Intranasal Drug Delivery for Children with Acute Illness

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Abstract: Management of pain and anxiety for children requiring urgent care has progressed dramatically in the past decade. However, the administration of analgesia and sedation in children is inconsistent, with significant practice variation among practitioners, and especially amid younger children who receive less than optimal analgesia.

Nasal administrations of drugs have several significant advantages over current practices. The nose has a very rich vascular supply, it facilitates direct absorption to the systemic blood supply and increases bioavailability of the drug, compared to oral administration.

The current review summarizes available information on the use of intranasal drug delivery for children in acute illness. Midazolam (Versed), Fentanyl, Diamorphine and Ketamine are discussed, as well as pitfalls and caveats of intranasal drug use.

INTRODUCTION

Significant strives have been made in recent years in the management of pain and anxiety among children requiring urgent treatment in the Emergency Department and the Intensive Care Unit [1]. However, the road to pain-free or even a decreased suffering of children with acute illness or injury is still paved with impediments [2]. The administration of analgesia and sedation in children is inconsistent, with significant practice variation among practitioners, and especially amid younger children who receive less than optimal analgesia [3].

Inadequate analgesia and sedation have not only immediate disadvantage during a medical procedure or due to tissue damage, but have been shown to induce long-term complications. Young infants who undergone a procedure with inadequate analgesia had long-standing increased response to painful experiences [4,5].

In the quest for the ultimate pharmacological agent for children, one should consider many factors. The ideal agent should have a rapid onset of action, adequate depth of sedation and anxiolysis, maintenance of spontaneous breathing, complete lack of response to the painful stimulus, complete amnesia to the procedure, rapid recovery, and an excellent safety profile [6]. However, this drug is yet to be discovered, and current management of procedures in children is usually done using a combination of drugs. Today, in order to achieve adequate depth of sedation and anxiolysis, most health care providers in the acute care setting are using intravenous or intramuscular drugs for procedural sedation.

While these routes of administration are considered more effective compared to oral administration, due to rapid systemic distribution of the medication, they are painful to children and could increase the anxiety associated with the treatment. Hence, new routes of administration are gaining momentum in the pediatric acute realm.

TRANS-NASAL TREATMENTS

Ayurveda, the science of life, has been practiced in India for hundreds of years. It comprise of changes in daily living practices to 'promote health'. Ayurvedic practices are said to restore the balance and harmony of the individual, resulting in self-healing, good health and longevity. Ayurveda practitioners believe that the nose is 'the door to the brain' and using nasal drops (Nasya) improve voice, vision, and mental clarity. Intranasal administering sesame oil, calamus oil, sunflower oil, coconut oil, or Ghee (butter without any solid milk particles or water) has been suggested as medically beneficial [7].

While we could find no randomized controlled trials looking at assessing these hypotheses, nasal administration of drugs is known for many years. Nasal administrations have several significant advantages over current practices. First, the nose has a very rich vascular supply, with immediate passage of drugs to the blood stream. Direct absorption to the systemic blood supply is important since this avoids first pass metabolism through the gastrointestinal system, and increase bioavailability of the drug, compared to oral administration.

Intranasal drug administration is also relatively easy. While most young children are not cooperative during the actual administration of the drug, this is relatively a short procedure, as the volume of the drug is less than 2-3 mL. No sterile technique is needed and due to fast absorption, the child can sit up immediately after the drug has been given.

ENHANCING BIOAVAILABILITY

Several key factors affect bioavailability of the intranasal administered drug. The drug itself, the delivery technique and the anatomy of the nasal cavity.

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The Drug

Molecular size as well as the drug's pH should be considered when deciding on intranasal administration [8]. McMartin *et al.* found good availability of intranasal drugs, without adjuvant, for all molecules up to 1000 molecular weight [8]. They reported that for water soluble compounds, there is a linear correlation between the log of molecular weight and the log of percent drug absorption [8].

The Delivery Technique

Intranasal medications can be delivered in several methods. Drops can be applied from a syringe, the drug can be nebulised or given through pressurized aerosol. All have been demonstrated to be effective [9]. Recently, an atomizer, delivering the drug in a pushed atomized spray was developed. While it is believed that metered-dose systems provide the greatest dose accuracy and reproducibility, the device ease of use vary significantly.

