Use of Intranasal Medications in Pediatric Patients

Susan E. Warrington, PharmD; Robert J. Kuhn, PharmD, FPPAG

Abstract: A growing body of evidence supports the intranasal administration of atomized medications for a wide variety of pediatric indications. This article describes their use applicable to orthopedic specialists in the areas of pediatric pain management, as well as pre- and intraoperative sedation. As a quick, painless alternative to more invasive routes of administration, intranasal drug delivery has shown similar time to clinical effect compared to the intravenous route, while minimizing anxiety in both patients and their parents.

The administration of medications in pediatric patients is not always an easy task. Barriers can be as simple as poor palatability of oral medications, or a patient who has difficulty swallowing pills. Rectal administration is another option, but this can often be socially undesirable, especially in older children. More invasive routes of delivery, such as intramuscular, subcutaneous, intravenous (IV), or intraosseous, provide optimal drug delivery but often cause associated pain and anxiety; therefore, an alternative route of administration is often desired in the pediatric patient population.

Intranasal drug administration offers a quick, painless, noninvasive way to give medications, with onset of action generally comparable to that of IV administration where the central nervous system is the site of action.[1] An increasing body of literature investigates the applications of intranasal delivery for many indications (eg, seizures, epistaxis, pretreatment for nasogastric tube insertion, and naloxone administration for narcotic overdose reversal). This article describes their use applicable to orthopedic specialists in the areas of pediatric pain management, as well as pre- and intraoperative sedation.

Drs Warrington and Kuhn are from University of Kentucky HealthCare, Lexington, Kentucky.

Drs Warrington and Kuhn have no relevant financial relationships to disclose.

Correspondence should be addressed to: Susan E. Warrington, PharmD, 800 Rose St, H110, Lexington, KY 40536-0293 (susan.warrington@uky.edu)

doi: 10.3928/01477447-20110427-20

Pharmacokinetics

Delivery to the highly vascularized nasal mucosa allows for rapid transport of medications into the bloodstream and across the blood brain barrier. Intranasal administration has faster absorption compared to oral.[2] Due to direct absorption into the bloodstream, the intranasal delivery route also bypasses first-pass metabolism in the liver. In general, pharmacokinetic studies show that the bioavailability of intranasal medications is less than that of IV administration, but direct absorption into the central nervous system and comparable time to desired clinical effect indicate that this route still achieves similar outcomes regarding onset of action.[3-5] It is important to note, however, that due to incomplete absorption of intranasal administration, doses for intranasal medications are higher than those recommended for IV administration (Table).

Droplets vs Atomized Spray

Studies have compared the use of atomized spray vs droplet delivery into the nasal cavity. Drops into the nose are noted to be primarily deposited onto the ciliary surface with excess runoff down the throat. In comparison, atomized particles cover more surface area and are better distributed into the nasal mucosa, resulting in better bioavailability.[6,7] From the perspective of patient acceptance, administration of atomized spray has also been shown to produce significantly less aversive behavior in young children, making it a practical option.[8]

ADMINISTRATION

A key concept to consider for intranasal drug delivery is selecting a formulation concentration that allows for minimization of volume. Volumes of 0.2 to 0.3 mL per nostril are ideal, but volumes up to 1 mL per nostril can be used. Small volumes divided between both nostrils optimizes absorption and reduces mucosal surface saturation and runoff down the throat. However, this issue is more apparent in adults vs children due to weight-based dosing.[1]

Another consideration for intranasal administration is the patient's mucosal environment and potential barriers to drug delivery. Mucous, blood, and the use of vasoconstrictors impair absorption via intranasal route; therefore, alternative delivery methods should be considered in these cases if nasal suctioning is inadequate or not possible.

Atomized intranasal administration is achieved by using a product known as a Mucosal Atomizer Device (MAD; Wolfe Tory Medical, Inc, Salt Lake City, Utah).[9] This latex-free device attaches directly to a luer-lock syringe and atomizes medications to a particle size of 30 to 100 μ. When drawing up medications to be given via atomizer device, an additional 0.1 mL of volume should be included to account for estimated dead space in the device. Cost per atomizer device is approximately $4 to $5.

