Does the Intranasal Route Pass the Sniff Test?

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0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2017.06.003

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[Ann Emerg Med. 2017;70:212-214.]

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ANNALS CASE

Medication Route Options

Physicians and scientists have developed creative and varied routes of medication administration to patients. Some of the many options include intravenous, intramuscular, intrathecal, intraosseous, per os, subcutaneous, intravaginal, and per rectum routes. The intravenous route is further divided into peripheral and central and use, depending on the clinical situation. For example, line infiltration of specific drugs can lead to necrosis; thus, these drugs should be given only through central access. Another intravenous access, the umbilical line, is available only at certain times, typically only within the first week of life.[1] The latest up-and-comer is the intranasal route, which has increased application in many different clinical scenarios and is potentially underused in many emergency departments (EDs). But does it pass the sniff test?

How do we choose the ideal route for each medication and each patient? There are so many factors to consider that we may not even consciously acknowledge the many decision points in choosing a route. Different routes vary in bioavailability and time of onset of drug effect. Some routes are more operator dependent and some take longer to obtain. Some routes cause more discomfort, are more invasive, or can put patients at risk for adverse events. Certain drugs can be administered to target specific body parts and limit systemic absorption and adverse effects, such as the intrathecal route or nebulized medications. In a pinch, the intraosseous route can be lifesaving for many resuscitation medications, but taking a drill to a patient's bone is less palatable to the general public for obvious reasons. Although the per os route clearly uses the fewest resources and has minimal patient discomfort, the bioavailability is delayed and patients who cannot protect their airway are clearly not candidates. We rely on the intramuscular route when per os is less effective but intravenous placement is unnecessary. In the ED, the careful, longer process of obtaining intravenous access is much less preferable for agitated patients because a great benefit is placed on decreasing time during which a provider wields a sharp object in a small tornado of chaos.

Anecdotally, the intranasal route is frequently discussed in the literature and used in pediatrics, but less often for adults, despite their having the same pain receptors and perhaps a more matured and refined fear of needles. Considering that the intranasal route is well tolerated, easy to administer, and effective, perhaps it should be more frequently used for adult patients. Aren't they just big kids anyway?

WHY INTRANASAL?

The purpose of this review is to reflect specifically on the intranasal route as described as well in the recent publication by Rech et al.[2] Let's (nose) dive right into it!

The benefits of intranasal administration are clear: absorption is independent of body habitus, hydration, or nutrition. There is no need for painful and potentially dangerous needles, and a minimal level of technical skill is needed to administer medications.

Intranasal medications vary from pain control (fentanyl), to sedation (eg, midazolam, dexmedetomidine), to opioid overdose reversal (naloxone), to seizure cessation (midazolam). A free Web site called Intranasal.net[3] is a helpful resource to learn more about intranasal medication administration and to review available references supporting its use.

Here are 3 general pharmacokinetic or pharmacodynamic principles that explain why intranasal administration is effective. First, the nose contains a full vascular plexus that provides a straight path into the bloodstream. Small-molecule, nonionized, lipid-soluble drugs can cross mucous membranes more easily and work

better for intranasal administration. Second, most orally administered medications undergo first-pass metabolism before reaching their target within the body. Intranasal administration, on the other hand, bypasses this first-pass effect, which can produce higher drug concentrations (bioavailability) faster. So intranasal administration might be the best route in emergency settings such as seizure, trauma, agitation, or severe pain. Similarly, drugs that must undergo first-pass metabolism for activation would not be ideal candidates for intranasal administration. Third, as you will remember from your rigorous medical school anatomy training, the nose is geographically close to the brain. Therefore, absorption across the nasal mucosa produces cerebrospinal fluid drug concentrations that in some studies exceeded plasma concentrations. This is particularly useful in centrally acting drugs such as antiepileptics. There is also some evidence that some drugs administered intranasally are directly transported to the brain.[4-6]

For intranasal administration, a potential drawback is that only 1 mL can be maximally absorbed per naris, with ideal volume less than 0.5 mL. Therefore, depending on the medication, higher concentrations may be needed than are normally stocked in the ED or by emergency medical services (EMS). For example, the midazolam used for intravenous or intramuscular administration is commonly a solution of 1 mg/mL, but for intranasal administration, the 5 mg/mL concentration is preferred. Stocking more than one concentration in the ED can increase the risk for medication errors. When intranasal protocols or guidelines are created, it is important to consider how and where different concentrations will be stocked and how staff will be trained to minimize the risk of error.

Here are 4 important concepts to consider with intranasal administration[7,8]: minimize barriers to absorption and ensure that the nasal mucosa is available and free of secretions and blood, minimize the volume and maximize drug concentration to stay below the 1-mL volume limitation, take advantage of maximal absorption by using both nostrils, and use a delivery system that maximizes drug dispersion.

WHAT IS AN ATOMIZER?

Next, to highlight real-life application, let's discuss how to administer intranasal medications and options for delivery systems. One time-saving factor is that the nose is not sterile (far from it!); hence, intranasal delivery does not require sterilization. A huge relief compared with the enormous time and resource investment for sterility in central venous line placement! Furthermore, as you may recall from your gross anatomy class, there are 2 nostrils, both of which can be taken advantage of for drug administration. There are many ways to administer this volume intranasally, including nasal drops and sniffing of medications. But of all the methods to actually administer the drug, an atomizer is the most efficient. According to the often-used and rarely cited (despite rigorous peer review) Web site Wikipedia, atomization is the process of "making an aerosol, which is a colloid suspension of fine solid particles or liquid droplets in a gas."[9] The reason for the preference for atomization is that the smaller droplet size maximizes spread of the medication across more of the mucosal area. This allows you to take advantage of all the real estate available! And as you know, real estate is all about location, location, location! And of course, in this case, the nose is Park Place and Boardwalk.

