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Time Course of Reversal of Fentanyl-Induced Respiratory Depression in Healthy Subjects by Intramuscular Nalmefene and Intramuscular and Intranasal Naloxone

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Abstract

The increase in opioid overdose deaths, particularly involving potent, long-acting synthetic opioids, has led to calls for stronger, longer-acting opioid-overdose-reversal agents. Using an opioid-induced respiratory depression model, we investigated the onset and time course of action of naloxone and a long-acting opioid antagonist, nalmefene, in reversing the effects of an ongoing intravenous fentanyl infusion over a period of up to 100 min. Healthy, moderately experienced opioid users received intramuscular (IM) nalmefene 1 mg, IM naloxone 2 mg, or intranasal (IN) naloxone 4 mg after fentanyl-induced respiratory depression was established based on reduction in respiratory minute volume (MV). Each participant received each opioid antagonist twice per a randomized crossover schedule. Reversal of respiratory depression, pharmacokinetics, and safety were investigated. Participants showed rapid increases in plasma opioid antagonist concentrations, and meaningful reversal of depressed MV tended to occur earlier with IM nalmefene and IM naloxone than with IN naloxone. Compared to naloxone, nalmefene provided extended exposure, and mean MV was maintained at a higher level. All participants experienced treatment-related adverse events, but none were severe, serious, or led to study drug discontinuation. This study provides evidence that IM nalmefene 1 mg achieves reversal of fentanyl-induced respiratory depression similar to or better than that achieved with standard-of-care naloxone treatments. No new safety concerns were raised for IM nalmefene at the tested dose. The pharmacokinetic and pharmacodynamic properties of IM nalmefene position it as an important treatment option in opioid overdose reversal, particularly given the increasing prevalence of overdoses involving potent, long-acting synthetic opioids.

Keywords

fentanyl, nalmefene, naloxone, opioid antagonist, opioid overdose, pharmacodynamics, pharmacokinetics, respiratory depression reversal

Introduction

The increasing prevalence of fatal overdoses in the United States involving potent synthetic opioids such as illicitly manufactured fentanyl and carfentanil (and chemical analogs thereof) is a growing crisis.[1–5] Overdose involving single and/or multiple synthetic opioids is particularly dangerous given their potency, rapid absorption and onset of action, long duration of action, and the increasing prevalence of counterfeit dosage forms and illicit drug supplies being mixed with varying amounts of fentanyl and fentanyl analogs and then sold as heroin or other illicit drugs.[2,6]

The toxicity associated with synthetic opioids including fentanyl and its analogs relates to their high affinity for mu-opioid receptors (MOR) and also to their lipophilicity, which contributes to a rapid onset of respiratory depression.[7,8] The lipophilicity of fentanyl also leads to its rapid redistribution from plasma to adipose tissue. Slow release back into the plasma results in an elimination half-life of approximately 2 to 8 h.[9–11] In contrast to fentanyl, the clinical behaviors of many current and emerging illicit synthetic opioid analogs are poorly characterized.[7]

The opioid receptor antagonist naloxone is the current standard of care for reversing opioid overdoses. As the potency and doses of abused opioids have increased, so have multiple naloxone administrations,[12–14] and the FDA has approved high-dose injectable and intranasal (IN) naloxone products.[15,16] The increasing number of overdose deaths involving long-acting, potent synthetic opioids and increasing use of multiple opioids suggest the need for stronger, longer-acting opioid antagonist treatments.[17] Indeed, in 2017, the

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National Institutes of Health and the National Institute on Drug Abuse jointly issued a call for the development of such treatments.[18] However, knowledge gaps continue to exist with regard to alternate opioid antagonist options for known or suspected high-potency synthetic opioid overdose, and there is a lack of real-world evidence that higher naloxone doses are effective in reversing overdoses involving higher exposures to potent synthetic opioids with longer durations of action. Importantly, the short elimination half-life of naloxone (30 to 90 min[19]) suggests that opioid agonists with a longer half-life than naloxone have the potential for renarcotization following an initial successful reversal.[7,20,21]

Nalmefene[22] is an opioid antagonist with the same pharmacological mechanism of action as naloxone but with certain attributes that may increase its effectiveness in reversing overdoses resulting from high doses of potent, long-acting synthetic opioids. These attributes include nalmefene's longer half-life of 8 to 11 h and greater affinity for MOR.[19,21,23] Because nalmefene and naloxone lack agonist activity at MOR, their potency as opioid antagonists derives from their receptor affinities. In analyses of nalmefene and naloxone using CHO-K1 cells stably expressing recombinant human MOR, nalmefene's MOR affinity ranged from 3.6 to 5.4 times that of naloxone.[23]

Injectable nalmefene hydrochloride (Revex, 1 mg/mL) was originally approved by the FDA in 1995 for the complete or partial reversal of opioid drug effects induced by natural or synthetic opioids.[24] However, the US marketing authorization holder discontinued the distribution of nalmefene in 2008 for reasons unrelated to safety or effectiveness.[25] In the face of a deepening opioid crisis fueled largely by increases in overdoses involving fentanyl and other synthetic opioids, nalmefene has received renewed interest. In February 2022, the FDA approved a generic nalmefene hydrochloride injection vial (2 mg as a 1 mg/mL solution) for the complete or partial reversal of opioid drug effects induced by either natural or synthetic opioids and for the management of known or suspected overdose.[26,27] Based on the available clinical studies conducted more than 25 years ago, intravenous (IV) nalmefene doses of 0.5 to 1 mg effectively reversed respiratory depression within 2 to 5 min of opioid overdose.[28,29] However, there is a lack of recent clinical experience because of the absence of nalmefene from the market during the period over which overdose deaths involving synthetic opioids have increased dramatically. Moreover, data on nalmefene's onset of action following intramuscular (IM) administration are limited.