Table

Dosing of Intranasal Medications in Children

Medication	Dose	Onset of Action, min	Duration of Action, min	Considerations
Dexmedetomidine	1-2 μ/kg	15-30	55-100	May be preferred when more than mild sedation is desired; monitor for hypotension and bradycardia
Fentanyl	1.5-2 μ/kg	10-20	30	Monitor for hypoxia
Ketamine	5-8 mg/kg	5-10	Up to 60	Monitor for hypoxia
Midazolam (anxiolysis)	0.4-0.5 mg/kg	10-20	20-40	Use 5 mg/mL concentration; may cause nasal burning for 30-45 seconds

PAIN CONTROL

Orthopedic fractures and joint dislocations are some of the most painful pediatric emergencies, and time to administration of analgesics is of primary concern. Opiates via IV administration for orthopedic trauma pain provide rapid onset of analgesia and can be titrated to effect; however, other considerations regarding this route are additional associated pain and anxiety, as well as the time required to gain IV access. The use of intranasal fentanyl in the emergency room setting has gained favor in recent years as a fast, painless alternative to IV administration. Intranasal opiates also appear to be most useful for acute pain management for wound-dressing changes, large abrasions, and burns.

Fentanyl is an opiate analgesic with the most evidence to support intranasal administration. Use in pediatric patients has shown comparable efficacy to IV fentanyl and IV morphine in postoperative pain management and acute fractures in the emergency department, respectively.[4,10]

A study by Saunders et al[11] also shows efficacy in pain control and overall patient satisfaction with use following traumatic orthopedic injury. Lipophilic drugs with low-molecular weight generally achieve plasma levels similar to those from IV delivery. Pharmacokinetic data for intranasal fentanyl suggests approximately 71% bioavailability, reflecting findings that relatively higher doses are required for intranasal vs IV routes of administration (ie, 1.5-2 μ/kg). As with IV administration, intranasal fentanyl also allows for titration to effect while monitoring appropriately for potential respiratory depression and chest wall rigidity.

PRE- AND INTRAOPERATIVE SEDATION

Minimizing distress over parental separation and induction of anesthesia are challenges associated with pediatric patients in the preoperative period. Therefore, the administration of a sedative/anxiolytic agent is common practice prior to IV cannulation and transfer to the operating room. Oral midazolam is one of the most commonly used agents for this purpose, but only 70% of pediatric patients will accept this therapy.[12] Therefore, the use of intranasal midazolam, intranasal dexmedetomidine, and intranasal ketamine have been investigated for pre- and intraoperative sedation.

Anxiety during medical procedures is also a common scenario in pediatric patients, and procedures where intranasal sedation and anxiolysis have proven beneficial include: magnetic resonance imaging and computed tomography scans, laceration repair, burn-dressing changes, dental extractions, and venipuncture.

Midazolam is a water-soluble benzodiazepine known to have a rapid onset and short duration of action, as well as properties of amnesia and anxiolysis. Administered intranasally, midazolam is an effective option for conscious sedation.[13-16] When compared to oral midazolam, intranasal administration has shown a more rapid absorption and time to onset of action due to

THE BOTTOM LINE

- Intranasal medication administration is a practical option for pediatric patients as a noninvasive alternative to the intravenous route.
- Atomized spray vs droplet delivery is noted to be superior in the literature due to better nasal distribution and absorption.
- In the areas of pain control and pre- and intraoperative sedation, inhaled medications have shown similar efficacy to intravenous options regarding time to onset of desired effect.

systemic absorption via close communication between the vascular plexus cavity and the subarachnoid space by way of the olfactory nerve.[2]

