The Journal of Clinical Pharmacology
2016, 00(0) 1–11

DOI: 10.1002/jcph.759

Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose

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Abstract

Parenteral naloxone has been approved to treat opiate overdose for over 4 decades. Intranasal naloxone, administered "off label" using improvised devices, has been widely used by both first responders and the lay public to treat overdose. However, these improvised devices require training for effective use, and the recommended volumes (2 to 4 mL) exceed those considered optimum for intranasal administration. The present study compared the pharmacokinetic properties of intranasal naloxone (2 to 8 mg) delivered in low volumes (0.1 to 0.2 mL) using an Aptar Unit-Dose device to an approved (0.4 mg) intramuscular dose. A parallel study assessed the ease of use of this device in a simulated overdose situation. All doses of intranasal naloxone resulted in plasma concentrations and areas under the curve greater than those observed following the intramuscular dose; the time to reach maximum plasma concentrations was not different following intranasal and intramuscular administration. Plasma concentrations of naloxone were dose proportional between 2 and 8 mg and independent of whether drug was administered to 1 or both nostrils. In a study using individuals representative of the general population, >90% were able to perform both critical tasks (inserting nozzle into a nostril and pressing plunger) needed to deliver a simulated dose of naloxone without prior training. Based on both pharmacokinetic and human use studies, a 4-mg dose delivered in a single device (0.1 mL) was selected as the final product. This product can be used by first responders and the lay public, providing an important and potentially life-saving intervention for victims of an opioid overdose.

Keywords

intranasal, naloxone, opioid overdose, pharmacokinetics, Narcan® Nasal Spray

Opioid overdose is a serious and evolving public health problem in the United States.[1,2] Thus, more than 28,000 overdose deaths[3] and 750,000 annual emergency department visits[4] have been attributed to prescription opioids (eg, oxycodone, methadone) and heroin. Although the introduction of abuse deterrent formulations has apparently stabilized the death rate due to prescription opioids, an unintended consequence has been a dramatic rise in the rate of heroin-induced fatalities.[1,5] As part of a comprehensive effort to limit opioid-induced fatalities, multiple government agencies[6] have endorsed wider access to naloxone (17-allyl-4,5α-epoxy-3,14-dihyroxymorphinan-6-one HCl), a high-affinity opiate receptor antagonist that has been used to treat the symptoms of opioid overdose, including respiratory depression, for over 40 years.[7,8]

Naloxone has been approved by the US Food and Drug Administration (FDA) for parenteral administration, but in an attempt to reduce the morbidity and mortality associated with opioid overdose, there has been a dramatic increase in its off-label use by the intranasal (IN) route.[9–11] Although most morbidity and mortality incidents are the result of accidental overdose involving prescription opioids,[12] the distribution of improvised IN naloxone "kits" has largely been confined to individuals with opiate (eg, heroin) use disorders at high risk of overdose, the friends and family of these individuals, and first responders.[10] These improvised IN naloxone kits generally consist of 1 or 2 prefilled syringes, each containing 2 mL of naloxone HCl (1 mg/mL) and a mucosal atomizing device. Individuals

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Submitted for publication 26 February 2016; accepted 27 April 2016.

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administering the naloxone are instructed to give half a vial, or 1 mL, in each nostril (for a total dose of 2 mL); a second dose can be administered if the patient has not responded to the first dose.[9,10] Despite multiple reports describing the effectiveness of using these improvised intranasal devices in reversing opiate overdose,[9–11,13,14] a high error rate has been associated with both kit assembly and proper IN administration, even in individuals receiving training.[15] Moreover, it is not known if the pharmacokinetic (PK) properties of naloxone produced by these improvised IN devices are equivalent to the approved dose of parenterally administered naloxone. Here, we describe the PK properties and usability profile of an IN naloxone HCl formulation delivered in low volume (0.1 mL) that was recently approved by the FDA for the treatment of opioid overdose.

Methods

Pharmacokinetic Study

Study Participants. The PK study was approved by the MidLands Independent Review Board (Overland Park, Kansas); all subjects gave written informed consent before participation. The study was carried out in accordance with the International Conference on Harmonisation for Good Clinical Practices guidelines.[16] This trial was registered as NCT02572089 (www.clinicaltrials.gov).

