Report of a Field Trial of a New Intranasal Naloxone Delivery Device

[1]Emma Furlano, M.D., [2]Emily Payne, MPH, [1]Erin Caffrey, M.D., Kim Donahue, M.D., [2]Kirsten Rowe, M.S., [2]Sharon Stancliff, M.D., [1]Heather Long, M.D., [1]Michael W. Dailey, M.D.

1. Albany Medical College, Department of Emergency Medicine
2. NYS Department of Health, AIDS Institute

Please address all correspondence to Michael W. Dailey, M.D., daileym@amc.edu
Tel. 518-262-3773

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Abstract

Objectives

The United States faces an opioid epidemic. Naloxone (NLX) is the reversal agent for opioid overdose and can be administered by community members, public safety officers, and healthcare providers alike. Opioid overdose reversal can induce withdrawal and be dangerous to both patients and treating personnel. Higher dose intranasal (IN) naloxone appears to offer advantages because of its single-step contained delivery device. We conducted an equipoise study comparing the efficacy and safety of the newer product to the standard.

Methods

Advanced life support agencies were enrolled in this field trial comparing the previous formulation (2mg/2ml) with the higher dose formulation (4mg/0.1ml). On a weekly basis they used either the 2/2 or the 4/0.1 for the first and, if indicated, second administration of NLX to suspected opioid overdoses. Patient encounters were timed. Basic statistical analysis was performed on the results. A panel of experts independently reviewed each administration to look for potential confounders, treatment errors or trends of concern.

Results

Total encounters: N = 176; 97 (4/0.1) and 79 (2/2). Populations were statistically similar. Heroin was the suspected agent in 80% of cases. There was a significant difference in mean time to first administration; 32 seconds in the 4/0.1 group and 64 seconds in 2/2 ($p<0.05$). There was no difference in number of patients that received a second dose, 42.3% patients in the 4/0.1 compared with 38.0% in the 2/2. 49.5% of patients became responsive and alert after administration of the 4/0.1 and 48.1% after administration of the 2/2. In the 4/0.1 group, 7.2% became responsive and angry and 9.3% were combative and in the 2/2 group 8.9% became responsive and angry and 3.8% combative, these differences are not statistically significant. There were no injuries and no assaultive behavior towards responders.

Conclusion

Our field trial of a single step intranasal naloxone product given by EMS providers demonstrated that 4mg/0.1ml concentrated naloxone given intranasally did not lead fewer repeat doses, or precipitous withdrawal, significantly worse experiences for patients, or injury to EMS personnel compared to 2mg/2ml.

Introduction

Opioid overdose is a public health crisis. Drug overdoses have steadily increased since the 1990s, with the percentage involving opioids representing strong majority of these events. According to CDC data, roughly 75% of the more than 106,000 drug overdoses in 2021 were attributable to opioids.[1] While the early 2000-2010s saw a shift in the opioid landscape from prescription opioids to heroin with an increase in associated overdose deaths, the introduction of synthetic opioids since approximately 2015 has created a far more potent and volatile opioid landscape. [1-3] Overdose treatment must evolve with this landscape to address this crisis in our communities.

In response to this crisis, highly successful community access and public safety opioid overdose treatment programs have been established across the country which equip and train individuals to recognize and treat suspected overdoses with naloxone.[4] Historically, two different formulations were used in these programs – naloxone 0.4mg in 1ml given intramuscularly (IM) and 2mg in 2ml given intranasally (IN). Owing to safety concerns associated with needlestick injuries and training issues for some potential responders, the intranasal route became increasingly popular and has demonstrated great success. Administration of naloxone 2mg/2ml IN via mucosal atomizer device (MAD) is standard of practice and has been deployed in New York by emergency medical services (EMS) providers since 2005, with the newer 4mg/0.1mL single step atomizer acceptable as a substitute.[5] Prior studies have attempted to determine an ideal dose and route of administration, with the data suggesting that relatively higher doses of naloxone are more frequently associated with adverse effects such as patient withdrawal and potential harm to caregivers.[6,7]

