Intranasal Drug Delivery: An Alternative to Intravenous Administration in Selected Emergency Cases

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Nasal transmucosal medication delivery is an active area of research, both in new drug development by the pharmaceutical industry and by clinicians using already available intravenous medications. The nasal mucosa is an attractive area in which to deliver medications because the procedure is painless and needleless, which eliminates the risk of needle-stick injuries and reduces patient discomfort. The delivery system does not require sterile technique or intravenous catheters, and the route is immediately available in all patients. In addition, the nasal mucosa offers a large absorptive surface that has considerable blood flow, allowing rapid drug absorption into the bloodstream and cerebral spinal fluid.[1,2] In addition, because intranasal drug delivery results in direct medication absorption, gastrointestinal destruction and hepatic first-pass metabolism (ie, destruction of drugs by the liver enzymes) are avoided, allowing more drug to be available more rapidly than if it were administered orally.[1] The result is that many medications delivered intranasally achieve absorption rates and plasma concentrations comparable with that obtained by intravenous administration.[1]

Factors affecting nasal drug absorption

The percentage of medication that ends up in the bloodstream after administration is termed "bioavailability." Intravenous medication is 100% bioavailable after administration. Oral medications are about 5% to 10% bioavailable because of gastrointestinal and hepatic destruction. Intranasal medication bioavailability varies from negligible to almost 100%.

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TABLE 1
Nasal medication delivery device options

Device type	Advantages	Disadvantages	Per patient cost
Cotton swabs	Inexpensive	Unmeasured dose (swab)	Pennies
Syringe droppers	Measured dose (syringe)	No atomization Uncomfortable (swab) Bioavailability problem: limited area of mucosal contact	
Single use syringe-driven devices MAD Nasal (Figure 1)	Improved bioavailability: atomized drug delivery Measured dose	More expensive than dripping in with a syringe or using a cotton swab	$2.45*
Positive displacement pump atomizers MADomizer* (Figure 2) Go Medical† Nasal Inhaler (Figure 3)	Improved bioavailability: atomized drug delivery Measured dose Inexpensive (MADomizer)	More expensive than dripping in with a syringe or using a cotton swab	MADomizer tip: $0.84 Go Medical Nasal Inhaler costs approximately $10 US; entire pump is disposable †
Venturi Atomizer De Vilbiss‡	Improved bioavailability: atomized drug delivery	Expensive, unmeasured dose; potentially substantial medication wasting; resterilization prior to reuse§	Cleaning, sterilization, replacement parts and reassembly costs§; capital expenditure§

*Manufacturer: Wolfe Tory Medical, Inc, Salt Lake City, Utah.
†Manufacturer: Go Medical, Subiaco, Western Australia.
‡Manufacturer: De Vilbiss Atomizers, Sunrise Medical, Carlsbad, Calif.
§Venturi devices pose infectious risk unless cleaned between each patient. Therefore, per patient costs include labor involved in disassembly, cleaning/sterilization, and reassembly. Capital expenditure may include autoclave, air compressor, and atomizer cart purchase and upkeep, compressed air hosing routed to every location, and device purchase.

If a drug molecule can cross the nasal mucosa, the primary factors influencing bioavailability are medication concentration and volume, delivery method, and nasal mucosal health.[1] The most concentrated form of the medication available should be used, because large volumes (more than .5 to 1 mL per nostril) will run out of the nose, reducing total absorption. If volumes greater than 1 mL are required, they should be applied as divided doses, allowing a few minutes for the first dose to absorb. On the other hand, if small volume doses are used, be aware that delivery devices have a "dead space" in the applicator tip where some medication will remain. This should be kept in mind when calculating the volume of medication to be administered.

To optimize drug absorption, the delivery system must allow maximal surface area coverage with a thin layer of drug.[1] The easiest method is to deliver half the dose into each nostril, doubling the absorptive surface area. Atomized drug delivery systems result in superior surface area coverage compared with drops or spray methods and will improve medication bioavailability[3] (Table 1; Figures 1-3). Nasal mucosal destruction and copious mucous or blood secretions inhibit medication absorption. With a quick look into the nostril, the nurse can notice mucosal abnormalities and predict in advance whether nasal drug absorption will be less effective.

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FIGURE 1
The MAD 100 single-use, syringe-driven atomizer allows the administration of a measured dose of intranasal medication. (Photo courtesy of Wolfe Tory Medical, Inc.)

FIGURE 2
A positive displacement pump atomizer, the MADomizer, is an inexpensive system for administering medications across the nasal mucosa. (Photo courtesy of Wolfe Tory Medical, Inc.)

Intranasal medication delivery in the emergency department

A number of commonly used ED medications are effective when delivered intranasally. These medications include the synthetic opiates fentanyl and sufentanil for the treatment of acute pain; midazolam, for procedural sedation and for the treatment of seizures; naloxone, for opiate overdose; and topical anesthetics/vasoconstrictors for use prior to nasal intubation or nasogastric tube (NGT) placement or for the treatment of epistaxis (Table 2).

Pain control: intranasal opiates

Many patients who visit the emergency department fail to obtain adequate pain relief.[4] One reason is the lack of a rapid, effective, painless method for pain control. Nasal opiates offer an effective, inexpensive solution. The synthetic opiates fentanyl and sufentanil are uniquely suited for transmucosal delivery because of their high lipid solubility and their high potency (100 to 1000 times more potent than morphine).[2,5-7] Sufentanil is probably the best opiate medication currently available for intranasal drug delivery because of its high concentration, rapid mucosal absorption, and large therapeutic index.[2] Dipping a cotton swab tip into sufentanil and applying it to the nasal mucosa produces an effect within seconds.[2] In addition, it produces longer lasting analgesia with less persistent respiratory depression than does fentanyl.[2] Situations in which intranasal opiates may be particularly useful are for minor fractures and contusions, wound dressing changes, and in children with acutely painful conditions.[6,7] Most of these patients never get an intravenous line, and intramuscular injections or oral medications are too painful or too slow to allow timely interventions. Spraying atomized fentanyl or sufentanil intranasally will result in rapid pain control and allow the nurse to proceed with care.

