Intranasal Medication Delivery for Children: A Brief Review and Update
Timothy R. Wolfe and Darren A. Braude

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abstract

With the exception of oral medications, most traditional forms of drug delivery outside the operating suite require an injection with a needle—a process that is painful and anxiety-provoking, risks needle stick injury, and consumes valuable staff time. In addition, intravenous access in pediatrics may be difficult for inexperienced providers. Intranasal medication delivery offers an alternative method of drug delivery that is often as fast in onset as intravenous medication, usually painless, inexpensive, easy to deliver, and effective in a variety of acute pediatric medical conditions. This article briefly reviews the most common uses for intranasal medication delivery in pediatrics: pain control, anxiolysis, and seizure control. *Pediatrics* 2010;126:532–537

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**KEY WORDS**

 pediatrics, administration, intranasal, narcotics, fentanyl, midazolam, analgesia, anticonvulsants

**ABBREVIATIONS**

 ED—emergency department

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Traditionally, pediatric medications are delivered via oral, rectal, subcutaneous, intramuscular, intravenous, and, occasionally, intraosseous routes. Oral medication delivery is slow in onset, difficult when patients are vomiting, and problematic when the patient’s oral intake is restricted. In addition, children often refuse to swallow oral medications, potentially limiting their reliability. The highly vascularized mucosal surfaces at the nasal mucosa and the olfactory tissue in direct contact with the central nervous system allow nasally administered drugs to be rapidly transported into the bloodstream and brain, with onsets of action approaching that of intravenous therapy. First-pass drug metabolism via the liver is also avoided, resulting in high bioavailability of many medications. Delivery of intranasal medication is also relatively painless, inexpensive, and easy to deliver with a minimum of training. This article briefly reviews the literature on intranasal medication delivery for pediatric pain, anxiety, and seizure control. Other potential uses for intranasal medication delivery that are not included in this review include the treatment of epistaxis, pretreatment before nasogastric tube insertion, and reversal of narcotic overdose with naloxone. This review is intended to expose the clinician to the concept of intranasal medication delivery at the bedside. This is not intended as a comprehensive literature review or meta-analysis.

**METHODS**

Relevant studies were identified from 3 sources: (1) a key word search of Medline including nasal; intranasal; intra-nasal; and matching medications including fentanyl, sufentanil, diamorphine, midazolam, and lorazepam; (2) a Google Scholar search with the same key words; and (3) a review of the references from each identified article. Only clinical trials of humans published in English were included. Although we reviewed articles for adults as well as pediatrics, we generally included only pediatric-focused articles in this review. Because this was intended as a brief topic review rather than a comprehensive literature review or meta-analysis, we included only articles that made unique and meaningful contributions, in the opinion of the authors.

**General Delivery Technique**

Successful intranasal medication delivery requires a basic understanding of delivery techniques to optimize medication bioavailability and effectiveness. These techniques include minimizing drug volume while maximizing drug concentration, adequate dosing, use of both nostrils to double the absorptive mucosal surface, and use of atomized particles to enhance medication absorption. Concentrated medications in a small volume (0.2–0.3 mL per nostril) are ideal, whereas volumes in excess of 1 mL per nostril are not reliably absorbed as a result of mucosal surface saturation and runoff from the nasal cavity. These volume issues tend to be of more importance in adults than in children because of weight-based dosing. For example, the generic fentanyl concentration is 50 μg/mL, which limits total dosing to 100 μg if delivering 1 mL per nostril. This represents a 1.5-μg/kg dose for a 66-kg patient. Patients whose ideal body weight exceeds 66 kg—rare until adolescence—would require delivery in divided doses, allowing a few minutes for absorption between doses. Some investigators have used compounded fentanyl with higher concentrations (150–300 μg/mL) than generic fentanyl to allow delivery of optimal doses with a smaller total volume. Diamorphine, a powdered opiate that is not available in the United States, may be reconstituted in smaller liquid volumes to accomplish the same purpose.

Because of incomplete and slower absorption with nasal administration, higher medication doses than those given intravenously are also required to achieve similar efficacy (Table 1). Failure to deliver an adequate intranasal drug dose because of a provider’s previous experiences with intravenous medication dosing may result in lack of efficacy. Delivering half of the medication into each nostril maximizes the absorptive mucosal surface, further enhancing drug bioavailability. Finally, the delivery method should maximize surface area coverage with a thin layer of drug. This can be achieved by converting the drug to an atomized spray (rather than drops), resulting in less drug loss to the oropharynx, higher cerebrospinal fluid levels, better patient acceptability, and improved clinical effectiveness. Nasal mucosal abnormalities should also be noted. Large amounts of mucous or blood will inhibit medication absorption. A quick look into the nostril will reveal these problems, and the clinician can either suction the nostril before administering the medication or select an alternative method of drug delivery.
Acute pain is extremely common in pediatric patients. Intranasal opiates fill one niche in the therapeutic armamentarium of pain control, offering one of the most interesting and perhaps broadly useful indications for intranasal medications. Situations in which intranasal opiates may be particularly useful are for minor fractures, large abrasions, burns, wound-dressing changes, and other acutely painful conditions. Data now clearly support the role of intranasal opiates as a rapidly effective alternative to intravenous or intramuscular opiate therapy in these situations.4,6–8,15–23

