Intransal drug administration is a viable alternative for drug delivery.

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INTRANASAL DRUG ADMINISTRATION: AN INNOVATIVE APPROACH TO TRADITIONAL CARE

Intranasal drug administration offers all levels of EMS providers a safe and effective alternative for drug delivery

Emergency medical providers across the country use a variety of drugs to help manage patients in the prehospital setting. Depending on each service's region and level of care, the number of drugs available to a given provider can range from as few as five to as many as 100. As prehospital care grows and expands, medical directors, EMTs, paramedics and managers are all looking for ways to grow the quality of care delivered prior to emergency department arrival. Improving the quality of care does not always mean expanding someone's scope of practice by adding more interventions and more drugs to a provider's toolbox. It can also mean finding new ways to deliver current interventions more efficiently and safely. Previously, this has included the transition to needleless intravenous (IV) line med-ports, auto-retracting IV needles, utilization of emergency medical dispatch to eliminate the unnecessary use of lights and sirens, and the ever-changing tweaks to cardiopulmonary (perhaps soon to be called cardiocerebral) resuscitation.

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OBJECTIVES

- Explain the physiology of intranasal drug administration.
- List the benefits of intranasal drug administration.
- Identify three methods for intranasal drug delivery.
- Explain the rationale for utilizing the intranasal drug route.
- Identify five drugs that can be safely administered intranasally.

Photo courtesy LMA North America

This continuing education article will discuss intranasal drug administration—a delivery route that has not seen widespread EMS utilization, but which offers all levels of EMS providers a safe and effective alternative for drug delivery in a variety of emergency settings.

Intranasal Drugs

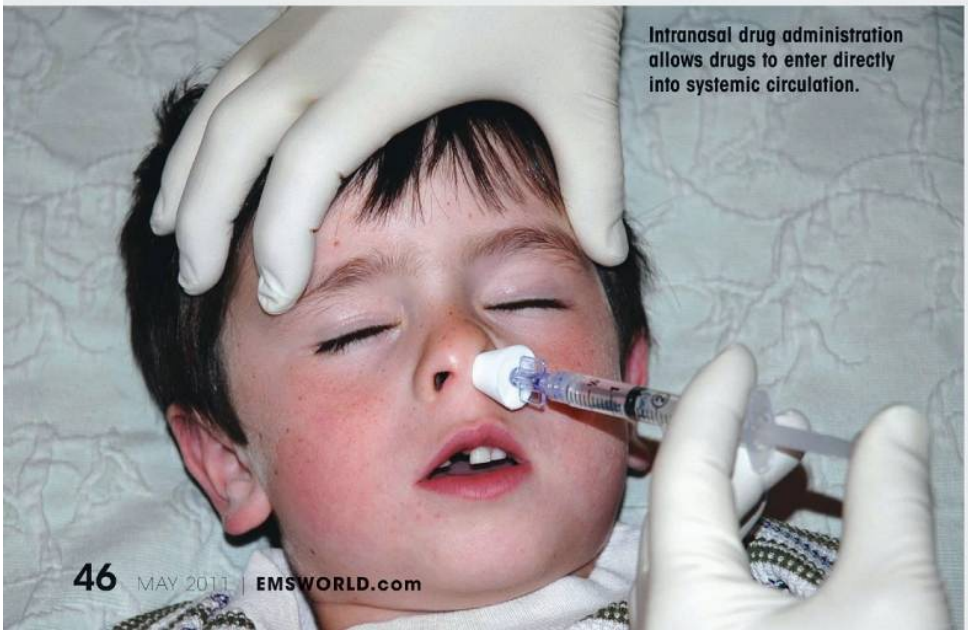
The idea of intranasal (IN) drug administration is not completely new. An article in the April 2007 issue of *EMS* Magazine by Rob Curran called for its widespread introduction and use.[1] Curran cited then-recent research that suggested IN drug administration was safe and could be nearly as effective as IV administration; however, to date, widespread use has not caught on. While there are a variety of reasons that could be argued, probably the most simple is that EMS as a system can be slow to change. Another reason is that the administration of intranasal drugs is considered off-label, since few drugs have been specifically presented to the FDA for approval via the intranasal route. Remember, though, many drugs used in emergency medicine are considered off-label. Since Curran's article, more research has been completed on both understanding how IN drug administration works and what drugs are effective via the IN route.