Male and female volunteers aged 18 to 55 years with body mass index (BMI) 18 to 30 kg/m^2 participated in the PK study. Subjects were currently not taking either prescription or over-the-counter medications; nonsmokers and subjects who smoked 20 or fewer cigarettes per day were enrolled. Screening procedures conducted within 21 days of study initiation included the following: medical history, physical examination, evidence of nasal irritation, 12-lead electrocardiogram, complete blood count, clinical chemistry, coagulation markers, hepatitis and human immunodeficiency screening, urinalysis, and urine drug screen. Female subjects were tested for pregnancy at screening and admission to the clinic. Subjects were excluded if they had either abnormal nasal anatomy or 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. Subjects were required to abstain from grapefruit juice and alcohol from 72 hours prior to admission to the end of the last blood draw of the study and from nicotine- and caffeine-containing products and food for at least 1 hour prior to and 2 hours after dose administration. On days of dosing, a subject's vital signs were required to be within the normal range before administration of naloxone, defined as systolic blood pressure >90 mm Hg and ≤140 mm Hg; diastolic blood pressure >55 mm Hg and ≤90 mm Hg; resting heart rate >40 beats per minute (bpm) and ≤100 bpm; and respiratory rate >8 respirations per minute (rpm) and ≤20 rpm.

Study Design. The PK study was an inpatient, open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study conducted at Vince & Associates Clinical Research (Overland Park, Kansas). Subjects were randomly assigned to 1 of the 5 sequences to ensure at least 6 subjects in each sequence. On the day after clinic admission, participants were administered the study drug in randomized order with a 4-day washout period between doses. Subjects remained in the clinic for 19 days until all 5 treatments were administered and returned 3 to 5 days after discharge for a follow-up visit. Subjects were fasted overnight before each dosing day and received 1 of the following 5 treatments:

A. 2 mg naloxone IN (a single 0.1-mL spray of the 20 mg/mL formulation in 1 nostril)
B. 4 mg naloxone IN (a single 0.1-mL spray of the 20 mg/mL formulation in each nostril)
C. 4 mg naloxone IN (a single 0.1-mL spray of the 40 mg/mL formulation in 1 nostril)
D. 8 mg naloxone IN (a single 0.1-mL spray of the 40 mg/mL formulation in each nostril)
E. 0.4 mg naloxone IM (1.0 mL of the 0.4 mg/mL naloxone HCl for injection in the gluteus maximus)

These doses were chosen based on a pilot study using 2 mg and 4 mg naloxone delivered in low volumes (0.1-0.2 mL) with a different device (data not shown). The IN devices were coded so that neither the staff nor the subjects knew the concentration of naloxone solution administered. IN naloxone was administered in the supine position, and subjects remained in this position for approximately 1 hour after dosing. Subjects were instructed not to breathe when the drug was administered to simulate an opioid overdose with a patient 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, 4, and 24 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). Twelve-lead ECGs were collected predose and at 1 hour and 6 hours postdose. Venous blood samples were collected for the analyses of plasma naloxone concentrations predose and at 2.5, 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, 360, 480, and

720 minutes postdose using Vacutainer® tubes containing sodium heparin. The plasma was stored at –20°C until analyzed.

Study Drugs. Naloxone HCl powder (cGMP grade, 99.8% purity) was purchased from Mallinckrodt (St. Louis, Missouri); naloxone HCl for injection was manufactured by Hospira, Inc (Lake Forest, Illinois). Nasal devices (Aptar Unit-Dose device for liquids, Louveciennes, France) were supplied by Lightlake Therapeutics, Inc (New York, New York). The devices, containing naloxone HCl concentrations of 20 mg/mL and 40 mg/mL, were manufactured by DPT Laboratories, Ltd (Lakewood, New Jersey) and delivered a volume of 0.1 mL.

