Received: 14 April 2024 | Revised: 21 June 2024 | Accepted: 17 July 2024

DOI: 10.1002/psp4.13215

ARTICLE

Mechanistic pharmacokinetic–pharmacodynamic modeling and simulations of naloxone auto-injector 10 mg reversal of opioid-induced respiratory depression

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Abstract

The purpose of the analysis was to evaluate if 10 mg naloxone, administered intramuscularly, could reverse or prevent opioid-induced respiratory depression (OIRD), including OIRD associated with the administration of lethal doses of high-potency opioids. A naloxone population pharmacokinetic (PK) model was generated using data from two naloxone auto-injector (NAI) clinical PK studies. Mechanistic OIRD PK-pharmacodynamic (PD) models were constructed using published data for buprenorphine, morphine, and fentanyl. Due to the lack of published carfentanil data in humans, interspecies allometric scaling methods were used to predict carfentanil PK parameters in humans. A PD model of a combined effect-compartment and receptor kinetics model with a linear relationship between ventilation and carbon dioxide was used to predict the respiratory depression induced by carfentanil. Model-based simulations were performed using the naloxone population PK model and the constructed mechanistic OIRD PK–PD models. Changes in ventilation were assessed after opioid exposure and treatment with 2 mg naloxone or one or two doses of 10 mg naloxone. A higher percentage of subjects recovered back to the rescue ventilation thresholds and/or had a faster recovery to 40% or 70% of baseline ventilation with 10 mg compared with 2 mg naloxone. A second dose of 10 mg naloxone, administered 60 min post-opioid exposure, expedited recovery to 85% of baseline ventilation and delayed time to renarcotization compared with a single dose. In addition, when 10 mg naloxone was administered at 5, 15, 30, or 60 min before fentanyl or carfentanil exposure, rapid and profound OIRD was prevented.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The increased prevalence of high-potency opioids, their possible use as chemical weapons, and the potential threat to public health and national security suggest the need for higher initial naloxone doses.

WHAT QUESTION DID THIS STUDY ADDRESS?

PK–PD models based on naloxone auto-injector clinical data combined with opioid PK–PD models were used to provide insight as to how IM-administered 10 mg naloxone (NAI 10 mg) can reverse OIRD caused by high-potency opioids.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Model-based simulations demonstrated that NAI 10 mg administration resulted in subjects returning to predefined ventilation thresholds faster than with NAI 2 mg. A second dose administered at 60 min post-opioid exposure expedited ventilation recovery and delayed renarcotization. NAI 10 mg administered up to 60 min before fentanyl or carfentanil exposure helped prevent rapid and profound OIRD.

HOW MIGHT THIS CHANGE DRUG DISCOVERY DEVELOPMENT, AND/OR THERAPEUTICS?

The use of PK–PD modeling, including the identification of relevant mechanistic and physiological components, is a valuable tool to assess the effects and gain insight into the clinical effectiveness of opioid antagonists.

INTRODUCTION

The increased prevalence of more potent illicitly manufactured fentanyl and other synthetic opioids (e.g., nitazenes), also classified as high-potency opioids, presents public health and national security threats to civilians and military communities,[1–4] and has created new challenges for the adequate treatment of opioid exposures. In general, opioids that are at least 50 times more potent than morphine are defined as high-potency opioids[5] and include semi-synthetic opioids like the partial agonist buprenorphine and synthetic opioids like fentanyl and carfentanil. These potent opioids bind to the mu-opioid (MOP) receptor in the central nervous system (CNS) and cause respiratory depression within min of exposure.[6] In addition, high-potency opioids may increase the likelihood of renarcotization (the return of respiratory depression and CNS symptoms after initial naloxone administration and response).

Naloxone was approved by the US Food and Drug Administration (FDA) in 1971 and has been used for over five decades to quickly and effectively reverse opioid-induced respiratory depression (OIRD) and opioid-induced CNS depression without widely reported or serious adverse effects. Naloxone is an opioid antagonist that competitively binds to the MOP receptors in the CNS preventing opioids from binding and exerting their effects. When administered in the absence of opioids, naloxone exhibits essentially no pharmacologic activity. Prior to 2021, the FDA defined initial naloxone dosing as 0.4–2 mg for intravenous (IV), intramuscular (IM), or subcutaneous (SC) administration and 2 or 4 mg for intranasal (IN) administration.[7,8] As more potent opioids become available, higher doses of naloxone hydrochloride (HCl) are needed to reverse OIRD and opioid-induced CNS depression. In a previously published simulation study using an opioid receptor quantitative systems pharmacology model, 2 mg IM naloxone was unable to reduce MOP receptor occupancy to 50% within 10 min when the fentanyl plasma exposure was 75 ng/mL. However, higher doses of naloxone, 5 mg and 10 mg IM, decreased MOP receptor occupancy by fentanyl to below 50% in 5.5 and 4 min, respectively, which are within a window for a potential successful resuscitation.[9] In 2021, the FDA approved two new out-of-hospital prescription naloxone products that deliver 5 mg of naloxone IM/SC or 8 mg IN.[10,11] Dosage and administration instructions for these out-of-hospital use products state that, if the desired response is not obtained or maintained after a single dose, subsequent naloxone doses can be administered every 2–3 min as necessary, with no defined upper limit on the amount of naloxone that can be administered.

