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Comparison of the Pharmacokinetic Properties of Naloxone Following the Use of FDA-Approved Intranasal and Intramuscular Devices Versus a Common Improvised Nasal Naloxone Device

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Abstract

For more than a decade, first responders and the general public have been able to treat suspected opioid overdoses using an improvised nasal naloxone device (INND) constructed from a prefilled syringe containing 2 mg of naloxone (1 mg/mL) attached to a mucosal atomization device. In recent years, the U.S. Food and Drug Administration (FDA)–approved Ezvio, an autoinjector that delivers 2 mg by intramuscular injection and Narcan nasal spray (2- and 4-mg strengths; 0.1 mL/dose) for the emergency treatment of a known or suspected opioid overdose. The present study was conducted to compare the pharmacokinetics of naloxone using the FDA-approved devices (each administered once) and either 1 or 2 administrations using the INND. When naloxone was administered twice using the improvised device, the doses were separated by 2 minutes. The highest maximum plasma concentration was achieved using the 4-mg FDA-approved spray. The highest exposures at 5 minutes postdose, based on AUC values, were after administration with the autoinjector and the 4-mg FDA-approved spray; at 10, 15, and 20 minutes postdose, the latter yielded the greatest exposure. Even after 2 administrations, the INND failed to achieve naloxone plasma levels comparable to the FDA-approved devices at any time. The ease of use and higher plasma concentrations achieved using the 4-mg FDA-approved spray, compared with the INND, should be considered when deciding which naloxone device to use.

Keywords

intranasal, naloxone, opioid overdose, pharmacokinetics

Deaths from opioid overdoses have increased substantially over the last 20 years. Of the 60 000 opioid-related deaths in 2017 in the United States, 14 958 were because of natural and semisynthetic opioids, 15 958 were because of heroin, and 29 406 because of synthetic opioids, much of which was fentanyl.[1] Fentanyl, which is approximately 50- to 100-fold more potent than morphine on the mu-opioid receptor,[2,3] is being detected in an increasing percentage of overdose cases and found in other recreational drugs such as methamphetamine and cocaine.

Naloxone (17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one HCl) is a high-affinity opiate receptor antagonist that has been used by the parenteral route of administration to treat the symptoms of opioid overdose for more than 40 years.[4] An increasing number of government jurisdictions have endorsed the use of naloxone for intranasal administration by nonmedical personnel, such as police and the general public population, to treat opioid overdoses.[4,5] An improvised nasal naloxone device (INND), consisting of a prefilled naloxone syringe intended for parenteral use attached to a mucosal atomization device, was first described in 1994.[6] Since then, it has often been prepared by pharmacists, dispensed to patients, and provided to first responders, either with an individual physician's prescription or with a standing order authorizing dispensing by pharmacies. The INND has not been approved for use by the U.S. Food and Drug Administration (FDA).

In recent years, the FDA has approved 2 types of devices that can be used by nonmedical personnel for

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the administration of naloxone. Evzio, approved in April 2014, is an autoinjector for intramuscular injection of 2 mg of naloxone that gives audible instructions for its use. The initial approval was for administration of 0.4 mg in 0.4 mL, but subsequent approval was for a 2-mg dose in the same volume; the lower-dose autoinjector was withdrawn from the market. Narcan devices for nasal administration of 4 and 2 mg of naloxone in 0.1 mL (hereafter referred to as FDANxSpray) were approved by the FDA in November 2015 and January 2017, respectively. As of the time of this writing, only the 4-mg product is available; the manufacturer has not marketed the 2-mg product and has no current plans to launch it (personal communication, Fintan Keegan, Adapt Pharma).

The present study was designed to directly compare the pharmacokinetics (PK) of the FDA-approved naloxone devices and the INND. This study was also designed to compare the PK of naloxone following 1 and 2 administrations of the INND with repeated doses separated by the recommended time of 2-3 minutes. It was hypothesized that because of the large volume of fluid (2 mL) and incomplete absorption prior to the second dose, 2 administrations using the INND would not yield a substantial increase in the naloxone C_{max} compared with a single administration.

Methods

Study Participants

The study protocol was approved by the MidLands Independent Review Board (Overland Park, Kansas), and all participants gave written informed consent before participation. The study site was Vince & Associates Clinical Research (Overland Park, Kansas), and the study was conducted in accordance with the International Conference on Harmonization for Good Clinical Practices guidelines.[7] This trial was registered as NCT03386591 (www.clinicaltrials.gov).