To inform these issues, we developed an opioid-induced respiratory depression (OIRD) model in which we administered a three-step fentanyl infusion to safely induce respiratory depression in healthy participants with histories of prior nonmedical opioid exposure. We investigated the onset and time course of reversal of fentanyl-induced respiratory depression by IM nalmefene versus standard-of-care naloxone (IM and IN). Similar studies of OIRD have used fentanyl or other opioid agonists to induce respiratory depression and assessed its reversal by opioid antagonists using minute volume (MV) or other measures of respiratory depression.[30–34] We also assessed the pharmacokinetics (PK) of nalmefene and naloxone, as well as the safety of fentanyl when co-administered with nalmefene or naloxone.

Methods

Study Overview

The study protocol and informed consent form were reviewed and approved by the IntegReview (now Advarra) institutional review board (IRB) in Austin, TX (protocol reference number NAL1003). All participants provided written informed consent. This was a randomized crossover study in healthy participants with a history of recent nonmedical opioid use. It was conducted at a single site in the United States (Ohio Clinical Trials, Columbus, OH) between October and November 2020. The study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), local regulatory requirements, and the most recent revision of the Declaration of Helsinki.

Participants

Eligible participants were healthy males and females, ages 18 to 55 years, weighing 50 to 100 kg and with a body mass index of 18 to 30 kg/m^2 inclusive. Only subjects who, in the opinion of the investigator, were free of any clinically significant active or chronic disease based on medical history, physical examination, vital signs, clinical laboratory testing, and electrocardiography (ECG) were eligible. Per protocol, they were also required to be moderately experienced opioid users who had used opioids for nonmedical purposes on at least 10 occasions in the previous year, including at least three times in the previous 12 weeks, and who had taken an opioid at a dose equivalent to at least 30 mg oxycodone immediate release at least once in the previous year. Reasons for exclusion included opioid dependence, as indicated by DSM-IV-TR (drug and alcohol abuse/dependence questionnaire), medical history, or a positive result on the screening naloxone challenge test (assessed using the Objective Opioid Withdrawal Scale); history of increased intracranial pressure, brain tumor, seizures, or head trauma with sequelae; hospitalization for any pulmonary condition

within the previous 2 years; history of obstructive sleep apnea; oxygen saturation (SpO_2) <95% as measured by pulse oximetry on room air; consumption of more than half a pack of cigarettes per day; resting heart rate <45 or >100 bpm; history of allergy or hypersensitivity to fentanyl, naloxone, nalmefene, or other opioid agonists or antagonists, or any of their excipients; self-reported substance use disorder in the previous 2 years; and participation in a drug rehabilitation program (other than for smoking cessation). In addition, subjects had to have completed a qualification session during which they tolerated IV fentanyl (5 μg/min) well while experiencing sufficient respiratory depression (documented by measurements of MV) to participate in the study.

Study Design

The study consisted of three phases: screening, treatment, and follow-up. The treatment phase consisted of a six-period crossover sequence in which each of the three opioid antagonist treatments was administered on two separate occasions. The three treatments were nalmefene HCl 1 mg IM (1 mg/mL solution with the same active and inactive ingredients as Revex; supplied by Purdue Pharma L.P.), naloxone HCl 2 mg IM (1 mg/mL solution; International Medication Systems, Limited), and naloxone 4 mg IN (Narcan; Adapt Pharma Inc.). All three antagonist treatments and doses studied are approved for the reversal of known or suspected opioid overdose. For each period (experimental session), following induction of OIRD (a ~50% reduction in MV from baseline) with fentanyl, nalmefene or naloxone was administered according to a randomly assigned treatment sequence. The three treatments (A = nalmefene 1 mg IM, B = naloxone 2 mg IM, C = naloxone 4 mg IN) were administered in replicates, randomized across six sequences (ABCABC, ACBACB, BACBAC, BCABCA, CABCAB, CBACBA) to minimize order effects and allow unbiased comparison of treatment outcomes. The washout time between periods was ≥ 72 h.

Each treatment period began with an IV infusion of a saline solution (0.9%) administered 30 to 45 min before the start of the first fentanyl infusion. This allowed baseline measurements to be collected and was also intended to blind participants to the precise timing of the start of fentanyl administration. Participant MV was monitored continuously using a noninvasive ExSpiron ventilation monitor (model 1Xi; Respiratory Motion Inc., Waltham, MA).[35,36] Additional real-time continuous monitoring included SpO_2 and transcutaneous CO_2 (both measured using a Sentec Digital Monitoring System, Sentec AG, Therwil, Switzerland). Participants received continuous supplemental oxygen (2 L/min) via a simple mask during the entire experimental session.

Following the baseline period, participants received fentanyl administered as a sequence of three successive IV infusions designed to maintain approximately constant fentanyl concentrations once OIRD was achieved during the first fentanyl infusion. The second and third infusion rates were successively reduced to maintain the fentanyl concentration approximately equal to that attained at the end of the first infusion. The total duration of the fentanyl infusions was individualized (i.e., based on each participant's response to fentanyl in each treatment period) using continuous real-time assessments of MV to monitor respiratory depression and the attainment of OIRD. The maximum total duration of the three successive fentanyl infusions in each treatment period was 230 min.

