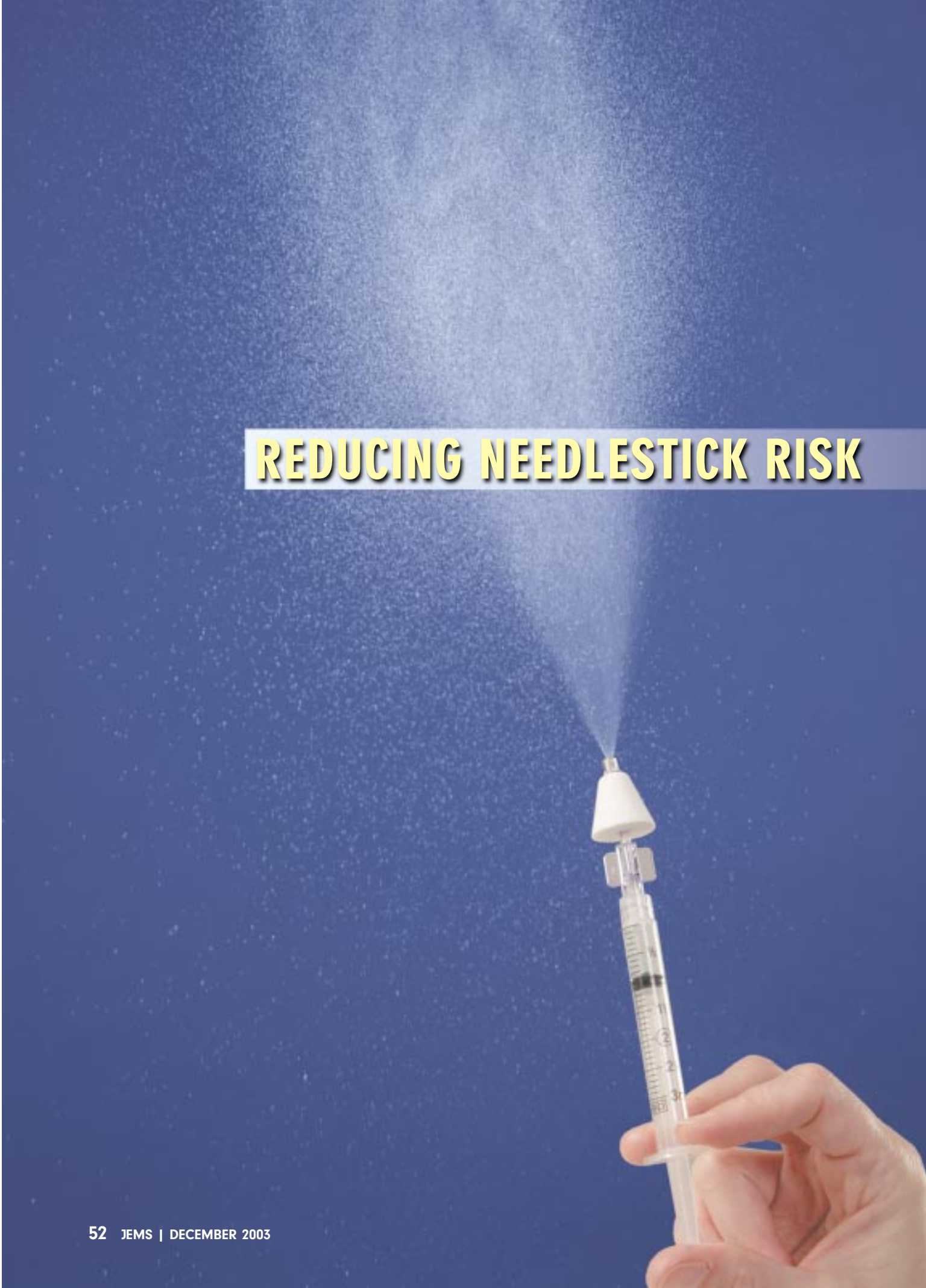
REDUCING NEEDLESTICK RISK



NASAL DRUG DELIVERY IN EMS

By Tim Wolfe, MD, & Erik Barton, MD

Scenario #1: Rescue 9 responds to a residence to evaluate a seizing patient. On arrival, the crew finds an obtunded three-year-old girl suffering a grand mal seizure. The hysterical mother informs the crew that her daughter has been seizing for at least 10 minutes. Clinical assessment reveals an intact airway, grunting respirations, tachycardia and 88% saturation on pulse oximetry.