The FDA approved a prescription 10 mg naloxone auto-injector (NAI 10 mg) for IM/SC use in 2022.[12] The pharmacokinetic–pharmacodynamic (PK–PD) modeling analysis described here was used to demonstrate that administration of NAI 10 mg can help reverse or prevent OIRD, including OIRD associated with the administration of lethal doses of high-potency opioids.

METHODS

Naloxone population PK model development

The naloxone population PK model was developed using a total of 2063 PK measurements from two clinical studies in 48 healthy adult subjects evaluating the PK profiles of four naloxone doses administered IM/SC using naloxone auto-injectors (NAI): EVZIO® 0.4 mg (one or two doses), EVZIO® 2 mg (NAI 2 mg), and NALOXONE HYDROCHLORIDE injection (NAI 10 mg). The clinical study protocols were approved by an accredited Institutional Review Board and all study subjects signed informed consent forms prior to participating. Detailed methods are provided in the Appendix S1.

Construction of mechanistic OIRD PK–PD models and reversal by naloxone

Mechanistic OIRD PK–PD models were constructed using published models for buprenorphine (a partial agonist with a long duration of response and slow receptor dissociation),[13] morphine (a full agonist considered the "standard" opioid),[14] and fentanyl (a fast-acting, synthetic, high-potency opioid),[15] and further validated with external clinical observations from the literature. Detailed methods are provided in the Appendix S1.

Carfentanil, a synthetic, high-potency opioid with slow receptor dissociation, has limited published PK and PD data in humans. Available data from studies evaluating IV fentanyl and carfentanil doses and PK time profiles in mice[16] and rabbits[17,18] were used with interspecies allometric scaling to predict carfentanil PK parameters in humans, based on the similarities of fentanyl and carfentanil (i.e., carfentanil is a structural analogue of fentanyl). The PD parameters of the MOP receptor binding model for carfentanil and naloxone were obtained from an FDA source.[19] Detailed methods for the carfentanil mechanistic PK–PD model creation are provided in the Appendix S1.

The final naloxone population PK model was incorporated into the constructed PK–PD models of OIRD to conduct the simulations.

Model-based simulations

The effect of NAI 10 mg on the reversal of OIRD was evaluated in three clinical simulation scenarios using different IV-administered opioids and doses. The opioids evaluated were buprenorphine (0.9, 9.9, 18.9 μg/kg), morphine (0.2, 2.2, 4.2 mg/kg), fentanyl (2.1, 23.1, 44.1 μg/kg), and carfentanil (0.2, 2.2, 4.2 μg/kg). The lowest doses of buprenorphine, morphine, and fentanyl were selected based on published data as corresponding to 50% suppression in ventilation when administered IV. The lowest dose of carfentanil was the human equivalent of the half maximum effective concentration (defined by bradypnea and/or loss of posture) in non-human primates when administered SC.[20] For all four opioids, the middle dose was the mid-point between the low and high doses and the highest doses were 21 times the lowest dose. The 21-fold difference was based on unpublished data on renarcotization of non-human primates after administration of carfentanil (SC) and 10 mg naloxone (IM). The highest doses represent lethal doses of morphine, fentanyl, and carfentanil.

In the first modeling simulation scenario, all opioid doses were evaluated. Naloxone (NAI 2 mg and NAI 10 mg) was administered IM/SC when there was a 60% reduction in ventilation (i.e., 40% ventilation) following morphine, fentanyl, or carfentanil exposure. Below the 40% threshold for spontaneous breathing was defined as unsafe with the potential for respiratory complications.[19,21] For buprenorphine, naloxone was administered after a 30% reduction in ventilation due to buprenorphine's slow respiratory depressant effect onset.[22] The effect of NAI 2 mg, NAI 10 mg, or no naloxone on OIRD was assessed by the time required to recover to the 40% or 70% ventilation threshold and the percentage of subjects that recovered to each threshold.