The first fentanyl infusion was delivered at a fixed rate of 5.0 μg/min and was stopped when MV had decreased by ~50% from baseline for ~5 min or when the maximum permitted duration of the first fentanyl infusion of 2 h was reached. Immediately thereafter, a second fentanyl infusion with a fixed duration of 20 min was started, followed by a third infusion with a duration of up to 90 min. The infusion rates for the second and third fentanyl infusions were always lower than that of the first infusion, and the exact rates were dependent on the duration of the first fentanyl infusion. Concentration data from IV bolus fentanyl doses administered in a prior study (data on file) were used to fit a 3-compartment PK model for fentanyl. This model was used to simulate fentanyl concentration profiles for constant-rate (5.0 μg/min) IV infusion for the full range of possible first infusion durations (5, 10, 15, …115, and 120 min). For each of these possible durations, the fentanyl PK model was used to empirically determine rates for the second and third infusions necessary to maintain fentanyl concentrations at approximately the level attained at the end of the first fentanyl infusion over the entire duration of the second and third fentanyl infusions. Thus, for each participant, the total fentanyl dose administered was individualized based on measured changes in MV. Transcutaneous CO_2 and potentially other parameters (e.g., adverse events) during the fentanyl infusion were used to assist in determining when to end the first infusion.

At 10 min (the midpoint) following the start of the second fentanyl infusion, an opioid antagonist treatment was administered. IM doses of antagonists were administered as direct injections into the anterolateral thigh using a prefilled syringe with a staked stainless steel needle (22 gauge, 5/8 inch length). Each antagonist was administered as a single dose. Administration of opioid antagonists was single-blinded (participants had been informed that they might receive nalmefene,

naloxone, or placebo; however, no participant received placebo). Informing participants about the potential administration of a placebo was intended to reduce bias in their responses to the administered IM and IN treatments.

Experimental sessions followed an overnight fast or light breakfast. Because they were wearing an oxygen mask (and to avoid the need to use the restroom), participants were not permitted to eat or drink beginning 2 h before dosing or during dosing. They remained upright for 4 h after the end of fentanyl administration. To minimize the potential for drug interactions, participants were required to abstain from the following during the study: products containing caffeine and xanthine, poppy seeds (beginning 1 week prior to study start), alcohol (beginning 48 h before the first dose of study drug), recreational drugs, and tobacco/nicotine. They were also required to abstain from strenuous exercise during the study.

Pharmacokinetics

In each experimental session, blood samples were collected into K_2EDTA-coated Vacutainer tubes immediately before nalmefene/naloxone administration (predose) and at the following times after nalmefene/naloxone administration: 2, 3, 5, 10, 15, 20, and 30 min and 1, 2, 4, and 8 h. Within 30 min of each blood draw, samples were centrifuged (3000 rpm at 4°C for 15 min), and the resulting plasma was stored at −20°C prior to analysis.

Analytes were extracted from plasma by liquid–liquid separation and were measured using validated high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) detection methods with positive ion electrospray ionization. The assays were linear from 10 to 5000 pg/mL for fentanyl, 0.1 to 100 ng/mL for nalmefene, and 0.025 to 20 ng/mL for naloxone. The lower limit of quantitation was 10 pg/mL for fentanyl, 0.1 ng/mL for nalmefene, and 0.025 ng/mL for naloxone.

For each treatment period, the following model-independent PK metrics were calculated based on the antagonist plasma concentrations (naloxone or nalmefene): area under the plasma concentration–time curve $(AUC)_{0\text{-}2min}$, $AUC_{0\text{-}5min}$, $AUC_{0\text{-}10min}$, $AUC_{0\text{-}15min}$, $AUC_{0\text{-}20min}$, $AUC_{0\text{-}t}$ (where t was the time of the last measurable plasma concentration), C_{max} (peak plasma concentration), and T_{max} (time to peak plasma concentration).[37] The duration of PK sampling (8 h) was too short to reliably estimate $t_{\frac{1}{2}}$ for the antagonists; therefore, $t_{\frac{1}{2}}$ (terminal half-life) and $AUC_{0\text{-}inf}$ (extrapolated to infinity) were not reported. AUC values were calculated by the linear trapezoidal method. PK metrics were not calculated for fentanyl.

Pharmacodynamics

Pharmacodynamic (PD) assessments were based on real-time assessment of MV (L/min), as calculated by the ExSpiron device.

Safety

Safety assessments included treatment-emergent adverse events (TEAEs), which were assigned to an administered study drug according to their time and date of onset. The study drug was fentanyl alone or fentanyl with IM nalmefene, IM naloxone, or IN naloxone. Adverse events that started within 7 days after a participant's last dose of study drug were assigned as TEAEs to the last study drug administered. TEAEs were assessed for severity, seriousness, and causality. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 and were classified by System Organ Class (SOC) and Preferred Term (PT). Each PT and SOC was counted only once per participant. Severity was assessed according to Common Terminology Criteria for Adverse Events. For each participant, only the worst severity was counted.

Other safety assessments included laboratory safety assessments (biochemistry, hematology, and urinalysis); vital signs, which included systolic and diastolic blood pressure, pulse rate, breathing rate, body temperature, and SpO_2 (measured by pulse oximetry); physical examination; and ECG.