There are several commercially available devices that can be used in the ED for intranasal administration. If you do not have access to one of these devices and you want to improvise your own, there are some "MacGyver" methods using a nebulizer kit and either oxygen or suction tubing.[10,11] However, the fine mist from the nebulizer will take much longer than a commercial mucosal atomizer; dosing can be imprecise as condensated droplets accumulate within the lumen and drip from the tubing, and a cooperative patient is a must! These caveats limit the utility in many scenarios in which we may opt for the intranasal route. You can watch the technique and its flaws on our EM:RAP-HD video available on YouTube and EMRAP.org.

ATOMIZERS AND THE LAY PUBLIC

Intranasal drugs are easy to use and have a high safety profile; hence, the reason public discussion has started on intranasal prescriptions. The most discussed medication in this realm is naloxone for opioid overdose. There have been countless opinion pieces and medical publications during the last few years describing how safe and potentially lifesaving naloxone could be to curb deaths related to overdose. Unfortunately, there is opposition to unlimited access to naloxone for the general public as a result of concerns that naloxone would have the unintended effect of increasing or, worse, encouraging opioid abuse. Regardless of the debate, it cannot be overstated that with intranasal naloxone's ease of use and safety profile, it has great potential to save lives.[12]

For parents and caregivers of children with epilepsy, some recommendations include home prescriptions of intranasal midazolam through nasal atomizer to abort seizures.[13] This makes sense, especially in more remote communities in which response times for EMS are longer.

Intuitively, the intranasal route seems to be a more practical option than rectal administration of diazepam, and previous studies have shown intranasal midazolam to be a safe and effective option.[14-17]

CONCLUSION

Intranasal drugs are not a new method of drug delivery; however, it is not one that physicians necessarily think of reflexively when considering options for drug administration. But there is really no reason for that to be the case! Most people have noses and nostrils (sorry, Voldemort). Think about it; it is much easier and quicker to squirt a medication up a nose than it is to place an intravenous line, even in the most experienced hands. Over time, more applications for the intranasal route will be sniffed out as research continues and imaginations are sparked. Until then, find out whether your ED has an atomizer, and if not, no worries: just make your own!

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REFERENCES

1. Hansen M. Intravenous and intraosseous access in infants and children. In: Tintinalli JE, Stapczynski J, Ma O, et al, eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 8th ed. New York, NY: McGraw-Hill; 2016.
2. Rech MA, Barbas B, Chaney W, et al. When to pick the nose: out-of-hospital and emergency department intranasal administration of medications. *Ann Emerg Med*. 2017;70:203-211.
3. Wolfe T. Therapeutic intranasal drug delivery. Available at: http://Intranasal.net. Accessed May 22, 2017.
4. Dale O, Hjortkjaer R, Kharasch ED. Nasal administration of opioids for pain management in adults. *Acta Anaesthesiol Scand*. 2002;46:759-770.
5. Hussain AA. Mechanism of nasal absorption of drugs. *Prog Clin Biol Res*. 1989;292:261-272.
6. Sakane T, Akizuki M, Yamashita S, et al. The transport of a drug to the cerebrospinal fluid directly from the nasal cavity: the relation to the lipophilicity of the drug. *Chem Pharm Bull (Tokyo)*. 1991;39:2456-2458.
7. Corrigan M, Wilson SS, Hampton J. Safety and efficacy of intranasally administered medications in the emergency department and prehospital settings. *Am J Health Pharm*. 2015;72:1544-1554.
8. Bailey AM, Baum RA, Horn K, et al. Review of intranasally administered medications for use in the emergency department. *J Emerg Med*. 2017; http://dx.doi.org/10.1016/j.jemermed.2017.01.020.
9. Wikipedia. Atomization. Available at: https://en.wikipedia.org/wiki/Atomization. Accessed May 22, 2017.
10. Bond C. SOCMOB how to: make an atomizer [video]. YouTube. Available at: https://www.youtube.com/watch?v=VcRBRr11hrU. Published March 23, 2013. Accessed May 22, 2017.
11. Walker G. How and why to use intranasal medications. Available at: https://www.youtube.com/watch?v=K1vGuNHrjo4. Published December 13, 2012. Accessed May 22, 2017.
12. Doyon S, Aks SE. Expanding access to naloxone in the United States. *Clin Toxicol (Phila)*. 2014;52:989-992.
13. Smith R, Brown J. Midazolam for status epilepticus. *Aust Prescr*. 2017;40:23-25.
14. Holsti M, Dudley N, Schunk J, et al. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. *Arch Pediatr Adolesc Med*. 2010;164:747-753.
15. Holsti M, Sill BL, Firth SD, et al. Prehospital intranasal midazolam for the treatment of pediatric seizures. *Pediatr Emerg Care*. 2007;23:148-153.
16. Brigo F, Nardone R, Tezzon F, et al. Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: a systematic review with meta-analysis. *Epilepsy Behav*. 2015;49:325-336.
17. Humphries LK, Eiland LS. Treatment of acute seizures: is intranasal midazolam a viable option? *J Pediatr Pharmacol Ther*. 2013;18:79-87.