Intranasal opiate efficacy and speed of medication onset are not issues; intranasal opiates are as effective as intravenous morphine and faster than intramuscular morphine for treating acute pain.4,6,7 Kendall et al7 compared a 0.1-mg/kg intranasal diamorphine spray with a 0.2-mg/kg intramuscular morphine injection among 404 children who were aged 3 to 16 and presented with clinical fractures. They found intranasal diamorphine to be faster in onset; less painful to deliver; and more acceptable to patients, parents, and nursing staff, prompting them to state that intranasal opiates should be the standard method for emergency department (ED) pain control for children with extremity fractures. Borland et al24 compared a 1.7-μg/kg intranasal fentanyl dose with a 0.1-mg/kg intravenous morphine dose in 67 children in the ED with long bone fractures. Both interventions were equivalent in terms of onset of action, adequacy of pain control, and lack of serious adverse effects. They concluded that intranasal fentanyl was superior to intravenous morphine for acute fracture care because it is easier to administer, is painless, and results in more rapid control of pain as a result of elimination of the need for an intravenous line. After implementation of intranasal fentanyl as their standard treatment for moderate to severe pain, Borland et al24 found that the mean time to opiate delivery in their ED decreased from 53 to 25 minutes, and intravenous line starts for pain control dropped from 100% to 42%. Holdgate et al19 also found a significant reduction in time to analgesia by using 1.5 μg/kg intranasal fentanyl compared with intravenous morphine (32 vs 63 minutes), and younger children were also nearly twice as likely to receive opioid analgesia when intranasal fentanyl was available. Other studies confirm both the efficacy and the safety of intranasal fentanyl for acute pain relief in children.20–25 Intranasal fentanyl has also been shown to be an effective and safe alternative to intravenous morphine for adults in the traditional prehospital setting and for both adults and children in more austere environments, such as ski patrol.6,25

### Anxiolysis

Light procedural sedation and anxiolysis by using intranasal medications has been evaluated for a variety of procedures, including but not limited to laceration repair, MRI and computed tomography scans, burn-dressing changes, dental extractions, endoscopies, and accessing central venous ports.26–32 Intranasal midazolam is the most commonly studied medication for this indication, although data on fentanyl, ketamine, sufentanil, dexmedetomidine, and combinations of these drugs are available.30,33–36 Lane and Schunk28 recently reviewed 205 cases of intranasal midazolam use for procedural anxiolysis among children who were aged 1 to 60 months and seen in the ED. They found that 95% of patients who were treated with intranasal midazolam achieved anxiolysis and required no additional sedative to complete the procedure. There were no adverse events among the 194 patients who received only intranasal midazolam. Abrams et al33 compared 4 different intranasal medications for sedation before dental procedures: midazolam 0.4 mg/kg, ketamine 5 mg/kg, sufentanil 1.5 μg/kg, and sufentanil 1 μg/kg. Midazolam and sufentanil at the lower dose (1 μg/kg) were most effective and had the fewest complications. Hogberg et al37 had a different experience with using intranasal mi-

### TABLE 1 Intranasal Medications and Doses on the Basis of Published Literature

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Intranasal Medication and Dose</th>
<th>Important Reminders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain control</td>
<td>Fentanyl 1.5–2.0 μg/kg4,20–22</td>
<td>Monitor for respiratory depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Titration is possible every 15 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider administering oral medications to take effect as intranasal wears off</td>
</tr>
<tr>
<td></td>
<td>Midazolam 0.4–0.5 mg/kg27–28</td>
<td>Anxiolysis only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use concentrated form (5 mg/ml) because other concentration may not work</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warn patient and family that burning sensation may last 30 s</td>
</tr>
<tr>
<td></td>
<td>Midazolam 0.2 mg/kg5,41</td>
<td>Use the concentrated form (5 mg/ml) because other concentration may not work</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deliver immediately to allow absorption to occur while you support airway</td>
</tr>
</tbody>
</table>

Before using a nasal medication, inspect the nostril for significant amounts of blood or mucous discharge. Presence of these will limit medication absorption. Suctioning the nasal passage before delivery and/or alternate delivery options should be considered. Deliver half of the medication dose up each nostril. This doubles the available mucosal surface area (over a single nostril) for drug absorption and increases rate and amount of absorption. Use the MOST concentrated form of the medication available—dilute forms are less effective (eg, use midazolam 5 mg/ml, not 1 mg/ml). Do not use more than 0.5 to 1.0 mL of medication per nostril (0.2–0.3 is the ideal volume). When a higher volume is required, apply it in 2 separate doses, allowing a few minutes for the first dose to absorb.
diazepam for bowel biopsies. These authors found that intravenous midazolam was preferable to intranasal midazolam because of both the nasal discomfort and the need for repeat dosing associated with intranasal midazolam. Intranasal sedatives in general and midazolam specifically are a safe and rapid means of relieving a child’s anxiety in the health care setting, although they result in only minor sedation.