In opioid-dependent patients, rapid reversal with an opioid antagonist like naloxone can precipitate acute withdrawal, which can involve violent and aggressive behavior. In severe cases, acute opiate withdrawal may be characterized by sudden onset of adult respiratory distress syndrome, seizures and cardiac dysrhythmias.[8] One retrospective case series demonstrated that in opioid-dependent patients, IV doses of naloxone as low as 0.08 mg precipitated symptoms of withdrawal.[9] A prospective study from Norway examined adverse reaction in out-of-hospital treatment of suspected heroin overdose with naloxone. In nearly 1200 patients assessed for confusion, headache, aggression, tachycardia and seizures, this study found an adverse reaction rate of 45%.[8] While these data emphasize a very real risk for naloxone-precipitated withdrawal, newer data find that in the age of synthetic opioids, patients are found with lower initial Glasgow Coma Scale (GCS) following overdose, and require more frequent pre-hospital dosing of naloxone

to achieve a similar post-administration respiratory rate and GCS.[10] In light of these new data and the evolving opioid landscape, perhaps the higher dose, single step naloxone may be a more appropriate option for first responders if the safety profile for patients and bystanders is not significantly different.

In 2016, the State Emergency Medical Advisory Committee (SEMAC) in New York approved use of this single-step naloxone 4mg/0.lml atomizer for substitution in EMS protocols in place of the 2mg/2ml with the MAD which requires assembly and is thus a multistep product. Prior to considering statewide distribution to public safety and community responders, we conducted a field trial to test clinical equipoise between current standard naloxone, 2mg in 2ml with MAD (2/2) and this newer one step (4/0.1) naloxone product.

Methods

NYS EMS protocols allow for 2mg in 2ml IN naloxone administration at both the basic and advanced life support levels for initial intervention in cases of suspected opioid overdose where patients are hypoventilatory or in respiratory arrest. For this New York State Department of Health (NYSDOH) sponsored field trial, advanced life support agencies were enrolled to compare the current formulation (2/2) with the new formulation (4/0.1). Each agency received a supply of pre-assembled packets that included a timer, a color-coded data sheet, and one of the two naloxone formulations. Blue packets were used during odd-numbered weeks and green packets for even weeks. On a weekly basis, responders used either the 2/2 or the 4/0.1 for the first and, if indicated, the second administration of naloxone to patients with suspected opioid overdose. All providers were trained on the study procedures and on the use of the new one-step nasal spray. Care was otherwise provided as currently recommended in the state approved EMS protocols. The field trial was restricted to advanced life support agencies to ensure that if any patient went into precipitous opioid withdrawal, medical consequences would be identified and could be adequately treated in the prehospital environment. Because this was comparing a new FDA approved formulation of medication against the off-label but current standard use formulation, the field trial was determined to be exempt from the DOH Institutional Review Board (IRB). All medication administrations were reviewed by a data safety monitoring board.

Upon arrival at the scene of a suspected opioid overdose, the packet was opened, the digital timer was started, and the designated formulation removed. Timer operation was managed by the designated data collector, who recorded time and events on the provided data collection sheet. Points for data collection included an initial patient evaluation, initial responder intervention, time of first dose of study medication, and two post-medication reassessments. The initial evaluation

included qualitative assessment of responsiveness, as well as respiratory and pulse rates. Initial intervention measures included administration of verbal and/or noxious stimuli, supplemental oxygen, assisted ventilations, or CPR. Response to each intervention was observed and recorded as 'unchanged', combative', 'responsive and angry', 'responsive and alert', 'responsive but sedated', or 'unresponsive and breathing'.