The nasal cavity has two primary functions: olfaction, or sense of smell, and warming, humidifying and filtering the air we breathe. It is the latter function that is important when discussing intranasal drug administration. Inside the nasal cavities are turbinates, which are highly vascular and convoluted passageways lined with a warm, moist mucosal layer. The moist mucosal layer moisturizes air as it passes though the turbinates, and the dense capillary beds allow heat transfer into the air. Additionally, the highly vascular turbinates allow for rapid drug absorption into the bloodstream because the capillaries within the turbinates are specifically designed to allow the rapid shift of fluids (medicines) across the capillary membranes. Turbinates increase the nasal mucosal surface area from what would likely be only a few square inches to over 180 cm^2.[2]

Intranasal drug administration, like intravenous administration, avoids first-pass metabolism by allowing drugs to enter directly into systemic circulation rather than requiring them to be absorbed through the GI tract and filtered by the liver. When a drug is absorbed through the gastrointestinal tract, it must pass through the liver prior to entering central circulation. When a drug passes through the liver, it is filtered. Liver filtration leads to a portion of the drug dose being metabolized into waste before it can be beneficial for the patient. Intravenous drug administration, like intranasal drug administration, avoids first-pass metabolism by introducing the drug directly into the central circulation. Avoiding first-pass metabolism increases the amount of drug that can benefit the body, because first-pass metabolism is a process by which the drug's serum concentration is greatly decreased as it passes through the liver for the first time.

Drugs in central circulation are still eventually metabolized by the liver into other chemicals. The goal of therapeutic drug administration is to have enough of the drug remaining after it circulates through the liver so the drug is beneficial to the patient. Because the nasal mucosa is so close to the central nervous system, drugs given IN have an opportunity to reach their target organ, which is often the brain, prior to being exposed to first-pass metabolism.

Additionally, the olfactory tissues relay sense of smell signals directly to the central nervous system. Olfactory mucosa is on the superior aspect of the nasal cavity and actually extends through the skull's cribiform plate and into the cranial cavity. When drugs impact this olfactory mucosa, they are absorbed directly through these tissues into the cranial cavity and are diffused in the cerebral spinal fluid. This pathway allows for the rapid onset of drugs that impact the central nervous system and also allows drugs to bypass the blood-brain barrier.[2]



Intranasal drug administration allows drugs to enter directly into systemic circulation.

Photo courtesy LMA North America

Delivery Methods

There are three primary methods for drug delivery to the IN route. Many EMS providers have managed patients who have snorted drugs like cocaine. While inhaling dry powder is a method for delivering drugs to the nasal mucosa, crushing up and snorting medications is not routinely recommended, as there is little control over the actual amount of medication delivered, and it should not be employed by prehospital providers.

Another delivery method is with a syringe and dropper; the syringe can double as the dropper. With this method, a specific drug amount can be drawn up using the syringe, which allows for precise drug dosing. However, to properly deliver the drug using this method, drops of the medication must be delivered onto the mucosa one at a time. Delivering the

drops too fast will cause the drug to drip into the back of the throat and it will not be absorbed into the bloodstream. Proper delivery also requires that the patient be positioned with their head tilted backward so the medicine drips through the turbinates and not back out of the nose. This can pose a problem with patients who cannot lie still with their head backward—particularly seizing patients, children and noncooperative patients. For years this was the preferred nasal delivery system and is one reason IN delivery did not become popular.

