When to Pick the Nose: Out-of-Hospital and Emergency Department Intranasal Administration of Medications

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The intranasal route for medication administration is increasingly popular in the emergency department and out-of-hospital setting because such administration is simple and fast, and can be used for patients without intravenous access and in situations in which obtaining an intravenous line is difficult or time intensive (eg, for patients who are seizing or combative). Several small studies (mostly pediatric) have shown midazolam to be effective for procedural sedation, anxiolysis, and seizures. Intranasal fentanyl demonstrates both safety and efficacy for the management of acute pain. The intranasal route appears to be an effective alternative for naloxone in opioid overdose. The literature is less clear on roles for intranasal ketamine and dexmedetomidine. [Ann Emerg Med. 2017;70:203-211.]

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INTRODUCTION

Intranasal medication administration is an increasingly popular route in the emergency department (ED) and out-of-hospital transport because of ease of use. It obviates the need for invasive routes of administration in patients without intravenous access, those seizing or combative, and where obtaining intravenous lines is difficult and time intensive (Table 1). Additionally, it offers a relatively painless alternative to intravenous or intramuscular access, which is of particular benefit to children.[1]

The intranasal route offers direct drug transport into the central nervous system circulation.[2] Medications must possess the following properties to effectively cross the blood-brain barrier: physiologic pH, un-ionized state, high lipophilicity, and small molecular weight.[3] Intranasal administration thus largely bypasses hepatic first-pass metabolism and permits rapid and predictable bioavailability compared with oral medications and some intramuscular medications.[4] We review the literature and indications for out-of-hospital and ED administration of intranasal midazolam, fentanyl, naloxone, ketamine, and dexmedetomidine.

Medications can be delivered intranasally by an atomizer that sprays the surface of the nasal mucosa. Atomizers are preferable to a syringe dropper, pipette, or soaked pledget because they do not require patient cooperation in head positioning and they maximize bioavailability and absorption by distributing the medication across a large surface area.[3,5,6] The volume administered should not exceed 1 mL per nostril (ideally 0.2 to 0.5 mL) to avoid runoff and swallowing.[4,7] Commonly used brands of mucosal atomization devices (sometimes referred to as "MAD")[3] have Luer-lock syringe connections that permit precise dosing (Figure). For optimal bioavailability, doses should be administered during a few seconds and divided evenly between nostrils, even at small volumes. Atomizers have 0.1 mL of "dead space," so providers should overfill to account for this loss.[3]

MIDAZOLAM

Midazolam is a benzodiazepine with sedative, anxiolytic, hypnotic, muscle relaxant, antegrade amnestic, and anticonvulsant activity.[8] Although aqueous and acidic (pH <4) in solution, at physiologic pH it becomes highly lipophilic, allowing rapid absorption and penetration through the blood-brain barrier (Table 2).[8] Two studies found that doses between 0.1 and 0.2 mg/kg produced adequate serum concentrations in children within 10 to 12 minutes.[9,10] A randomized trial found that 0.5 mL (5 mg/mL) per nostril had faster onset compared with 1 mL, whereas 0.2, 0.5, and 1 mL all produced similar clinical effects.[7] Thus, sedation can be rapidly achieved with intranasal midazolam[9]; however, the maximal volume (5 mg/mL, allowing 10 mg/dose) may limit sedative dosing in patients weighing greater than 50 kg and require repeated doses.

Table 1. Advantages and disadvantages of intranasal administration.[1-5]

Advantages	Disadvantages
Less painful than intravenous or intramuscular routes of administration	Volume limits dose
Needleless	Limited data compared with other routes
Fast delivery	More costly than intravenous route
Pharmacokinetics preferable to intramuscular:	Cannot be used in certain situations:
Obesity	Nasal trauma or septal defects
Children	Recent use of intranasal vasoconstrictors (eg, cocaine, phenylephrine)
Elderly	Intravenous or intraosseous pharmacokinetics more reliable
Minimizes spread of infectious diseases	Variable palatability
	May cause nasal mucosa irritation (eg, midazolam)

