Intranasal Naloxone Is a Viable Alternative to Intravenous Naloxone for Prehospital Narcotic Overdose

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Abstract

Objective. To compare the prehospital time intervals from patient contact and medication administration to clinical response for intranasal (IN) versus intravenous (IV) naloxone in patients with suspected narcotic overdose. **Methods.** This was a retrospective review of emergency medical services (EMS) and hospital records, before and after implementation of a protocol for administration of intranasal naloxone by the Central California EMS Agency. We included patients with suspected narcotic overdose treated in the prehospital setting over 17 months, between March 2003 and July 2004. Paramedics documented dose, route of administration, and positive response times using an electronic record. *Clinical response* was defined as an increase in respiratory rate (breaths/min) or Glasgow Coma Scale score of at least 6. Main outcome variables included time from medication to clinical response and time from patient contact to clinical response. Secondary variables included numbers of doses administered and rescue doses given by an alternate route. Between-group comparisons were accomplished using t-tests and chi-square tests as appropriate. **Results.** One hundred fifty-four patients met the inclusion criteria, including 104 treated with IV and 50 treated with IN naloxone. Clinical response was noted in 33 (66%) and 58 (56%) of the IN and IV groups, respectively ($p = 0.3$). The mean time between naloxone administration and clinical response was longer for the IN group (12.9 vs. 8.1 min, $p = 0.02$). However, the mean times from patient contact to clinical response were not significantly different between the IN and IV groups (20.3 vs. 20.7 min, $p = 0.9$). More patients in the IN group received two doses of naloxone (34% vs. 18%, $p = 0.05$), and three patients in the IN group received a subsequent dose of IV or IM naloxone. **Conclusions.** The time from dose administration to clinical response for naloxone was longer for the IN route, but the overall time from patient contact to response was the same for the IV and IN routes. Given the difficulty and potential hazards in obtaining IV access in many patients with narcotic overdose, IN naloxone appears to be a useful and potentially safer alternative.

Received January 19, 2009, from the Department of Emergency Medicine, UCSF–Fresno, Medical Education Program (TMR, GWH, GS, MS), Fresno, California. Revision received March 2, 2009; accepted for publication March 17, 2009.

The authors have no conflicts of interest for this study.

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doi: 10.1080/10903120903144866

Key words: naloxone; narcotic overdose; emergency medical services; intranasal

PREHOSPITAL EMERGENCY CARE 2009;13:512–515

Introduction

Naloxone (Narcan) is a competitive antagonist of the mu-opioid receptor.[1] It has long been used in the emergency setting to reverse the effects of opioid toxicity, and can be lifesaving for patients who have significant respiratory and mental status depression. There are a number of possible modes of administration for naloxone, including intravenous (IV), intramuscular (IM), subcutaneous (SQ), endotracheal, sublingual, inhaled, and intranasal (IN).[2,3] The IV route is the most commonly used because it is both rapid and predictable in its clinical effects.

To date, there have been only a handful of studies comparing the different modes of naloxone administration. Wanger et al. compared the prehospital use of naloxone by the IV and SQ routes.[4] They found that although the IV route had a more rapid effect once given, SQ naloxone was administered more quickly, and the overall time from patient contact to clinical effect was nearly the same. A prospective study of 30 patients in Denver evaluated IN naloxone as the first-line agent in the prehospital setting in narcotic overdose.[5] Of the 11 patients who responded to either IN or IV naloxone, 91% responded to IN naloxone alone. Of those treated with IN naloxone, 64% did not require IV access in the field. Kelly and Koutsogiannis compared IN naloxone with IM naloxone in Australia. In a preliminary report, they noted a 100% response rate with IN naloxone for six trial patients.[6] In a subsequent prospective randomized trial, Kelly et al. found the IM route to be faster than IN administration (6 vs. 8 minutes).[7] The success rate for the patients treated with IN naloxone was 74%, and there was no difference between the groups in rescue doses needed.

