REVIEW OF INTRANASALLY ADMINISTERED MEDICATIONS FOR USE IN THE EMERGENCY DEPARTMENT

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Abstract—Background: Intranasal (IN) medication delivery is a viable alternative to other routes of administration, including intravenous (IV) and intramuscular (IM) administration. The IN route bypasses the risk of needle-stick injuries and alleviates the emotional trauma that may arise from the insertion of an IV catheter. Objective: This review aims to evaluate published literature on medications administered via the IN route that are applicable to practice in emergency medicine. Discussion: The nasal mucosa is highly vascularized, and the olfactory tissues provide a direct conduit to the central nervous system, bypass first-pass metabolism, and lead to an onset of action similar to IV drug administration. This route of administration has also been shown to decrease delays in drug administration, which can have a profound impact in a variety of emergent scenarios, such as seizures, acutely agitated or combative patients, and trauma management. IN administration of midazolam, lorazepam, flumazenil, dexmedetomidine, ketamine, fentanyl, hydromorphone, butorphanol, naloxone, insulin, and haloperidol has been shown to be a safe, effective alternative to IM or IV administration. As the use of IN medications becomes a more common route of administration in the emergency department setting and in prehospital settings. © 2017 Elsevier Inc. All rights reserved.

Keywords—emergency department; intranasal; medication; nasal; prehospital

INTRODUCTION

The oral route of drug administration is the most widely available and often the preferred route for systemic drug delivery. However, in the emergency department (ED) setting, it is likely that the oral route may not be available because of different clinical factors (e.g., level of consciousness, intolerance, obstructions, and trauma), and an alternative route is needed. Intranasal (IN) medication delivery has been shown to be a viable alternative to other invasive routes of administration, including intravenous (IV) and intramuscular (IM) administration (1,2). IN drug administration requires less technical skill compared to the IV route. The IN route bypasses the risk of needle-stick injuries and attempts to alleviate the potential emotional trauma that may arise from pain caused by insertion of an IV catheter if an IV is not necessary otherwise. In addition to safety concerns, the reviewed medications has been shown to be a safe and effective alternative to IM or IV administration. Use of IN is becoming more commonplace in the emergency department setting and in prehospital settings.
delivery of IM medications depends on accurate drug delivery into the IM space rather than the subcutaneous tissues. In addition, IN drug delivery can be used in a variety of patient populations, regardless of age, body habitus, clinical condition, or level of patient cooperation. IN administration has also been shown to decrease time to drug administration compared to IV administration, which can have a profound impact in certain emergent scenarios, such as seizures, acutely agitated or combative patients, and trauma management (3). In addition, IN medication administration may be useful in patients where obtaining IV access is challenging, such as those who abuse IV drugs.

**DISCUSSION**

**Physiology of Intranasal Drug Administration**

The nose is divided into two halves, and each half consists of four areas: the vestibule, atrium, respiratory region, and the olfactory region. The respiratory mucosa is primarily responsible for systemic drug delivery. The nasal mucosa receives an extensive amount of blood flow per unit of tissue compared to other major organs, such as the liver or brain. The nasal cavity can hold approximately 15–20 mL and has a surface area of ≤150 cm² (2). This extensive network of highly vascularized territories, combined with the olfactory tissues, provides some pharmacokinetic advantages for drug administration. Specifically, there is a direct conduit for the drug to enter the central nervous system and systemic circulation (4,5). This, in addition to bypassing first-pass metabolism by the liver, leads to an onset of action similar to IV drug administration. However, because of the slower rate of absorption, larger IN doses may be necessary wherein safety features should be put into place to limit medication errors related to dosing differences between IV and IN administration. In addition, not all medications are suitable for IN administration. Drug product characteristics that are considered advantageous include poor gastrointestinal solubility or those that undergo extensive first-pass metabolism (2).

