged from the emergency department, or a non-IN hydromorphone rescue analgesic is administered (see following paragraph regarding first and second rescue medication assessments at 15- and 30-minutes). This non-IN hydromorphone rescue analgesic will be considered after 60 minutes, and its administration will be determined at the discretion of the primary attending physician. If a non-IN hydromorphone rescue analgesic is administered, the time when it

was given will be recorded. The attending physician may administer an analgesic of their choice as a rescue analgesic (e.g. IV hydromorphone, IV morphine) as per standard practice.

At the 15- and 30-minute marks, the patient will undergo a first and second rescue IN hydromorphone assessment. They will be asked if their pain is, “much less, a little less, the same, or worse” compared to before they received the IN hydromorphone. If they reply, “the same”, or “worse”, they will receive an additional rescue dose of IN hydromorphone at 0.015 mg/kg, maximum single dose of 2 mg. We will also ask the patient, " "Do you want more medicine to make your pain less?", as patients who report that their pain is "a little less" or "a lot less" may still not have achieved adequate pain relief, and this deficit will not be identified without asking this specific follow-up question to confirm adequacy of pain relief. Intranasal hydromorphone has been shown to reliably produce adequate analgesia by 10 minutes when an adequate dose has been administered. Therefore, determining whether additional analgesia is required at 15 minutes is a reasonable amount of time to wait after administering a dose of IN hydromorphone to see if a patient experienced any improvement in pain intensity. This methodology has been used in prior pilot studies of analgesics, to prevent patients from receiving inadequate analgesia if the initially selected dose was not sufficient, and so that an effective dose can be determined. In addition, administering additional reduced doses (i.e. half initial dose) after 15 minutes of receiving a dose of parenteral opioid analgesic, if there has been no improvement in pain intensity, is standard practice when administering IV opioid analgesics as part of typical clinical care when treating pain in children.

Adverse events will be assessed and recorded by the research assistant or study investigator, in conjunction with the nursing staff and treating physician. These adverse events will include those considered minor and major. The specific adverse events being assessed are detailed on pages 8 and 9 of the data collection form. All adverse events will be assessed every hour.

Patients will receive IN hydromorphone (2 mg/mL concentration) at a dose of 0.03 mg/kg, maximum single dose 4 mg. This dose was obtained from prior studies demonstrating that the bioavailability of IN hydromorphone was 55%, and clinical studies showing that at least 4 mg was required to achieve clinically meaningful improvement in pain in adults, with no incidence of serious adverse events, and no significant difference in adverse events compared to lower doses. The usual pediatric dosing of IV hydromorphone is 0.015 mg/kg, so the use of 0.03 mg/kg is consistent with this demonstrated bioavailability of IN hydromorphone. In addition, other commonly-used IN analgesics and sedatives (e.g. fentanyl, midazolam, ketamine) are dosed in a similar fashion: that is, at least double (and for some medications, up to five times) the IV dose is used when administering the medication by the IN route. This dosing strategy and interpretation of the bioavailability and pharmacokinetic data for intranasal hydromorphone was discussed with Dr. Serge Cremers (Director of Biomarkers Core Laboratory of the Irving Institute for Clinical and Translational Research).

Statistical Procedures:

We will use descriptive statistics (mean/SD, median/IQR) to describe our patient population and their characteristics. Our primary outcome of median change in pain intensity will be measured using the Faces Pain Scale – Revised (FPS-R), a validated pain scale in children ages 4 to 17 years old, which allows a child to report their pain intensity on a scale from 0 (no pain) to 10 (most pain). Median change in pain intensity will also be measured using the verbal Numeric Rating Scale (vNRS), which assesses pain by asking how much pain they have on a scale from 0 to 10. We will report the median

change in pain intensity of our patients who receive intranasal hydromorphone. Our secondary outcome of adverse events will be reported using descriptive statistics, i.e. the proportion of patients who experienced each type of adverse events. We will also be recording the time at which rescue analgesics are administered, and report the results as a Kaplan-Meier curve. For the purposes of this pilot study, we will enrol 40 patients, which has been previously demonstrated to be sufficient in similar pilot studies evaluating the analgesic efficacy of other medications.

Potential Risks:

The risks associated with receiving intranasal hydromorphone are the same as if administered by another route (e.g. intravenous). There is a chance that the patient may not experience the same degree of pain relief that they may have experienced if they had received intravenous hydromorphone. However, patients will have their pain assessed as per usual standard care, and can receive additional required analgesics at any point in time if their pain relief is inadequate. The procedures involved in this study do not increase the risk for adverse events normally associated with receiving hydromorphone. Potential Benefits: Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of Risks, Benefits & Monitoring THe most common adverse events reported by patients who have received intranasal hydromorphone include bad taste in mouth (21%), dizziness (14%), somnolence (15%), nausea (6%), and vomiting (2%). Except for bad taste in mouth, the incidence of these adverse events associated with intranasal hydromorphone were all less than that experienced by patients who received the same dose of intravenous hydromorphone (Coda et al. 2003)

Coda BA, Rudy AC, Archer SM, Wermeling DP. Pharmacokinetics and bioavailability of singledose intranasal hydromorphone hydrochloride in healthy volunteers. Anesth Analg 2003;97(1):117–23.

Potential Benefits:

If the treating physician was going to initiate an intravenous line for the sole purpose of administering a parenteral opioid analgesic to treat the child's pain, one potential benefit is that receiving intranasal hydromorphone instead would spare the child a painful and distressing needle stick. Another benefit is that the patient may receive longer duration of analgesia than if they had received intranasal fentanyl, which is a commonly-administered parenteral opioid analgesic in the pediatric emergency department.

Alternatives:

An alternative to participation in this study is to choose not to participate, or to receive an opioid analgesic by an alternate route (e.g. oral, intramuscular, or intravenous).

Data and Safety Monitoring:

Data will be reviewed on an ongoing basis by the PI with each patient enrolled. On an ongoing basis, the investigators will monitor accrual of study subjects, assess adherence to study protocol, assess

data quality, and collect and review adverse events and other subject safety matters. We will submit to the IRB protocol deviations and any requested protocol modifications. A data safety monitoring board (DSMB) consisting of two physicians unrelated to the study will be formed to evaluate safety and adherence to the protocol (Drs. Colin Carter and Maria Kwok, Division of Pediatric Emergency Medicine). The first review will be conducted after the first 10 patients are enrolled, and then the DSMB will convene every 6 months until the study is completed.

Adverse Event Reporting: An adverse event is any untoward medical occurrence by a subject. For each patient, the investigators will evaluate adverse events after completion of enrollment. All unanticipated problems (i.e. unexpected events, outcomes, or occurrences, at least possibly related to the research, and suggest an increase in risk of harm to subjects or others) will be reported to the IRB. This reporting will be done promptly, but no later than one week after the occurrence or after the PI acquiring knowledge of the unanticipated problem, and will also be reported at time of continuing review. All data will be maintained on password-protected computers and in locked file cabinets in a locked room to which only authorized study personnel will have access. Only approved research staff will view the clinical information of children enrolled in this study. We will retain study records and documentation for 3 years after the last enrolled patient has completed all study procedures.