Assisted ventilation with 100% oxygen results in improved O_2 saturation. Despite several attempts, the crew cannot establish an IV. The providers administer a dose of rectal diazepam (Valium) and rapidly transport the patient to the hospital. Seizure activity persists en route. The emergency department (ED) staff are also unsuccessful at establishing an IV. However, they administer a dose of nasal midazolam (Versed) and the child stops seizing within three minutes of drug delivery.

Scenario #2: Rescue 7 responds to a "man down" call in the downtown area. They find an unkempt male in his mid-30s lying in an alley. He has slow respirations, pinpoint pupils, cool dusky (i.e., dark bluish tinged) skin and obvious IV drug abuse needle track marks on both arms.

Bag-mask ventilation is instituted, and an IV line is attempted. While establishing the IV, the paramedic accidentally sticks his left index finger with a blood-contaminated needle.

The paramedic administers naloxone (Narcan) to the patient, who is successfully resuscitated. The patient admits that he's infected with both human immunodeficiency virus (HIV) and hepatitis C (HCV). He is transported to the ED and discharged within two hours, with no further therapy given in the ED.

The paramedic is checked into the ED and given the first dose of HIV prophylactic medications. He learns that treatment to prevent HIV after a needlestick is not 100% effective. Further, no preventive therapy exists to reduce his chances of contracting HCV. The paramedic spends additional time filling out worker's compensation paperwork and scheduling follow-up with employee health.

The next few months will be difficult: He faces the substantial side effects that accompany HIV medications, and his personal life is in turmoil due to issues of safe sex with his wife and the mental anguish of waiting to see if he'll contract HIV or HCV. A friend informs him that new evidence suggests that naloxone is effective at reversing heroin overdose if it's given intranasally—with no risk of a needlestick.

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Needlestick injury in EMS

Both of these scenarios demonstrate clinical situations in which intranasal (IN) drug delivery may enhance patient care while simultaneously eliminating the risk of a contaminated needlestick to an EMS provider. Although this delivery option is not necessarily more effective than traditional SQ, IM or IV injection methods, it is easier to deliver and often works as well as an injection. Most importantly, IN drug delivery eliminates the risk of a contaminated needlestick to the EMS provider.

Needlestick injury is not a minor issue. Bloodborne exposures are an occupational hazard that health-care providers face daily. The CDC estimates that 600,000 percutaneous injuries involving contaminated sharps occur each year. With the increasing prevalence of bloodborne pathogens, such as HIV, hepatitis B virus (HBV) and HCV, accidental needlesticks now pose a life-changing, and possibly life-ending, event to health-care workers. This risk is of even more concern in the prehospital environment, where a combination of patient and environmental factors make serious EMS provider exposures more likely.

Although intranasal drug delivery is not necessarily more effective than traditional SQ, IM or IV injection methods, it is easier to deliver & often works as well as an injection. Most importantly, IN drug delivery eliminates the risk of a contaminated needlestick to the EMS provider.

Many patients who utilize EMS for transport to the ED have chosen lifestyles that place them at particularly high risk for contracting bloodborne infections. Marcus, et al found that 4.1–8.3% of emergency patients in one inner city environment were infected with HIV.[1] Kelen et al studied the risk of HIV, HBV and HCV in another inner city ED and found that 24% of all patients were infected with at least one of those viruses.[2] Two subgroups had particularly high risks of viral infection: critically ill trauma victims (HIV seroprevalence of 16%)[3] and IV drug abusers (HCV seroprevalence of 83%).[2]

These data are more than 10 years old, but, given the continued progression of the HIV and hepatitis epidemics, it is apparent that patients transported by EMS systems (at least those in inner city areas) are at high risk of carrying bloodborne pathogens. Unique EMS environmental conditions, such as combative patients, uncontrolled scene issues, poor lighting and moving ambulances, make the probability of suffering a needlestick even more likely than in more controlled medical settings.

Effective interventions that reduce the risk of accidental needlestick injury to EMS providers should be welcomed. However, despite more than 20 years of focus on reducing needlestick injuries, health-care workers continue to injure themselves. To address this problem, Congress implemented the Needlestick Safety and Prevention Act in November 2000.[4] This act implements minimum requirements for all states and focuses heavily on "engineering controls," such as safer medical devices.