Analytical Methods. Plasma naloxone concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Plasma samples (0.2 mL) were added to individual wells of a 96-well plate along with 0.05 mL methanol:water (3:7) containing the internal standard (0.1 ng naloxone-d_5) and 0.2 mL 1 M potassium phosphate (pH 7.2). After vortex mixing, the plate was loaded onto a preconditioned 96-well SPE plate and washed sequentially with 0.1% formic acid, acetonitrile, and dichloromethane:isopropanol (8:2). Naloxone was eluted with dichloromethane/isopropanol (8:2) containing 2% ammonium hydroxide to a new 96-well plate. After evaporation, the residue was reconstituted in 0.2 mL methanol:water (9:1) and submitted to LC-MS/MS analysis. Naloxone was analyzed using an AB MDS Sciex API-5000 LC-MS/MS system (Framingham, Massachusetts) with an atmospheric pressure chemical ionization source operated in the positive ion mode. The mobile phase consisted of a gradient increasing from 60% mobile phase A (0.04% ammonium hydroxide):40% mobile phase B (methanol:acetonitrile, 1:1) to 20% A/80% B with a flow rate of 0.4 mL/min through a 50×2.1 mm XBridge C18 column. Naloxone eluted at approximately 2 minutes. Ions monitored were m/z 328.3 and 212.1 for naloxone and m/z 333.3 and 212.1 for the internal standard. The calibration curves (peak area ratios) were linear ($r^2 > 0.980$) over the concentration range of 10.0 pg/mL to 10 ng/mL; the lower limit of quantitation (LLOQ) was 10.0 pg/mL. The interday precision of the calibration curves and quality control samples ranged from 2.1% to 7.9%, and the accuracy ranged between –2.4% and 3.8% during the analysis of the samples.

Data Analyses. The safety population included all subjects who received at least 1 dose of naloxone; the PK population included all subjects who received at least 1 dose of naloxone 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, St. Louis, Missouri). Values of peak plasma concentrations (C_{max}) and the 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 0 to the last quantifiable concentration ($AUC_{0\text{-}t}$) was determined by the linear trapezoidal method and extrapolated to infinity ($AUC_{0\text{-}\infty}$) by adding the value of the last quantifiable concentration divided by the terminal rate constant (λ_z). The extrapolated percentage of $AUC_{0\text{-}\infty}$ was less than 20% for all concentration profiles; therefore, only $AUC_{0\text{-}\infty}$ is reported. The apparent total body clearance (CL/F) was calculated as the dose divided by $AUC_{0\text{-}\infty}$. PK comparisons were performed using a mixed-effects model in which sequence, period, and treatment were independent factors. Dose proportionality for all IN doses of naloxone was accessed using C_{max} and $AUC_{0\text{-}\infty}$ parameters. In this analysis the mixed-effects power model $[\ln(PK) = \beta 0 + \eta_i + \beta 1 \times \ln(Dose) + \varepsilon_{ij}]$ was used, and 90% confidence intervals (90%CI) were constructed for the ratio of the dose-normalized geometric mean values (R_{dnm}) of the parameters.[17] All analyses of demographic and safety data were performed using SAS® statistical software, version 9.3 (SAS Institute, Inc, Cary, North Carolina).

Human Factors and Usability Studies

Study Participants. The study was reviewed and approved by Concentrics Institutional Review Board (Indianapolis, Indiana); participants or a guardian reviewed and gave written informed consent before participation. The study was carried out in accordance with the Draft Guidance for Industry and Food and Drug Administration Staff: Applying Human Factors and Usability Engineering to Optimize Medical Device Design, June 22, 2011[18] and the Guidance for Industry—Label Comprehension Studies for Nonprescription Drug Products, August 2010.[19]

Adolescents aged 12 to 17 years and adults 18 years of age or older participated in the 2 human use studies. The REALM test[20] and REALM-Teen test[21] were administered to the adults and adolescents, respectively, in order to screen literacy levels for information only in analyzing the population. The tests are based on a list of 66 words commonly found on medication labels. The subjects needed to be able to read, speak, and understand the nature of the study procedures. They were excluded if they had ever been trained or employed as a healthcare professional or had participated in any clinical trial, product label study, or market research study in the past 12 months.