The Anatomy

The nasal mucosa is very rich in blood supply, but also surrounded by adrenergic nerves, with mostly alpha receptors. Hence, combining the delivered drug with alpha-receptor-antagonists or beta-receptor-agonists, will enhance absorption. Administration of the drug should aim at maximal absorption through the mucous membranes of the nares, and to avoid swallowing the drug or dripping of the drug back through the nose.

PREVIOUS EXPERIENCE WITH PEDIATRIC INTRANASAL DELIVERY FOR ACUTE ILLNESS

Intranasal Benzodiazepins

The use of intranasal Benzodiazepins for cessation of seizures has gained interest in the last decade [10]. The prompt onset of action, in face of the urgent need for seizure cessation and potential difficulty in obtaining intravenous access, were the rational to start administering the drug intranasally. Among almost 50 children with seizures, admitted to one Emergency Department, intravenous diazepam worked more quickly to control the seizures, when compared with intranasal midazolam. However, the overall time to cessation of the seizures after arrival at the hospital was faster with intranasal midazolam [11]. As was suggested in a recent "evidence topic report" [12, 13, 14], intranasal midazolam should be considered in children with acute seizure.

Midazolam (Versed), the first water soluble benzo-diazepine, is widely accepted as a parenteral anxiolytic and surgery premedicant [15]. Midazolam was first given intranasally in 1988 by Wilton *et al.* [16]. The elimination half-lives of intranasal and intravenous midazolam were found to be similar (2.2 h IN and 2.4 h IV). Under optimal conditions, absorption of midazolam *via* the nasal mucosa is virtually complete [17,18] and rapidly achieving sedative plasma concentrations in children [19]. Intranasal midazolam is currently used for several indications in children.

When administered preoperatively at 0.2 and 0.3 mg/kg, midazolam was found to be a very potent anxiolytic and sedative. Similarly, when two doses of 0.2 mg/kg (total 0.4 mg/kg) were given to children undergoing outpatient echocardiography [20], midazolam was found to be effective and safe.

In two studies [21,22] a combination of midazolam and ketamine was used. When intranasal midazolam (0.2 mg/kg) and rectally administered ketamine (9.0 mg/kg) were given, only 22% (7/32) of children required further ketamine and in only 6% (2/32) halothane was introduced. When midazolam (0.56 mg/kg) and ketamine (5 mg/kg) were administered nasally to 30 children under 16 Kg weight undergoing computerized tomography, 83% (25/30) had satisfactory sedation. The onset of sedation was rapid and there were no respiratory complications. Intranasal midazolam at 0.3 mg/kg gave the fastest effect when compared to oral midazolam (0.5 mg/kg), rectal midazolam (0.5 mg/kg) and sublingual midazolam (0.3 mg/kg) for children randomly assigned to receive midazolam before an elective operation [21].

In a randomized, double-blind, controlled trial, intranasal midazolam (0.4 mg/kg) was found to be effective in facilitating suturing of lacerations in 59 preschool children in the ED [22]. The group of children receiving intranasal midazolam had a lower mean heart rate, maximum heart rate, maximum systolic blood pressure, lower cry, motion and struggle scores and a higher parental satisfaction, when compared to children receiving intranasal normal saline (placebo) or children receiving no intervention. In a study comparing intranasal midazolam at 0.5 mg/kg and intramuscular ketamine for sedation during laceration repair [23], none of the children receiving midazolam could remember the suturing. Intramuscular injection of ketamine was associated with more vomiting (9/50 *vs* 4/50) and a longer median time for discharge (82 *vs* 75 minutes) compared to intranasal midazolam ($P < 0.05$).

Recently, in a randomized, double-blind, placebo-controlled crossover study in children with cancer receiving needle sticks for blood work [26], children, parents and nurses – all reported reduced anxiety and discomfort in the children who received 0.2 mg/kg intranasal midazolam. Even though midazolam has no analgesic properties, the children reported pain reduction.

The accumulated evidence suggests that intranasal administration of midazolam is as efficacious and is safer than intravenous administration. The onset of action is faster compared to the oral route.

Intranasal Fentanyl

Fentanyl is highly fat soluble, achieves therapeutic levels within 10 min of administration and have a half-life of an hour. When fentanyl is used in analgesic doses it has a good safety profile. No hemodynamic instability or respiratory compro-mise has been reported. Previous reports documented its advantageous pharmacokinetic profile for quick and effective analgesia [27, 28].