Healthy volunteers of both sexes aged 18-55 years with body mass index of 18-32 kg/m^2 participated in this study. Participants were not taking either prescription or over-the-counter medications, and they were either nonsmokers or they smoked 20 or fewer cigarettes per day. Screening procedures conducted within 21 days of study initiation included the following: medical history, physical examination, evaluation for evidence of nasal irritation or nasal symptoms, 12-lead electrocardiogram, complete blood count, clinical chemistry, coagulation markers, hepatitis and human immunodeficiency screening, urinalysis, and urine drug screen. Female participants were tested for pregnancy at screening and admission to the clinic. Participants were excluded if they had either abnormal nasal anatomy or nasal symptoms, an upper respiratory tract infection, used opioid analgesics for pain relief within the previous 14 days, or, in the judgment of the investigator, had significant acute or chronic medical conditions.

Study Design

The study was an inpatient, open-label, randomized, 5-period, 5-treatment crossover study. Participants were randomly assigned to 1 of 5 sequences to ensure at least 6 participants in each sequence. On the day after clinic admission, participants were administered the study drug in randomized order with a 2-day washout period between doses. Participants remained in the clinic for 10 days until all 5 treatments were administered; they were contacted by telephone 3 to 5 days later as a follow-up. Participants were required to abstain from alcohol from admission to the end of the last blood draw of the study and from nicotine- and caffeine-containing products for at least 1 hour prior to and 2 hours after dose administration. Participants fasted overnight from midnight the day prior to until 4 hours after dose administration.

On days of dosing, a participant's vital signs were required to be within the acceptable range before receiving naloxone, defined as systolic blood pressure < 160 mm Hg and diastolic blood pressure < 100 mm Hg. Each participant received each of the following treatments according to the randomization scheme:

Treatment A — 2 mL of naloxone of a 1 mg/mL solution (one 1-mL spray in each nostril) at 0 minutes using the INND;
Treatment B — 2 mL of naloxone of a 1 mg/mL solution (one 1-mL spray in each nostril) at 0 and 2 minutes using the INND;
Treatment C — 2 mg of naloxone intranasally at 0 minutes using the 2-mg FDANxSpray (0.1 mL of a 20 mg/mL solution);
Treatment D — 4 mg of naloxone intranasally at 0 minutes using the 4-mg FDANxSpray (0.1 mL of a 40 mg/mL solution);
Treatment E — 2 mg of naloxone intramuscularly at 0 minutes using the autoinjector (0.4 mL of a 5 mg/mL solution).

Intransal naloxone dosing was administered in the supine position, and participants remained in this position for approximately 1 hour after dosing. Participants were instructed not to breathe when the drug was administered to simulate an opioid overdose of a person in respiratory arrest. The nasal passage was examined by medical personnel for irritation using a 6-point scale at predose and at 5 minutes and 0.5, 1, and 4 hours postdose. Nasal irritation was scored as follows: 0, normal-appearing mucosa, no bleeding; 1, inflamed mucosa, no bleeding; 2, minor bleeding that stops within 1 minute; 3, minor bleeding taking 1 to 5 minutes to stop; 4, substantial bleeding for 4

to 60 minutes, does not require medical intervention; and 5, ulcerated lesions, bleeding that requires medical intervention. The intramuscular injection was into the anterolateral aspect of the thigh, as indicated in the package instructions. Twelve-lead electrocardiograms were performed predose and 1 and 8 hours postdose. Venous blood samples were collected for the analyses of plasma naloxone concentrations predose and 3, 5, 10, 15, 20, 30, 45, and 60 minutes and 2, 3, 4, 6, 8, and 12 hours postdose using Vacutainer tubes containing sodium heparin. The plasma was stored at −60°C until analyzed.

Study Drugs

Naloxone HCl, USP for injection, 2 mg/mL, in Leuer-Jet prefilled syringes (International Medication Systems, Ltd, South El Monte, California), LMA mucosal atomization devices (Teleflex, Morrisville, North Carolina), 2-mg autoinjectors (kaleo, Inc., Richmond, Virginia), and 4-mg FDANxSpray devices (Adapt Pharma, Radnor, Pennsylvania) were purchased from commercial sources. The 2-mg FDANxSpray devices were generously provided by Adapt Pharma. Each INND was constructed by attaching a mucosal atomization device to a prefilled syringe.