Statistical Analyses

Descriptive statistics were calculated using SAS software version 9.4 or later (SAS Institute, Cary, NC). PK analyses were performed using Phoenix WinNonlin version 8.0 or higher (Certara, Princeton, NJ). Plasma concentrations below the lower limit of quantification were set to zero. If two or more successive PK samples gave concentrations below the lower limit of quantification, the PK profile was terminated at the last quantifiable concentration. Actual blood sampling times were used in the analysis.

The primary PD outcome measure was change in MV from opioid-induced nadir (defined as the median MV over the 5-min interval beginning 10 min before opioid antagonist administration). The change in MV from opioid-induced nadir was assessed at prespecified time points of 2.5, 5, 10, 15, 20, 30, and 90 min after administration of the opioid antagonist. Median MV during a 1-min window around each time point was used. For example, MV for a nominal time point of 5 min was calculated as the median of the values obtained between 4.5 and 5.5 min. In the absence of an accepted standard defining clinically meaningful reversal of respiratory depression, the time to onset of reversal was estimated for various reversal thresholds (25%, 33%, 50%, 67%, 75%, 90%, and 100%). The X% reversal threshold was

calculated as nadir + [X% × (baseline − nadir)], where baseline was defined as the median MV during the 10 min before the start of the first fentanyl infusion and nadir as the median MV in the 10 to 5 min before opioid antagonist administration. For example, for a participant whose baseline MV was 8 L/min with an MV of 4 L/min at nadir, an increase in MV to 6 L/min first observed at 5 min after antagonist administration would represent a 50% reversal with a time of onset of 5 min:

$$4\text{L/min} + [50\% \times (8\text{L/min} - 4\text{L/min})] = 6\text{L/min} \quad (1)$$

Post Hoc Inferential Statistical Analysis. Hypothesis #1: Non-inferiority test

The null hypothesis is that IM nalmefene (μT) is inferior to the reference treatment (μR). The alternative hypothesis is that μT is not inferior to μR.

H0: $\mu T - \mu R \leq -0.5$ versus H1: $\mu T - \mu R > -0.5$

Hypothesis #2: Superiority test

The null hypothesis is that IM nalmefene (μT) is not superior to the reference treatment (μR). The alternative hypothesis is that μT is superior to μR.

H0: $\mu T - \mu R \leq 0$ versus H1: $\mu T - \mu R > 0$

In this post hoc testing, IM nalmefene was compared with each of the two reference treatments: IM naloxone and IN naloxone. In addition, the two reference treatments were also compared with each other for noninferiority and superiority. Least-square means and 95% confidence intervals (CIs) were calculated using a generalized linear model that included change in MV from nadir at each time point as the outcome and subject, treatment, treatment sequence, and period as factors.

Results

Disposition and Participant Characteristics

Thirteen subjects (two females and 11 males) were screened, and the eight who were eligible (all males) were randomized in the study. All eight participants completed the study and were included in the PK, PD, and safety analyses. Median age was 40.5 years (range 30 to 50) (Table 1). Most participants were White (50.0%) or Black or African American (37.5%) and one was Hispanic or Latino. Median body mass index was 23.62 kg/m^2 (range 21.1 to 25.8).

Table 1. Participant Characteristics

	N = 8
Age (years)	
Mean (SD)	40.5 (7.05)
Median (range)	40.5 (30 to 50)
Age group (years), n (%)	
18 to 34	2 (25.0)
35 to 49	5 (62.5)
50 to 55	1 (12.5)
Male, n (%)	8 (100)
Ethnicity, n (%)	
Hispanic or Latino	1 (12.5)
Not Hispanic or Latino	7 (87.5)
Race	
Black or African American	3 (37.5)
White	4 (50.0)
Other[a]	1 (12.5)
Weight (kg)	
Mean (SD)	73.75 (10.22)
Median (range)	72.25 (58.4 to 91.5)
Body mass index (kg/m^2)	
Mean (SD)	23.63 (1.45)
Median (range)	23.62 (21.1 to 25.8)

SD, standard deviation.
[a] Mixed white and American Indian.

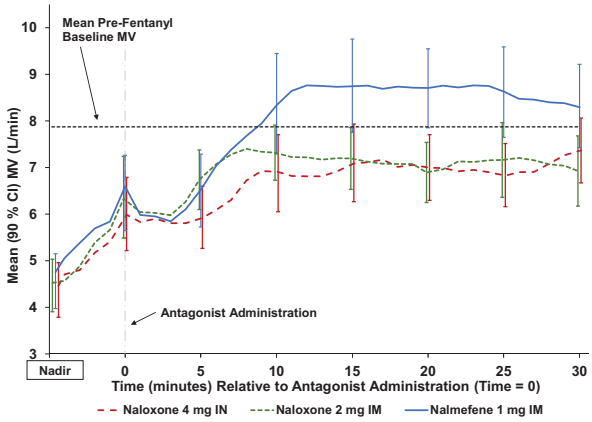

Figure 1. Time course of mean minute volume by treatment, pooled across experimental sessions, from 0 to 30 min after opioid antagonist administration. CI, confidence interval; IM, intramuscular; IN, intranasal; MV, minute volume. The dashed line represents the mean MV (7.87 L/min) prior to fentanyl administration (mean pre-fentanyl baseline MV). Mean fentanyl infusion rate during antagonist administration was 5.0 μg/min for infusion #1, 4.2 μg/min for infusion #2, and 3.2 μg/min for infusion #3.