**Preparation and Administration**

Unlike IV drug administration, IN medication administration does not require a sterile access site or medications prepared in a sterile manner. This enhances the rapidity of drug preparation and drug delivery. Using both nostrils when administering medications also helps optimize medication delivery because a limited volume can be administered in a single nostril at one time. Products that are more concentrated are preferred, because volumes >1 mL per nostril have a higher propensity to satu-rate the mucosal surface and result in drug runoff into the proximal pharynx. In addition, if less concentrated products are used it would necessitate dividing the dose into several attempts at administration, therefore delaying care and potentially increasing anxiety for the patient. Some common IN administration considerations are outlined in Table 1 (6,7).

For systemic drug absorption to occur, a drug has to pass the mucus layer and the epithelial membrane. In addition, the extent of drug absorption is reliant upon several factors, most importantly placement of the drug and the rate of mucociliary clearance of drug out of the nasal cavity. A variety of delivery methods have been used for IN administration, including manual application of drug (usually topical preparations), sniffing, insertion of drops, or use of atomization/spray devices. Atomizers are often the most efficient method for systemic drug delivery because they reduce drug runoff and enhance drug delivery over a larger surface area to improve nasal bioavailability. The administration of drugs using atomizers generally results in higher success rates because of patient comfort and successful drug delivery being independent of head position; however, they are not required for IN drug administration (8). Manual application or sniffing typically results in reduced drug delivery because larger proportions land on the external nostrils or anterior aspects of the nasal cavity.

Patients should first be evaluated to determine if they are a candidate for IN medication administration. Potential contraindications would include any condition in which the nasal passages, mucosa, or airway are compromised (Table 2). The majority of patients appear to tolerate IN medication administration well; few adverse events have been reported. Local irritation is the most common adverse event, but others include poor taste, increased lacrimation, and a burning sensation. Some medications may have other known drug-specific adverse effects that may not be limited to the route of administration (Table 3).

<table>
<thead>
<tr>
<th>Table 1. Intranasal Medication Administration Considerations</th>
</tr>
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<tbody>
<tr>
<td><strong>Strategy</strong></td>
</tr>
<tr>
<td>Concentrated products are preferred, ideally volumes &lt;1 mL per nostril should be used</td>
</tr>
<tr>
<td>Divide doses between both nostrils</td>
</tr>
<tr>
<td>Products administered by this route should not be inhaled</td>
</tr>
<tr>
<td>Avoid blowing nose or sniffing postadministration</td>
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Table 2. Potential Contraindications to Intranasal Medication Administration

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
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<tbody>
<tr>
<td>Abnormal neurologic examination or developmental delay</td>
</tr>
<tr>
<td>Allergy or sensitivity to the medication being administered</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td>Facial trauma</td>
</tr>
<tr>
<td>Medical conditions that affect ciliary function (e.g., cystic fibrosis)</td>
</tr>
<tr>
<td>Nasal obstruction (e.g., nasal polyps, significant facial trauma)</td>
</tr>
<tr>
<td>Rhinitis</td>
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</table>

PHARMACOLOGIC AGENTS

There is a myriad of medications that can be given via the IN route. Many are used for symptomatic relief of nasal conditions, including epistaxis, rhinitis, or preparation for nasopharyngoscopy or nasotracheal intubation. Not all are applicable to emergency medicine providers. Therefore, the scope of this review will encompass medications most commonly used in emergent or urgent situations and those that have a potential for application in the ED.

SEDATIVE-HYPNOTICS

Midazolam

Use in the Emergency Department. The use of IN midazolam in the ED has broadened to include several indications, including procedural sedation, chemical anxiolysis, and seizures. The greatest utility in the ED is in the areas of procedural sedation and seizures. The IN route has been shown to be less invasive than the IM route, and this is particularly helpful in pediatric patients who are undergoing painful procedures in the ED, including IV catheter placement.

Midazolam is an excellent candidate for the IN route because it has a more rapid onset of action than other benzodiazepines given via the IN route. IN midazolam reaches plasma concentrations similar to IV midazolam administration, with a peak concentration attained in 25 min and clinically significant concentration within 10 min (9). Most data are limited to use in children. IN midazolam has been studied in the preanesthesia setting for use in minor procedures, such as laceration repair or dental trauma, seizures, and before radiologic imaging (10–12).