In the second modeling simulation scenario, using only the highest opioid doses, the cumulative effect of administering two NAI 10 mg on OIRD and renarcotization was evaluated. The second NAI 10 mg was administered IM/SC at 60 min after opioid exposure in all subjects who received an initial naloxone dose. Timing for administration of the second naloxone dose was based on data from the first modeling simulation scenario. The time required to reach 85% of baseline ventilation (considered near normal ventilation) and the time to renarcotization were assessed in all subjects who received naloxone. Renarcotization was defined as ventilation recovering to 85% and then dropping below 85%.

The last modeling simulation scenario evaluated the ability of NAI 10 mg administered prophylactically to minimize the impact of OIRD. NAI 10 mg was administered IM/SC at 60, 30, 15, and 5 min before exposure to the highest fentanyl and carfentanil dose. Maximum ventilation suppression and time to reach maximum ventilation suppression were calculated.

In all simulations, NAI was administered at the defined thresholds or designated times without delay as these products are ready-to-use and do not require assembly. Two hundred simulation trials of 100 subjects each were conducted. The inter-individual variability (IIV) for PK and PD parameters and baseline ventilation identified

from the literature[13–15] was used for buprenorphine, morphine, and fentanyl. The IIVs of relevant carfentanil PK and PD parameters were assumed to be 15%. The statistical summaries and plots focused on the central tendency (median) and its uncertainty (90% confidence interval [CI]).

Analysis software

The naloxone population PK and OIRD mechanistic PK–PD analyses were performed in an environment interfaced by Pirana (version 2.9.4) in which NONMEM (version 7.3), PsN (version 4.6.0), xpose (version 4.5.3), and R (version 3.3.1 or later) were incorporated in an integrated manner for data manipulation, estimation, simulation, and for graphical and statistical summaries.

RESULTS

Population PK modeling of NAI

Following IM/SC administration of naloxone via NAI, the naloxone concentration–time profiles were best described by a two-compartment PK model with three transit absorption compartments and linear first-order elimination from the central compartment. Apparent clearance (CL/F) was allometrically scaled with body weight; no other covariates were found to be significant. Detailed results are provided in the Appendix S1.

Mechanistic PK–PD models of OIRD

The mechanistic PK–PD models for buprenorphine and morphine are three-compartment PK models with combined effect-compartment and receptor kinetics models with linear transduction functions. The fentanyl model is a two-compartment PK model with an effect-compartment link model with a fractional E_{max} PD model. Validation results for the mechanistic PK–PD models of buprenorphine, morphine, and fentanyl are provided in the Appendix S1.

Interspecies allometric scaling was used to predict carfentanil PK parameters due to lack of carfentanil PK in humans. Two PK scenarios were evaluated: Scenario 1 was human carfentanil PK based on mouse data ($t_{1/2}$ ~ 5 h) and Scenario 2 was human carfentanil PK based on rabbit data ($t_{1/2}$ ~ 1 h). The mechanistic carfentanil PK–PD model was a two-compartment PK model with a PD model of a combined effect-compartment and receptor kinetics model with a linear relationship between ventilation and carbon dioxide. Human carfentanil PK and PD model parameters are presented in Table S8. Validation of the constructed model could not be conducted due to a lack of published carfentanil human clinical data.

PK–PD model-based simulations

Different opioid doses

In this simulation, most to all of the subjects met the ventilation thresholds to receive naloxone after exposure to the middle and highest opioid doses, while the lowest opioid doses resulted in a smaller percentage of subjects reaching the predefined ventilation threshold to receive naloxone (Table S9). The ventilation time courses of OIRD reversal with NAI 10 mg, NAI 2 mg, and no naloxone are presented as medians and 90% CIs in Figure 1. The percentage of subjects who recovered and the rescue time required to recover to the predefined ventilation thresholds after NAI administration following opioid exposure are presented in Table 1. For morphine, fentanyl, and carfentanil, a higher percentage of subjects recovered to predefined ventilation thresholds after NAI 10 mg administration compared with NAI 2 mg, except in situations where all subjects recovered. Furthermore, NAI 10 mg resulted in a faster recovery to 40% or 70% of baseline ventilation than when no naloxone or NAI 2 mg was administered for all opioids and doses.