The act empowers health-care workers by allowing them to insist on implementation of procedural and technological changes to reduce needlestick injury risks. It specifically states, "non-managerial employees responsible for direct patient care must have input into employer decisions about *which* engineering controls to adopt" regarding reduction of needlesticks, "not *whether* or not to adopt them."[4]

The health-care industry has responded to this mandate in a number of ways, including the creation of needleless IV solution sets, self-retracting needles and methods of delivering injectable medications via the nasal mucosa without using a needle. Like nitroglycerine, which is rapidly absorbed across mucosal membranes, many medications easily cross mucosal membranes. The nasal mucosa offers a large, well-perfused, absorptive surface that is ideal for delivering medications directly to the bloodstream via absorption. The remainder of this article focuses on the topic of intranasal drug delivery and medications of particular interest to EMS providers.

Basic concepts in intranasal medication delivery

IN medication delivery, an active area of pharmaceutical research, is emerging as an attractive alternative to both oral and injectable drug delivery for selected medications. IN medication delivery has a number of advantages over more traditional drug delivery methods.

First, it's easy and convenient. The nose is an easily accessed area of the body—even more accessible than the arm is for IV therapy.

Second, unlike IV and IM therapies, no special training skills are required for IN medication delivery.

Third, serum levels of many nasally administered medications are comparable to injectable therapies and much higher than oral or rectal drugs.

Finally, IN medication delivery poses a minimal amount of discomfort to the patient and does not expose the health-care provider to a needlestick risk. However, IN medication delivery is not always effective and will never completely replace traditional medication delivery methods.

To fully understand the strengths and weaknesses of IN drug delivery, a number of concepts need to be discussed, including first pass metabolism, nose-brain pathway and bioavailability.

First pass metabolism

First pass metabolism (see Figure 1) is a concept that deals with the body's inborn method of destroying medications that enter the circulation through the intestinal mucosa. When a medication is ingested by mouth, it enters the stomach, where it's stored for 30–45 minutes. The drug then passes into the small intestine, where it's absorbed across the intestinal mucosa into the