Syringe and atomizer devices have been developed over the past several years and have drastically simplified the delivery route. Spray-tipped atomizers can be attached onto syringes and break the drug into fine particles. These particles more broadly distribute the medication across the nasal mucosa, which increases the drug's bioavailability compared to the syringe and dropper method. Bioavailability refers to the amount of drug that actually makes it into the bloodstream and is available to the body. There is an increased bioavailability because the atomizer reduces the loss of drug droplets into the back of the throat. Also, with an atomizer the drug can be delivered with the patient's head in any position; it does not have to be tilted backward like with the syringe and dropper.

"Intranasal administration allows for more rapid drug delivery when IV access is not available."

Ideally, intranasal medications administered by prehospital providers should be administered with an atomizer device. However, even with these devices, there are a few keys to delivery to keep in mind:[2]

- Use as highly concentrated a form of the drug as possible
- Limit the fluid volume delivered to a nostril to 1 mL or less
- Divide the total amount of fluid to be delivered evenly between both nostrils
- Atomizers may have "dead space" within them and should be flushed with saline to deliver all of the medication
- Allow 15 minutes before administering subsequent intranasal doses.

The intranasal drug route is more than just an administration route. There are unique benefits for IN delivery. The anatomy of the nasal mucosa allows for rapid drug absorption, and its location allows drugs to be delivered directly into the bloodstream and bypass the blood-

brain barrier, all without the need for establishing IV access. Bypassing the blood-brain barrier allows many drugs to more rapidly benefit the patient by speeding their action on the central nervous system. This is particularly beneficial when administering benzodiazepines for patients experiencing seizures.

Another benefit of the route is its safety. No needles are needed, such as with IV, subcutaneous and intramuscular drug delivery. The absence of needles increases provider safety, particularly when the need arises to administer drugs to combative or seizing patients. Eliminating needles decreases the chances of accidental needlesticks both on scene and while managing patients during transport.

The disadvantage to intranasal drug delivery is that a limited number of drugs can be delivered to the nasal mucosa. Not every drug used by prehospital providers can be atomized for absorption and provide the same intended effects. Additionally, patients with diseased or unhealthy nasal mucosa, such as from long-term drug abuse or cancer, will likely have impaired drug absorption, as their turbinates can be destroyed or damaged from disease processes. Foreign debris, such as blood and other fluids in the nasal cavity, can also impair drug absorption.

Figure 1: Indications and Drugs Available for Intranasal Administration

- Pain management
  - Ketorolac
  - Fentanyl
- Seizure management
  - Midazolam
- Narcotic overdose
  - Naloxone
- Hypoglycemia
  - Glucagon

Intranasal drug administration has a variety of beneficial prehospital indications, including pain management, seizure control, narcotic drug reversal and hypoglycemia management.

Pain Management

A great deal of research has demonstrated that pain control can be obtained through intranasal drug administration in a safe and effective manner with few side-effects.[2] There are a variety of different pain medication choices, including opiates and nonsteroidal antiinflammatory drugs that provide analgesia and can be administered intranasally.

One of the most serious concerns with opiate drug administration is the potential for significant respiratory depression leading to hypoxia. However, the slower absorption of IN drugs, compared to IV administration, is enough of a delay that the risk of respiratory depression decreases significantly. When a drug is administered at the recommended intranasal dose, which is 1.5–2 times the IV dose, respiratory depression does not occur.[3,4] Additionally, despite the slower absorption rate, the time saved by eliminating the need for IV access actually allows for the patient to experience a drug's effects faster.[5]

Analgesic Options

Recently, ketorolac (Toradol) was FDA-approved for intranasal administration. Ketorolac is a nonsteroidal antiinflammatory drug that is effective in managing short-term moderate and severe pain. When given via IV, it has near-immediate onset, with full effect reached in 20–45 minutes, and has a half-life of 6–8 hours. When administered intranasally, ketorolac has the same onset and half-life. In one study, ketorolac was found to reduce the need for opiate analgesia when 30 mg was administered intranasally.[6] This represents great potential benefit for EMS providers. Since ketorolac does not have any of the side-effects opiate drugs have, including hypotension and potential respiratory depression, it may be a reasonable drug for basic and intermediate life support providers to administer intranasally. By decreasing the number of patients requiring opiates for analgesia, fewer patients require intravenous access for analgesia, and fewer needles means increased safety. Ketorolac also does not have the addictive property of opioids, which decreases the potential for provider theft and misuse.