Seizure Control

Intranasal midazolam also offers an effective treatment option for patients with prolonged seizures. Midazolam easily crosses the nasal mucosa and the blood-brain barrier, resulting in a rapid rise in both the plasma and the cerebrospinal fluid concentrations. Fişgin et al compared rectal diazepam with intranasal midazolam and found intranasal midazolam faster in onset and more effective at seizure cessation (60% vs 87%). Compared with intravenous diazepam, intranasal midazolam had similar efficacy (92% vs 88%) and faster onset as a result of the lack of need to start an intravenous line. Intranasal midazolam and lorazepam are also safe for treating seizures outside of the hospital setting. Ahmad et al compared intranasal lorazepam with intramuscular paraldehyde in 160 pediatric patients at a rural African clinic, most of whom were experiencing seizure for an extended period (>2 hours) as a result of cerebral malaria or bacterial meningitis. Intranasal lorazepam stopped 75% of the seizures within a few minutes, whereas intramuscular paraldehyde was effective 61% of the time. Holsti et al reported their results after conversion of their emergency medical services system protocols from rectal diazepam to intranasal midazolam for treatment of pediatric seizures. The rates of prehospital seizure control (62% vs 28%), need for emergent intubation (11% vs 42%), and requirement for hospital admission (40% vs 89%) and ICU admission (16% vs 59%) all were substantially better in the intranasal midazolam group compared with the rectal diazepam group. Home seizure therapy is also effective, safe, and preferred over rectal diazepam by families who have relatives with epilepsy. These findings suggest that intranasal midazolam should be adopted as an option for treating patients who experience status epilepticus in situations in which intravenous access in not immediately available.

Adverse Effects and Costs

Adverse effects of nasal medications are infrequent. The most common adverse effect noted is nasal burning and irritation after administration of midazolam. Although this discomfort is transient, parents and older patients should be forewarned of this adverse effect before drug delivery. With the exception of delivery of high doses of intranasal sufentanil for induction during surgery, oversedation has not been reported for intranasal medications, including fentanyl or midazolam. In Australia, intranasal midazolam is commonly provided to parents for home therapy for status epilepticus without reported concerns, and fentanyl is a standard pediatric pain medication delivered at triage to children with severe pain. Intranasal medication delivery is also quite cost-effective, especially when time and resource use as well as patient satisfaction are concerned. Costs of intranasal medication delivery differ little from that of intravenous delivery: total costs for supplies and effective generic medications typically run <$5.00 to $7.00 US.

CONCLUSIONS

Intranasal medication delivery is an effective method of delivering analgesia, anxiolysis, and anticonvulsants to pediatric patients. In the properly selected patient, nasal administration can reduce time to medication delivery and onset, reduce medical staff resource use, eliminate needle-stick exposure risk, and eliminate pain from the injection, thereby leading to improved patient and parent satisfaction. Pediatricians, pediatric emergency physicians, and emergency medical services medical directors should consider adopting this delivery method for medications and indications that are appropriate to their practice setting.

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Algae at the Pump?: Algae, the microorganisms that are the basis of the aquatic food chain and producers of more than 40% of the world’s oxygen, may soon have yet another critically important role to play—that of oil producer. As reported in The New York Times (Pollack A, July 26, 2010), the race is on to develop algae that can convert sunlight and carbon dioxide into oils that can be refined and used as fuel. While algae are currently more expensive to purchase, they can potentially produce 10 to 100 times more fuel per acre than either corn or soybeans. Finding the right algae for production can either be through selection and enhancement of naturally occurring strains with the preferred properties or through genetic engineering. The benefit to using algae for the production of hydrocarbons is that they are remarkably efficient, absorb enormous amounts of carbon dioxide, and can be grown under a variety of seemingly hostile conditions. Even after burning of the end product, there would be no net increase in carbon dioxide production. The downside, other than cost and technical issues, include possible disruption of the food chain or oxygen production by mutated or accidently released “super algae” that out-compete naturally occurring forms. With oil reserves running low and the toxic effects of released oil on the nation’s mind, it seems only time before we’ll see signs at the pump noting “at least 10% from algae”.

Noted by WVR, MD