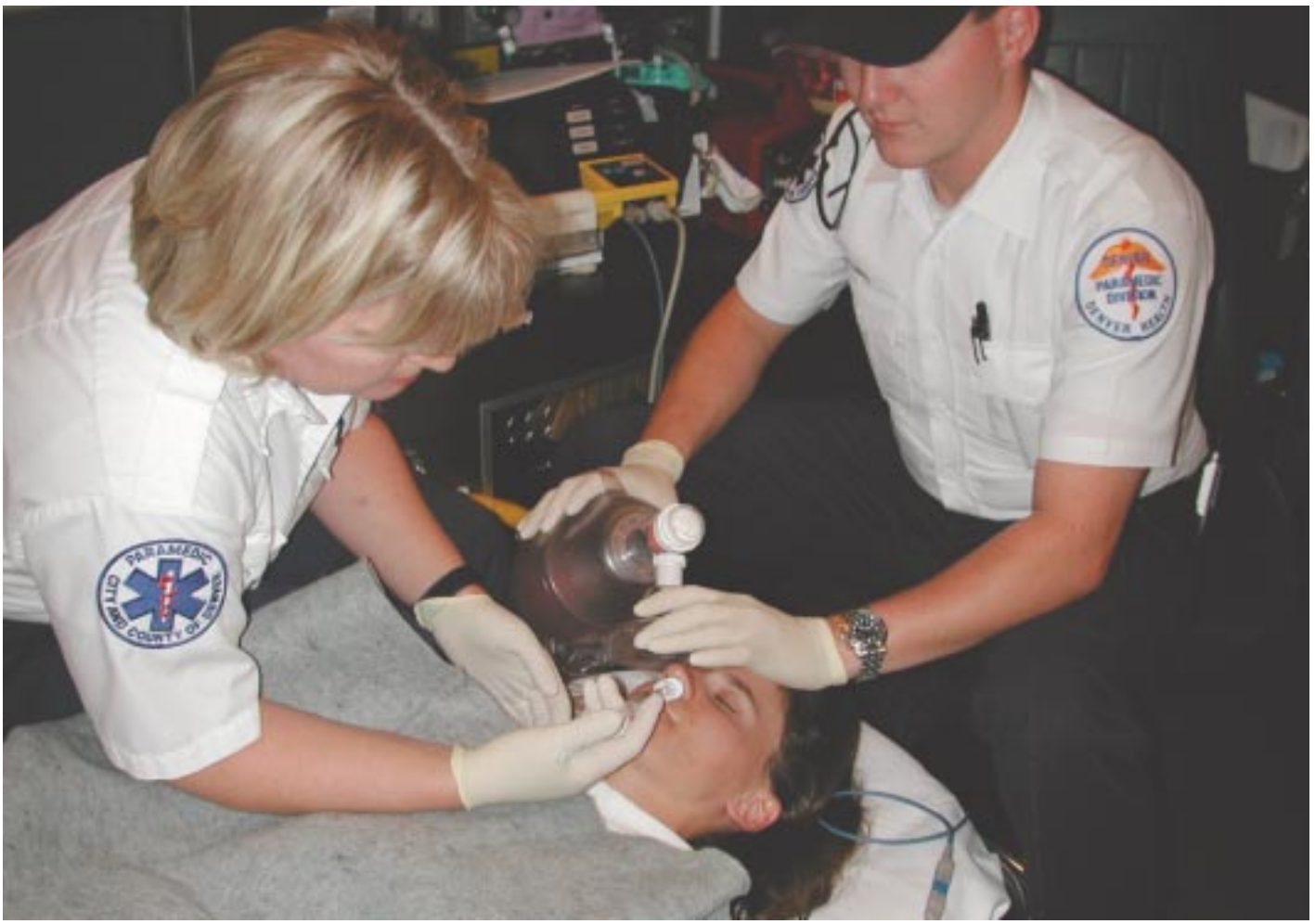
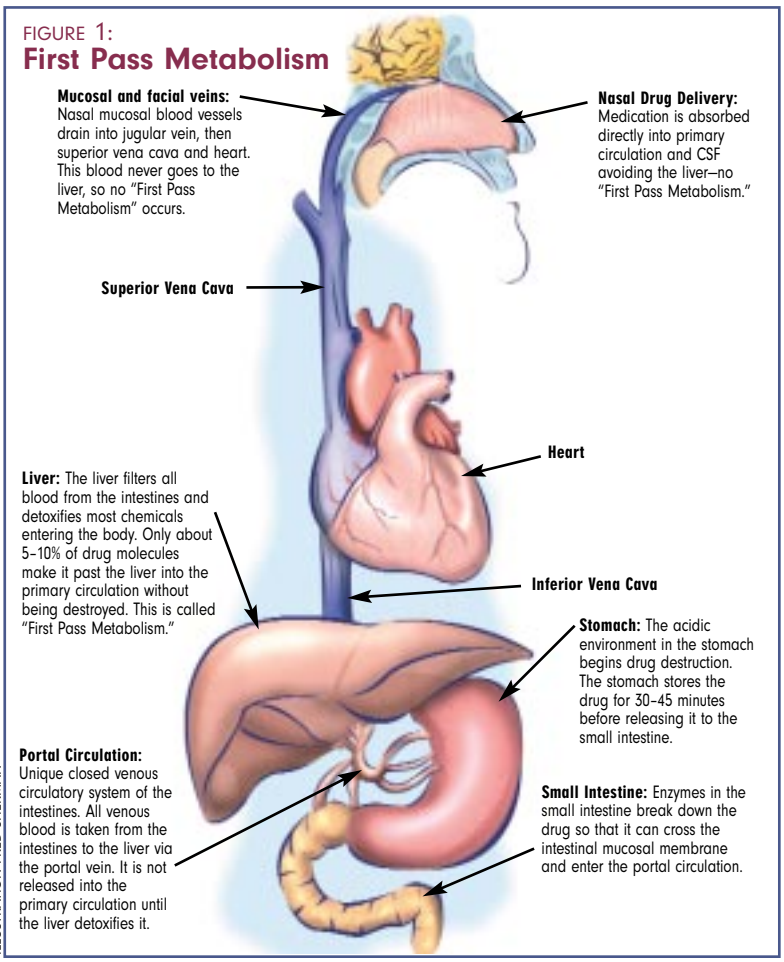


FIGURE 1:
First Pass Metabolism



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Needlestick injury is not minor. ... The CDC estimates that 600,000 percutaneous injuries involving contaminated sharps occur each year.

intestinal venous circulation.

