
Original Contributions

EFFICACY OF INTRANASAL NALOXONE AS A NEEDLELESS ALTERNATIVE FOR TREATMENT OF OPIOID OVERDOSE IN THE PREHOSPITAL SETTING

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□ **Abstract**—Prehospital providers are at increased risk for blood-borne exposure and disease due to the nature of their environment. The use of intranasal (i.n.) medications in high-risk populations may limit this risk of exposure. To determine the efficacy of i.n. naloxone in the treatment of suspected opiate overdose patients in the prehospital setting, a prospective, nonrandomized trial of administering i.n. naloxone by paramedics to patients with suspected opiate overdoses over a 6-month period was performed. All adult patients encountered in the prehospital setting as suspected opiate overdose (OD), found down (FD), or with altered mental status (AMS) who met the criteria for naloxone administration were included in the study. i.n. naloxone (2 mg) was administered immediately upon patient contact and before i.v. insertion and administration of i.v. naloxone (2 mg). Patients were then treated by EMS protocol. The main outcome measures were: time of i.n. naloxone administration, time of i.v. naloxone administration, time of appropriate patient response as reported by paramedics. Ninety-five patients received i.n. naloxone and were included in the study. A total of 52 patients responded to naloxone by either i.n. or i.v., with 43 (83%) responding to i.n. naloxone alone. Seven patients (16%) in this group required further doses of i.v. naloxone. In conclusion, i.n.

naloxone is a novel alternative method for drug administration in high-risk patients in the prehospital setting with good overall effectiveness. The use of this route is further discussed in relation to efficacy of treatment and minimizing the risk of blood-borne exposures to EMS personnel. © 2005 Elsevier Inc.

□ **Keywords**—Prehospital; intranasal; naloxone; overdose; exposure; needlestick

INTRODUCTION

In 1991, the Occupational Safety and Health Administration (OSHA) published the Occupational Exposure to Bloodborne Pathogens standard. This regulation outlines employer requirements necessary for the implementation of an exposure control plan to reduce or eliminate hazards from bloodborne pathogens and infectious materials (1). The regulation specifically targets engineering controls as a primary means of eliminating or minimizing employee exposures. These controls include implementation of safer medical devices such as needleless systems and shielded needles. Despite advances in medical device technology that reduce needlestick risk, employee exposures continue to be of concern. Frequency of these

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exposures remains high, and the potential long-term mental and physical health effects can be severe (2–5).

In response to the continued prevalence of bloodborne pathogen exposures from accidental sharps injuries in the workplace, OSHA developed The Needlestick Safety and Prevention Act (Pub. L. 106-430), which was signed into law in November 2000 and became effective in April 2001 (6). It set forth in greater detail the requirements for employers to identify, evaluate, and implement safer medical devices.

Most recently, needleless technology has been implemented in hospitals, clinics, and other healthcare offices. To date, however, very few needleless systems are being used in the prehospital setting. Ambulances, including air and ground programs, rarely find one needleless system that has universal compatibility with the various devices used in the hospitals they service. For this reason, most prehospital providers still rely on needle-type devices to access peripheral intravenous (i.v.) lines and to administer subcutaneous (s.q.), and intramuscular (i.m.) medications.

Intranasal (i.n.) medication delivery is an alternate delivery route for injectable medications. When used with carefully selected medications, this delivery route has the advantage of rapid onset, high plasma bioavailability, direct transport to the central nervous system (CNS) across the olfactory mucosa, elimination of first pass metabolism and, perhaps most importantly, elimination of all needles (7–13). Access to the nose is also relatively immediate, especially in the prehospital setting where access to extremities through clothing can be highly variable from one patient to the next. Intranasal medication administration in the emergent setting is a rapid and a safe method for both the patient and the provider that has been underutilized to date.

We investigated the use of i.n. naloxone (Narcan[®]) by paramedics to assess its efficacy and safety as an alternative (needleless) medication delivery route. Narcan is commonly used in patients suffering from a suspected opioid overdose. These patients often have limited peripheral venous access, making the intranasal route potentially very advantageous. The preliminary data, published in January 2002, was very promising (14). This study reports the final data from that series and makes the recommendation that the intranasal route should be considered as a safer method of administering naloxone in high-risk patients encountered in the field. Additionally, we will briefly discuss other intranasal medications that hold promise in the prehospital setting.