Fentanyl is a synthetic opioid analgesic that has a shorter duration and half-life than morphine. It is associated with less cardiac instability than morphine, but otherwise functions similarly and has effects on the body nearly identical to morphine and is effective in treating moderate to severe pain. The typical IN dose for fentanyl is 2–4 micrograms per kilogram. Remember, intranasal doses are 1.5–2 times normal doses.

A team led by Australian ambulance researcher Paul Middleton compared the effectiveness of IV morphine to IN fentanyl and inhaled methoxyflurane for prehospital analgesia and found that IV morphine dosed initially at 5 mg and repeated at 2.5–5mg every 2 minutes was slightly more effective than an initial IN dose of 240 micrograms of fentanyl. Both were significantly more effective than methoxyflurane. Prior to beginning the study, the researchers noted that IN absorption rates of fentanyl can be variable. To control this they limited IN fentanyl doses to 90 micrograms (0.3 mL) per medication atomization per nostril. Subsequent doses of 60–90 micrograms were given every 5 minutes as needed. Results demonstrated that while IV morphine was more effective, IN fentanyl does not require IV access and can be administered more rapidly. Further, when a statistical analysis was performed, morphine was not statistically more effective than IN fentanyl for total pain control, which in practical terms means the drugs provide equivalent relief. Morphine was, however, more effective for a greater number of patients.[7] This study demonstrated that intranasal fentanyl provides analgesia as effectively as intravenous morphine. Also, no untoward effects were observed during the study period, helping to demonstrate that IN fentanyl is safe as well.

Interestingly, both fentanyl and morphine failed to adequately control pain in nearly 20% of patients who received the drugs. This truly signals an area for improvement in prehospital pain management and suggests the need for advanced providers to have multiple analgesic medicines available, with the ability to switch medicines when the first is not working.

Another study compared morphine and fentanyl for safety and effectiveness and found that both produced similar pain control; however, more fentanyl was required compared to morphine to achieve the same level of pain control when doses were standardized. This study used 5 mg morphine as equivalent to 50 mcg fentanyl. Fentanyl was associated with fewer adverse effects, 6.6% to 9.9%, with nausea being the most common adverse effect for both medicines. The researchers also concluded that both medicines provide adequate prehospital analgesia with low rates of side-effects.[8]

Seizure Control

Traditionally, prehospital providers manage status epilepticus with rectal diazepam when IV access cannot be obtained. Our anecdotal experiences support the claim that rectal diazepam does not always provide seizure control. A 2007 study compared administration of rectal diazepam to intranasal midazolam (Versed) for management of prehospital pediatric seizures. This study found that IN midazolam achieved 100% seizure control compared to 78% for rectal diazepam. Diazepam was also associated with a 33% intubation rate, while no patients managed with midazolam required intubation.[9] The researchers determined that IN midazolam was more effective in seizure control, was safer to administer, faster, and more socially acceptable than rectal diazepam administration. This study does not compare intravenous diazepam administration to IN midazolam. When an IV is already in place, IV benzodiazepines remain the gold standard for seizure management. However, when no IV is in place, as when prehospital providers arrive on scene, it is just as safe and faster to attempt IN drug administration than to attempt IV access in an actively seizing patient.