Of importance, the intestinal venous circulation—called the *portal circulation*—is a separate circulatory compartment from the body's major venous circulation. All molecules absorbed into the portal circulation are initially transported to the liver for detoxification and packaging. Liver enzymes destroy most of the drug molecules, and a small fraction, perhaps 5–10%, enters the body's circulation as active drug. The remainder is excreted into the bile or as inactive molecules into the bloodstream and is excreted from the body in the stool or urine. This process is called *first pass metabolism*.

The point: Orally delivered medications take a long time to enter the body's circulation, and most of the medication is destroyed en route. Nasally delivered medications avoid

the gut entirely, so medications delivered across the nasal mucosa are minimally delayed in their absorption and don't suffer first pass metabolism. The result is more rapid medication delivery and much higher blood levels of the medication.

Nose-brain pathway

The upper aspects of the nasal cavity are covered with sensory nerves (for smelling) called the olfactory mucosa. Medication distributed onto these sensory nerves is absorbed directly into the cerebral spinal fluid (CSF), allowing for immediate effect on the central nervous system. This is called the *nose-brain pathway* (see Figure 2, p. 59). The nose-brain pathway is of importance to the clinical effect that occurs with centrally acting medications used to treat seizures (midazolam) and comas (naloxone).

Bioavailability

The amount of medication that ends up in the bloodstream as a percentage of how much was originally administered is termed *bioavailability*. IV medication, in which all the medication is injected directly into the bloodstream, is considered to be 100% bioavailable. All other delivery methods are compared to the IV method to determine the amount that ends up in the bloodstream. Most oral medications are about 5–10% bioavailable due to first pass metabolism. Nasal medication bioavailability varies. Not all drugs can be delivered via the nasal mucosa—primarily due to problems with bioavailability. Table 1 (below) lists a number of the factors that affect bioavailability.

Assuming that a medication is appropriate for nasal absorption, the most important factors to EMS personnel regarding bioavailability are medication concentration and volume, the method used to deliver the drug into the nose and characteristics of the nasal mucosa.

The concentration and volume of a drug significantly impact the

TABLE 1: Factors Influencing Drug Bioavailability

Drug Molecular Characteristics
- Molecular size
- Molecular structure, complexity
- Lipophilicity
- pKa of molecule

Drug Formulation Characteristics
- Drug concentration and volume*
- pH of drug solution
- Addition of absorptive enhancers

Delivery System Characteristics*
- Total area of drug deposition
- Drug solution particle size
- Drug loss anteriorly, posteriorly

Nasal Mucosal Characteristics**
- Nasal mucosal volume
- Presence of active bleeding
- Scarring, chronic mucosal damage
- Ciliary activity
- Nasal mucosal blood flow

* Items that can be influenced or assessed by the EMS provider; choose the correct concentration and an appropriate delivery system.
** Be aware of the nasal mucosal condition to assist in predicting its ability to absorb medication.

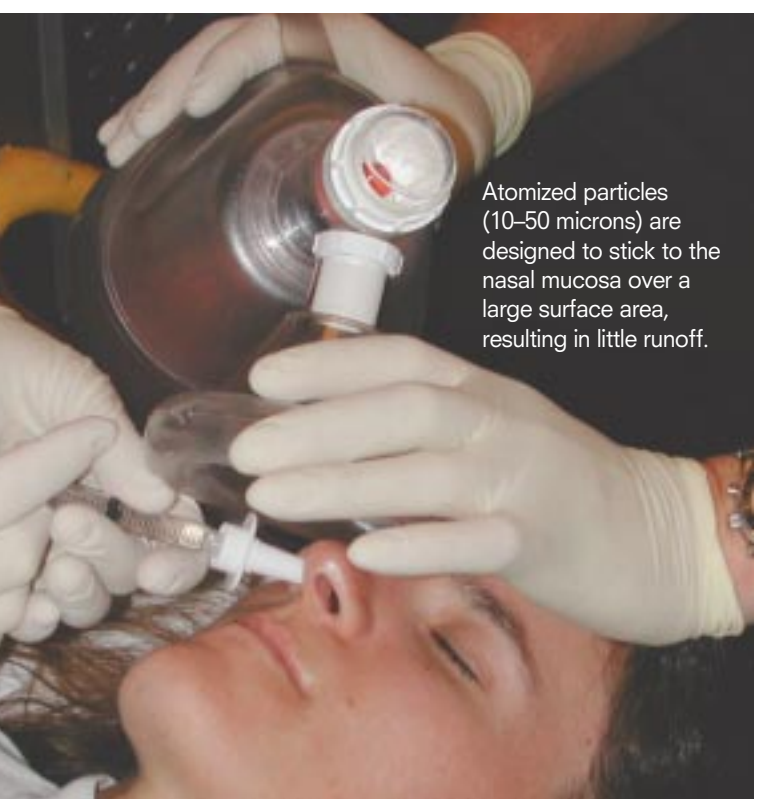
amount that can be absorbed intranasally. In general, highly concentrated medications in a small volume of solution are best. If too much fluid is used, it just runs out the nose or down the back of the throat and is wasted. Therefore, volumes of more than 0.5–1.0 mL per adult nostril aren't available for absorption.