IN midazolam alone has been used for procedural sedation both alone and in combination with other agents, including analgesics (7,13–15). It has also been used successfully for laceration repair in the ED setting. IN midazolam alone experienced no adverse events and that 11 of 60 patients included also received adjunctive ketamine for sedation, which shows that midazolam can be used safely when combined with other agents (16). Tsze et al. evaluated the optimal volume of administration in pediatric patients receiving midazolam (0.5 mg/kg) for laceration repair in the ED. They compared volumes of 0.2, 0.5, and 1 mL with respect to time to minimal sedation. They determined that all volumes produced comparable outcomes, but provider satisfaction was compromised with the 0.2-mL volume of administration (7). It is advisable to use a maximum dose of 10 mg to avoid oversedation or respiratory depression.

IN midazolam has been evaluated in several studies for use in seizure and status epilepticus (17–20). In a systematic review performed by Brigo et al. in 2015, there was no difference in clinical seizure cessation between IN midazolam, IV diazepam, and rectal diazepam, with a mean time to seizure cessation after midazolam administration ranging from 3 to 4 min. The authors concluded that IN midazolam was as efficacious and as safe as IV diazepam in treating status epilepticus (21). McMullan et al. confirmed the effectiveness of IN midazolam for seizures in a 2010 meta-analysis that included six studies with a total of 774 patients. This analysis examined all types of non-IV benzodiazepines in children (22). For seizure cessation, midazolam by any route was determined to be superior to diazepam by any route (relative risk = 1.52 [95% confidence interval 1.27–1.82]). Midazolam was administered faster than diazepam and respiratory complications requiring intervention were similar, regardless of administration route (22).

Dosage. Dosing for seizures is 0.2 mg/kg (maximum of 10 mg), while total doses for procedural sedation range from 0.2–0.8 mg/kg with initial doses starting at 0.2–0.3 mg/kg, and providers can repeat doses if adequate sedation is not achieved or prolonged sedation is necessary (9). Higher doses are more likely to produce a deeper sedation for a longer duration. Onset for sedation is typically 5–15 min, with most studies reporting a mean onset of around 10 min (9). The duration of effect is typically 45 min, allowing for most patients to be discharged from the ED or outpatient area without complications.