For the highest opioid doses, the median rescue times to restore ventilation to predefined thresholds after NAI 10 mg or NAI 2 mg administration, respectively, were 17 or 212 min (40% of baseline ventilation) and 24 or 370 min (70% of baseline ventilation) for 18.9 μg/kg buprenorphine; 162 or 451 min (40% of baseline ventilation) and 478 or 541 min (70% of baseline ventilation) for 4.2 mg/kg morphine; and 9 or 36 min (40% of baseline ventilation) and 13 or 312 min (70% of baseline ventilation) for 44.1 μg/kg fentanyl. With the middle and highest doses of carfentanil, ventilation was quickly suppressed to ~10% of baseline. As expected, the time course of OIRD reversal after

FIGURE 1 Effect of NAI 10 mg, NAI 2 mg, and no naloxone on ventilation time course for opioid-induced respiratory depression. As soon as the ventilation response dropped below the horizontal dotted line, the naloxone dose was given (i.e., 30% reduction for buprenorphine and 60% reduction for morphine, fentanyl, and carfentanil from ventilation baseline). The solid lines and shaded areas represent the medians and 90% CIs of the median, respectively.

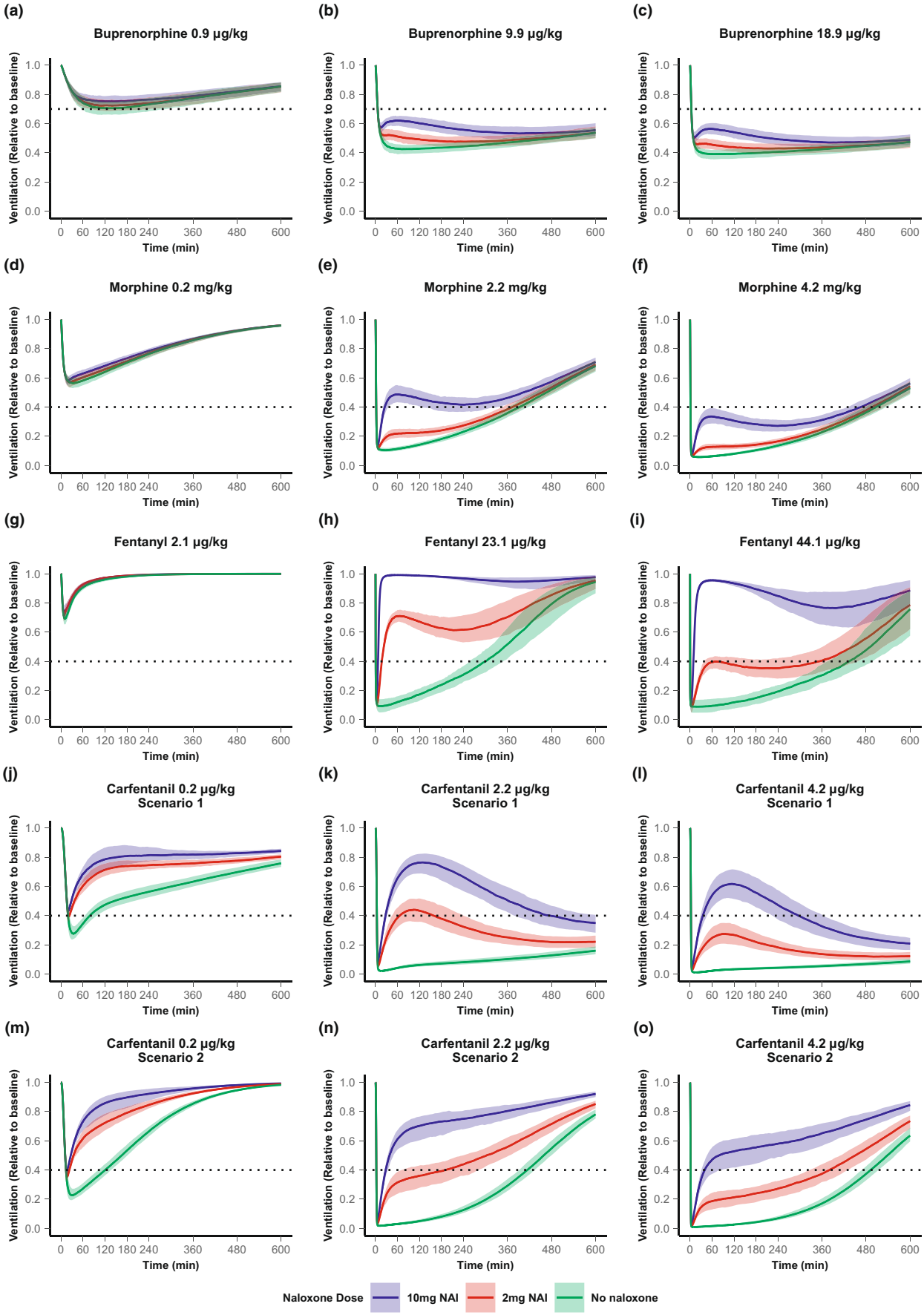
(a)
Buprenorphine 0.9 µg/kg
(b)
Buprenorphine 9.9 µg/kg
(c)
Buprenorphine 18.9 µg/kg
(d)
Morphine 0.2 mg/kg
(e)
Morphine 2.2 mg/kg
(f)
Morphine 4.2 mg/kg
(g)
Fentanyl 2.1 µg/kg
(h)
Fentanyl 23.1 µg/kg
(i)
Fentanyl 44.1 µg/kg
(j)
Carfentanil 0.2 µg/kg
Scenario 1
(k)
Carfentanil 2.2 µg/kg
Scenario 1
(l)
Carfentanil 4.2 µg/kg
Scenario 1
(m)
Carfentanil 0.2 µg/kg
Scenario 2
(n)
Carfentanil 2.2 µg/kg
Scenario 2
(o)
Carfentanil 4.2 µg/kg
Scenario 2
Ventilation (Relative to baseline)
Time (min)
Naloxone Dose
10mg NAI
2mg NAI
No naloxone