Analytical Methods

Plasma naloxone concentrations were determined using a validated liquid chromatography-tandem mass spectrometry assay as detailed in Krieter et al.[8] The calibration curves (peak area ratios) were linear ($r^2 > 0.980$) over the concentration range of 0.01 to 10 ng/mL, and the lower limit of quantitation was 0.01 ng/mL. The interday precision of the calibration curves and quality control samples ranged from 2.21% to 4.66%, and the accuracy ranged between -3.88% and 1.50% during the analysis of the samples.

Data Analyses

The safety population included all participants who received at least 1 dose of naloxone; the PK population included all participants who completed all 5 dosing periods with sufficient data to calculate meaningful PK parameters. PK parameters were calculated using standard noncompartmental methods and a validated installation of WinNonlin Phoenix, version 6.3 (Pharsight Corp., Mountain View, California). Values of peak plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were the observed values obtained directly from the concentration-time data. The terminal elimination half-life ($t_{½}$) was estimated by linear regression analysis. The area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}t}$) was determined by the linear up/log down trapezoidal method and extrapolated to infinity (AUC) by adding the value of the last quantifiable concentration divided by the terminal rate constant. The extrapolated percentage of AUC was less than 20% for all concentration profiles; therefore, only AUC is reported. The apparent total clearance (CL/F) was calculated as the dose (D) divided by AUC. Within an analysis of variance framework, comparisons of ln-transformed, dose-normalized PK parameters were performed using a mixed-effects model in which sequence, period, and treatment were the independent factors. The 90% confidence interval (CI) for the ratio of the geometric least-squares means of C_{max} and AUC were constructed for comparison of the 4 intranasal treatments with the intramuscular formulation. The 90%CIs were obtained by exponentiation of the 90%CIs for the differences between the least-squares means based on an ln scale.

Table 1. Participant Demographics

	All	Female	Male
N	30	13	17
Age (years), mean (range)	33.7 (19–55)	30.3 (19–54)	36.2 (19–55)
Race			
White	12	3	9
Black/African American	17	9	8
Native American	1	1	0
Ethnicity			
Hispanic or Latino	2	2	0
Not Hispanic or Latino	28	11	17
Weight (kg), mean (range)	77.7 (50.3–109.6)	68.2 (50.3–79.7)	85.0 (61.8–110)
BMI (kg/m^2), mean (range)	26.6 (19.7–31.9)	26.0 (19.7–31.9)	27.1 (21.5–31.4)

BMI, body mass index.

Results

Participant Characteristics

Seventeen male and 13 female participants received at least 1 dose of naloxone (Table 1), and 27 of the 30 participants completed the study. One female participant discontinued for personal reasons after the second treatment period, and another female participant was removed from the study after the first treatment period because of an episode of mild syncope during blood draws. A male participant was removed after the second period because of disruptive behavior.

Pharmacokinetics

C_{max} was highest after intranasal administration of 4 mg of naloxone using the 4-mg FDANxSpray device (5.9 ng/mL; Table 2). It was similar when 2 mg of naloxone was administered using the autoinjector and the 2-mg FDANxSpray device (3.8 and 3.6 ng/mL, respectively) and lowest when 2 and 4 mg was given

Table 2. Pharmacokinetics of Naloxone in Healthy Participants After Administration Using the INND, the 2-mg and 4-mg FDANxSpray Devices, and the Autoinjector