Pharmacokinetic studies have noted the bioavailability of intranasal midazolam to be approximately 60%; however, similar outcomes for time to clinical effect are noted when compared to IV midazolam. Intranasal midazolam has been used since 1988 with repeatable positive outcomes. The most commonly reported adverse effects of intranasal midazolam are nasal burning for 30 to 45 seconds and bitter taste. In some instances, 10 μ of 10% lidocaine administered intranasally to each nostril has shown benefit in reducing reported burning sensations.[17,18]

Dexmedetomidine is a tasteless, colorless, and odorless agent that acts as a selective alpha-2 adrenergic agonist with both sedative and analgesic effects via actions in the central nervous system. It is commercially available as a concentration of 100 μ/mL, which makes it easy to administer in volumes <1 mL. A benefit noted with the use of this agent is that it has minimal to no effect on respiratory rate or tidal volume.

Although time to effect is relatively delayed when compared to IV administration, pharmacological effects are considered comparable.[19] The most notable adverse effects that occur with IV administration in pediatric patients include dose-dependent hypotension and bradycardia. With intranasal dexmedetomidine, moderate decreases in blood pressure and heart rate have been noted in healthy children during the first hour after administration.[20,21]

Talon et al[6] compared intranasal dexmedetomidine given via atomizer with oral midazolam in children younger than 18 years. Both products had similar effects on preoperative sedation and anxiolysis for induction of general anesthesia with no significant adverse effects, and only modest hemodynamic effects. Yuen et al[22] investigated time to onset and duration of sedative effects for intranasal dexmedetomidine administered via droplets with similar sedative efficacy and pharmacodynamic results (Table).

Ketamine is a dissociative anesthetic that creates a trance-like state with properties of sedation, amnesia, analgesia, and catalepsy. In a study by Kazemia et al,[23] sedative effects of intranasal ketamine 5 mg/kg were compared to intranasal midazolam 0.2 mg/kg. In 130 children aged 2 to 5 years who received the study medication 20 minutes preoperatively, 89% of the ketamine group vs 90% of the midazolam group vs 47.5% of placebo group were sedated at the time of separation from parents, and 80%, 86%, and 22.5%, respectively, were sedated at the time of intravenous line insertion. Therefore, intranasal midazolam and intranasal ketamine were deemed equally effective for the purpose of easy parental separation and IV line placement.

Efficacy of intranasal ketamine and midazolam were compared by Gharde et al[24] in children with tetralogy of Fallot. Dosing up to 10 mg/kg of ketamine was used in this study vs 0.2 mg/kg of midazolam, as well as a mixture of ketamine 7.5 mg/kg and midazolam 0.1 mg/kg. Sedation was assessed at 30 minutes post-dose. In the ketamine alone study group, sedation, separation, and acceptance of IV cannulation were all good, compared with good sedation but poor separation and acceptance in the midazolam alone group. Overall, the use of higher than typically recommended intranasal ketamine was deemed better than intranasal midazolam for purposes of preparation for induction in the preoperative period.[24]

Although the delivery of medications for pain and sedation via intranasal route does not have current approval by the United States Food and Drug Administration, when used in the proper patients and settings, this route appears to be a viable option for pediatric drug delivery. As with any sedation or narcotic analgesic use in pediatric patients, these procedures should be done with trained personnel who have the expertise and equipment to monitor patients; therefore, it would seem prudent to make these agents part of standard protocols when used. The ability to monitor patients during the time peak effects of these agents are obtained is critical for both efficacy and safety. As an effective component of care, this method of delivery not only helps to expedite pain control and pre- or intraoperative sedation in pediatric patients, but also helps to alleviate anxiety in pediatric patients and their parents.

REFERENCES

1. Wolfe TR, Braude DA. Intranasal medication delivery for children: a brief review and update [published online ahead of print August 9, 2010]. *Pediatrics*. 2010; 126(3):532-537.
2. Rey E, Delaunay L, Pons G, et al. Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *Eur J Clin Pharmacol*. 1991; 41(4):355-357.
3. Wermeling DP, Record KA, Archer SM, Rudy AC. A pharmacokinetic and pharmacodynamic study, in healthy volunteers, of a rapidly absorbed intranasal

midazolam formulation [published online ahead of print November 29, 2008]. *Epilepsy Res*. 2009; 83(2-3):124-132.