TABLE 1 Recovery to 40% or 70% of baseline ventilation following naloxone administration after opioid-induced respiratory depression.

Opioid (IV)	Recovery ventilation threshold (%)	% Subjects who recovered to threshold[a] Median [90% CI]		Rescue time (min)[b] Median [90% CI]	
		NAI 2 mg	NAI 10 mg	NAI 2 mg	NAI 10 mg
Buprenorphine 0.9 μg/kg	40	92.3 [80–100]	93.55 [80–100]	47.65 [13.99–158.39]	9 [6.39–23.4]
	70	55.9 [39.95–73.11]	66.7 [47.34–81.2]	198.1 [44.93–417.19]	29.7 [17.58–75.14]
Buprenorphine 9.9 μg/kg	40	71.1 [62.99–78.03]	69.75 [61.39–78.01]	200.25 [97.5–263.84]	16.15 [8.4–279.4]
	70	16.95 [11–24.11]	25.15 [17.39–32.61]	339.9 [46.5–476.11]	25.95 [16.36–41.62]
Buprenorphine 18.9 μg/kg	40	62.5 [54.89–70.51]	62.3 [53.8–70.21]	212.1 [84.5–286.86]	17.3 [8.6–268.62]
	70	9.8 [5.4–15.11]	16.5 [10.99–23.11]	370 [40.88–504.05]	23.7 [15.98–48.1]
Morphine 0.2 mg/kg	40	100 [100–100]	100 [100–100]	15.8 [11.2–25.41]	8.4 [6.39–11.01]
	70	100 [100–100]	100 [100–100]	237.1 [160.15–299.99]	25.3 [19.5–45.72]
Morphine 2.2 mg/kg	40	94 [90.67–98]	97 [93.86–99]	351.35 [312.77–385.01]	21.9 [18.18–30.83]
	70	48.5 [37.4–55.03]	58 [49–65.03]	506.8 [480.79–529.82]	413.9 [264.69–477.62]
Morphine 4.2 mg/kg	40	77 [69–83]	83 [78–89]	450.9 [422.06–477.07]	161.8 [29.8–365.07]
	70	21 [14.95–27]	29 [21.95–37.1]	540.65 [514.99–563.08]	477.9 [288.23–526.33]
Fentanyl 2.1 μg/kg	40	100 [100–100]	100 [100–100]	3.4 [2.7–4.4]	2.2 [1.7–2.8]
	70	100 [100–100]	100 [100–100]	6 [5.2–7]	3.7 [3.2–4.3]
Fentanyl 23.1 μg/kg	40	95.8 [92.5–99]	100 [98.9–100]	16.7 [14.8–18.7]	6.4 [5.8–6.8]
	70	75.5 [68.8–81.92]	100 [98.9–100]	31.95 [28–37.9]	8.8 [8–9.4]
Fentanyl 44.1 μg/kg	40	72 [65.28–79.41]	99 [97.8–100]	36.2 [29.2–45.81]	9 [8.4–9.8]
	70	54.25 [45.18–63.51]	98.9 [96.8–100]	311.8 [220.55–383.42]	13.4 [12.4–14.6]
Carfentanil Scenario 1 0.2 μg/kg	40	100 [96.2–100]	100 [98.09–100]	15.2 [13.1–17.41]	9.9 [8.59–11.61]
	70	85.7 [79.08–92.5]	96.6 [92.2–100]	41.85 [37.59–48.1]	32.6 [30.09–35.6]
Carfentanil Scenario 1 2.2 μg/kg	40	54.5 [46.5–62.01]	81 [73.98–87]	26 [22–30.23]	19.85 [17.8–22.8]
	70	26.3 [19.19–34.33]	58 [49–65.32]	48.6 [41.8–56.43]	42.45 [39–47.01]
Carfentanil Scenario 1 4.2 μg/kg	40	37 [30–46]	68 [59.95–75]	28.2 [23.59–33.6]	22 [19.09–24.61]
	70	15 [9.96–22.05]	43 [34.28–52]	50.45 [41.4–59.9]	45 [39.79–49.2]
Carfentanil Scenario 2 0.2 μg/kg	40	100 [100–100]	100 [100–100]	15.4 [13.29–18.21]	10.2 [8.8–11.91]
	70	100 [100–100]	100 [100–100]	47.45 [41.58–59.78]	33.4 [30.9–37.2]
Carfentanil Scenario 2 2.2 μg/kg	40	98 [95–100]	99 [97.95–100]	165.6 [55.99–266.11]	24.8 [22.1–30.22]
	70	81 [75–87]	91.9 [87–95]	417.7 [360.81–453.61]	78.75 [57.4–192.11]
Carfentanil Scenario 2 4.2 μg/kg	40	91 [86–95]	96 [92–99]	338.5 [277.43–389.6]	34.75 [27.09–57.44]
	70	57 [48–65]	76 [68.95–82]	474.9 [431.74–507.18]	175.35 [68.53–320.04]