Parameter (Units)[a]	One Dose INND 2 mg Intransally (Treatment A)		Two Doses INND 4 mg Intranasally[b] (Treatment B)		2-mg FDANxSpray Intranasally (Treatment C)		4-mg FDANxSpray Intranasally (Treatment D)		Autoinjector 2 mg Intramuscularly (Treatment E)	
C_{max} (ng/mL)	1.4	(45.4)	2.3	(36.7)	3.6	(42.6)	5.9	(34.3)	3.8	(33.4)
C_{max}/D (ng/mL/mg)	0.8	(45.4)	0.6	(36.7)	2.0	(42.6)	1.6	(34.3)	2.1	(33.4)
T_{max} (h)	0.3	(0.1–0.8)	0.3	(0.2–0.8)	0.3	(0.2–0.8)	0.3	(0.2–1.0)	0.5	(0.1–3.0)
AUC (ng·min/mL)	125	(27.2)	214[c]	(23.9)	329[d]	(22.1)	583	(29.5)	532	(18.5)
AUC /D (ng·min/mL/mg)	69.0	(27.2)	59.3[c]	(23.9)	183[d]	(22.1)	162	(29.5)	296	(18.5)
$AUC_{0\text{-}5\ min}$ (ng·min/mL)	0.7	(133)	0.8	(67.9)	1.2	(131)	2.0	(111)	2.6	(84.4)
$AUC_{0\text{-}10\ min}$ (ng·min/mL)	4.0	(81.8)	5.4	(52.1)	8.8	(80.3)	12.8	(72.7)	12.3	(55.2)
$AUC_{0\text{-}20\ min}$ (ng·min/mL)	16.0	(55.3)	23.5	(44.4)	37.3	(60.4)	55.4	(49.3)	43.0	(41.4)
$t_{½}$ (h)	1.5	(40.3)	2.2[c]	(36.9)	1.5[d]	(33.5)	2.2	(38.2)	1.4	(18.4)
CL/F (L/h)	866	(27.2)	1010[c]	(23.9)	328[d]	(22.1)	370	(29.5)	203	(18.5)

%CV, percent coefficient of variation; AUC, area under the plasma concentration-time curve from time zero to infinity; $AUC_{0\text{-}5\ min}$, AUC from time zero to 5 minutes; $AUC_{0\text{-}10\ min}$, AUC from time zero to 10 minutes; $AUC_{0\text{-}20\ min}$, AUC from time zero to 20 minutes; CL/F, apparent clearance; C_{max}, maximum plasma concentration; $t_{½}$, terminal half-life; T_{max}, time to C_{max}; relative BA, bioavailability relative to intramuscular injection; INND, improvised nasal naloxone device.
n = 27.
[a]Geometric mean values (%CV) for all except T_{max}, which is median (minimum, maximum).
[b]Second dose using INND administered 2 minutes after the first dose.
[c]n = 21.
[d]n = 26.

Table 3. Statistical Summary of Naloxone Treatment Comparisons (Intranasal Versus Intramuscular Administration)

Parameter	Intranasal Administration (Test)	Comparison (E as Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90%CI for Ratio
C_{max}/dose	INND 2 mg × 1 IN (treatment A)	A vs E	37.2	32.1–43.0
	INND 2 mg × 2 IN (treatment B)	B vs E	29.6	25.5–34.2
	2 mg FDANxSpray IN (treatment C)	C vs E	93.2	80.6–108
	4 mg FDANxSpray IN (treatment D)	D vs E	76.4	66.0–88.4
AUC /dose	INND 2 mg IN (treatment A)	A vs E	23.3	21.2–25.7
	INND 2 mg × 2 IN (Trt B)	B vs E	19.6	17.7–21.8
	2 mg FDANxSpray IN (treatment C)	C vs E	61.7	56.0–68.0
	4 mg FDANxSpray IN (treatment D)	D vs E	54.6	49.7–60.1

AUC/dose, AUC per milligram of naloxone administered; C_{max}/dose, C_{max} per milligram of naloxone administered; CI, confidence interval; INND, improvised nasal naloxone device; IN, intranasally.
[a]Geometric least-squares mean ratio between treatments, expressed as a percentage of reference (treatment E, 2 mg intramuscularly using an intramuscular 2-mg autoinjector device).

by 1 and 2 intranasal doses using the INND (1.4 and 2.3 ng/mL, respectively). The median T_{max} value was 20 minutes for all the intranasal doses and slightly longer after the intramuscular dose. The elimination half-life of naloxone ranged between 1.4 and 2.2 hours.

Values of AUC were approximately the same when 2 mg of naloxone was given by the autoinjector and when 4 mg of naloxone was administered by the 4-mg FDANxSpray device. Values of AUC were lowest after 2 or 4 mg of naloxone was delivered by the INND. When the dose of naloxone was considered, both C_{max}/D and AUC/D were highest for the intramuscular dose (2.1 ng/mL/mg and 296 ng·min/mL/mg) and lowest for the 1 and 2 doses using the INND. The relative bioavailability of intransal naloxone compared with the intramuscular dose was 54%–62% for FDANxSpray spray devices and 19%–23% using the INND (Table 3).