4. Borland M, Jacobs I, King B, O'Brien D. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department [published online ahead of print October 25, 2006]. *Ann Emerg Med*. 2007; 49(3):335-340.
5. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomized study. *BMJ*. 2000; 321(7253):83-86.
6. Talon MD, Woodson LC, Sherwood ER, Aarsland A, McRae L, Benham T. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. *J Burn Care Res*. 2009; 30(4):599-605.
7. Ljung B, Adreassen S. Comparison of midazolam nasal spray to nasal drops for the sedation of children. *J Nucl Med Technol*. 1996; 24(1):32-34.
8. Primosch RE, Guelmann M. Comparison of drops versus spray administration of intranasal midazolam in two- and three-year-old children for dental sedation. *Pediatr Dent*. 2005; 27(5):401-408.
9. MAD Nasal Mucosal Atomization Device. Wolfe Tory Medical, Inc, Web site. http://www.wolfetory.com/MAD/MADNasal.aspx. Accessed March 12, 2011.
10. Manjushree R, Lahiri A, Ghosh BR, Laha A, Handa K. Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anesth*. 2002; 49(2):190-193.
11. Saunders M, Adelgais K, Nelson D. Use of intranasal fentanyl for the relief of pediatric orthopedic trauma pain. *Acad Emerg Med*. 2010; 17(11):1155-1161. doi: 10.1111/j.1553-2712.2010.00905.x.
12. Khalil SN, Vije HN, Kee SS, Farag A, Hanna E, Chuang AZ. A paediatric trial comparing midazolam/Syrpalta mixture with premixed midazolam syrup (Roche). *Paediatr Anaesth*. 2003; 13(3):205-209.
13. Wilton NC, Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology*. 1988; 69(6):972-975.
14. Lane RD, Schunk JE. Atomized intranasal midazolam use for minor procedures in the pediatric emergency department. *Pediatr Emerg Care*. 2008; 24(5):300-303.
15. Lloyd CJ, Alredy T, Lowry JC. Intranasal midazolam as an alternative to general anaesthesia in the management of children with oral and maxillofacial trauma. *Br J Oral Maxillofac Surg*. 2000; 38(6):593-595.
16. Yealy DM, Ellis JH, Hobbs GD, Moscati RM. Intranasal midazolam as a sedative for children during laceration repair. *Am J Emerg Med*. 1992; 10(6):584-587.
17. Lugo RA, Fishbein M, Nahata MC, Lininger B. Complication of intranasal midazolam. *Pediatrics*. 1993; 92(4):638.
18. Chiaretti A, Barone G, Rigante D, et al. Intranasal lidocaine and midazolam for procedural sedation in children [published online ahead of print October 27, 2010]. *Arch Dis Child*. 2011; 96(2):160-163.
19. Iirola T, Vilo S, Manner T, et al. Bioavailability of dexmedetomidine after intranasal administration. *Eur J Clin Pharmacol*. In press.
20. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. *Anesth Analg*. 2008; 106(6):1715-1721.
21. Yuen VM, Irwin MG, Hui TW, Yuen MK, Lee LH. A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. *Anesth Analg*. 2007; 105(2):374-380.
22. Yuen VM, Hui TW, Irwin MG, Yao TJ, Wong GL, Yuen MK. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. *Anaesthesia*. 2010; 65(9):922-929. doi: 10.1111/j.1365-2044.2010.06453.x.
23. Kazemia AP, Kamalipour H, Seddighi M. Comparison of intranasal midazolam versus ketamine as premedication in 2-5 years old paediatric surgery patients. *Pak J Med Sci*. 2005; 21(4):460-464.
24. Gharde P, Chauhan S, Kiran U. Evaluation of efficacy of intranasal midazolam, ketamine and their mixture as premedication and its relation with bispectral index in children with tetralogy of fallot undergoing intracardiac repair. *Ann Card Anaesth*. 2006; 9(1):25-30.