Studied sedation and anxiolysis indications for intranasal midazolam in children include laceration repairs, imaging, induction of general anesthesia, and reduction of nasal and limb fractures.[11-20] One ED study of 169 children aged 6 months to 7 years who required laceration repair in the ED randomized patients to receive oral midazolam at 0.5 mg/kg up to 15 mg or intranasal or buccal midazolam, both 0.3 mg/kg up to 10 mg.[15] The buccal group showed significantly less distress compared with the oral group, whereas the intranasal group did not. The intranasal group experienced the most local irritation and the smallest proportion of patients who willingly accepted the medication; however, it yielded a faster onset of sedation and higher parental satisfaction. A retrospective study of 205 pediatric ED patients sedated for procedures (laceration repair in 89%) found that a mean dose of 0.4 mg/kg was required to achieve adequate sedation and that the intranasal route appeared to be well tolerated.[16] A third series of 58 children requiring imaging (aged 1 to 40 months) noted effective sedation averaging an onset of 15 minutes after administration of 0.4 mg/kg, with recovery averaging 51 minutes.[12]

Two studies compared intranasal midazolam with other regimens. The first allocated 100 children aged 1 to 7 years and requiring wound suturing to receive either midazolam 0.5 mg/kg intranasally or ketamine 2.5 mg/kg intramuscularly and found that significantly more patients receiving midazolam required restraints of the head, arms, or legs during the procedure (86% versus 14%).[21] In the second study, 50 children received either midazolam 0.4 mg/kg intranasally or a combination of ketamine and midazolam intravenous (1 and 0.1 mg/kg, respectively).[22] Although 92% of patients in the midazolam group were believed to have achieved adequate sedation, this group showed lower sedation satisfaction scores from parents and physicians. Patients receiving midazolam had a longer onset of sedation and a shorter recovery.

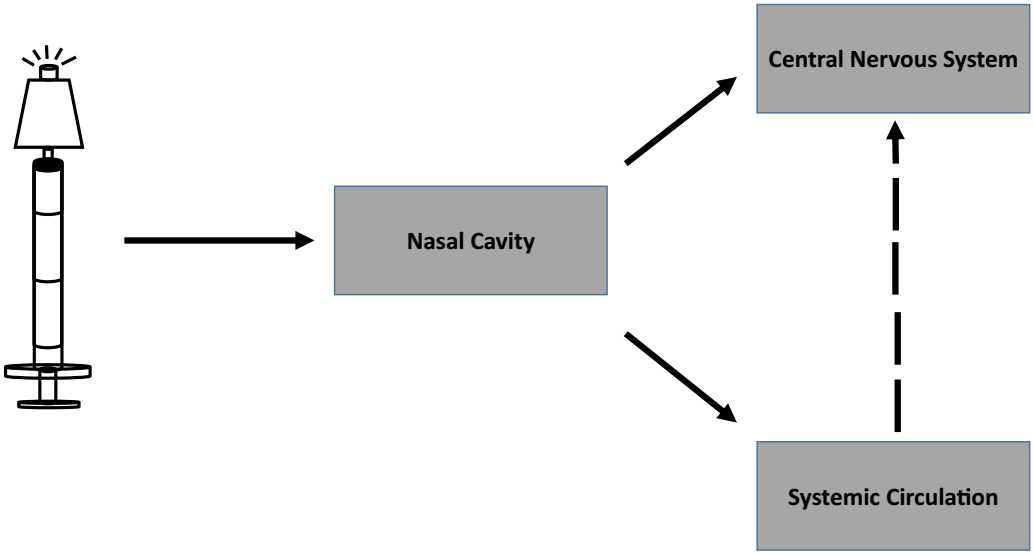

Figure. Mucosal atomization device. Once in the nasal cavity, the spray from this device expels across a large surface area of the nasal mucosa. Medications with optimal pharmacokinetic properties rapidly cross the blood-brain barrier and enter the central nervous system and systemic circulation.