Study Design. The study was conducted in rooms equipped with 1-way mirrors for observation. To simulate a real-life emergency, study participants were challenged with administering the medication to an unconscious victim, simulated by a full-sized mannequin. No training on the use of the device was provided prior to the usability assessment.

Intranasal devices (Aptar Unit-Dose device, Louveciennes, France) were filled with 0.1 mL of water and packed into a blister card. The blister card, along with a Quick Study Guide (QSG) and patient information section of the package insert were packed into a carton.

Study A (2 devices) was slightly more complex and was conducted prior to study B (1 device) in order to determine if individuals were able to perform critical tasks without reviewing the QSG. The objective of the QSG was to provide clear and concise instructions (combined with pictures) for use in a crisis situation with limited time to interpret the directions (Figure 1). Subjects in study A were randomized to 1 of 2 arms: subjects in arm 1 were given an opportunity to read the QSG in advance of the simulation, whereas subjects in arm 2 did not review the QSG in advance. Subjects in study B (1 device) did not review the QSG in advance of the simulation.

Subjects were presented with a scenario of an unconscious overdose victim simulated by a life-sized mannequin similar to those used for cardiopulmonary resuscitation training. Subjects were given the product with labeling and asked to proceed as they would in a real-life emergency; no training or coaching was provided either prior to or during the simulation. Background noise, in the form of TV and radio, was introduced into the scenario to simulate voices and noise from onlookers. A trained observer (located behind a 1-way mirror) documented the steps that the subject took during the simulation. Once the subject completed the simulation, an interview was conducted in a separate room to evaluate comprehension of key concepts in the patient information section of the package insert. After the comprehension interview, additional questions were asked about any incorrect actions that were observed during the human factors testing; this information was obtained in order to identify any potentially confusing sections of the labeling.

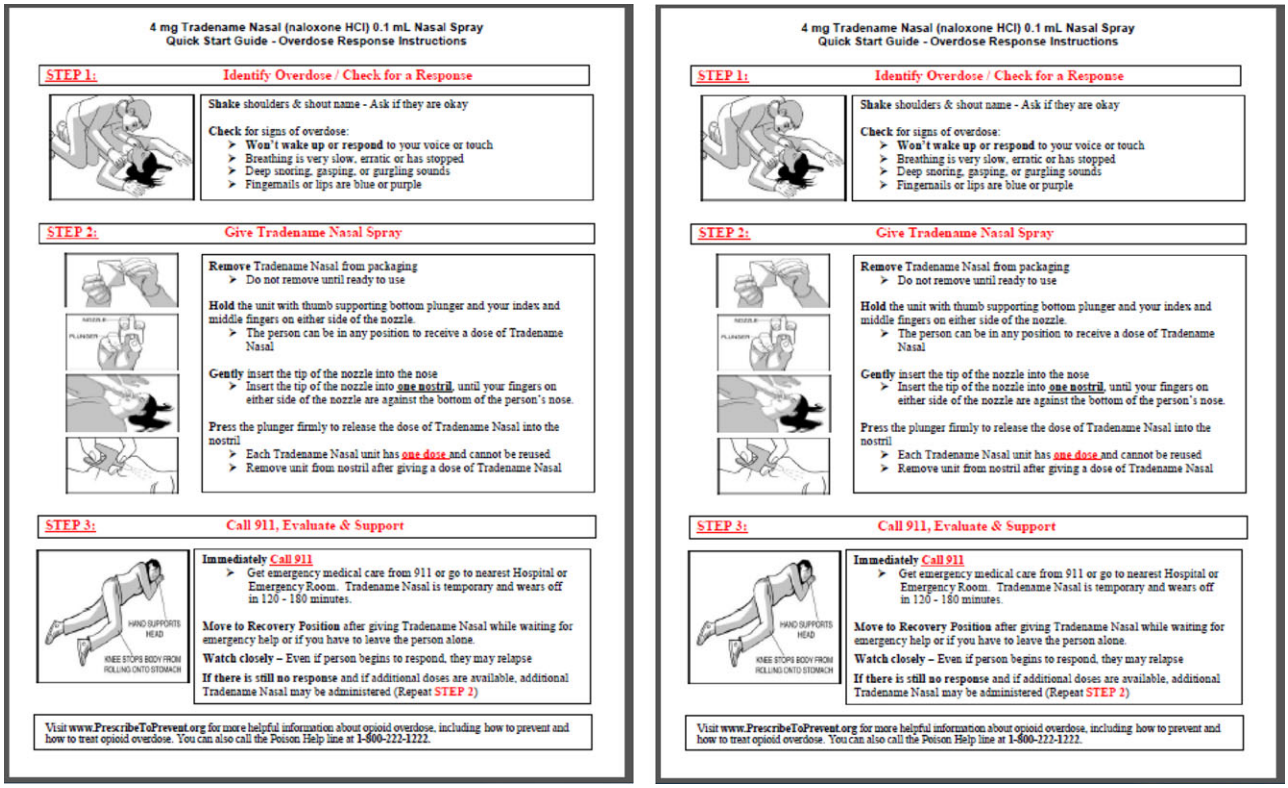
Data Analyses. The primary endpoints for the critical tasks were (1) inserting the device nozzle into a nostril and (2) pressing the plunger to release a dose into the nose. Secondary endpoints included (3) checking for response, (4) calling 911, and (5) moving to a recovery position after administering dose. Study A also included (6) waiting 2 to 3 minutes to assess the effectiveness of the first dose and (7) readministration using a new unit (if needed). As a subject interfaced with a mannequin rather than a person, the observer was able to make judgments on mitigating circumstances in which the subject was either restricted or confounded by the mannequin. This allows a response that is "not perfect or technically correct" to be considered as "correct" if the subject's intent indicates that he or she either understood the correct action or that the apparent incorrect action has no safety risk. An example would be partial insertion into the mannequin's nose because it lacked flexibility of a human nose. These were added to the final correct performance scores of primary and secondary tasks.