Lorazepam

Use in the Emergency Department. Much of the literature supporting the use of IN lorazepam is in the setting of seizures or status epilepticus (23). However, clinical use of lorazepam spans multiple indications, including anxiolysis, preoperative adjunct, and add-on therapy for nausea and vomiting (24,25). The most common use for IN
<table>
<thead>
<tr>
<th>Drug*</th>
<th>Indication†</th>
<th>Intranasal Dose</th>
<th>Time to Peak Effect (Intranasal IN vs. Intramuscular IM)‡</th>
<th>Volume Range§</th>
<th>Adverse Events</th>
<th>Relative Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications Commonly Used in the Emergency Department</strong></td>
<td></td>
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<tr>
<td>Fentanyl (50 μg/mL)</td>
<td>Analgesia</td>
<td>0.5–2 μg/kg</td>
<td>5 min&lt;sub&gt;IN&lt;/sub&gt;; 1–5 min&lt;sub&gt;IV&lt;/sub&gt;</td>
<td>0.5–3 mL</td>
<td>Nasal irritation, rhinitis, and headache</td>
<td>$</td>
</tr>
<tr>
<td>Ketamine (100 mg/mL)</td>
<td>Agitation, analgesia, depression, migraine, and sedation</td>
<td>3–6 mg/kg</td>
<td>5–10 min&lt;sub&gt;IN&lt;/sub&gt;–&lt;sub&gt;IM&lt;/sub&gt;</td>
<td>2–4 mL</td>
<td>Poor taste, dizziness, hypersalivation, hypertension, agitation, and emergence reactions</td>
<td>$</td>
</tr>
<tr>
<td>Lorazepam (2 mg/mL)</td>
<td>Agitation and seizures</td>
<td>0.1 mg/kg (usual range of 1–2 mg with a max of 4 mg)</td>
<td>30 min&lt;sub&gt;IN&lt;/sub&gt;; 60 min&lt;sub&gt;IM&lt;/sub&gt;</td>
<td>0.5–2 mL</td>
<td>Poor taste, cool feeling in the nose and throat, lacrimation, and nasal irritation</td>
<td>$</td>
</tr>
<tr>
<td>Midazolam (5 mg/mL)</td>
<td>Agitation, sedation, and seizures</td>
<td>0.1–0.4 mg/kg (usual range of 2–5 mg with a max of 10 mg)</td>
<td>5–10 min&lt;sub&gt;IN&lt;/sub&gt;–&lt;sub&gt;IM&lt;/sub&gt;</td>
<td>0.4–2 mL</td>
<td>Nasal irritation, conjunctival congestion, and increased salivation</td>
<td>$</td>
</tr>
<tr>
<td>Naloxone (1 mg/mL)</td>
<td>Reversal of opioid-induced respiratory depression</td>
<td>0.1 mg/kg (usual range of 0.4–2 mg)</td>
<td>1–5 min&lt;sub&gt;IN&lt;/sub&gt;–&lt;sub&gt;IM&lt;/sub&gt;</td>
<td>0.4–2 mL</td>
<td>Nausea, vomiting, headache, tremor, sweating, agitation, cardiac dysrhythmias, myocardial infarction, and seizures</td>
<td>$</td>
</tr>
<tr>
<td><strong>Other Medications</strong></td>
<td></td>
<td></td>
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<tr>
<td>Dexmedetomidine (100 μg/mL)</td>
<td>Sedation</td>
<td>1–2 μg/kg</td>
<td>20 min&lt;sub&gt;IN&lt;/sub&gt;; 1–5 min&lt;sub&gt;IV&lt;/sub&gt;</td>
<td>0.7–1.5 mL</td>
<td>Bradycardia and hypotension</td>
<td>$$$</td>
</tr>
<tr>
<td>Flumazenil (0.1 mg/mL)</td>
<td>Reversal of benzodiazepine-induced respiratory depression</td>
<td>0.025–0.04 mg/kg (max of 0.1–0.2 mg)</td>
<td>5–10 min&lt;sub&gt;IN&lt;/sub&gt;–&lt;sub&gt;IM&lt;/sub&gt;</td>
<td>1–2 mL</td>
<td>Gastrointestinal symptoms and agitation</td>
<td>$</td>
</tr>
<tr>
<td>Hydromorphone (2 mg/mL)</td>
<td>Analgesia</td>
<td>2–10 mg</td>
<td>10–15 min&lt;sub&gt;IN&lt;/sub&gt;–&lt;sub&gt;IM&lt;/sub&gt;</td>
<td>1–5 mL</td>
<td>Poor taste</td>
<td>$</td>
</tr>
</tbody>
</table>

* Concentrations listed reflect the recommended concentration for use during intranasal administration.
† Indications commonly utilizing the intranasal route were included. The listed indications are not meant to be a comprehensive list.
‡ If intramuscular administration was not an available option, intranasal was compared to the listed route.
§ Assuming weight of 70 kg; volume listed is the total volume, which would then be divided between each nostril.
|| Dollar amount based on average wholesale acquisition cost per dose; $ <$50 (US); $$ = $50–100 (US); $$$ >$100.
lorazepam in the ED is for seizures or chemical anxiolysis.

The pharmacokinetic profile of IN lorazepam indicates that there is potential for broader clinical utility, similar to midazolam. Studies of IN lorazepam found similar pharmacokinetic profiles to the injectable routes of administration, including IV and IM routes (24,25). Lorazepam has ~80% bioavailability when given via the IN route and has a time to peak concentration of 30 min, which is nearly two times faster than IM administration (24,26,27).

Ahmad et al. compared IN lorazepam to paraldehyde for treatment of seizures in Malawi where children (>2 months of age) were randomized to receive either lorazepam (0.1 mg/kg) IN or 0.2 mL/kg paraldehyde administered via the IM route. In this study, use of IN lorazepam also reduced the need for repeat doses of other antiepileptics (28). Arya et al. conducted a study comparing IN lorazepam to IV lorazepam for control of acute seizures in children. They randomized 141 children to receive 0.1 mg/kg of either IN or IV lorazepam (maximum of 4 mg). They determined that IN lorazepam was not inferior to IV lorazepam with producing cessation of seizure activity, time to administration to termination of seizure activity, or duration of seizure-free period after lorazepam administration (25).