After the first dose of naloxone was administered, the individual's response was again noted, and vital signs were recorded. Providers noted any adverse effects of drug administration including vomiting, seizure, diaphoresis and complaints of pain. Providers were also allowed to record the subjective adverse effect of "dope sickness" which was not defined. If at 5 minutes adequate reversal was not achieved and the patient was still hypoventilatory, a second dose of the study medication was administered by the same route. Following this, the patient would receive intravenous naloxone if indicated or otherwise managed in accordance with local protocol. Study sheets were entered into Survey Monkey (San Mateo, CA). All EMS crews that completed the survey sheet were provided with a coupon good for one large pizza in compensation for participating in the field trial. Basic statistical analysis was performed using IBM SPSS Statistics, Version 25.0. Data collection sheets were reviewed for completeness and clarification by the study coordinator and paramedics were contacted to collect missing data.

Cases were considered for exclusion if naloxone was administered prior to EMS arrival, the patient presented in cardiac arrest or there was a protocol violation. A panel of experts independently reviewed each administration record to assess for potential confounders, treatment errors or trends of concern.

Results

This field trial included six fire departments and three emergency medical agencies around northeast New York. A total of 176 forms were completed over 64 weeks, from June 2016 to August 2017. There were 79 forms submitted for the 2/2 group and 97 forms submitted for the 4/0.1 group. Five cases were excluded from the final study results. Two patients received naloxone prior to arrival of the paramedic crews. One presented as a traumatic cardiac arrest after the patient jumped from a balcony. Another patient in cardiac arrest was given naloxone after providers achieved return of spontaneous circulation after following the EMS protocols. In the last case, responders administered naloxone despite adequate respiratory effort on initial assessment and this was deemed a protocol violation and an inappropriate use of the medication.

Populations treated were very similar, there was no statistical difference in age range (mean 36 years old, SD 11) or gender (70% male) and there was no difference in initial level of responsiveness following noxious stimuli (Table 1). The mean time to first dose was significantly different between the two formulations at 1:04 minutes for the 2/2 group versus 0:32 minutes for the 4/0.1 group ($p<0.05$). However, the mean number of naloxone doses used (1.7) and mean time of response to naloxone were very similar (2:57 minutes in the 2/2 group versus 2:59 minutes in the 4/0.1 group). There was no statistical difference of response or symptoms between these groups, nor was there a difference between initial patient contact time and patient responsiveness (Table 2). After the first dose of naloxone administration, 41 of 97 (42.3%) patients received a second dose in the 4/0.1 group compared with 30 of 79 (38.0%) in the 2/2 group. This was not statistically significant.

Following the first dose of naloxone, no patients in either group were identified as "dope-sick" by EMS, beyond the noted reactions. Symptoms of opioid withdrawal were observed in both groups, including vomiting and diaphoresis. A third dose was required in 16 patients in the 4/0.1 group and 11 patients in the 2/2 group. Overall, 49.5% of patients became responsive and alert after administration of the 4/0.1 formulation and 48.1% after administration of the 2/2 formulation. While in the 4/0.1 group, 7.2% became responsive and angry and 9.3% were combative and in the 2/2 group 8.9% became responsive and angry and 3.8% combative, these differences are not statistically significant. Further investigation into the cases of combative patients revealed that they were flailing erratically without an intended target and were not directly combative to the responding providers. Heroin was the most common suspected agent in both groups (Table 3). There were no statistically significant differences in response to naloxone or symptoms between these groups.

Discussion

In an epidemic of opioid overdoses facing our communities, the availability of a safe and effective opioid reversal agent is integral to saving lives. In response to this burgeoning issue, community outreach programs across the country have worked relentlessly to educate the public and increase availability of naloxone to patients and families as well as to law enforcement, fire departments and other EMS personnel. Naloxone has now been used for decades and is demonstrated safe and effective in the community setting with thousands of lives saved. The 4mg/0.1ml naloxone device delivers twice the dose of medication delivered by the widely accepted device, and in much higher concentration, leading to blood levels over 4 times greater than IM

dosing.[11] Knowing that the opioid epidemic is also evolving, can this higher dose of naloxone be used with minimal or no adverse effects for patients or caregivers?

