Introduction

Intranasal (IN) drug delivery is a non-invasive and versatile method of drug delivery, and has emerged as a safe and effective alternative to traditional routes of delivery in pediatric emergency departments (PEDs) (1,2). Procedural sedation and analgesia (PSA) may present a clinical challenge where anxiety and pain perception in children can be strengthened by parental anxiety, unfamiliar environments, and anticipation of pain (1,3). Intravenous (IV) administration in children is associated with delays, parental dissatisfaction, and distress in establishing access (3). PSA is often inadequate with less than one-third of children receiving PSA for painful procedures (1,2). To mitigate these pitfalls of IV PSA, IN drug delivery has been shown to improve patient comfort and reduce the need for more invasive procedures (1,2). Similarly, ongoing emotional consequences can result from procedures in PEDs, which can be mitigated by appropriate pain control and anxiolysis via IN medications (4). PEDs are appropriate settings for the rapid acting, easily delivered, relatively safe option of IN medication, especially when time, resources, and vascular access are all important considerations. As it has been spread more widely in PEDs a review of IN drug delivery is warranted.

This review aims to provide an overview and update of current literature on the use of intranasal (IN) drug delivery in pediatric emergency medicine (PEM), in terms of the anatomy, physiology, pharmacokinetics, limitations, drug delivery methods, necessary training, safety, contraindications, effectiveness, current indications and trends, and implications for clinical practice and future developments in IN drug administration. We evaluate how IN medication use in PEM has recently evolved, what recent research has revealed about the utility of IN drug delivery in PEM, and what the future of IN drug delivery might look like.

Abstract

This review aims to provide an overview and update of current literature on the use of intranasal (IN) drug delivery in pediatric emergency medicine (PEM), in terms of the anatomy, physiology, pharmacokinetics, limitations, drug delivery methods, necessary training, safety, contraindications, effectiveness, current indications and trends, and implications for clinical practice and future developments in IN drug administration. We evaluate how IN medication use in PEM has recently evolved, what recent research has revealed about the utility of IN drug delivery in PEM, and what the future of IN drug delivery might look like.

Key words: Administration, Intranasal; Analgesia; Conscious Sedation; Emergency Service, Hospital; Fentanyl
of IN drug delivery might look like. With this review article, we hope to increase awareness and understanding of this route of administration, and to encourage further research, clinician familiarity, and innovation in this field to advance capabilities in pediatric emergency medicine.

Main subject

1. Anatomy, physiology, and pharmacokinetics

The human nose is made up of paired nasal bones, and upper and lower lateral cartilages, with the nasal septum dividing the cavity into left and right sides (5,6). The lateral nasal wall contains the inferior and middle turbinates, with the openings of most sinuses located beneath the middle turbinates. The adult nasal cavity has a large surface area of about 150 cm², which is further increased by epithelial microvilli, while the pediatric nasal cavity surface area varies by age (7). The sub–epithelium of the nasal mucosa is thin, highly vascularized, and permeable (8). The proximity of the nasal mucosa to the central nervous system (CNS) and the unique innervation of the nasal mucosa are what make IN medications effective and promising for future drug development. IN administration offers a non–invasive way to bypass the blood–brain barrier, providing direct contact between the olfactory tissue and CNS, and allowing drugs to rapidly enter the brain (5).

The nasal mucosa is close to multiple key structures in the cranium, including the cribriform plate, cerebrospinal fluid, olfactory nerves and bulbs, meninges, and trigeminal nerves (8,11,12). The intracellular route, through the olfactory nerves to the bulbs, is a slower route compared to the extracellular route where drugs can cross the gaps between olfactory nerves or be transported along the trigeminal nerves more rapidly. It is theorized that these various routes allow for IN medications to permeate the CNS more rapidly, easily, and in greater concentration than conventional drug delivery (8,11,12).

IN medications generally reach higher concentrations in the brain than other routes of drug delivery in patients of all ages (6,13). The primary appeal and utility of IN drug delivery is twofold: increased central concentrations and decreased systemic concentrations of a drug, relative to other methods (11,12). For example, a study found that IN dantrolene resulted in significantly increased peak concentrations and longer duration in the brain without an adverse effect (AE) on the olfaction or motor function when compared with per os (PO) administration in animal trials (14). However, measuring CNS concentrations of a drug is challenging in humans, and thus objective data are limited on the effectiveness of IN medications compared to other methods (6). Nevertheless, it should be clear based on the above discussions that IN medications have great potential in clinical medicine, especially in emergency circumstances.