METHODS

Study Design

This study was performed by the Denver Health Paramedic Division as a prospective evaluation of intranasal



Figure 1. The Mucosal Atomizer Device (MAD[®]) attached to a syringe showing the spray pattern of medication.

naloxone in all patients who presented with potential opiate drug intoxication. The study was performed from February 1 to August 30, 2001 as part of a Paramedic Division Quality Assurance Evaluation of i.n. naloxone. There was an interruption in the study (March to June) due to a national shortage of naloxone in the 2 mg/2 mL concentration doses. Data collection occurred for a total of 3 months during the study period. All paramedics went through a brief training curriculum that taught the use of the i.n. naloxone device and the appropriate documentation required before the start of the study. Institutional Review Board (IRB) approval was granted (protocol #01-635).

Procedure

All adult patients (> 14 years) encountered in the field with a prehospital encounter diagnosis of “altered mental status” (AMS), “found down” (FD), or “suspected opioid overdose” (OD) were eligible for the study. The standard protocol called for these patients to have an i.v. placed and to receive i.v. naloxone (1–2 mg) based on the paramedic’s assessment of a possible overdose. For the study this protocol was modified so that these patients initially had 2 mg of intranasal naloxone administered using a disposable Mucosal Atomizer Device (MAD[®], Wolfe-Tory Medical, Inc., Salt Lake City, UT) (Figure 1). One mL of the 1 mg/mL naloxone solution was administered into each naris by inserting the MAD[®]

approximately ¼ to ½ inch, for a total volume of 2 mL. Immediately after i.n. naloxone, the standard protocol including airway management, i.v. line placement and i.v. medications was followed. The standard protocol was discontinued only if the patient responded and no further treatment was required. Data sheets were completed for all patients (Figure 2) and included: times of initial patient encounter, i.n. naloxone administration, i.v. insertion, i.v. naloxone administration, and patient response. In addition, paramedics were asked to report any obvious abnormalities noted in the patient's nasal mucosa (such as bleeding, deformity, mucus, etc.) at the time of i.n. drug administration.

Outcomes

The number of patients responding to i.n. naloxone, defined as a significant improvement in level of consciousness as determined by paramedics, before i.v. administration of a second dose of naloxone was recorded. Additionally, the time of response to naloxone (to the nearest minute) was measured by paramedics. Results were analyzed using McNemar Change test and two-tailed *t*-tests for independent samples.

RESULTS

Ninety-five patients met study criteria and received i.n. naloxone. Fifty-two of these patients responded to either i.n. or i.v. naloxone ("Naloxone Responders"). Table 1 lists the category to which the paramedics assigned the patients and the percentage that responded to naloxone. The majority of patients (63%) were suspected of having an opiate overdose upon initial assessment by the paramedic. Three patients were assigned to two categories. Forty-three (83%) of the 52 "Naloxone Responders" ($p = 0.0011$) awoke with intranasal naloxone before the paramedics could administer the naloxone intravenously. Table 2 lists mean and median response times from paramedic arrival and from drug administration for all naloxone responders. Twelve of the 43 i.n. "Naloxone Responders" (29%) received no i.v. placement in the field after i.n. naloxone delivery. Seven patients (16%) in the i.n. naloxone response group required additional doses of i.v. naloxone after initial response due to "recurrent somnolence" or "slow response," whereas 36 patients (84%) required no further naloxone therapy (69% of all "Naloxone Responders"). None of the "Naloxone Responders" was reported to have severe withdrawal reactions from either i.v. or i.n. naloxone.

There were nine patients (17%) who responded only to i.v. naloxone and not to i.n. naloxone. Five of these

nine (56%) i.n. nonresponder patients had "epistaxis" (2), "nasal mucus" (1), "trauma" (1), or "septal abnormality" (1), as noted by paramedics. None of the i.n. naloxone responders had any nasal abnormality noted by paramedics.

DISCUSSION

With the increasing seroprevalence of bloodborne pathogens, accidental needle sticks now pose a life-changing and possibly life-ending event to health care providers. This risk is especially high in the Emergency Medical Services (EMS) environment. Marcus et al. found a human immunodeficiency virus (HIV) seroprevalence rate of 4.1 to 8.9 per 100 patient visits in three inner-city Emergency Department (ED) populations (15). The annual blood contact for an individual EMS worker has been estimated to be as high as 12.3 per year in populations where over 90% of patients' HIV status are unknown (16). There is much concern that this high exposure rate can result in viral seroconversion of EMS providers. Valenzuela et al. reported a fivefold higher prevalence of Hepatitis B (HBV) infection in paramedics than that observed in a comparable population from the same city in 1985 (17). Pepe et al. confirmed this correlation in Houston EMS personnel, noting a strong association between years of employment and the rate of HBV infections (18). Although there is less risk today with the advent of HBV vaccines and use of universal precautions, the risk for other exposures remains significant.