One study released in February 2011 compared IN and IV lorazepam for seizure management in pediatric patients. Using the same drug for both administration routes allowed researchers to directly compare administration routes. Results demonstrated that from the time the drug is given there is no statistical difference in the time it takes to terminate seizures between IV and IN lorazepam. The researchers also noted that there was a delay (median 4 minutes) to establish IV access for IV lorazepam administration, while there is no delay for IN administration.[10]

> **"Intranasal analgesia is not associated with respiratory depression."**

This study demonstrates that the

overall fastest time from recognizing status epilepticus to termination with drugs can be achieved with administration of intranasal benzodiazepines when an IV is not already in place. A patient can rapidly become hypoxic during a seizure, and rapid seizure termination is essential. Research now shows there is a faster method to achieve this, and it is important to consider implementing this into prehospital seizure management.

Narcotic Overdose

Patients who overdose on narcotic-based drugs can range from the chronic IV drug abuser or experimenting teenager to an elderly woman who mismanages her pain medications. At times, it can be very difficult to establish IV access on these patients, and some can be quite combative, creating a situation where introducing an IV needle is unsafe. Additionally, narcotic overdose can cause serious respiratory depression leading to hypoxia. It is not uncommon for patients who overdosed on narcotics to require ventilations. Fortunately, this respiratory depression can be rapidly reversed with the administration of naloxone, which is an opioid antagonist that blocks the opioid receptor sites in the central nervous system. Traditionally, 0.4–2 mg of naloxone is given intravenously; however, it can also be given IN when no IV is available.

The difference between effects of IN and IV naloxone was recently studied. This study looked at the time from patient contact until respiratory depression was reversed for the two administration routes. The researchers found that the total time from patient contact to clinical response was shorter when naloxone was given IN. The time from administration to response is faster with IV administration, but this was an expected result. Additionally, they felt that IN administration was safer because the need for needle use around a drug abuser is eliminated.[5]

During a 2002 prospective study of 30 patients in Denver, IN naloxone was evaluated as a first-line agent for prehospital narcotic overdose. This study found that 91% of patients responded to IN naloxone alone, and 64% did not require prehospital IV access.[11] This study raises debate over the potential benefit for basic life support providers to have a prefilled syringe of naloxone available for IN administration to patients with respiratory depression following opioid overdose. Currently, New Mexico allows BLS providers, police officers and family members of known addicts to carry naloxone for IN administration. Boston EMS also provides its BLS providers with IN naloxone.[2]

Hypoglycemia Management

When prehospital providers cannot establish IV access for dextrose administration to patients experiencing hypoglycemia, their options include oral glucose or administration of glucagon. Oral glucose, as is well known, cannot be given when patients lack the ability to swallow (although it can be applied along the gum line and absorbed buccally in extreme situations).

Traditionally, glucagon is given as a 2 mg intramuscular injection; it can also be administered intranasally (2 mg IN is comparable to 1 mg intramuscular glucagon). Several studies have demonstrated that intramuscular glucagon produces a faster and larger rise in blood glucose levels than IN glucagon.[2] Thus, when providers are properly trained, IM glucagon is preferred. First responders, however, can benefit from having a needleless system available for glucagon administration in unresponsive hypoglycemic patients. Additionally, IN glucagon may be beneficial in some unique circumstances. One example is when a patient is hypothermic and has poor peripheral circulation. Administering an IM drug to that patient would cause an extremely delayed drug response. Other examples of situations where nasal administration may be preferred include when a patient is contaminated and an adequate site cannot be cleaned, when a patient is combative, or when, because of extenuating circumstances, clothing cannot be removed to access an IM administration site.

Summary

Intranasal drug administration is safe and effective and has many applications to prehospital providers of all levels. Administered drugs do take longer to take effect than drugs administered intravenously; however, the time saved by not needing to establish an IV offsets this difference. When evaluating your system's protocols, consider adding IN drug administration, and particularly consider its benefit in patients who may be seizing, hypoglycemic, experiencing a narcotic overdose or in pain.

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