The method chosen to deliver medication to the nasal mucosa is also important. A device that results in maximal surface area coverage with a thin layer of the drug results in higher drug bioavailability.[5] Options for nasal drug delivery include droppers, spray bottles, atomization devices and nebulizers. Droppers and spray bottles create large particle droplets and tend to cover a smaller surface area of the nasal mucosa than atomizer devices. In addition, a substantial amount of the drug delivered via these methods runs back into the throat, where it's not effectively absorbed.[6]

Atomized particles (10–50 microns) are designed to stick to the nasal mucosa over a large surface area, resulting in little runoff.[7] Nebulized particles (<5 microns) are designed to stay entrained (i.e., caught up and carried along) in the airflow and move down into the throat, trachea and lungs. Research studies demonstrate that nasal medication bioavailability increases as the drug delivery system is changed from a drop form to a spray form to an atomized form.[6–8]

To further enhance absorption, half the medication should be placed into each nostril, effectively doubling the surface area.

The health of the patient's nasal mucosa is also critical to absorption.[5] Large amounts of nasal mucous or a bloody nose inhibit medication absorption. Mucosal destruction from prolonged cocaine abuse or previous surgery can also result in reduced mucosal surface available for drug absorption. Nasal vasoconstrictors, such as Afrin and Neo-Synephrine, can also be problematic because they cause nasal blood vessel constriction, resulting in reduced absorption rates. Often, a quick look into the nostril reveals these problems, enabling the



Atomized particles (10–50 microns) are designed to stick to the nasal mucosa over a large surface area, resulting in little runoff.

EMS provider to predict whether nasal drug absorption may prove ineffective.

Nasal medication delivery in EMS

Although not all medications are readily transported across the nasal mucosa, a number of commonly used EMS drugs have proven effective in emergent settings. Implementation of the nasal delivery route for these drugs enhances an EMS provider's ability to care for patients and reduces their risk of needlestick injuries.

EMS medications that can be delivered intranasally include:

- Naloxone for opiate overdose;
- Midazolam (Versed) for the treatment of seizures and for procedural sedation;
- Glucagon for hypoglycemia;
- Opiates for pain control; and
- Topical anesthetics/vasoconstrictors prior to nasal intubation, NG tube placement or treatment of epistaxis.

Nasal naloxone

IV drug abusers requiring injectable naloxone are a patient population that places EMS providers at especially high risk for bloodborne pathogen exposure.[1–3] Because these patients rarely need an IV for any reason beyond the administration of naloxone, a method of administering naloxone without a needle is a welcome alternative.[9]

Fortunately, naloxone is a small molecule that easily crosses the nasal mucosal membranes. After IN administration, naloxone exhibits opiate antagonist effects almost as rapidly as it does via the IV route, with bioavailability approaching 100%.[10,11]

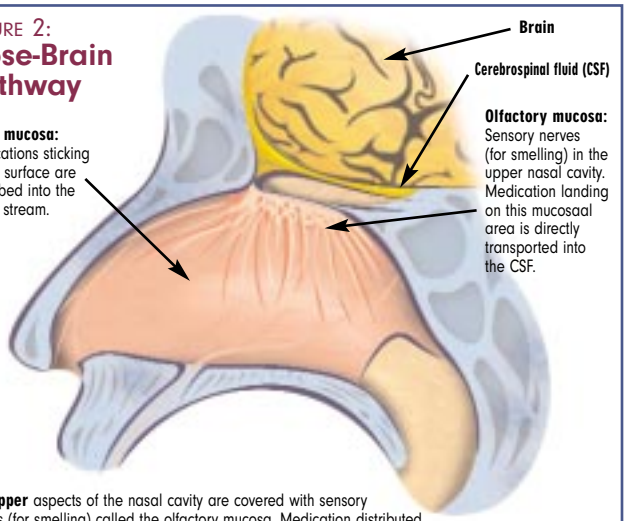
The Denver Health Paramedic system used the high nasal bioavailability of naloxone to design a prehospital study investigating the efficacy and safety of IN naloxone for the treatment of suspected opiate overdose. Their preliminary data was published in the January issue of *Prehospital Emergency Care*, and final data are being written for publication.[12]