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FIGURE 3
The Go Medical Nasal Inhaler is a disposable pump atomizer for delivering intranasal medications. It costs approximately US $10. (Photo courtesy of Go Medical.)

[Intranasal medication administration] is painless and needleless, which eliminates the risk of needle-stick injuries and reduces patient discomfort.

Procedural sedation: intranasal opiates, benzodiazepines, and ketamine

Procedural sedation also can be achieved using intranasal medications.[5,7,8] Midazolam is the most commonly studied medication for this indication, although data on fentanyl, ketamine, sufentanil, and combinations of these drugs are available.[5] The data allow a few generalizations. First, intranasal medications are effective for mild to moderate sedation but not for deep sedation. Second, benzodiazepines and opiates produce varying levels of patient sedation, regardless of the route of delivery. For this reason, a combination of medications and the ability to titrate their effect is attractive. Third, respiratory depression is still a risk, especially when potent opiates are used. Therefore, staff must monitor the patient closely. Finally, adverse effects, such as nasal burning, are common with nasal midazolam.[8] Nevertheless, in the pediatric setting, where mild sedation is often enough to relieve the anxiety of the parents as well as the child, intranasal medications are effective sedatives.

Many medications delivered intranasally achieve absorption rates and plasma concentrations comparable with that obtained by intravenous administration.

Seizure control: intranasal benzodiazepines

In situations where an intravenous line is not available, intranasally administered benzodiazepines offer a rapid, effective method to treat an acutely seizing patient. Fisgin et al[9] found that intranasally administered midazolam was effective in 87% of patients with prolonged seizures, whereas rectally administered diazepam was only effective 60% of the time ($P < 0.05$). The authors concluded that intranasal midazolam is more effective, socially acceptable, and convenient than rectally administered diazepam. A similar study compared intranasal midazolam to intravenous diazepam.[10] These authors found that nasally administered midazolam stopped 88% of seizures, whereas 92% were controlled with intravenously administered diazepam (P = NS). Although similarly effective, intranasally administered midazolam worked more rapidly: The mean time to seizure cessation was 6.1 minutes with midazolam and 8.0 minutes with diazepam. The single study that has investigated intranasal lorazepam absorption suggests that it should be effective for seizure control.[11] However, its use remains investigative. Based on these studies, many EMS agencies have adopted intranasal midazolam as the first-line therapy for treating seizures in the field.[12]

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TABLE 2
Intranasal medications and doses for treatment of emergency conditions

Clinical scenario	Intranasal medication and dose	Important reminders
Pain control	Sufentanil 0.2 to 1.0 μg/kg Fentanyl 1.5 to 3.0 μg/kg	Always monitor for respiratory depression Only use a device that can deliver an exact dose of medication Titration is possible
Sedation	Midazolam 0.5 mg/kg Sufentanil 0.2 to 1.0 μg/kg Fentanyl 1.5 to 3.0 μg/kg Ketamine 6-8 mg/kg	Always monitor for respiratory depression Combination therapy probably more effective than single drug therapy Titration is possible
Seizures	Midazolam 0.2 to 0.3 mg/kg (Use 10 mg in teenagers and adults)	ALWAYS use the concentrated form of midazolam: 5 mg/mL Deliver immediately to allow absorption to occur while you support the airway
Opiate overdose	Naloxone 2 mg (2 mL)	ALWAYS use the concentrated form of naloxone: 1 mg/mL Deliver immediately to allow absorption to occur while you support the airway
Epistaxis	Oxymetazoline 0.5-1.0 mL to affected nostril (2 squeezes of bottle or measure it and deliver with atomizer) Add 1.5 mL lidocaine 4% if cautery will be performed	Have patient blow nose to remove all clots from nostril prior to delivery of the medication Spray 0.5-1.0 mL of medication up affected nostril(s) Soak a cotton swab with additional oxymetazoline and insert into nose Pinch nose for 5-10 minutes then re-examine and cauterize, if necessary Have patient purchase oxymetazoline over the counter and use at home
Nasal procedures (nasogastric tube, fiberoptics, nasopharyngeal airway, nasal intubation)	Lidocaine 4% (plus oxymetazoline 0.5 mL)	Spray both the nose (1.5 mL lidocaine) and the throat (3 mL lidocaine) Wait 3 minutes for full anesthetic effect before doing the procedure; repeat half the dose, if necessary

Nasopharyngeal procedures: nasal and oral 4% lidocaine

Nasogastric tube placement is a very painful procedure. Nevertheless, it is routinely performed with little or no analgesia.[13] A number of prospective studies demonstrate that topical 4% lidocaine applied to both the nose and the throat results in dramatic reduction in pain compared with lidocaine jelly alone.[13,14] The addition of a topical vasoconstrictor also appears beneficial because of nasal mucosal shrinkage and the prevention of epistaxis. These data strongly suggest that topical nasal and oral anesthetics/vasoconstrictors should be considered for all conscious patients before NGT placement. Be aware that vasoconstrictors can be absorbed and cause hypertension problems, especially in patients taking β-blockers who receive phenylephrine (Neosynephrine).[15] Although oxymetazoline (Afrin) has milder cardiovascular effects than does phenylephrine, care should be taken when administering vasoconstrictors to patients with significant cardiovascular disease or hypertension.

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