An especially high-risk patient population to EMS providers is the intravenous drug abuser (IVDA). These patients have HIV, HBV and Hepatitis C (HBC) seroprevalence rates that are far higher than the baseline population and the serostatus is typically unknown to EMS workers (19). In addition, EMS personnel commonly are involved in their care for life-threatening illnesses such as respiratory arrest from opiate overdose. Because opiate overdose patients rarely need an i.v. for any reason beyond the administration of naloxone (20–22), a needleless method of administering naloxone would eliminate needlestick risk and potential transmission of bloodborne pathogens.

As this study demonstrates, such a delivery method exists. Like nitroglycerine, which is rapidly absorbed across mucosal membranes, naloxone also easily crosses the mucosal membranes. After intranasal mucosal administration, naloxone exhibits opiate antagonist effects almost as rapidly as the i.v. route with a bioavailability and clinical response approaching 100% in animal and human studies (7–9). The current series is a report of routine i.n. naloxone use in the emergent setting of opiate

PREHOSPITAL INTRANASAL NARCAN

(For Quality Assurance/Performance Improvement Purposes Only)

PROTOCOL FOR DEVICE USE:

- 1) Time of first contact noted as accurately as possible.
- 2) Load syringe with 2 mg of Narcan and nasal atomizer.
- 3) Administer intranasal Narcan via rapid intranasal mist spray of 1cc to each nostril.
- 4) Time of administration accurately noted and whether patient responded.
- 5) Continue normal attempt(s) to gain IV access and secure airway as needed.
- 6) Record time of IV Narcan if given and whether patient responded.

NOTE: Protocol stops after patient response.

PATIENT DATA:

DATE: _____ TRIP #: _____

INDICATION for Narcan: Opioid overdose Altered mental status Found down

Other: _____

- 1) TIME OF FIRST PATIENT CONTACT: _____
- 2) TIME INTRANASAL NARCAN ADMINISTERED: _____
- 3) TIME IV LINE STARTED: _____
- 4) DID THE PATIENT AROUSE AFTER INTRANASAL NARCAN: Yes No
(If No, then continue with Intravenous Narcan)
- 5) TIME IV NARCAN GIVEN: __ RESPONSE: Yes No
- 6) RESPONSE TO OTHER MEDICATION: Yes (med) _____ No
- 7) TIME OF PATIENT RESPONSE: _____

NASAL abnormalities noted: Septal abnormality Epistaxis Mucous

Trauma Other: _____

COMPLICATIONS/COMMENTS: _____

***** NOTE *** PLEASE ATTACH COMPLETED FORM TO TRIP SHEET**

Figure 2. Paramedic recording sheet for Prehospital Intranasal Narcan study.

overdose. This study shows that intranasal naloxone is a clinically effective, rapid, needleless approach for administering naloxone to patients suffering an opiate over-

dose and is easily implemented in the prehospital setting. Our results demonstrate an 83% response rate to i.n. naloxone in patients suffering an opiate overdose. In

Table 1. Numbers of Patients who Presented with Altered Mental Status (AMS), Found Down (FD) or as a Suspected Opiate Overdose (OD), and the Number of Patients who Responded to Naloxone (“Naloxone Responders”)

	AMS (n = 40)	FD (n = 20)	OD (n = 38)
Total patients (n = 95)			
“Naloxone responders”	11 (22%)	8 (15%)	33 (63%)

Note: three patients were listed in two categories.

actual practice, response rates to i.n. naloxone may be greater than 83%. By study design, no delays for i.v. naloxone were allowed, resulting in a number of cases where i.v. naloxone was administered shortly after i.n. naloxone due to rapid i.v. placement. Four of the nine patients (44%) reported to have responded only to i.v. naloxone received the i.v. dose within 4 min or less after the i.n. dose. Because i.n. naloxone often takes 4 min to arouse a patient, some of these patients may have responded to i.n. naloxone but were identified as nonresponders because they received i.v. naloxone within such a short time period.