Study patients received 2 mg IN naloxone (1mg/mL up each nostril) upon initial contact. A mucosal atomization device (MAD, Wolfe Tory Medical, Salt Lake City) was used to deliver the naloxone to enhance absorption. After IN naloxone, standard protocols, including airway management, IV placement and administration of IV naloxone, were followed.

Ninety-five patients were enrolled. Fifty-two patients responded to naloxone: 43 (83%) to IN naloxone alone, and nine (17%) to IV following IN naloxone. Four of the "non-responders" received IV naloxone so rapidly (in less than three minutes) that it's likely the nasal naloxone did not have time to produce a clinical effect. An additional four of the nine non-responders had anatomic abnormalities that may have prevented IN medication absorption (e.g., epistaxis, nasal trauma, nasal septal abnormalities).

The median times from arrival at patient side to awakening and from administration of IN naloxone to patient awakening were 8.0 minutes and 3.0 minutes, respectively. These median times to awakening after arrival and naloxone administration are less than those reported by Wanger et al for IV naloxone (9.3 minutes and 3.8 minutes) or SQ naloxone (9.6 minutes and 5.5 minutes).[13] The authors conclude that IN naloxone can be effective in the field (83% initial response rate), acts rapidly and reduces the risk of paramedic needlesticks in this population.

FIGURE 2:
Nose-Brain Pathway



The **upper** aspects of the nasal cavity are covered with sensory nerves (for smelling) called the olfactory mucosa. Medication distributed onto these sensory nerves is absorbed directly into the CSF, allowing immediate effect on the CNS. This is called the "**nose-brain pathway**."

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These results are important in terms of risk reduction. Accidental needlesticks resulting from a source patient who is an IV drug abuser are emotionally draining for the EMS provider and their family. Months of distress are spent worrying about the possibility of contracting HIV, hepatitis B or C and prevention of any possible transmission to the employee's family.[14,15]

In addition, the medications used for post-exposure prophylaxis for HIV are expensive and frequently result in major side effects.[16] Administering naloxone intranasally eliminates needlestick risk, improves the safety of the work environment and avoids the professional, personal and family turmoil that may occur should a provider incur a needlestick from an IV drug abuser.

Nasal midazolam

Status epilepticus is a common neurological emergency, resulting in significant complications that can be reduced by early EMS intervention.[17,18] Diazepam is the most widely used drug for the emergent management of seizures in both adults and children. Diazepam must be given intravenously or rectally because absorption is slow and erratic if given via the intramuscular route.[19,20] Due to the difficulties of establishing an IV in a seizing patient, IV administration of diazepam may result in delayed seizure control, especially in children.[21,22]

Rectal diazepam offers an alternate method of delivery, but has a low peak concentration and slow onset of action.[23–25] It's also considerably more expensive than generic diazepam or midazolam due to patent protection. Finally, rectal drug administration is less socially acceptable and less effective than other routes.[24,26,27]

IN midazolam delivery offers an attractive alternate method for the administration of benzodiazepines in seizing patients.[22,24,27] Midazolam easily crosses the nasal mucosa and the blood brain barrier, resulting in a rapid rise in both plasma and CSF concentrations.[8,23] Peak plasma midazolam concentrations occur approximately six to 12 minutes after IN administration.[23]

Two prospective studies compared IN midazolam to rectal or IV diazepam for the treatment of seizures. Fisgin et al compared IN midazolam to rectal diazepam in pediatric patients suffering prolonged seizures.[24] IN midazolam was used to treat 23 seizures, and rectal diazepam was used to treat 22 seizures. Midazolam stopped 20 (87%) of 23 seizures and diazepam 13 (60%) of 22 seizures ($p < 0.05$). No

clinically important adverse events occured in the two groups. The authors conclude that administration of midazolam via the nasal mucosa is more effective, socially acceptable and convenient than rectal diazepam.