Additionally, IN administration of naloxone may reduce the risk of needlestick in a clinical setting where hepatitis, human immunodeficiency virus (HIV), and difficult IV access are common. Patients with altered mental status or narcotic overdose may require IV access for other reasons. However, as noted by Barton et al., those with isolated narcotic overdose who rapidly respond to IN naloxone may not require IV access at all.[5]

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The main objective of our study was to compare the IV and IN routes of naloxone administration with respect to the time from patient contact and medication administration to clinical effect in patients with suspected narcotic overdose. We also sought to assess the positive clinical response rate, need for repeat or rescue doses, and whether any needlesticks occurred during the care of the study patients.

METHODS

We performed a retrospective review of electronic emergency medical services (EMS) records. In March 2004, the local EMS protocol was changed, making IN naloxone the first-line route of administration in patients with suspected narcotic overdose. (See Table 1 for the protocol.) The study period included March 2003 through July 2004. Thus, in the first year of the study period, IV naloxone was the first-line agent, and in the final five months, IN naloxone was the first-line agent. The patient population selected for this study included those patients transported by EMS during the study period who were treated with naloxone for suspected narcotic overdose. In our system, patients must be clinically suspected of opiate intoxication and have a respiratory rate (RR) of 8 breaths/min or less to receive naloxone. Exclusion criteria consisted of failure to be treated with naloxone and altered mental status that was not thought to be secondary to narcotic overdose.

The prehospital record is entirely electronic, with all patient care data uploaded into a single EMS database. We extracted the data relevant to our study, including all prehospital times, vital signs, patient assessments, and medications administered. We imported the extracted data into a Microsoft Excel 2000 spreadsheet (Microsoft Corp., Redmond, WA) and stripped it of unique patient identifiers.

Main outcome measures included time from naloxone administration to clinical response and time from patient contact to clinical response. Secondary outcome measures included numbers of doses administered, rescue doses given by an alternate route, and needlesticks reported during the care of study patients. We defined a positive *clinical response* as an increase in RR of at least 6 breaths/min or improvement in the Glasgow Coma Scale (GCS) score of at least 6 points.

Between-group comparisons were accomplished using t-tests and chi-square tests as appropriate. The study was approved by the hospital institutional review board and the Central California EMS Medical Control Committee.

TABLE 1. Intranasal Naloxone Protocol from the Central California EMS Agency

Naloxone
Intranasal (IN)—Administer 2 mg intranasally (1 mg per nostril) using a mucosal atomizer device (MAD) if suspected narcotic intoxication and respiratory depression (rate 8 breaths/min or less) are present. This dose may be repeated in 5 minutes if respiratory depression persists. Respirations should be supported with BVM until the respiratory rate is >8 breaths/min.
Intramuscular (IM)—Administer 1 mg if unable to administer intranasally. May repeat once in 5 minutes.
Intravenous (IV)—Administer 1 mg via slow IV push if there is no response to intranasal or intramuscular administration after 10 minutes.
Pediatric dose—Administer 0.1 mg/kg intranasally, if the patient weighs less than 10 kg and is less than 1 year old.

BVM = bag–valve–mask; EMS = emergency medical services.

TABLE 2. Characteristics of the Study Group

	IN Naloxone	IV Naloxone	p-Value
All patients (*N*)	50	104	
Age—mean (range), years	41 (18–72)	44 (3–96)	0.21
Gender—male (%)	71%	60%	0.14
Initial GCS score—mean	6.2	6.9	0.28
Initial RR—mean, breaths/min	8.6	10.9	0.06
Initial SBP <100 mmHg (%)	10%	20%	0.11
Responders only (*n*)	33	58	
Initial GCS score—mean	5.2	5.8	0.36
Initial RR—mean, breaths/min	7.0	9.1	0.08

GCS = Glasgow Coma Scale; IN = intranasal; IV = intravenous; RR = respiratory rate; SBP = systolic blood pressure.