Note: Scenario 1: carfentanil $t_{1/2}$ = ~5 h; Scenario 2: carfentanil $t_{1/2}$ = ~1 h.

Abbreviations: CI, confidence interval; IV, intravenous; NAI, naloxone auto-injector.

[a]Based on subjects who received a naloxone dose at the threshold level (i.e., at a 30% reduction from baseline ventilation for buprenorphine and a 60% reduction from baseline ventilation for morphine, fentanyl, and carfentanil).

[b]Rescue time: The difference between the timepoint when naloxone is first administered and when ventilation first recovered back above the threshold (40% or 70% of baseline ventilation).

NAI administration was different based on the half-life of carfentanil. Specifically, for Scenario 1 ($t_{½}$ ~ 5 h), ventilation rapidly recovered initially to 40% or 70% of baseline but, by 2 h post-carfentanil exposure, it began to decline again due to the long carfentanil half-life, whereas in Scenario 2 ($t_{½}$ ~ 1 h), the ventilation also rapidly recovered initially, then continued recovering toward baseline rather than declining (Figure 1). Median rescue times after NAI

10 mg or NAI 2 mg administration, respectively, for 4.2 μg/kg carfentanil were 22 or 28 min (40% of baseline ventilation) and 45 or 50 min (70% of baseline ventilation) for Scenario 1 and 35 or 339 min (40% of baseline ventilation) and 175 or 475 min (70% of baseline ventilation) for Scenario 2.

Second dose of NAI 10 mg

The cumulative effect of a second dose of NAI 10 mg on OIRD was evaluated to represent situations where a single dose is not sufficient to reverse respiratory depression and/or there is a risk of renarcotization. A second NAI 10 mg was administered at 60 min after exposure to the highest opioid doses in subjects who received an initial dose of NAI 10 mg. Ventilation versus time profiles (medians and 90% CIs) for the effect of two NAI 10 mg on OIRD are presented in Figure 2. The time for renarcotization to occur after administration of a second NAI 10 mg at 60 min was compared with a single NAI 10 mg in Table 2. The data for buprenorphine and morphine should be interpreted with caution as there were low percentages of subjects who recovered to 85% ventilation with one or two doses of NAI 10 mg.

A second NAI 10 mg contributed to further recovery from buprenorphine-induced respiratory depression, but the reversal effect was minimal, and eventually, the ventilation declined again due to the slow dissociation kinetics of buprenorphine. A larger percentage of subjects recovered to at least 85% of baseline ventilation when administered two NAI 10 mg versus one. Regardless of the number of naloxone doses received, the percentage of subjects who experienced renarcotization was similar, but the time to renarcotization was prolonged when two NAI 10 mg were administered instead of one (259 vs. 184 min, respectively).