The safety and efficacy of intranasal fentanyl has been previously demonstrated in the setting of a pediatric Emergency Department. Forty five children, 3-7 years old, with fractures or abdominal pain were given a median dose of 1.5 mcg/kg of intranasal fentanyl (range 0.5-3.4 mcg/kg). Pain scores on a 100mm visual analogue scale decreased

from 61mm pre-intervention (95% CI 53.2-69.4mm) to 45mm at 10 min (95% CI 24.6-39.9) after administration of intranasal fentanyl. When using the Wong-Baker face scale [29] in children under 7 years old, the scores were 4.0 (95% CI 3.3-4.7) and 2.2 (95% CI 1.3-3.1) out of 5 at time of administration and at 10 minutes after administration, respectively. There was no significant difference in the mean systolic and diastolic blood pressure, pulse rate, respiratory rate or oxygen saturation when compared at intervals of 5 minutes up to 30 minutes following administration of the intranasal fentanyl [30].

In one prospective, open-label study with 47 children 3-10 years old with limb fractures, intranasal fentanyl provided effective pediatric analgesia that was comparable to intramuscular morphine, but was better tolerated [31].

Intranasal Diamorphine

Diamorphine hydrochloride is twice as potent as morphine and has similar onset of action and duration. It is highly solubale in water, a quality that facilitates its preparation in high concentration. The volume administered can be relatively small (many times as small as 0.1 ml) and can be given intranasal.

Two randomized controlled trial have shown Diamorphine (0.1 mg/kg spray) to induce the same degree of pain relief as intramuscular morphine (0.2 mg/kg). The first was among 58 children aged between 3 and 16 years with clinically suspected limb fractures [32] and the second was a multi center trial in the UK that included over 400 patients [33]. Both found no significant adverse events.

Intranasal Ketamine

Ketamine is used for sedation in children for many years and has been established as an effective and safe drug [34], since analgesic doses of ketamine have minimal adverse impact upon cardiovascular or respiratory function [35].

In a pharmacokinetic study, nasal administration of low doses of ketamine (3 mg/kg) produced plasma concentrations associated with analgesia, but using high doses *via* the nasal route (9 mg/kg) produced high plasma concentrations of ketamine similar to anesthesia, but the latter needed large volume of the drug given intranasal [36].

Intranasal ketamine was also found useful for dental procedure in children, and administration of the drug (3 mg/kg) resulted in a good sedation score and a short recovery period [37].

In a double-blinded, placebo-controlled study, intranasal ketamine premedication in 40 children resulted in a significantly better (P = 0.013) cooperation index, compared to intranasal placebo, permitted pleasant and rapid separation of children from their parents, cooperative acceptance of monitoring and of mask inhalation induction, and did not cause prolonged post-anesthetic recovery or delayed discharge home [38].

PITFALLS AND CAVEATS

The use of intranasal drugs is not without limitations. Intranasal drugs may cause temporary nasal irritation as reported by adults [39]. In children, 77% (23/30) cried during intranasal administration of midazolam in one report [25] and 45% (17/38) complained of temporary discomfort in another report [40]. Nevertheless, adults reported the irritation acceptable and not painful [41]. In children, it is difficult to determine if crying was due to the drug itself or due to anxiety from physician presence, the temperature of midazolam relative to the temperature in the nasal mucosa, or the fact that the child was held while administering the medication [26]. Paradoxical behavioral reaction was described in children receiving midazolam in about 1% of the cases [41], but this was reported only after using midazolam in its intravenous route.

It is also possible that some of the drug administered through the nasal mucosa, especially if given in drop formulation, might be swallowed or absorbed through the mucous membranes in the pharynx or distally. This potentially can cause unpredictable analgesia or sedation. However, delivery *via* aerosol can overcome this phenomenon.

In summary, in a continuous attempt to diminish pain associated with intravenous and intramuscular drug administration, investigators have been looking for new routes to administer drugs. In recent years, nasal administration of drugs is becoming more common and multiple clinical trials have shown promising results. The no-needle technique reduces iatrogenic pain and can be administered even at home. Future studies will explore new drugs and accurate dosaging and formulations that can be delivered for the best analgesia to our young patients.

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