RESULTS

There were 154 patients during the study period who met inclusion criteria. Characteristics of the study group are reported in Table 2. Per protocol, 104 received IV naloxone as first-line therapy, and 50 received IN naloxone. Positive clinical response, as previously defined, was seen in 33 of 50 (66%) patients in the IN group and in 58 of 104 (56% patients in the IV group ($p = 0.3$). Changes in GCS score and RR in patients with a positive clinical response to naloxone are reported in Table 3.

Time intervals are reported in Fig. 1. It took longer for the IN naloxone to take effect (12.9 vs. 8.1 min, $p = 0.02$), but the total time from patient contact to

TABLE 3. Changes in Mean Glasgow Coma Scale Score and Respiratory Rate after Treatment of Positive Responders to Naloxone

	Pretreatment	Posttreatment	p-Value
Intranasal ($n = 33$)			
GCS score	5.2	13.1	0.0001
RR, breaths/min	7.0	16.9	0.0001
Intravenous ($n = 58$)			
GCS score	5.8	12.7	0.0001
RR, breaths/min	9.1	17.8	0.0001

GCS = Glasgow Coma Scale; RR = respiratory rate.

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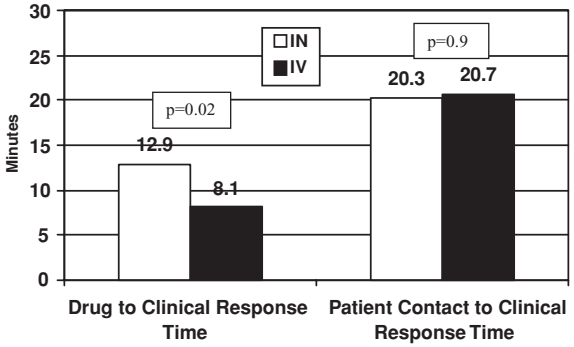

FIGURE 1. Time intervals in minutes. IN = intranasal; IV = intravenous.

clinical response was the same for the two groups (20.3 vs. 20.7 min, p = 0.9). We performed a post-hoc power calculation based on our data and found that we had a power of 83% to detect a difference of 20% (4 minutes) in the time from patient contact to clinical response.

In the IN group, 34% (17/50) of patients were given a second dose of naloxone, while in the IV group, 18% (19/104) required a second dose (p = 0.05). In addition, three patients in the IN group received a rescue dose of naloxone by an alternate route, while no patients (6% vs. 0%, p = 0.19) in the IV group received a rescue dose by another route (Fig. 2). No needlestick injuries were reported by EMS providers in either group.

DISCUSSION

We found that the administration of naloxone by the IN route is a useful alternative to the IV route in the prehospital setting. Prior to the initiation of the protocol change, there were some concerns by the medical control committee and the medics themselves regarding the efficacy of IN naloxone. However, IN administration of naloxone is now well received by our prehospital community. In addition, the EMS system has implemented protocols that utilize IN midazolam and glucagon.

There are a number of potential advantages to the IN administration of naloxone in the prehospital setting, in the emergency department, in the clinic, and even in layperson applications. IN naloxone offers a needleless alternative that may be lifesaving or spare a patient intubation if IV access cannot be quickly established. Other potential applications include clinics for drug users, rehabilitation programs, patients at home on high-dose opioids, methadone clinics, drug resource centers, or needle exchange programs. Such uses would require careful study, because it may create other problems, such as emboldening users to be more cavalier with narcotic dosing. IN naloxone could potentially be used by laypersons in emergency situations when access to health care is limited or unavailable. This has already been done with IN glucagon in diabetic patients.[8] However, one potential concern is that a false sense of security that lay rescue naloxone will cure "any case" of altered mental status could lead to harmful delays in EMS activation when the change in mental status is not secondary to narcotic intoxication.