**Dosage.** The literature supports doses of IN lorazepam similar to those used for IV administration (0.1 mg/kg), and these have been shown to be effective in producing seizure cessation (23,28). Available studies used doses ranging from 2–4 mg per dose.

**Dexmedetomidine**

*Use in the Emergency Department.* This agent has been used in clinical practice for its sedative, analgesic, and anxiolytic properties (29). IN dexmedetomidine has specifically been used for procedural sedation in adult and pediatric patients (1,30,31). Time to satisfactory sedation was noted to be as long as 20–30 min, limiting the use of dexmedetomidine in the ED (31,32). Infusions of dexmedetomidine are commonly targeted for cost-containing initiatives. However, the cost of one-time doses in the ED are far less expensive, opening up the possibility for use in this setting.

Dexmedetomidine, a selective α-2 adrenergic agonist, binds to both peripheral and centrally located α receptors (29). Yuen et al. conducted a study evaluating the use of IN dexmedetomidine in 18 volunteers in attempts to elucidate whether this route could be utilized in premedication for anesthesia. They compared placebo to 1 µg/kg IN dexmedetomidine and 1.5 µg/kg of IN dexmedetomidine. Although the authors concluded that both doses of dexmedetomidine were safe, produced appropriate levels of observed sedation (via visual analog scale for sedation), and were well-tolerated, they were not able to evaluate whether either dose was an effective anxiolytic because the subjects were healthy volunteers (30). Therefore, Yuen et al. conducted another evaluation of IN dexmedetomidine in 116 pediatric patients undergoing elective surgery (primarily circumcision, urologic surgery, or laparoscopic abdominal surgery). They found that children 5–8 years of age benefited more from 2 µg/kg, whereas children 1–4 years of age experienced satisfactory sedation at doses from 1–2 µg/kg (31). One of the noted limitations with use of IN dexmedetomidine appears to be the time to onset.

IN dexmedetomidine has been compared to other sedatives, including midazolam and ketamine (1,33). Sheta et al. compared IN dexmedetomidine (1 µg/kg) to IN midazolam (0.2 mg/kg) for premedication prior to dental extraction. The authors found that IN dexmedetomidine produced a significantly deeper level of sedation at the time of separation (77.8% vs. 44.4%, respectively), but IN midazolam produced a shorter time to onset of sedation (15 min vs. 25 min) (33). Both ketamine and dexmedetomidine were found to be equally efficacious in producing anxiolysis prior to imaging studies performed in one study. Both reduced total propofol requirements during the imaging study and both had a shorter time to awakening and discharge as compared to placebo (1).

**Dosage.** Dexmedetomidine is not labeled for use via the IN route. The doses studied range from 1–2 µg/kg, which mirror IV loading doses seen with mechanical sedation, procedural sedation, or emergence delirium in adult patients (29). The duration of action is dose-dependent, with a range of 45–90 min (31).

**Ketamine**

*Use in the Emergency Department.* The clinical application of ketamine in the ED is extensive and continues to expand beyond rapid sequence intubation or procedural sedation in pediatric patients. Ketamine is a phenylcyclohexyl derivative that has been used for analgesia during procedural sedation or traumatic pain, for chemical anxiolysis in acute agitation, for neuropathic pain, migraine headache, adjunctive treatment of major depressive disorders, and general anesthesia (34–36). The more practical applications of IN ketamine in the ED include analgesia, procedural sedation, or for chemical anxiolysis in acute agitation. Subdissociative doses of ketamine for pain lend themselves nicely to IN administration given the lower doses and subsequent lower volumes of administration. Ketamine is available in two
concentrations (10 and 100 mg/mL), both of which can be used for IN administration.

IN ketamine has been studied both as monotherapy and in combination with other sedatives or analgesics in both adults and children (1,34–39). Ketamine acts as a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. IN ketamine has an onset of action between 5–10 min and the bioavailability via this route can vary significantly being anywhere from 25–50% (35). Use of IN ketamine has been studied in novel areas including acute pain in the ED, migraine headache, and for major depressive disorders.