Pharmacodynamics

Figure 1 shows the mean (90% CI) MV profiles over time (0-30 min) for the three antagonist treatments. Mean MV profiles over the 0-90-min time course across the three antagonist treatments are shown in Figure S1. Mean MV was similar at baseline for the three treatments (mean pre-fentanyl baseline MV = 7.87 L/min), as was MV at the opioid-induced nadir, defined as the 5-min interval (−10 to −5 min) beginning at the start of the second fentanyl infusion.

All three MV profiles show an increase in MV over the 5 min prior to antagonist administration. This likely reflects transient subject stimulation as preparations were made for IM or IN administration of the assigned antagonist treatment. Similarly, the MV profiles for all three treatments show a brief positive spike at the time of antagonist administration (0 min),

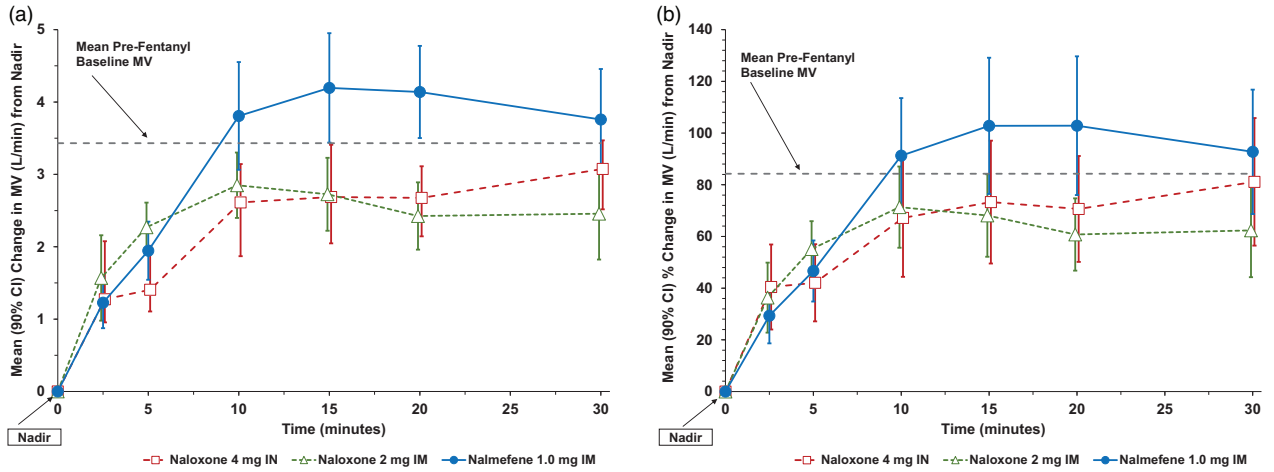

Figure 2. Mean absolute and percentage change in minute volume from opioid-induced nadir. (a) Absolute change and (b) percentage change. CI, confidence interval; IM, intramuscular; IN, intranasal; MV, minute volume. Dashed lines represent the mean MV prior to fentanyl administration (mean pre-fentanyl baseline MV): 3.43 L/min in (a) and 84.3 L/min in (b).

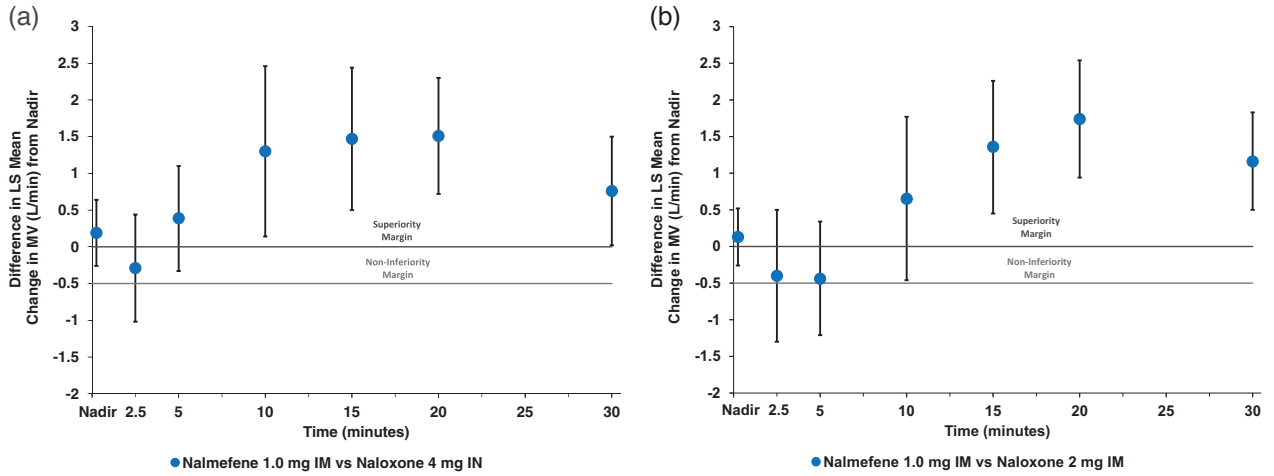

Figure 3. Differences in least-square mean change in MV from nadir at specified time points. (a) IM nalmefene versus IN naloxone and (b) IM nalmefene versus IM naloxone. IM, intramuscular; IN, intranasal; LS, least-square; MV, minute volume. Error bars represent 95% confidence intervals.

followed by a decline over the interval immediately following antagonist administration. This decline likely represents the waning of subject stimulation caused by dosing at time 0 and ends when the mounting antagonism overtakes the return of fentanyl-induced respiratory depression that would otherwise be maintained by the ongoing fentanyl infusion had the treatment administered included no opioid antagonist.