The correct score and lower boundary of the 95%CI were calculated for each of the 2 human factors primary endpoints. The correct score was the point estimate for execution of both critical tasks, defined as the total number of subjects who correctly completed both critical tasks, divided by the number of subjects who performed the tasks, multiplied by 100. Success criteria for the combined primary endpoints had a lower bound threshold of at least 69% for the correct scores in study A (2 devices) or at least 73% for the correct scores in study B (1 device). This was based on sample size and CIs around a mean, a point estimate of the population mean. For all remaining human factors tasks and comprehension objectives, correct scores and 2-sided 95%CIs were computed; however, no thresholds were established. Subgroup analyses were conducted to evaluate any potential differences between subjects with low literacy and adolescent subjects aged 12 to 17 years. An error rate of 6% for each task was estimated based on preliminary qualitative work using untrained users completing each task. This led to a projected probability of completing both critical core tasks correctly for any particular subject to be at least 88%. This estimate is consistent with rates accepted by the FDA for other approved products expected to be used by the lay public, including nasal sprays. With a sample size of 30 subjects per arm, the probability of having the lower bound of the 2-sided 95%CI (of the estimated proportion of subjects correctly completing all core tasks) above the predefined 69% threshold was 87%, assuming the true correct demonstration of the core tasks rate was 88%. With a sample size of 50 subjects, the probability of having the lower bound of the 2-sided 95%CI (of the estimated proportion of subjects correctly completing all core tasks) being above the predefined 73% threshold was 88%, assuming the true correct simulated use demonstration of the core tasks rate was 88%.