Because quick absorption of naloxone is important in reversing respiratory depression in persons who have overdosed on an opioid, Table 2 includes the AUC during the first few minutes after naloxone administration. Exposure during the first 5, 10, and 20 minutes was approximately 2- to 3-fold higher using either the 2- and 4-mg FDANxSpray device or the autoinjector compared with exposure following use of the INND. Higher mean concentrations were apparent after only 5 minutes when naloxone was administered using any of the 3 FDA-approved devices compared with either 1 or 2 doses using the INND (Figure 1).

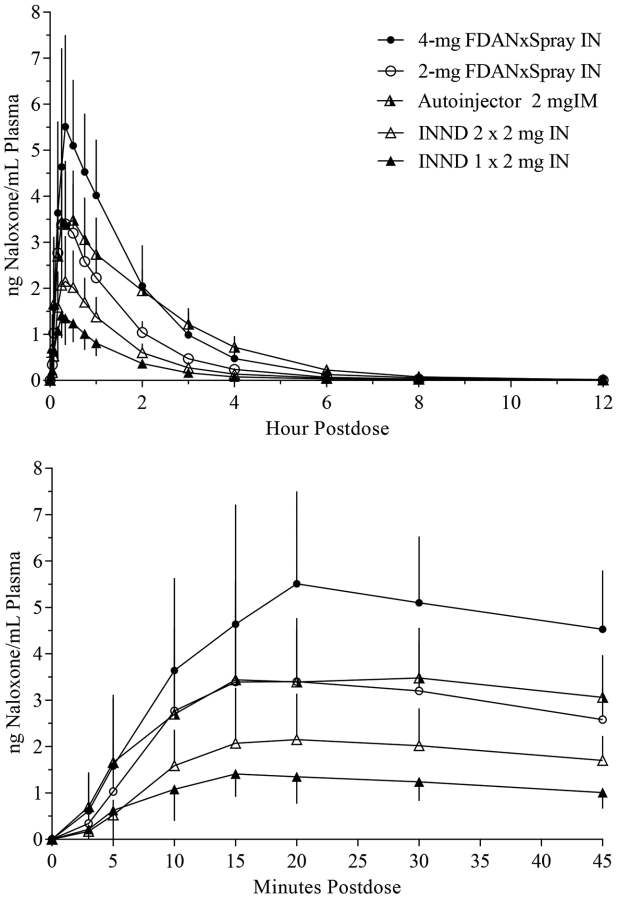

Figure 1. Mean ± SD plasma concentrations of naloxone in healthy participants using the INND, 2- and 4-mg FDANxSpray devices, and the autoinjector. Naloxone was administered intranasally either once (at time zero) or twice (at zero and 2 minutes) using the INND. Naloxone was administered only once (at time zero) using the nasal spray devices and intramuscular autoinjector. The bottom panel displays the mean plasma concentrations during the first 45 minutes after administration.

There were no clinically relevant differences in the pharmacokinetic parameters of naloxone because of sex (Table 4).

Safety

A total of 8 treatment-related adverse events were reported by the participants; all were mild and resolved quickly. There were 2 instances each of dizziness and headache.

Discussion

To reverse an opioid overdose, the plasma concentration of naloxone needs to achieve an adequate concentration quickly after administration. The dose of naloxone necessary for a reversal is because of a number of variables, such as duration of effect, the specific potency and type of opioid consumed, the route of administration, any other ingested drugs, and the patient's underlying opioid tolerance.[9]

Table 4. Pharmacokinetics of Naloxone in Female and Male Participants After Administration Using the INND, Nasal Spray 2-mg, and Nasal Spray 4-mg Nasal Spray Devices, and Intramuscular 2-mg Autoinjector