Mean MV was maintained at a higher level over time after administration of IM nalmefene versus IM or IN naloxone (Figure 1). For each opioid antagonist treatment, the MV time course generally showed limited variation between experimental sessions (Figure S2). Overall, the time to onset of reversal in MV was similar for IM nalmefene and IM naloxone (Table S1). IM nalmefene and IM naloxone both consistently produced shorter mean reversal times compared to IN naloxone.

The change in MV from nadir at 5 min was similar for the three opioid antagonist treatments (Figure 2a). The mean change in MV from nadir at 5 min was 1.97 L/min for IM nalmefene, 2.14 L/min for IM naloxone, and 1.41 L/min for IN naloxone (Table S2). The change in MV from nadir for the different opioid antagonist treatments at 10 to 30 min was higher for IM nalmefene than for IM and IN naloxone (Table S2). Similar results were observed for percent change in MV from nadir (Figure 2b).

Post Hoc Inferential Statistical Analysis

When comparing IM nalmefene versus IN naloxone (Figure 3a), the change in MV from nadir was estimated to be greater for IM nalmefene than for IN naloxone starting from 10 min, with an associated 95% CI above the superiority margin (0 reference line), representing a statistically significant finding of

superiority. Superiority was also demonstrated at the 15-, 20-, and 30-min time points, while non-inferiority was demonstrated at all time points except 2.5 min.

When comparing IM nalmefene versus IM naloxone (Figure 3b), the change in MV from nadir was estimated to be greater for IM nalmefene than for IM naloxone starting from 15 min, with an associated 95% CI above the superiority margin (0 reference line). Superiority was also demonstrated at the 20- and 30-min time points, while non-inferiority was demonstrated at all time points except 2.5 min and 5 min. [Correction added on October 22, 2024, after first online publication: In the first full paragraph, the last line has been corrected to "2.5 min and 5 min."]

When comparing IN naloxone versus IM naloxone (Figure S3), IM naloxone generally performed comparably or slightly better than IN naloxone and showed superiority at 5 min.

Inferential analyses of change in MV from nadir at specified time points for IM nalmefene versus IN naloxone, IM nalmefene versus IM naloxone, and IM naloxone versus IN naloxone are shown in Tables S3-S5, respectively.

Pharmacokinetics

Sequential fentanyl infusions produced similar, nearly constant plasma fentanyl concentrations from the time of opioid antagonist administration (t = 0 min) through 30 min postadministration (Figure 4a). Plasma concentrations of both naloxone and nalmefene increased rapidly (Figure 4b,d), although nalmefene showed an extended duration of relatively higher exposures (Figure 4c,e). Informed estimates of the relative opioid agonist reversal potential of the two naloxone treatments can be assessed by direct comparison of their respective PK profiles in Figure 4b,c. However, inferences regarding the relative agonist reversal potential of nalmefene versus naloxone treatments cannot be made solely from these PK profiles because these profiles do not account for the differences in various attributes of nalmefene and naloxone, the most important of which is nalmefene's greater MOR affinity.[23]

Geometric mean C_{max} for IM nalmefene was 2.6 ng/mL. Geometric mean C_{max} for IM naloxone (4.8 ng/mL) was similar for IN naloxone (4.1 ng/mL). Median T_{max} was lower for IM naloxone (9 min) than for IM nalmefene (15 min) and IN naloxone (30 min). Geometric mean $AUC_{0\text{-}t}$ was 572 ng×min/mL for IM nalmefene, 625 ng×min/mL for IM naloxone, and 626 ng×min/mL for IN naloxone (Table 2).

Safety

All eight participants reported at least one TEAE. TEAEs reported by more than one participant were hyperhidrosis (n = 4, 50.0%), nausea (n = 3, 37.5%), pruritus (n = 2, 25.0%), and vomiting (n = 2, 25.0%) (Table S6). All TEAEs were treatment-related. The maximum severity of TEAEs was mild in five participants (62.5%) and moderate in three participants (37.5%). The moderate TEAEs were vomiting in two participants (25.0%) and muscle spasms in one participant (12.5%). No TEAEs were serious or led to the study drug being discontinued. Overall, TEAEs were similar when each of the three antagonist treatments was administered to reverse fentanyl-induced respiratory depression.

Laboratory safety (biochemistry, hematology, and urinalysis), vital signs (including systolic and diastolic blood pressure, pulse rate, breathing rate, body temperature, and SpO_2), physical examination, and ECG showed no clinically significant abnormalities. All eight participants experienced sinus bradycardia as a nonclinically significant ECG abnormality during the study.

Discussion

In the current opioid overdose crisis, there is a paucity of PK/PD data on the reversal of life-threatening respiratory depression induced by misuse and abuse of fentanyl and its synthetic analogs. However, as the FDA acknowledges,[38] clinical research on opioid antagonists faces substantial ethical and practical barriers. For example, there is no satisfactory way to safely replicate or simulate real-world opioid overdoses in a controlled setting, and a placebo cannot be used in real-world studies. There are also ethical considerations in conducting an efficacy study of nalmefene when effective doses of naloxone are available.