A second NAI 10 mg contributed to further recovery from morphine-induced respiratory depression; however, ventilation began to decline again around 2 h and at ~6 h post-morphine exposure, ventilation slowly began to return toward baseline. A larger percentage of subjects recovered to at least 85% of baseline ventilation when administered two NAI 10 mg (12%) vs. one (6%) and the time to renarcotization was prolonged with two NAI 10 mg compared with one (190 vs. 122 min, respectively).

When exposed to fentanyl, a second NAI 10 mg resulted in 100% of subjects recovering to at least 85% of baseline ventilation compared with 94% with one NAI 10 mg. Two NAI 10 mg resulted in a lower percentage of subjects experiencing renarcotization compared with a single dose (40% vs. 51%, respectively) and a prolonged time to renarcotization (304 vs. 156 min, respectively).

Administration of a second NAI 10 mg contributed to a faster transient improvement in OIRD after exposure to carfentanil with a half-life of ~1 h (Scenario 2) and

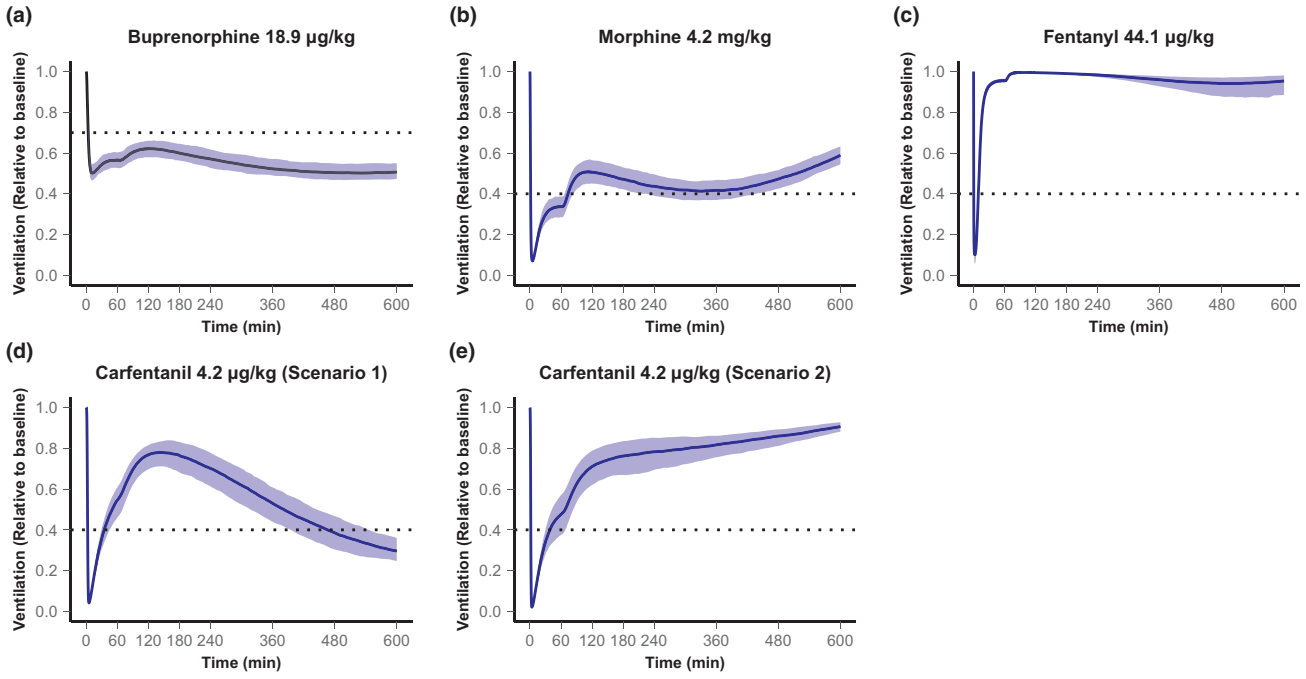

FIGURE 2 Effect of a second dose of NAI 10 mg on ventilation time course for opioid-induced respiratory depression. As soon as the ventilation response dropped below the horizontal dotted line, the first naloxone dose was given (i.e., 30% reduction for buprenorphine and 60% reduction for morphine, fentanyl, and carfentanil from ventilation baseline) and the second naloxone dose was given at 60 min following opioid exposure. The solid line and shaded area represent the median and 90% CI of the median, respectively.

TABLE 2 Impact of two NAI 10 mg doses on renarcotization following opioid-induced respiratory depression.