Table 2. Intranasal medication pharmacokinetics and adverse effects.[8,36,55,56,62,63,69,79,81,82]

Medication	Bioavailability, %	Onset, Minutes	Duration, Minutes	Dosing	Intranasal Adverse Effects
Midazolam	50	10–15	30	Procedural sedation: Pediatric: 0.1–0.5 mg/kg Adult: volume limits adequate dose Seizures: Pediatric: 0.2 mg/kg Adult: 10 mg Maximum single dose based on volume: 10 mg	Nasal burning, bitter taste
Fentanyl	89	6–7	30–60	Analgesia: Pediatric: 1–2 μg/kg per dose Adult: 100 μg Maximum single dose based on volume: 100 μg	Respiratory depression, lightheadedness, euphoria, nausea/vomiting
Naloxone	4–30	8–13	30–120	Opioid reversal: Pediatric: no data; recommend 0.2 mg/kg Adult: 2–8 mg Maximum single dose based on volume: 2 mg using IV solution for IN administration; 8 mg using new 4 mg/0.1 mL product	Nasal dryness, edema, congestion, and local inflammation
Ketamine	40–50	5–23	72	Procedural sedation: Pediatric: 3–9 mg/kg Adult: volume limits adequate dose Analgesia: Pediatric/adult: 0.5–1 mg/kg Maximum single dose based on volume: 100 mg (50 mg/mL solution); 200 mg (100 mg/mL solution)	Sore throat, bad taste
Dexmedetomidine	65	Pediatric: 13–25 Adults: 45	Pediatric: 85 Adults: 90–105	Procedural sedation: Pediatric: 1–2.5 μg/kg Adult: no data; volume limits adequate dose Maximum single dose based on volume: 200 μg	None reported

IV, Intravenous; *IN*, intranasal.

Thus, intranasal midazolam can provide anxiolysis and sedation for children; however, the maximum of 10 mg (concentration 5 mg/mL) per dose limits this modality in large children. Presently, there are no data for adults. The intranasal route causes a burning sensation or bitter taste in up to 66% of patients,[19,23] and it appears that 4% intranasal lidocaine (0.5 mL) given 5 minutes before midazolam can significantly decrease this discomfort—if multiple sequential intranasal medications can be tolerated.[24]

It is difficult to obtain intravenous access in an actively seizing patient, and rectal diazepam is commonly used for out-of-hospital seizures. This route is undesirable for patients or caregivers, and rectal diazepam is more costly than intranasal midazolam.[25-27] Recent guidelines for status epilepticus management in adults and children recommend intranasal midazolam as an alternative when intravenous lorazepam, intravenous diazepam, or intramuscular midazolam is unavailable (level B recommendation).[28] This is based on pediatric data and extrapolated to adults. Intranasal midazolam appears as effective as rectal and intravenous diazepam; however, to our knowledge there are no comparative trials against intravenous lorazepam or intramuscular or intravenous midazolam.[28]

Three studies compared intranasal midazolam with rectal diazepam. In the first, 45 children aged 1 month to 13 years and presenting to the ED with seizure activity greater than 5 minutes were randomized to receive either intranasal midazolam (0.2 mg/kg) or rectal diazepam (0.3 mg/kg).[29] The authors noted significantly greater resolution at 10 minutes with intranasal midazolam (87% versus 60%). This study used nasal drops (not atomizers) to administer midazolam, which may have blunted the benefit observed because of less adequate bioavailability

and risk of drug runoff. The second study compared intranasal midazolam (0.2 mg/kg) with rectal diazepam (0.3 mg/kg) in 188 seizure episodes in 46 children and found faster administration and seizure cessation with midazolam, as well as less respiratory depression.[30] A third trial compared intranasal midazolam (0.2 mg/kg) with rectal diazepam (0.3 to 0.5 mg/kg) for out-of-hospital treatment of 57 pediatric seizures.[31] Patients in the midazolam group had significantly shorter median seizure time and were less likely to have a repeated seizure in the ED, intubation, or hospital admission. Other studies support efficacy and high caregiver satisfaction for intranasal midazolam.[4,25,26]

Several studies have also evaluated intranasal midazolam against intravenous diazepam.[32-35] The most rigorous of these trials randomized 44 children aged 6 months to 5 years with febrile seizures lasting greater than or equal to 10 minutes to receive either intranasal midazolam 0.2 mg/kg (maximum 10 mg) or intravenous diazepam 0.3 mg/kg (maximum 10 mg).[32] The study found similar response between the 2 groups, but significantly faster administration (3.5 versus 5.5 minutes) and seizure cessation (6.1 versus 8 minutes) with midazolam. Similar findings have been found in additional trials, with one including adults and adolescents.[26,33-36] These results suggest that if intravenous access is not available in a seizing patient, intranasal midazolam is a rapid and effective alternative.