To overcome some of these challenges, we developed a clinical model of OIRD that uses PD endpoints to assess the onset and time course of antagonism of fentanyl-induced respiratory-depressant effects in a safe and controlled setting. MV profiles showed that the onset of reversal of fentanyl-induced respiratory depression occurred within the first 5 min following antagonist administration for all three treatments. However, the pace of early reversal was somewhat faster for IM nalmefene and IM naloxone compared to IN naloxone. Moreover, mean MV was maintained at a higher level, and the duration of reversal was longer, following administration of IM nalmefene compared to IM and IN naloxone, consistent with the former's longer half-life. This finding is in agreement with a previously published placebo-controlled morphine-induced respiratory depression reversal study in which nalmefene (0.4 mg/70 kg) and naloxone (0.4 and 1.6 mg/70 kg) were each administered IV to healthy volunteers according to a randomized crossover schedule 1 h after IM injection of morphine (10 mg/70 kg). MV was higher from 1.5 to

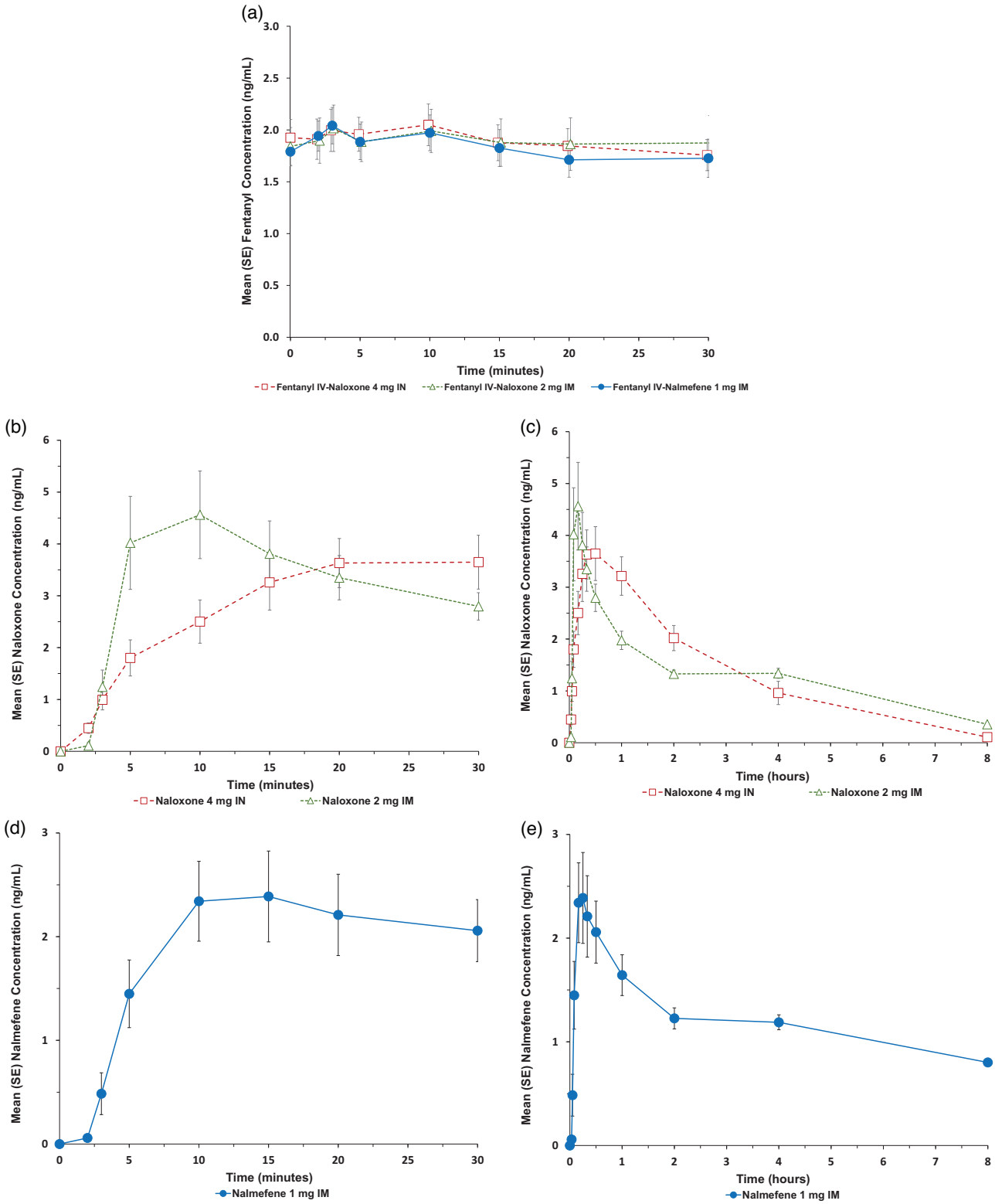

Figure 4. Time course of plasma fentanyl, naloxone, and nalmefene concentrations. (a) Mean plasma fentanyl concentrations from 0 to 30 min after opioid antagonist administration. Mean plasma naloxone concentrations from 0 to 30 min (b) and 0 to 8 h (c) after opioid antagonist administration. Mean plasma nalmefene concentrations from 0 to 30 min (d) and 0 to 8 h (e) after opioid antagonist administration. IM, intramuscular; IN, intranasal; IV, intravenous; SE, standard error.