When comparing time of response to i.n. naloxone to other routes of administration, it seems to be equivalent. Median times from arrival at the patient’s side to clinical response (8.0 min i.n. vs. 10.0 min i.v.) and from drug administration to clinical response (3.0 min i.n. vs. 3.0 min i.v.) were not significantly different between i.n. delivery and i.v. delivery. These median times to clinical response after naloxone administration are similar to those previously reported for intravenous naloxone and subcutaneous naloxone (23). Wanger et al. found that the median time from ambulance arrival to patient response (defined at a RR > 10) was 9.3 (± 4.2) minutes for i.v. naloxone, and 9.6 (± 4.58) min for s.q. naloxone. The median times from drug administration to clinical response were 3.8 min for i.v. naloxone and 5.5 min for s.q. naloxone. The authors conclude that the delay in re-

Table 2. Intranasal (i.n.) and Intravenous (i.v.) “Naloxone Responders” in the Prehospital Setting

	Response Times in minutes (± SD)		
	n = 52	Initial contact	Drug administration
i.n. Naloxone	43 (83%)	9.9 (± 4.4) (median 8.0)	4.2 (± 2.7) (median 3.0)
i.v. Naloxone	9 (17%)	12.8 (± 7.6) (median 10.0)	3.7 (± 2.3) (median 3.0)
p Value	0.0011	(ns)	(ns)

Note: times reported from initial patient contact and from drug administration to observed response.

Table 3. Intranasal Medications Previously Studied for Systemic Indications [adapted from Barton, et al. (3)]

Indication	Medications
Analgesia	Fentanyl
	Diamorphine
	Sufentanil
Antiemetics	Buprenorphine
	Meclizine
	Metoclopramide
Antihypertensives	Hydralazine
	Nifedipine
	Nitroglycerine
	Propranolol
	Verapamil
Cardiac arrest/ACLS	Atropine
	Epinephrine
	Lidocaine
Drug overdose	Naloxone
	Butorphanol
Headache therapy	Dihydroergotamine
	Lidocaine
	Sumatriptan
	Dextrose
	Glucagon
Sedation	Diazepam
	Ketamine
	Midazolam
Seizures	Diazepam
	Midazolam
Miscellaneous	Gentamycin
	Neostigmine

sponse to s.q. administration was compensated for by the time it took to establish i.v. access, making the delivery routes equivalent in efficacy. We believe the same logic applies to i.n. delivery with the added safety advantage that no needle is used.

Intranasal naloxone is not the only medication holding promise for needlestick risk reduction and improved patient care in the prehospital setting. Table 3 gives a listing of a number of medications routinely used in the EMS setting that are effective when delivered intranasally. One of the most important is i.n. midazolam for seizure control. A number of studies have demonstrated that emergent seizure control with i.n. midazolam is as effective as the long-held standard of intravenous diazepam and superior to rectal diazepam (24–27). Lahat et al. found i.n. midazolam to provide equivalent control of pediatric seizures compared to i.v. diazepam (28). In addition, due to the time it took to start an i.v. in a seizing child, the i.n. midazolam group (6.1 min) had a significant reduction in total time to seizure cessation compared to the i.v. diazepam group (8 min). Fisgin et al. noted a much better control of pediatric seizures using i.n. midazolam (87% cessation) when compared to rectal diazepam (60% cessation) (24).

Transmucosal drug delivery is emerging as a promis-

ing method of delivering medications directly to the blood stream. This method of delivery can eliminate the need for intravenous catheters, and effective drug levels can be delivered rapidly for a number of important medications. The nasal route is a particularly attractive area to deliver transmucosal medications due to the large absorptive surface (180 cm²), rich vascular plexus, blood flow rates that approach that of the brain, and rapid absorptive properties that allow titration of medication effect (29). Utilizing an "atomized" delivery system that enhances mucosal surface coverage and optimizes particle size for nasal distribution also increases drug absorption (30). Atomization provides a larger surface coverage to nonciliated surfaces for better absorption. Additionally, with nasal breathing, nearly all particles with a size of 10–20 μm ("atomized") are deposited on the nasal mucosa, those less than 2 μm pass through the nasal cavity and deposit in the lungs, whereas larger droplets often coalesce and run out of the nasal cavity.