A more concentrated formulation of midazolam is currently under development for seizure therapy,[37] with optimized volume and concentration, increased absorption, and 134% bioavailability relative to the current formulation.

FENTANYL

Analgesic therapy is not always optimal, particularly in out-of-hospital and pediatric populations.[38] Inadequate analgesia can modify the physiologic response to injury and may result in negative long-term effects.[39] Intranasal fentanyl has been studied for dental extractions, postoperative analgesia, chronic pain control for cancer patients, and burn wound management, and its use is increasing in the ED and out-of-hospital settings. The concentration of 50 μg/mL available in the United States limits the delivery of doses greater than 100 μg, thus leading to suboptimal analgesia or requiring multiple doses in patients weighing more than 50 kg.[40]

Fentanyl is a synthetic opioid that has selectivity for μ-opioid receptors. Because of its lipophilicity and 50- to 100-fold higher potency than morphine, it is ideally suited for intranasal administration (Table 2).[41,42]

In one observational study of 45 ED children given intranasal fentanyl (20 μg for those aged 3 to 7 years; 40 μg for those aged 8 to 12 years), pain reduction was achieved at 10 minutes and sustained through 30 minutes without important adverse effects.[43] A second study found similar improvement in 81 children (mean age 8 years) administered 2 μg/kg for orthopedic injuries.[44] A third noted safety and efficacy in 46 children aged 1 to 3 years and receiving intranasal fentanyl 1.5 μg/kg.[45]

In a randomized, double-blinded, placebo-controlled trial of intranasal fentanyl at 1.4 μg/kg versus intravenous morphine at 0.1 mg/kg in 67 ED children with long-bone fractures, there was no difference in analgesic efficacy at 5, 10, 20, or 30 minutes, and no serious adverse events in either group.[46] Two pediatric chart review studies found significantly faster time to administration of intranasal fentanyl compared with intravenous morphine,[47,48] attributable to the time required to obtain intravenous access.

The Pain in Children Fentanyl or Ketamine (PICHFORK) trial compared intranasal fentanyl (1.5 μg/kg) against intranasal ketamine (1 mg/kg) in a double-blind, randomized, controlled study of 73 children (3 to 13 years) with an isolated limb injury[49] and found similar analgesia at 30 minutes. The trial demonstrated a nonsignificant trend toward increased adverse effects with ketamine (78% versus 40%), mostly driven by minor issues (dizziness 30%, bad taste 25%, and drowsiness 16%) that did not appear to affect patient satisfaction.

Thus, intranasal fentanyl appears desirable for analgesia in situations in which intravenous access has not been established or is not warranted, particularly in children. Future trials should compare intranasal fentanyl with other analgesics and explore expanded indications, such as sickle cell crisis and other disease states.[50] Additional research should also include adults.

An out-of-hospital trial randomized 227 adults with pain scores greater than 2 of 10 (noncardiac) or greater than 5 of 10 (cardiac) to receive intranasal fentanyl (180 μg with the potential to receive 2 additional doses of 60 μg at ≥5-minute intervals) or intravenous morphine (2.5 to 5 mg with the potential to receive 2 additional doses of 2.5 to 5 mg at ≥5-minute intervals)[51] and found similar reductions in pain on ED arrival. The study noted a nonsignificant trend toward more serious adverse events (hypotension, respiratory depression, or altered level of consciousness) in the fentanyl group (15% versus 7%).

A prospective observational out-of-hospital study evaluated the safety of intranasal fentanyl (mean dose 114 μg) in 903 adults and children (>8 years) with severe pain from an orthopedic injuries, abdominal pain, or acute

coronary syndrome.[52] Thirty-six patients (4%) experienced adverse effects, none serious. Similarly, another study found no adverse effects in 94 children aged 1 to 16 years who received intranasal fentanyl 1.5 μg/kg.[53] Variations in adverse effects between studies likely result from differences in study design, dose, and adverse event definitions.