Table 2. Plasma Pharmacokinetic Parameters for the Opioid Antagonists (N = 8)

				(ng×min/mL)					
Treatment		T_{max}[a] (min)	C_{max} (ng/mL)	$AUC_{0\text{-}2min}$[b]	$AUC_{0\text{-}5min}$	$AUC_{0\text{-}10min}$	$AUC_{0\text{-}15min}$	$AUC_{0\text{-}20min}$	$AUC_{0\text{-}t}$
Naloxone 4 mg IN	GM	30 (20-37.5)	4.1	0.47	3.2	13	26	42	626
	GM CV (%)		41	67	117	90	77	64	31
Naloxone 2 mg IM	GM	9 (8-15)	4.8	0.11	5.0	24	43	60	625
	GM CV (%)		49	139	90	60	52	48	15
Nalmefene 1 mg IM	GM	15 (9-30)	2.6	0.31	1.7	11	22	32	572
	GM CV (%)		46	155	115	73	66	59	19

AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration; GM, geometric mean, GMCV, geometric mean coefficient of variation; IM, intramuscular; IN, intranasal; *t*, time of the last measurable plasma concentration; a concentration; T_{max}, time to peak plasma concentration.

[a] T_{max} is given as the median (Q1-Q3).

[b] $AUC_{0\text{-}2min}$ is given as the arithmetic mean, as many individual subject values for this parameter were 0.

6 h after administration of nalmefene versus either dose of naloxone.[39]

The safety analysis revealed no new safety concerns or signals. No TEAEs were severe, serious, or led to the study drug being discontinued. The small study sample precluded a formal analysis of safety trends by opioid antagonist treatment.

Although the OIRD model is not a simulation of real-world opioid overdoses, it allows the magnitude and time course of reversal of fentanyl-induced respiratory depression to be directly compared between opioid antagonists. The well-characterized PK and PD of fentanyl, combined with its ever-increasing prevalence as a primary agent in drug overdoses, support its selection as a model opioid agonist for assessing the reversal of OIRD in clinical models.[40] The OIRD model is particularly important given that inferences regarding the relative agonist reversal potential of nalmefene versus naloxone treatments cannot be made directly from the PK profiles because these profiles do not account for the differences in MOR affinity between the two antagonists. The differences and similarities in the onset and extent of reversal in the OIRD model are expected to correlate well with antagonist treatment data obtained from real-world overdoses.

The observed increase in MV in the 5 min before opioid antagonist administration likely reflects the stimulation of participants by activities that occurred during this time interval. These activities included a blood draw and preparing the participant for opioid antagonist administration. Since similar MV increases were observed prior to all three antagonist treatments, their impact on assessments comparing nalmefene IM with naloxone IM and IN was presumably minimal. As expected, in the interval shortly following antagonist administration, MV initially decreases, reflecting the waning of subject stimulation caused by predose and dosing activities. This is followed by increases in MV as the pharmacologic activities of the administered opioid antagonists begin to overcome the effect of the steady fentanyl concentrations that have been maintained by the ongoing infusion of fentanyl. Post hoc inferential analyses support the interpretation that IM nalmefene provided superior efficacy compared to IN and IM naloxone, at the studied dose levels. Overall, this clinical model of fentanyl-induced respiratory depression was found to be robust, with stable and comparable baselines and fentanyl concentration profiles between treatment groups, allowing for reliable characterization of antagonist treatment effects.

Limitations of the present study include the modest sample size, which precluded inferential statistical analysis of the primary variable. This was partially mitigated by administering each treatment twice, with the two administrations producing consistent results. The use of an ExSpiron device to measure MV introduced variability through its reliance on surface electrodes to assess chest wall motion. Another limitation is that fentanyl concentrations were maintained approximately constant, which would not be expected to occur in a real-world setting. Further, PD was only analyzed up to 90 min after opioid antagonist administration, which meant that the duration of reversal could not be assessed beyond this point. We also acknowledge that any statistical comparisons conducted post hoc and not pre-specified in our analysis plan were exploratory and hypothesis-generating in nature.

Collectively, our findings support the conclusion that the recent reintroduction of nalmefene injection provides a useful addition to the pharmacologic armamentarium of emergency physicians and other medically qualified personnel in the management of known or suspected opioid overdose. Furthermore, the more recently approved intranasal form of nalmefene (Opvee, Indivior Inc.) and the ongoing development of other injectable forms of nalmefene for opioid overdose reversal, including a prefilled syringe and an autoinjector, represent additional promising treatment options.

Conclusions

This study provides evidence that IM nalmefene (1 mg) achieves reversal of fentanyl-induced respiratory depression with a time to onset and a magnitude of reversal that is similar to, or better than, that achieved with standard-of-care naloxone products (IM naloxone 2 mg and IN naloxone 4 mg). The study raises no new safety concerns relating to IM nalmefene. These findings add to the foundational studies conducted with nalmefene IM injection and provide a contemporary perspective supporting the importance of IM nalmefene as an additional treatment option in responding to the current synthetic opioid overdose crisis. Subsequent formal studies and practical real-world experience will further inform the optimal use of nalmefene-based opioid overdose treatments.

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Conflicts of Interest

AC, EH, MS, and SCH are employees of Imbrium Therapeutics L.P., a subsidiary of Purdue Pharma L.P., the study sponsor. RPK was an employee of Imbrium Therapeutics L.P. at the time of the study. GA received no direct compensation for work related to the development of this manuscript. GA was directly compensated by Purdue Pharma L.P. for his involvement as the principal investigator for this study. SCH owns stock/stock options in Pfizer.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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