Based on the data collected, the 4/0.1 naloxone appears to be equivalent to the existing standard of care. There were no significant differences between the groups in terms of time from the initial naloxone dose to observed primary response. In both groups, the number of patients requiring a second dose of medication was equivalent. In addition, the difference in the rate of adverse reactions and behavioral responses was not significant. It can be concluded that either formulation can be administered safely and effectively without increased risks to patients or their caregivers.

There was a 32 second difference in the time between the initial evaluation of the patient and the administration of the first dose of naloxone between the two devices, presumably due to the assembly required for the 2/2 atomizer device. This difference was statistically significant, although likely not clinically meaningful. However, all providers had prior training and experience assembling the MAD, yet a statistically significant delay to administration was still observed. While the MAD currently in use requires proper assembly for successful drug administration, the 4/0.1 formulation is a single step delivery device that does not require assembly, conveying a time advantage. It seems likely that this time advantage would be amplified and perhaps clinically meaningful in the lay community, where prospective caregivers receive a single training on the use of the naloxone device and then attempt to locate and use it during a worst-case scenario. Regardless of the setting, avenues to minimize delay to warranted naloxone administration should be maximized.

Successful reversal efforts depend on awareness of the adverse effects of opioid medications, recognition of the signs of overdose and correct drug delivery. Owing to a relatively short half-life, naloxone can require serial dosing, a finding which was redemonstrated in the current study. Its near immediate efficacy when opioid overdose is correctly identified and treated, in conjunction with this short half-life, potentially induces a false sense of security in overdose patients. Patients who refuse medical transport following naloxone overdose are at increased risk for subsequent overdose.[12] To make matters more dire, during the COVID pandemic, patients who received naloxone in the community for overdose were more than twice as likely to refuse transport for to the hospital for further monitoring and evaluation.[13] This therefore places them at even greater risk for further overdose events in the community and need for recurrent attention and utilization of community resources. These compounded risks in the setting of an opioid landscape now hallmarked by more potent and readily available synthetic opioids make for a deadly combination.

While it is the responsibility of the medical community to mitigate the potential risk for harm, in this case as it relates to naloxone-induced withdrawal, it is also the responsibility of the

medical community to listen to its patients. A 2023 study involving 5 & 8 mg naloxone doses new to the market found that in patients receiving these doses, a combined majority had no dose preference (48%) or actually preferred the higher dose of medication (36%).[14] Although further data is needed to fully evaluate the efficacy of naloxone in reversal of these more potent agents, it seems that a majority the opioid-using community have acknowledged and are willing to assume the risks of naloxone-precipitated withdrawal in treatment of overdose, particularly when compared with the fatal alternative. The availability of the more potent and easier to administer naloxone formulation is a response to this acknowledgement, and represents an enormous potential to increase timely deployments of naloxone among public safety and untrained bystanders ultimately resulting in more lives saved.

Limitations:

While this was a prospective field trial, it was performed by experienced advanced life support (ALS) providers and not lay-persons, so the timing results for the 2/2 in particular may not be applicable to the lay public or other public safety personnel. As noted, we anticipate the assembly time and delay to drug administration would only be greater in this instance. The study design, which included weekly exchange of medication and data collection instruments was designed specifically to address public safety scheduling, with fire departments working a 24-hour, 4-day rotation. This was the simplest answer to gross randomization that could feasibly be implemented. As this was a simple field trial and not a blinded study, we recognize the potential for bias in the implementation of the intervention and the recording of data, however, medical care of overdoses is subject to continuous quality improvement. While this was supposed to be consecutive cases, there were several inadvertently missed patient contacts. When interviewed, the providers related that they wanted to titrate naloxone rather than give a large dose intranasally. This treatment was consistent with good medical care and has been encouraged as an approach to opioid overdose in the opioid dependent[5,14]. There was no consistent trend in these cases. We also acknowledge the potential Hawthorne effect from introducing the new device, or even additional patients being treated because of the pizza coupon, but there appeared to be only one over-zealous administration and there was no harm associated with it. Notably, there was also poor correlation between dispatch information and actual diagnosis – less than half of the cases where naloxone was administered were dispatched as overdose. This has been seen in previous studies and demonstrates the difficulty in collecting quality data from callers, as well as the variability in the presentation of overdoses. Oddly, over the study period there was a decreasing rate of all overdoses across the region; law enforcement, harm reduction personnel and emergency physicians have no explanation for this phenomenon. Also, while the field trial was ongoing, there