NALOXONE

Increases in opioid overdose and death necessitate early recognition and naloxone administration by lay persons and first responders.[54] Several states in the United States and countries in Europe dispense naloxone to at-risk patients (eg, intravenous drug users),[54] and these programs have shown success in saving lives.[55] The intranasal route is attractive for opioid overdose, given the difficulty of intravenous access in patients with compromised peripheral veins and the risk of infectious disease transmission.

Naloxone is a pure opioid antagonist with a higher affinity for the opiate receptor than exogenous opioids, competing with and displacing opioids primarily at the μ-receptor. Naloxone can be administered through intravenous, intramuscular, subcutaneous, and intranasal routes. A pharmacokinetic study of naloxone 2 mg administered intranasally and intramuscularly found a bioavailability of 4% and 36%, respectively; however, in this study the 2.5-mL volume per nostril far exceeded that which is optimal for nasal absorption (<1 mL). Such low bioavailability indicates that a concentrated solution or higher dosing is needed[56] and, indeed, another study using a higher concentration found a bioavailability between 24% and 30% (Table 2).[57] A new intranasal naloxone product at 4 mg/0.1 mL has been approved and appears an optimal formulation to overcome this relatively poor bioavailability.[58]

The efficacy of intranasal naloxone closely approaches that of the intramuscular route.[59,60] A randomized, unblinded trial of 155 overdose patients found less rapid time to respiratory rate greater than 10 breaths/min with the intranasal compared with the intramuscular route (mean 8 versus 6 minutes); however, there was no difference in mental status or need for supplemental naloxone.[61] Another randomized controlled trial of 172 patients noted a mean 8-minute response to improved respiratory recovery in both the intranasal and intramuscular groups; however, more intranasal patients received additional naloxone (18% versus 5%).[62] Thus, intranasal naloxone appears to be the preferred route in a patient without intravenous access, given the ease of administration and lessened risk of infectious disease transmission.

If intravenous access is already established, then this route is preferred over the intranasal route. A retrospective study of 96 patients with opioid overdose found greater need for supplemental naloxone with 2 mg intranasally compared with 0.4 to 2 mg intravenously (42% versus 20%), despite similar respiratory rates and Glasgow Coma Scale measures.[63] A second study randomized 100 patients to receive 0.4 mg/2 mL either intranasally or intravenously and found a longer mean response time in the intranasal group (2.6 versus 1.5 minutes).[64]

Despite this evidence of slightly longer time to onset and variable duration, intranasal naloxone can readily be considered as first-line therapy in suspected opioid overdose without intravenous access because of its ability to be simply and rapidly administered by lay persons and out-of-hospital personnel.

KETAMINE

Ketamine is a sedative and analgesic used for procedural sedation, postoperative and neuropathic pain, and, more recently, treatment of depression and migraines.[65-67]

Ketamine is a dissociative sedative that produces potent analgesia and amnesia while preserving spontaneous respiratory drive.[66-68] The time required for ketamine to reach maximum plasma concentration is substantially longer through the intranasal route compared with the intravenous one (10 to 23 minutes versus 2 minutes).[69] A pharmacokinetic study concluded that to yield serum concentrations high enough to produce sedation, ketamine would have to be administered at such high doses (9 mg/kg) and volumes that substantial quantities would be swallowed.[69] A high degree of patient variability has been noted, with sedation onset between 5 and 23 minutes and lasting up to 72 minutes, rendering the intranasal route impractical for this use.[65] Accordingly, intranasal ketamine is effectively limited to analgesia (Table 2).[49,70,71]

Ketamine sedation through the intranasal route has been studied for a variety of pediatric procedures, with variable success.[72-78] A previously described randomized trial compared intranasal fentanyl and ketamine and noted similar analgesia but a trend toward greater adverse effects with ketamine.[49] Another study randomized 72 adults undergoing nasogastric tube placement to receive intranasal water or ketamine 50 mg and found superior conditions with ketamine.[74]