Andolfatto et al. conducted a prospective, observational study using IN ketamine for acute analgesia in the ED. Patients >6 years of age diagnosed with moderate to severe pain were included and received an initial dose of 0.5 mg/kg but could receive a single repeat dose of 0.25 mg/kg 10 min after the initial dose if their pain scores were appropriately high. IN ketamine produced an acceptable decrease in the visual analog scale pain score within 30 min of administration and 57% of patients (n = 40) required a repeat dose to get adequate analgesia; the majority of adverse events were transient and minor in nature (35).

Graudins et al. conducted a prospective, randomized controlled, double-blind equivalence study comparing IN ketamine to IN fentanyl for relief of moderate to severe pain in children. The investigators compared IN ketamine at 1 mg/kg to IN fentanyl at 1.5 μg/kg. The authors found similar pain reductions between groups at all points in addition to similar sedation scores between the groups. There were more adverse events in the ketamine group (28/36; 78% vs. 15/37; 40%) although all were considered minor and insignificant (40).

Migraine headache in the ED is a common chief complaint, and several medications have utility in management of migraine including ketamine (41). Ketamine’s use in migraine headache can pose a pharmacologic advantage because it has a mechanism of action that differs from traditional nonsteroidal drugs or opioid narcotics. Afridi et al. conducted a double-blind, randomized trial investigating whether 25 mg of IN ketamine could be used as a treatment modality for preventing progression of migraine-related aura. They used 2 mg of IN midazolam as a control to blind the patients and providers to the psychotropic effects of ketamine. Once controlled, the patients were discharged to the outpatient setting where they were instructed to use the study drug during three attacks and record data on the duration and severity of their auras. The authors concluded that IN ketamine was effective in decreasing the severity of aura symptoms and this resulted in no major adverse events (42).

Dosage. Initial doses of IN ketamine range from 0.7–1 mg/kg, with repeat bolus doses of 0.5 mg/kg if necessary (for analgesia or sedation) (39). In pediatric patients, ≤5 mg/kg appears to be safe and effective via the IN route (1,39,43). For adults, 0.5–5 mg/kg has been recommended for procedural sedation followed by 0.25 mg/kg repeat boluses; however, lower doses ranging from 10–50 mg per dose have been used in the setting of chronic pain, major depressive disorder, and headache (34).

ALGESICS

Fentanyl

Use in the Emergency Department. Fentanyl has been extensively used in the prehospital and ED settings to provide rapid and easily titratable analgesia (44–46). IN fentanyl is rapidly absorbed into systemic circulation, making it ideal for acute or breakthrough pain. IN administration of fentanyl has a time to peak concentration of 5–15 min and has been shown to provide safe, efficacious, and well tolerated analgesia. IN administration represents a viable alternative to IV or buccal administration in the ED, perioperative, and periprocedural setting (44,45). Unlike benzodiazepines, nonparenteral routes of administration of fentanyl have data in both adult and pediatric patient populations (44–47).

Striebel et al. compared IV fentanyl with IN fentanyl for postoperative pain and again compared IN fentanyl to patient-controlled analgesia. In both evaluations, it was determined that IN fentanyl provided rapid analgesia without significant adverse events as compared to IV (48,49). Borland et al. compared IN fentanyl to oral morphine for analgesia during dressing changes in pediatric burn patients. IN fentanyl at a dose of 1.7 μg/kg was compared to 1 mg/kg of oral morphine. The authors concluded that IN fentanyl was as effective as oral morphine in providing pain relief without prolonging recovery time (50). Borland et al. also compared IN fentanyl to IV morphine in pediatric patients presenting to the ED for acute pain. IN fentanyl at 1.7 μg/kg was compared to IV morphine at 0.1 mg/kg. Fentanyl was found to be largely equivalent to morphine and alleviated the need for IV access (51).