was an FDA ordered recall of specific lot numbers of the MAD for failure to atomize correctly. This may have created potential for incorrect administration because of poor atomization or even bias if providers did not use the device during the recall. As there is such little variability, this likely did not impact our results. The last important limitation is that the study is underpowered, but after the experiences over the course of 64 weeks, the results were viewed by the expert review panel as being similar enough to move forward with the addition to the formulary of the 4mg/0.1ml naloxone product and to begin issuing it to the law enforcement, basic life support and community naloxone distribution programs.

Conclusion

As the country battles the opioid epidemic, increasing access to naloxone and ongoing engagement of multiple stakeholders will be key to saving lives. Decision making around naloxone formulation selection for law enforcement, fire department and EMS agencies includes considerations of the fiscal and operational impact of a product. Our field trial demonstrated that 4mg/0.1ml naloxone given intranasally did not lead to precipitous withdrawal, significantly worse experiences for patients, or injury to EMS personnel compared to 2mg/2ml. Because of the ease of use and clinical efficacy, we believe the deployment of this product may provide significant benefit for the lay public and for agencies with less medical experience such as basic life support (BLS), fire, and law enforcement personnel.

Table 1 Initial Level of Responsiveness Following Noxious Stimuli

Response	4/0.1mg	2mg/2mL	Total
No change	73	66	139
Responsive but sedated	6	4	10
Unresponsive and breathing	12	5	17
Unresponsive and not breathing	1	2	3
Responses not recorded	5	2	7
Total	97	79	176

Pearson chi2(4) = 3.4491 Pr = 0.486

Table 2 Time Difference between Initial Intervention and Response to Naloxone

	4mg/0.1mL	2mg/2mL	Total
<1 minute	0	1	1
	0.0%	1.3%	0.6%
1-3 minutes	15	14	29
	15.5%	17.7%	26.5%
3.01-5minutes	32	21	53
	33.0%	26.6%	30.1%
5.01-10 minutes	29	17	46
	29.8%	21.5%	26.1%
10.01-15 minutes	9	11	20
	9.3%	13.9%	11.4%
15.01-20 minutes	1	0	1
	1.0%	0.0%	0.6%
>20 minutes	2	1	3
	2.1%	1.3%	1.7%
No response to naloxone	9	14	23
	9.3%	17.7%	13.1%
Total	97	79	176
	100%	100%	100%

Pearson chi2(7) = 7.3037 Pr = 0.398

Table 3 Suspected Ingestion

Illicit Substance	4mg/0.1mL	2mg/2mL	Total
Alcohol	7.4	6.7	7.1
Benzodiazepine/Barbiturate	4.2	4.0	4.1
Buprenorphine/Suboxone	2.1	4.0	2.9
Cocaine/Crack Cocaine	5.	4.0	4.7
Heroin	80	77.3	78.8
Methadone	0	1.3	0.6
Pain Pills	7.4	6.7	7.1
Unknown Injection	1.1	2.7	1.8
Unknown Pills	5.3	5.3	5.3
Did not know	4.2	8.0	5.9
Other	16.8	8.0	12.9
Answered	98.0	94.9	96.6
Did not Answer	2.0	5.1	3.4

†Percent of responses within each group

† Responses are not mutually exclusive. Therefore, percentages may not total 100%.

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