With respect to prehospital personnel safety, body fluid exposures are a significant concern. A study done by the St. Louis EMS system reported 44 needlestick injuries in a 38-month period.[9] This equated to 145 injuries per 1,000 employee-years. Two of those employees developed clinically apparent hepatitis B during the study period. After accidental percutaneous exposure, the Centers for Disease Prevention and Control (CDC) reports a transmission rate of 1.8% for hepatitis C, 6–30% for hepatitis B, and 0.3% for HIV.[10] These statistics underscore the importance of implementing alternative methods of medication administration.

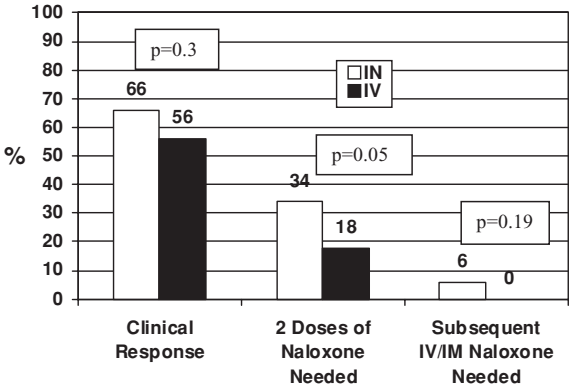

FIGURE 2. Clinical response rates (%) and rescue doses needed. IM = intramuscular; IN = intranasal; IV = intravenous.

LIMITATIONS AND FUTURE RESEARCH

There were a number of limitations to our study. First, because of the retrospective design of the study, we encountered missing data points for some patients. The time intervals we calculated were based on documentation by paramedics. The time intervals were longer than expected; however, the data-collection methods could have led to error in either direction. This observation is likely due to the fact that ongoing patient care is the top priority, and documentation frequently occurs after hospital arrival, with providers relying on memory and notes. The electronic record automatically records interactions with the dispatch

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center, such as the en route and hospital arrival times, but medication times and clinical responses are input individually. However, it seems unlikely that this type of error would bias the study results, as it presumably affected the IV and IN groups equally. Future studies in this area would be improved by accurate, real-time recording of treatment and clinical response times.

Another potential limitation is the inadvertent inclusion of cases that were not narcotic overdoses. We included all suspected cases of narcotic overdose in which paramedics treated the patient with naloxone, and we did not require confirmation of narcotics by toxicologic assays. However, the cases of misdiagnosis were likely spread equally between the two groups, thus enabling comparison without significant bias. Furthermore, our selection methodology may have missed some cases of narcotic overdose or cases in which naloxone was not administered. Although our choice to include all patients with suspected narcotic overdose per the assessment of the paramedic on scene may have resulted in some inaccuracies, it bolsters the external validity by mirroring the actual practice of prehospital medicine.

Our definition of a "positive response" to naloxone was arbitrary. We chose to define it in such a way that would represent a large, clinically significant change that was relatively objective by chart review. Although our definitions might have caused us to misclassify some responses as positive or negative, it is unlikely that the bias would favor either the IV or IN group. Also, our sample size was too small for meaningful subgroup analysis or to detect any needlesticks. Finally, we included only the more urban regions of our system, because these use an electronic record, which was used for data collection. Thus, patients in rural settings were disproportionately underrepresented. Inclusion of such patients might have altered the data in a number of ways, including more time to observe for clinical effects, establish IV access, or administer multiple doses of medication.

Conclusions

We found that although IN naloxone had a slower onset of action than the IV route, the overall time from patient contact to clinical effect was the same. Intranasal naloxone represents a more gradual and potentially safer way to reverse the effects of opioid overdose. Intranasal naloxone is a useful alternative in patients with suspected narcotic overdose in the prehospital setting and it potentially offers a decreased risk to the EMS providers caring for patients with difficult IV access and a relatively high prevalence of blood-borne pathogens.

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