Results

Pharmacokinetic Study

Subject Characteristics. Eighteen male and 12 female subjects (Table 1) received at least 1 dose of naloxone;



4 mg Tradename Nasal (naloxone HCl) 0.1 mL Nasal Spray
Quick Start Guide - Overdose Response Instructions
STEP 1: Identify Overdose / Check for a Response
Shake shoulders & shout name - Ask if they are okay
Check for signs of overdose:
Won't wake up or respond to your voice or touch
Breathing is very slow, erratic or has stopped
Deep snoring, gasping, or gurgling sounds
Fingernails or lips are blue or purple
STEP 2: Give Tradename Nasal Spray
Remove Tradename Nasal from packaging
Do not remove until ready to use
Hold the unit with thumb supporting bottom plunger and your index and middle fingers on either side of the nozzle.
The person can be in any position to receive a dose of Tradename Nasal
Gently insert the tip of the nozzle into the nose
Insert the tip of the nozzle into one nostril, until your fingers on either side of the nozzle are against the bottom of the person's nose.
Press the plunger firmly to release the dose of Tradename Nasal into the nostril
Each Tradename Nasal unit has one dose and cannot be reused
Remove unit from nostril after giving a dose of Tradename Nasal
STEP 3: Call 911, Evaluate & Support
HAND SUPPORTS HEAD
KNEE STOPS BODY FROM ROLLING ONTO STOMACH
Immediately Call 911
Get emergency medical care from 911 or go to nearest Hospital or Emergency Room. Tradename Nasal is temporary and wears off in 120 - 180 minutes.
Move to Recovery Position after giving Tradename Nasal while waiting for emergency help or if you have to leave the person alone.
Watch closely – Even if person begins to respond, they may relapse
If there is still no response and if additional doses are available, additional Tradename Nasal may be administered (Repeat STEP 2)
Visit www.PrescribeToPrevent.org for more helpful information about opioid overdose, including how to prevent and how to treat opioid overdose. You can also call the Poison Help line at 1-800-222-1222.

Figure 1. Quick Start Guide for use with 1 (left panel) and 2 (right panel) intranasal devices used in study B and study A, respectively.

Table 1. Pharmacokinetics of Naloxone: Subject Demographics

	All	Male	Female
Number	30	18	12
Mean age, years (range)	35.8 (22–55)	36.9 (22–55)	34.2 (24–46)
Race			
White	7	3	4
Black/African American	23	15	8
Ethnicity			
Hispanic or Latino	2	2	0
Not Hispanic or Latino	28	16	12
Mean weight, kg (range)	80.2 (56–102)	86.2 (56–102)	71.3 (57–85)
Mean BMI,[a] kg/m^2 (range)	26.5 (19.6–29.8)	26.8 (19.6–29.8)	26.1 (22.0–28.7)

[a]BMI, body mass index.

28 subjects completed the study. One male subject discontinued the study after 1 treatment period (treatment C) due to a systolic blood pressure greater than 140 mm Hg prior to the start of the second period. This predose elevation in blood pressure was judged to be unrelated to drug treatment. One other male subject withdrew for personal reasons after completing 4 treatments; this individual did not receive treatment C.

Pharmacokinetics. Naloxone plasma concentrations were above the lower limit of quantitation (10.0 pg/mL) at 2.5 minutes after IN administration, the first collection time point, in all but 1 (an individual receiving an 8-mg dose) of 114 samples collected; concentrations were measurable in 22 of 29 samples following IM injection (data not shown). The median t_{max} values after IN and IM doses ranged from 20 minutes to 30 minutes, indicating that naloxone was absorbed rapidly following either route of administration (Table 2; Figure 2). The mean C_{max} values increased from 3.1 ng/mL to 10.3 ng/mL as the IN dose increased from 2 mg to 8 mg; the mean C_{max} value following IM dosing was 0.9 ng/mL. $AUC_{0-\infty}$ increased from 4.7 ng·h/mL to 15.8 ng·h/mL as the IN dose increased 4-fold from 2 mg to 8 mg. The terminal elimination half-life of naloxone after all 4 IN regimens was approximately 2 hours; it was 1.3 hours after the IM injection. The geometric mean ratios of the dose-corrected C_{max} values of the IN doses compared to the IM dose ranged between 55.1% and 70.8%, whereas the ratio was approximately half for $AUC_{0-\infty}$ (Table 3). Based on the actual and dose-corrected values of C_{max} and AUC, the IM and IN doses were not equivalent. The pharmacokinetic properties of naloxone following IN administration were similar between male and female subjects for all 4 treatments (Figure 3, Table 4).

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