Lahat et al compared IN midazolam to IV diazepam in children seizing 10 minutes or longer.[22] Nasal midazolam stopped 23 of 26 (88%) seizures, while 24 of 26 (92%) were controlled with IV diazepam (p = NS). The mean time to seizure cessation was 6.1 minutes with midazolam and 8.0 minutes with diazepam. The authors concluded that IN midazolam was as safe and effective as IV diazepam, but the overall time to cessation of seizures after arrival at the hospital was faster with IN midazolam. Additional articles describe similar seizure control in adults.[27]

Other nasal medications

Glucagon, another medication in many EMS providers kits, can be effectively delivered via the nasal mucosa, avoiding the need to give an injection and resulting in normoglycemia much faster than if oral glucose is administered.[28,29] However, higher doses than the standard 1 mg dose may be required to obtain rapid resolution of hypoglycemia. Currently, glucagon is quite expensive, which may make an increase in the dosing requirements for IN delivery cost prohibitive.

Opiates also readily cross the mucosal membrane and can be used to control pain in a number of medical settings. Fentanyl is probably the most promising opiate for IN use in the United States, although more potent opiates, such as sufentanil, may be even better.[30]

A huge body of literature exists regarding the use of intranasal fentanyl in the anesthesia and post-operative setting.[30] More limited data exist regarding its use in the ED and prehospital setting. Jacobs et al published preliminary data of the use of IN opiates in a rural setting in Australia.[31] He found IN fentanyl effective and safe for pain control in his EMT-intermediate level EMS system. Borland et al, found that IN fentanyl resulted in early and sustained pain relief when it was used in the ED.[32]

For those agencies that perform nasotracheal intubation or place nasogastric tubes, pre-procedural intranasal and intraoral anesthetics/vasoconstrictors can significantly reduce a patient's adverse reactions (pain, gag, epistaxis) to the procedure, making it easier for the paramedic and easier on the patient.[33] Some systems may even consider treating nosebleeds with topical vasoconstrictors.[34]

Finally, terrorist events, nerve gas and cyanide poisoning are of concern. Little scientific information is available for IN nerve gas treatment options, but atropine is well-known to cross nasal mucous membranes.[35]

In situations where cyanide is a concern, the antidote used in Europe, hydroxocobalamin, is bioavailable

across the nasal mucosa.[36] Further investigation into the efficacy of nasally delivered antidotes for mass casualty situations would be welcome.

Take-away lessons for nasal drug delivery

Although IN medication delivery is an exciting new method for delivering medications in the EMS setting, it's not a panacea. Being aware of limitations is an important step to appropriate utilization of this therapy. Key issues that must be addressed up front are the medication dose, volume and delivery method.

Once the medication and delivery method are determined and the medication box is properly stocked, several other issues improve field experience. First, be aware of clinical situations where nasal delivery may be suboptimal. Inspect the patient's nostrils for large amounts of mucus, blood or other problems that might inhibit absorption. If abnormalities are present, consider other routes for drug administration because there may be an increased risk of failure.

Second, deliver the medication without delay to allow time for effective absorption.

Third, relax and reassess the patient for a few minutes. In many situations of opiate overdose and seizure therapy, no further care beyond brief airway support is necessary, and no needles need ever be used. If the clinical problem fails to resolve with the IN medication, consider two things: The nasal route was not effective, or the diagnosis is wrong.

In situations where a comatose patient fails to awaken with naloxone, continue to support breathing and circulation, administer naloxone via the IM or IV route and consider alternate causes for the coma.

In the case of seizures, remember that some seizures are hard to control and don't respond to IN midazolam or any medication in your drug box. In this setting, an IV will likely be needed. IV midazolam or other benzodiazepines should be administered, airway support should continue, and more complex seizure medication regimens may be required in the ED.

Conclusion

Nasal medication delivery is convenient and easy, but it may not always be effective. Nasal medication delivery won't replace the need for injections. However, awareness of its limitations combined with the correct equipment and medication concentrations will allow EMS providers to deliver a number of medications via the intranasal route. The result will be more rapid care and reduced needlestick exposure for prehospital personnel. JEMS

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See Dr. Wolfe lecture on intranasal medication delivery and adult intraosseous infusion at EMS Today in Salt Lake City, March 2–6, 2004.

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