Dosage. When administered via the IN route, peak plasma concentrations of fentanyl are higher and bioavailability was also higher as compared to buccal administration (45,47). The bioavailability of IN fentanyl is approximately 70%, therefore, doses evaluated are similar to that seen with IV administration (i.e., initial doses starting at 1–2 μg/kg) and are equally as efficacious (45).
Hydromorphone

Use in the Emergency Department. Hydromorphone is an opioid analgesic that is eight times more potent than morphine (52). Providers often consider this agent for IV administration when patients have moderate to severe pain or do not have adequate pain relief from morphine (3). IN use of hydromorphone in the ED would be appropriate in patients requiring multimodal pain control or who are nonresponsive to oral medications but who do not have IV access.

Two studies have evaluated the use of IN hydromorphone (52,53). The first was conducted in 24 healthy volunteers and revealed hydromorphone was rapidly absorbed when given IN. The time to reach maximum concentration ranged from 20–255 min (52). Wermeling et al. conducted a study of IN hydromorphone in patients with trauma-related pain. Single doses of 2, 4, 6, 8, and 10 mg were given via a single IN dose. All of the groups with the exception of those patients who only received 2 mg reported the following: initial pain relief within 10–15 min, a 30% reduction in their pain intensity within 30 min of administration, and a 50% reduction in pain intensity after an hour (53).

Dose. Hydromorphone is less lipophilic compared to other parenteral opioids, necessitating larger IN doses. Given the range of doses studied and the known bioavailability of IN hydromorphone, a dose of 4–10 mg IN hydromorphone may be considered for management of moderate to severe pain. However, it may be appropriate to start with 2 mg in elderly patients or patients with a perceived risk of respiratory depression, with the understanding that 2 mg may not provide adequate analgesia in those with severe pain. Practitioners should exercise extreme caution when administering IN hydromorphone. Particularly given the differences in IN dosing compared to IV administration.

AGENTs FOR REVERSAL SEDATION OR ANALGESIA

Flumazenil

Use in the Emergency Department. Flumazenil is a competitive benzodiazepine receptor antagonist. IN flumazenil has been used in reversing central nervous and respiratory depression from benzodiazepines after procedural sedation (54). As use of IN sedatives in the ED continues to grow, the stocking and use of IN reversal agents is logical.

Heard et al. documented the use of IN flumazenil used to reverse oversedation produced after administering 5 mg of IN midazolam and 15 μg (1 μg/kg) of IN sufentanil to a 3-year-old child (55). The authors document the successful use of IN flumazenil administered as two doses of 100 μg given in each nostril used to facilitate awakening of the pediatric patient after terminating a dental procedure (55).

McGlone et al. used IN flumazenil 0.025 mg/kg to reverse sedation produced by administration of 0.4 mg/kg of IM midazolam during suturing in pediatric patients in the ED (56). The patients were successfully reversed within 5–10 min of administration and reduced agitation and time to discharge in ED patients.

Dosage. The available literature on the use of IN flumazenil mostly involves administration in the periprocedural setting to reverse sedation from benzodiazepines in pediatric patients. Documented reports cite doses of 0.025–0.04 mg/kg flumazenil administered intranasally, which has been shown to produce similar serum concentrations as IV administration. The documented time to peak concentrations is approximately 2 min, with a half-life of up to 2 hours (54–56). The use of IN flumazenil in clinical practice has several limitations, including cost and volume of administration. The only available concentration of flumazenil is 100 μg/mL, thereby necessitating larger volumes of administration in pediatric patients.

Naloxone

Use in the Emergency Department. Naloxone is an opioid antagonist used emergently for the treatment of known or suspected opioid overdose (57). Naloxone works by competing with other opioids for the μ, κ, and σ opioid receptor sites in the central nervous system, with a greater affinity for the μ opioid receptor. Although multiple routes of administration are available (IV, IM, subcutaneous, inhalational, and IN), IN administration of naloxone can be useful in the setting of limited peripheral venous access associated with IV drug abusers and has a time to peak concentration of approximately 3 min (58,59). IN naloxone should be considered for use in the ED as the rising opioid epidemic presents an opportunity to rapidly reverse opioid-induced respiratory depression. In addition, IN naloxone can be used to reverse oversedation after opioids during procedural sedation in adult or pediatric patients.