2. Limitations

Mucus serves as a barrier for the nasal mucosa and can reduce drug permeability. Nasal secretion and mucociliary action clear particles from the nose in approximately 15–20 minutes (8,9). Against this barrier, mucoadhesive carriers, such as cellulose derivatives, polyacrylic acid, chitosan, and gelatin, can prolong the time that a drug remains in the nasal cavity (8,11,12). Although mucosal enzymes can degrade substances in the nasal cavity (8), the enzymes in the gastrointestinal tract degrade drugs more avidly than those in the nasal cavity (5). Further, IN administration bypasses the hepatic first–pass metabolism, resulting in a higher bioavailability.
3. Drug delivery methods

IN medications can be administered through drip devices or atomized sprays (1). Dripping IN medications requires a patient’s full compliance and involves using a dropper held close to the nostrils to deliver them into the nasopharynx (1). Currently, the mucosal atomizer device (MAD) is most widely used for IN delivery despite the ongoing development of many other devices (1,6,9). MAD is specialized to spray medication into a fine mist form to the nasal cavity and consists of a syringe, rubber bulb, and small nozzle. The nozzle is inserted into the nostril, and the medication is sprayed into the nasal cavity using the rubber bulb.

MAD use is preferred due to less drug loss to the oropharynx, higher drug concentrations in the cerebrospinal fluid, better tolerance, and improved efficacy (1). Using only small volumes of concentrated medication, ideally 0.2–0.3 mL per nostril, which is generally a tenth of the PO dose, will help to reach an IN concentration maximizing drug effectiveness. Fluid volumes in excess of 0.3 mL, which are instilled into the nasopharynx without an MAD, may result in excess drug deposition into the oropharynx (1,2,15). Using both nostrils to double the absorptive mucosal surface area enhances drug bioavailability (15).

4. Necessary training for IN drug administration

Emergency physicians (EPs) and nurses can administer IN medications effectively with minimal training (16). Perhaps more importantly, training increases awareness of IN medications as an option, increasing the frequency of its use (17). A simulation study comparing before training and after training on IN glucagon use for hypoglycemia shows 5.9% and 22.7% choosing and success rates of IN glucagon before the training respectively, compared to 58.8% and 100% of respective rates after the training (17). Another simulation study shows that IN glucagon had a success rate of 90.6% compared to IV glucagon at only 7.9%, regardless of the training level (18).

In a study looking at laceration repair in children, a combination of IN fentanyl and midazolam resulted in a treatment failure rate of 2.4%, where 2.0% required IV PSA and 0.4% required repair in the operating room (4). The low failure rates might stem from the relative ease of IN administration. Most training for IN administration is related to the specific drug being used. EPs and pharmacists should be aware of appropriate dosages and potential AEs of IN formulations. IN PSA may require additional training for EPs and nurses, as well as continuous monitoring and post-sedation observation. However, the training and personnel required for IN PSA are not unique to this route of drug delivery (19).

5. Safety and adverse effect profiles of IN medications

Across the literature review for this article, there were almost no reports of any serious AEs related to using IN medications in PEDs or elsewhere. There was 1 reported episode of hypotension with IN fentanyl, which spontaneously resolved, out of 276 patients receiving either IN ketamine or IN fentanyl (20). There were no serious AEs with IN ketamine. Among 181 children with a University of Michigan Sedation Scale, no child received a score of 3 (deeply sedated) or 4 (unarousable) on a scale of 0–4. In a study of 6,198 patients aged 3 years or younger receiving IN midazolam, IN fentanyl, or both, no serious AEs requiring reversal or respiratory support were reported (21).

A study comparing IN fentanyl and PO ibuprofen to IN ketamine and PO ibuprofen in pediatric patients with musculoskeletal injuries found no serious AEs reported (22). Another study found no serious AEs with IN diamorphine use in 226 children with fractures or other trauma (23). Among 1,855 children receiving IN fentanyl and IN midazolam for laceration repair, including those with complex medical histories, no serious AEs were reported with a 0.7% minor AE rate including 0.5% experiencing anxiety and 0.2% experiencing vomiting (4).
Inevitable AEs may be caused by the nasal mucosa’s complex anatomy, proximity to the brain, and innervation by sensory and cranial nerves. Minor AEs include nasal discomfort, unpleasant taste, and itchiness (4,24). With increased penetration of drugs into the brain, central AEs can pose more challenges, including nausea, vomiting, drowsiness, dizziness, headaches, lightheadedness, paradoxical agitation, vision changes, and nystagmus (20,25). Deterrent for EPs may be the frequency of vomiting as an AE of some drugs, including some opioids, ketamine, midazolam, and dexmedetomidine (3).