In a prospective observational study for use of ketamine as an analgesic, 40 mostly adult patients with orthopedic injuries received ketamine intranasally at 0.5 to 0.75 mg/kg, with 88% demonstrating a 13-mm visual analog scale pain reduction within 30 minutes.[70] In another study, 30

children aged 3 to 13 years with an isolated limb injury and pain score greater than or equal to 6 of 10 received ketamine intranasally at 0.7 mg/kg initially, with an additional dose of 0.5 mg/kg if necessary.[71] Aggregate dosing averaged 1.0 mg/kg, with median pain ratings decreasing from 74.5 to 30 mm after 30 minutes.

Thus, intranasal ketamine appears to be an effective analgesic (particularly in children), but substantial additional research is needed to establish comparisons with other agents and to optimize dosing.[72,73,75-78]

DEXMEDETOMIDINE

Dexmedetomidine is an α_2-agonist that produces sedation, hypnosis, analgesia, and sympatholysis while depressing respirations less than anesthetics, opioids, and benzodiazepines.[66,67] The clinical effect mirrors endogenous sleep. Patients sedated with dexmedetomidine are easier to rouse for neurologic examinations,[66] and this agent may cause lower rates of delirium compared with benzodiazepines.[79] When dexmedetomidine is administered intranasally, its bioavailability is 65% (Table 2),[80,81] with onset in children between 13 and 25 minutes and a duration of action of 85 minutes,[82,83] and onset in adults at 45 minutes, with 90 to 105 minutes for peak sedation.[84] The most common doses studied are between 1 and 2 μg/kg.[83,85-94]

Dexmedetomidine intranasally has been studied in the surgical, dental, and other periprocedural settings, primarily in children.[83,85-95] In the single ED study, 60 children aged 1 month to 5 years received 2.5 μg/kg intranasally before CT scanning, with a 13-minute average time to sedation.[82] Blinded radiologists considered the image quality excellent in all cases. No serious adverse events were observed; however, there was a single instance each of prolonged recovery (>2 hours after the initial dose), hypoxia, and vomiting.

Non-ED studies including more than 1,000 patients have shown no serious hemodynamic adverse events.[83,85-95] However, there is one case report[96] in which an 11-year-old girl without a cardiac history experienced syncope and bradycardia (a nadir of 36 beats/min) after receiving dexmedetomidine 2.4 μg/kg (100 μg) for sedation in advance of a voiding cystourethrogram. An additional report from the Food and Drug Administration's adverse event reporting system described a 9-year-old boy sedated with dexmedetomidine (route of administration unclear) for nuclear medicine who subsequently required hospitalization for syncope (further details are not provided).[94] Thus, idiosyncratic bradycardic or syncopal reactions with intranasal dexmedetomidine must be considered when this agent is selected.

CONCLUSION

The intranasal route of administration is becoming increasingly popular in the ED and out-of-hospital setting because it is easy, fast, and noninvasive. Several medications, including midazolam, fentanyl, naloxone, ketamine, and dexmedetomidine, possess pharmacologic properties that allow intranasal use and have been studied for a variety of indications.

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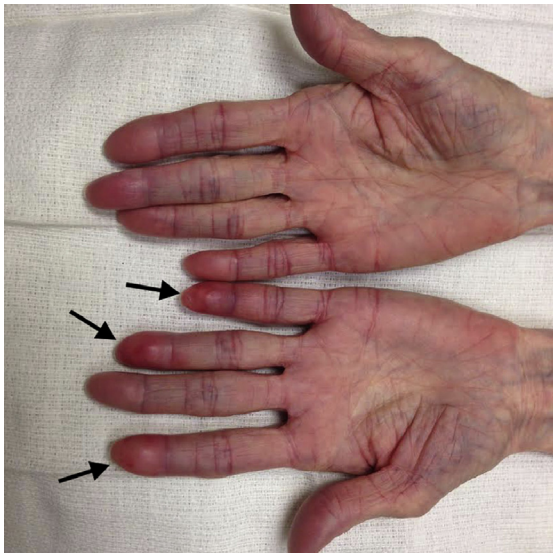

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