	INND 1 × 2 mg Intramuscularly (Treatment A)				INND 2 × 2 mg Intranasally (Treatment B)				2-mg FDANxSpray Intranasally (Treatment C)				4-mg FDANxSpray Intranasally (Treatment D)				Autoinjector 2 mg Intramuscularly (Treatment E)			
Parameter (Units)[a]	Female		Male		Female		Male		Female		Male		Female		Male		Female		Male	
C_{max} (ng/mL)	1.5	(30.2)	1.4	(55.0)	2.4	(19.8)	2.2	(45.9)	3.7	(44.5)	3.6	(42.7)	5.0	(24.0)	6.6	(35.8)	4.7	(27.0)	3.3	(29.7)
T_{max} (h)	0.3	(0.2–0.5)	0.3	(0.1–0.8)	0.3	(0.3–0.5)	0.3	(0.2–0.8)	0.3	(0.2–0.8)	0.3	(0.2–0.8)	0.5	(0.3–0.8)	0.3	(0.2–1.0)	0.5	(0.1–0.8)	0.5	(0.1–3.0)
AUC (ng·min/mL)	130	(19.8)	122	(31.8)	209	(16.6)	217	(28.1)	343	(21.8)	320	(22.7)	551	(36.9)	606	(23.8)	606	(14.3)	487	(15.7)
$t_{½}$ (h)	1.3	(16.5)	1.7	(48.1)	2.0	(37.9)	2.3	(36.1)	1.4	(27.4)	1.6	(37.6)	2.0	(39.3)	2.2	(38.3)	1.4	(10.4)	1.5	(22.3)
CL/F (L/h)	834	(19.8)	889	(31.8)	1040	(16.6)	997	(28.1)	315	(21.8)	338	(22.7)	392	(36.9)	356	(23.8)	179	(14.3)	222	(15.7)

%CV, percent coefficient of variation; AUC, area under the plasma concentration-time curve from time zero to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; $t_{½}$, terminal half-life; T_{max}, time to C_{max}; INND, improvised nasal naloxone device; relative BA, bioavailability relative to intramuscular injection.
n = 16 male and 11 female participants.
[a]Mean values (%CV) for all except T_{max} which is median (minimum, maximum)

Although an intravenous dose is the fastest means of achieving a high plasma concentration, the general public and many first responders such as police are not trained or equipped to administer naloxone intravenously. Loimer et al were the first to show that nasal administration of naloxone can be effective.[6] It can buy time while waiting for the arrival of trained medical personnel. Intranasal administration, which does not involve needles, is an advantage in the view of many individuals.[4] The prevalence in the last few years of fentanyl and other potent synthetic opioids, though, may require multiple administrations of naloxone to achieve reversal of an overdose.[10]

In Massachusetts during the first half of 2016, 74% of opioid overdose deaths involved fentanyl.[11] Of 64 persons who were trained by the Massachusetts Department of Public Health to use the INND, 75% reported witnessing, giving, or receiving administration of naloxone to successfully reverse an opioid or fentanyl overdose between October 2015 and April 2016. Of these events, 83% reported that 2 or more doses of naloxone using the INND per suspected fentanyl overdose were used before the person responded. In a retrospective study of 2166 patients treated by paramedics in New Jersey from 2014 to 2016 for a suspected opioid overdose, 91% experienced complete resolution of symptoms with a single dose of naloxone using an INND and 9% needed a second dose, generally by the intravenous route.[12]

Training is needed to understand how to assemble and use the INND, and even with training, there is a 45% failure rate in its use by the public.[13] A portion of the naloxone solution delivered using the device may be lost dripping down the nasopharynx or externally from the nose because of the introduction of a 1-mL solution into each naris. The optimum volume for nasal delivery is approximately 0.10 to 0.15 mL.[14] Approximately 90% of subjects in human use studies could use correctly either the autoinjector or the FDANxSpray device without any training.[8,13]

Previous data on the PK of naloxone following a single use of the INND were reported in a patent, but study details were minimal.[15] The results of the present study show that even with a second administration using the INND, maximum plasma concentrations were 60% less compared with the 4-mg FDANxSpray device. Previous PK data for the autoinjector can be found in the product label.[16] The current study was designed as a direct within-subject comparison of the FDA-approved devices and the INND.

The comparatively low plasma levels of naloxone observed following multiple administrations of the INND are a cause for concern. The use of fentanyl and its analogues, whether intended or unintentional,[17] necessitates rapid attainment of higher concentrations after it is determined that the person may have overdosed on an opioid. Because fentanyl has a fast onset,[11] the need to act in an expeditious manner has become more urgent. The ease of use[8] and higher plasma concentrations using the 4-mg FDANxSpray device compared with the INND should be considered when deciding which naloxone device to use. The likelihood that extreme overdoses with fentanyl, carfentanil, and related compounds may require even higher plasma concentrations of naloxone for reversal suggests there is merit in developing new products with similar ease of use that deliver higher and/or multiple doses of naloxone.

Declaration of Conflicting Interests

None of the authors have any disclosures.

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Data Sharing

For data sharing, please contact the corresponding author.

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