Despite the proven safety of abovementioned IN medications in PEDs, this is not always the case with newer uses, especially those prescribed to outpatients (26–28). In February 2022, the United States Food and Drug Administration put out a warning on the use of IN compounded ketamine, specifically esketamine, stating that the IN use of racemic ketamine is not approved and may place patients of all ages at risk of serious AEs, abuse, and misuse, especially in the home environment (26–28). Another study looking at the Food and Drug Administration Adverse Event Reporting System found that IN corticosteroids, alpha-adrenergic agonists, and antihistamines had over 100,000 AEs reported between 2014 and 2019 in patients of all ages, with steroids being most commonly reported (28). The most commonly reported AEs were dyspnea, headache, epistaxis, dysgeusia, and anosmia in descending order.

6. Contraindications

There are few reported absolute contraindications to IN drug delivery. Abnormalities in individual nasal mucosa or anatomy may alter drug absorption and can be relative contraindications if there is a concern that the anatomy would significantly impair absorption (5,14). Patients of all ages with moderate–to–severe trauma warrant IV or intraosseous medications and IN delivery should only be considered as a temporizing measure in emergency situations without other access readily available (29,30).

Similarly, IN administration should be avoided in facial trauma (5,14,30). Upper respiratory infection is a relative contraindication as it can lead to inflamed nasal mucosa, altering absorptive properties (5,14). Excessive mucus or blood is a relative contraindication as drug absorption is inhibited, although this can be minimized by suctioning the nostril before administration (5,14).

7. Effectiveness of IN medications

Comparable efficacy has been shown in studies comparing IN and other methods of drug delivery. One study showed that benzodiazepines, such as midazolam, are effective when administered IN, IV, or per rectal among patients of all ages (31). However, IN administration was found to be faster and more comfortable for patients without any significant difference in potency among the 3 routes. In a study comparing IN diamorphine with intramuscular morphine for pediatric patients with musculoskeletal injuries, no significant difference was found in pain control (32). These studies highlight the fact that, at least for these uses, IN drugs can be equally effective as IV drugs.

Reviewing studies on fentanyl, a widely studied IN medication, provides additional details. EPs in PEDs have concerns about the use of medications like IN fentanyl, possibly due to prejudice (1). However, IN fentanyl has been shown to be effective with a limited AE profile (33). IN fentanyl is rapidly acting, with a rapid onset (< 10 minutes) and short duration (< 1 hour). It has been found to provide more rapid yet equally effective pain control, compared to IV morphine or IV fentanyl in children (34). IN fentanyl can reduce pain scores by an average of 4 points (using Faces Pain Scale-Revised for 4–8 years of age or an 11-point Numeric Rating Scale over 8 years of age) and time to analgesia, compared to IV morphine, particularly in younger children who are twice as likely to receive opioid analgesia when IN fentanyl is available (35).

Other IN drugs and combinations of drugs have also been frequently studied and found to be similarly
effective. For example, no difference in pain control was found when using IN fentanyl with PO ibuprofen, compared to IN ketamine with PO ibuprofen in pediatric patients with musculoskeletal injuries (24). In a study, 95% of patients treated with IN midazolam achieved anxiolysis without additional sedatives (36). IN ketamine was found to provide adequate pain control 30 minutes after administration while preserving respiratory drive (34). When managing non-cooperative children during procedures, a combination of IN ketamine and IN midazolam was more effective than IN midazolam alone (37). In a study comparing IN ketamine, IN midazolam, and PO chloral hydrate for children undergoing transthoracic echocardiography, all 3 options provided adequate sedation (38). However, IN midazolam had a faster onset of sedation, while IN ketamine had a shorter duration of sedation (38). In a 2018 study evaluating pharmacokinetic and pharmacodynamic properties of IN and IV dexmedetomidine, the IV route displayed a faster onset compared to IN routes in adults (39). However, the delayed delivery of route offset the faster onset, without a significant difference in the sedation period or median onset time between the 2 routes (39).