The use of IN naloxone was first reported in 1991 by Loimer et al. The authors noted that naloxone was rapidly absorbed from the nasal cavity and was as effective as IV administration at reversing depression secondary to opioid overdose (60). There have been multiple studies evaluating the clinical efficacy of IN naloxone and all have determined IN naloxone to be a viable alternative for opioid reversal, especially in a prehospital setting (58,61).
Dose. IN naloxone is dosed as a range of 0.8–2 mg, instilling 0.4–1 mg in each nostril, followed by a repeat dose after 5 min if respiratory or central nervous system depression continues (62).

ANTIPSYCHOTICS

Haloperidol
Use in the Emergency Department. Haloperidol is a typical antipsychotic used extensively in the treatment of acute agitation. Data regarding IN use of antipsychotics in the ED are limited. However, the ease of administration, noninvasiveness, and pharmacokinetic properties make this an appealing route for an acutely agitated patient. Traditional routes of administration, such as oral or IV administration, may not be feasible in patients who are acutely agitated or even violent. Having a noninvasive route of administration is advantageous for health care providers and staff although there is limited evidence to suggest that IN administration is superior to IM (5).

There are limited data available regarding the use of IN haloperidol. In 2008, Miller et al. published a small pilot study of four healthy volunteers with the main objective to evaluate the pharmacokinetics of haloperidol after IN administration compared with IV and IM administration (63). Each subject received 2.5 mg of haloperidol via the IN, IV, or IM route in a randomized order. Peak concentrations were achieved within 15 min following IN and IV administration and within 37.5 min after IM administration, showing that the IN route provided higher and quicker peak concentration than the IM route. This study demonstrates that IN haloperidol absorption is rapid and can be used to obtain clinically relevant plasma levels (64).

Dose. The available literature indicates that doses of 2.5 mg produce serum levels similar to IV administration. However, most practitioners use doses ranging from 2.5–10 mg for agitation in the ED.

FUTURE DIRECTIONS
Given the number of advantages and the myriad of medications available for administration via the IN route, providers are becoming more accustomed to this method of drug delivery. It has had an impact on emergency triage and prehospital care. Also, as most ED annual censuses continue to increase, so do ED wait times. This has had direct effects on patient satisfaction, because it takes providers and staff longer and longer to address patient care issues, namely pain. Drug delivery via the IN route may be advantageous for use as an acute treatment for pain while waiting on an ED bed to become available. Nursing-driven protocols could be altered to include agents administered via this route to help provide early analgesia under appropriate conditions.

It is becoming increasingly feasible for parenteral medications to permeate into both prehospital and outpatient settings when given via the IN route (e.g., IN midazolam for control of acute seizures in pediatric patients). However, there are still barriers for the layperson to successfully use these medications. Especially as there are few commercially available IN products, current packaging typically involves those made for IV use that then requires someone to be able to draw up accurate doses, and there may issues with accessibility or beyond use dating when prepared by outpatient pharmacies.

CONCLUSIONS
IN administration of midazolam, lorazepam, dexmedetomidine, ketamine, fentanyl, hydromorphone, flumazenil, and naloxone has been demonstrated to be a safe, effective alternative to IM or IV administration. Use of IN medications is becoming a common alternate route of administration in the emergency department setting as well at the prehospital and outpatient settings; further showing the importance of providers becoming more familiar with this route of medication delivery.

REFERENCES


ARTICLE SUMMARY

1. Why is this topic important?
   Intranasal drug delivery is quickly becoming a more widely accepted route of medication administration. Intranasal drug delivery bypasses first-pass metabolism and avoids the risk of needle-stick injury.

2. What does this review attempt to show?
   This review attempts to broaden the readers’ appreciation for intranasal drug dosing and considerations for medication administration via this route.

3. What are the key findings?
   Intranasal medication delivery provides quick and effective medication delivery. Intranasal medication delivery offers a viable alternate route to intravenous administration and has been proven to demonstrate similar clinical benefits.

4. How is patient care impacted?
   Intranasal medication delivery increases therapeutic options for prehospital patient care. In addition, it can reduce time to medication administration and provides a needleless drug delivery system for a variety of skill levels.