Nasal drug administration also offers a number of advantages over parenteral and oral drug administration. The obvious advantage of nasal medication delivery over parenteral delivery is the elimination of an injection. This not only eliminates the risk of a needle stick exposure to the provider, but also eliminates the pain of injection experienced by the patient. The latter advantage is especially attractive in the pediatric setting. In addition, intranasal drug administration does not require sterile technique, clinical skills required for placing intravenous catheters or injecting medications, and it is immediately and readily available in almost all patients. Finally, for a number of parenteral medications, the rate and extent of absorption and plasma concentration vs. time profiles when the drug is delivered intranasally are comparable to those obtained by intravenous administration (31–35).

However, nasal drug delivery is not without its own problems. As demonstrated in our study, the clinical effect of i.n. drug delivery is not 100%. Even if an optimized medication form, concentration and delivery system are used, i.n. delivery will not always work due to uncontrollable patient factors. A patient's nasal blood flow and nasal mucosal characteristics have significant impact on drug absorption (36). If the patient used a street drug or OTC medication that decreases nasal blood flow (alpha agonists and anticholinergics), then the absorption of the therapeutic medication is likely reduced. Similarly, significant amounts of nasal secretions or nasal bleeding may inhibit drug absorption, and using higher drug volumes to try to overcome these factors would cause runoff into the hypopharynx and out of the nostril, making the extra medication volume unavailable for absorption.

The results of this study are important in terms of risk reduction to EMS providers. Accidental needle sticks, especially those resulting from a source patient who is an

i.v. drug abuser, are emotionally draining for employees as well as their families. Months of distress are spent worrying about the possibility of contracting HIV, hepatitis B or C, and concerns regarding prevention of any possible transmission to the employee's spouse (2–4). In addition, the medications used for postexposure prophylaxis for HIV are expensive and frequently result in major side effects (5). By administering naloxone intranasally, needlestick risk is eliminated. Prehospital systems in major metropolitan areas recognize the safety advantages of intranasal naloxone and are just now starting to implement this delivery route in their standard protocols for altered mental status and opiate overdose (37). These protocol changes will improve the safety of the work environment and eliminate the professional, personal, and family turmoil that might occur should a provider incur a needle stick from an i.v. drug abuser.

LIMITATIONS

There were significant limitations in designing such a study for use in the prehospital setting. First, because the efficacy of i.n. naloxone in the treatment of opiate overdose was an unknown, we were required to follow our standard procedure of rescue breathing, i.v. initiation and administration of i.v. naloxone in all patients encountered. The only adjustment to this protocol was to first administer i.n. naloxone before i.v. start. In some situations we may have administered i.v. naloxone before the i.n. drug had a chance to take effect. An ideal setting would have been the requirement to wait 5 min after i.n. drug delivery before i.v. naloxone was administered and provide rescue breathing with bagging if needed. This would have allowed us to be more certain of the clinical efficacy of i.n. naloxone. Despite this limitation, we still found an 83% response rate to i.n. naloxone.

A second limitation was the reliance on the subjective reporting from paramedics who were required to record times, administer medications, and assess appropriate patient responses. Although paramedics did an exemplary job, this type of data collection is subject to recording errors in such an uncontrolled setting. Additionally, times were recorded to the nearest minute, which may have limited exact analysis and statistical significance of the data.

A third limitation was lack of randomization or blinding. Patients were not randomized nor was drug administration blinded to the provider who was assessing patient response. Rather, we chose a "staged" protocol so that medical care of the patient would not be diminished if there was no response to the i.n. medication.

Finally, we did not look at confirmatory studies demonstrating the presence of opiate metabolites in the bloodstream of all patients who responded to i.n. or i.v.

naloxone upon hospital arrival. Because there are other overdose situations that may respond to naloxone, this could be a confounding variable in our study.

CONCLUSION

Several medications could be considered for routine intranasal administration in the prehospital setting. We have attempted to demonstrate the effectiveness of one medication, naloxone, with our study demonstrating an 83% response when used intranasally. Our recommendation is that i.n. naloxone should be considered in EMS settings as first-line therapy for opioid overdose patients, using parenteral naloxone as a secondary treatment, especially in high risk populations. The advantages to incorporating i.n. naloxone into a prehospital protocol include both 1) a rapid reversal of opioid overdose in a majority of patients, and 2) limiting the risk of needle-stick exposures. By employing intranasal medication administration with selected medications, bloodborne exposures may be reduced in prehospital practice.

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