8. Current indications and trends

Currently, IN medications have various indications in PEDs, including for sedation, analgesia, anxiolysis, anti-inflammation, abortive therapy for migraine, and initial treatment for status epilepticus (5). Patients with mild trauma can be ideal candidates for IN medications (14,30). IN opiates are particularly useful in treating minor fractures, large abrasions, burns, and wound dressing changes. Fentanyl is the most commonly used IN medication for acute analgesia (1). In some healthcare settings, such as Australia, fentanyl is the standard pediatric pain medication delivered at triage to children with severe pain (40).

The use of IN medications in PEDs has been increasing over the past 15 years. In detail, a 2010 survey of PEDs in England and Wales shows that 57.5% used IN medications, predominantly diamorphine (41). According to a 2017 Canadian survey performed on 136 pediatric EPs, 35% and 60% of respondents chose IN fentanyl as a first-line analgesic for moderate and severe pain, respectively (42). The survey also shows that as a second-line analgesic, 37%, 41%, and 18% chose IN fentanyl for mild, moderate, and severe pain, respectively (42). IN ketamine was not considered as a first-line agent and was considered as a second-line agent by 1% for moderate-to-severe pain.

A 2022 survey in New York City found that the treating pediatric EPs would prefer IN anxiolysis using any medication prior to laceration repair 89% of the time, and PO anxiolysis using any medication 11% of the time (43). In a 2023 study of 94 patients undergoing PSA in Spain, the treating EPs chose a single IN drug 16.6% of the time, and a combination of drugs including 1 or more IN medications 16.5% of the time (see Table 3 in Lorente et al. (44)). The combinations of drugs in additional 15% of cases were not individually listed and may have included IN medications.

The cited studies highlight the growing popularity of IN drug delivery around the world. Increased use of IN medications will spur further research and development to expand the applications, uses, and drugs available for IN delivery beyond what is currently available.

9. Implications for clinical practice and future developments

IN drugs can generally be divided into 3 categories: drugs with a central mechanism of action, drugs with a local mechanism of action, and drugs intended to treat CNS pathology (11,12). These categories can help to elucidate the possible future uses of IN medications. Various CNS pathology could be treated with IN drug delivery: encephalitis, meningitis, encephalopathy, hydrocephalus, neuritis, multiple sclerosis, autoimmune disorders, movement disorders, tumors, mass effect, congenital disorders, stroke, psychological disturbance, and cognitive impairment.
to name a few (11,12). IN delivery of antiviral, antimicrobial, anti-inflammatory, chemotherapeutic, steroidal, or other medications should be considered on a case-by-case basis (11–13,45). Similarly, IN drugs could treat symptoms related to the CNS, such as vertigo, nausea, vomiting, insomnia, headache, respiratory depression, autonomic instability, tremor, narcolepsy, migraines, psychosis, anxiety, agitation, and pain (11,12). Given the lists, the current use of IN medications is limited in scope. IN drug delivery has the potential of becoming the main option for acute and chronic CNS pathology in PEDs.

Medical advancement is promoted by new research. One area of research is looking at common medications and reformulating them to be maximally absorbed at the nasal mucosa and maximally permeable to the blood–brain barrier (31,46–48). Some of these formulations use lipid carriers, while others are attempting to miniaturize or "nanotize" drugs. IN administration, often combined with a nano-drug delivery system, can increase the brain concentration of drugs, including tramadol, paroxetine, duloxetine, venlafaxine, clobazam, buspirone, selegiline, and agomelatine (8). Many of these drugs could find a purpose in PEDs, IN tramadol could be an option for pain management, IN anxiolytics, antidepressants, and antiepileptics could be used for severe agitation, or suicidal or homicidal ideation (49).

10. Limitations of the study

This review is limited to the use of IN drugs in the PEDs, with some extrapolation from the data of preclinical or non–human research. Data from human clinical trials are still limited despite the growing popularity of IN medications. There may be studies and data not covered in this review. Additionally, some contents in this review are based on surveys and retrospective studies, which may not be as conclusive as the trials.

Conclusion

IN drug delivery is safe, effective, easy to administer, rapidly acting, and suited to the needs of pediatric emergency medicine. This delivery method has become more popular in PEDs. Moreover, IN medications have the potential to benefit patients beyond current popularity and applications. EPs must be aware of the facts surrounding IN medications to promote their use. Hopefully, with the increasing popularity of IN drug delivery, new efforts will be made to support the development of next–generation IN medications.

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