Opioid	Opioid dose (IV)	# of NAI 10 mg doses	% Subjects who recovered to at least 85% ventilation[a] Median [90% CI]	% Subjects who experienced renarcotization[b] Median [90% CI]	Time to renarcotization (min)[c] Median [90% CI]
Buprenorphine	18.9 μg/kg	1	6.2 [2.2–10.5]	66.7 [28.42–100]	183.65 [102.76–298.98]
		2	11.7 [6.5–16.8]	69 [45.4–90.9]	258.8 [177.5–340.3]
Morphine	4.2 mg/kg	1	6 [3–11]	25 [0–55.67]	121.65 [66.94–229.07]
		2	12 [7–18]	37.5 [14.25–62.5]	190 [143.72–301.66]
Fentanyl	44.1 μg/kg	1	93.6 [88.8–97.9]	51.2 [41.88–60.53]	155.5 [135.2–177.21]
		2	100 [98.9–100]	39.9 [31.2–48.52]	303.7 [279.6–338.18]
Carfentanil (Scenario 1)	4.2 μg/kg	1	26.3 [20–34.05]	90.25 [78.27–100]	296.2 [242.32–352.31]
		2	41.2 [33–48]	81.8 [72.06–91.72]	340.65 [295.39–390.62]
Carfentanil (Scenario 2)	4.2 μg/kg	1	50.25 [40.38–58]	4.3 [0–10.91]	289.8 [189.16–418.57]
		2	67 [59–74]	4.2 [0–7.53]	334.2 [218.6–438.98

Note: Scenario 1: carfentanil $t_{1/2}$: ~5 h; Scenario 2: carfentanil $t_{1/2}$: ~1 h.

Abbreviations: CI, confidence interval; IV, intravenous; NAI, naloxone auto-injector.

[a]Among subjects who received naloxone dose.

[b]Among subjects who recovered to at least 85% of baseline ventilation.

[c]If the percentage of subjects who experienced renarcotization was zero per simulation, it was excluded to calculate a statistical summary of the time of renarcotization. Renarcotization was defined by ventilation returning to above 85% baseline and then dropping below 85%.

prolonged improvement in ventilation after exposure to carfentanil with a half-life of ~5 h (Scenario 1), but only slightly decreased the percentage of subjects experiencing renarcotization for Scenario 1 (82% with two NAI 10 mg vs. 90% with one). In both carfentanil scenarios, a larger percentage of subjects recovered to 85% of baseline ventilation when administered two NAI 10 mg vs. one. Similarly, for both scenarios, two NAI 10 mg resulted in delayed renarcotization compared with a single NAI 10 mg (Scenario 1: 341 vs. 296 min, Scenario 2: 334 vs. 290 min, respectively).

Injection time of NAI 10 mg prior to opioid exposure

The ability of NAI 10 mg to impact ventilation when administered prior to fentanyl or carfentanil exposure was evaluated. NAI 10 mg was administered 60, 30, 15, or 5 min before exposure to 44.1 μg/kg fentanyl or 4.2 μg/kg carfentanil. Ventilation vs. time profiles (medians and 90% CIs) are presented in Figure 3 and maximum ventilation suppression and time to reach maximum ventilation suppression are presented in Table 3.

The impact of naloxone on fentanyl-induced respiratory depression is dependent on the time of naloxone administration relative to fentanyl exposure. When NAI 10 mg was administered 5 min prior to fentanyl exposure, fast-acting fentanyl caused a maximum ventilation suppression of 49% of baseline since naloxone was still being absorbed. Administration of NAI 10 mg at 15 or 30 min prior to fentanyl exposure minimized fentanyl-induced respiratory depression so ventilation remained near normal (83–84% of baseline). With administration of NAI 10 mg at 60 min prior to fentanyl exposure, the maximum ventilation suppression was 77% of baseline suggesting naloxone clearance is impacting its ability to suppress fentanyl-induced respiratory depression.

Overall, NAI 10 mg prevented the profound respiratory depression that is expected with a lethal carfentanil dose. When NAI 10 mg was administered 15 min prior to carfentanil, the maximum ventilation suppression was about 55% of baseline for Scenario 1 and 45% of baseline for Scenario 2. After initial stabilization in ventilation (at ~60–90 min post-opioid exposure), additional carfentanil toxicity was observed in Scenario 1 due to carfentanil's ~5-h half-life, resulting in more profound respiratory depression. In Scenario 2, severe respiratory depression was mitigated; however, the extent of initial ventilation suppression was greater than in Scenario 1 (36% vs. 46% of baseline, respectively). Additional carfentanil toxicity was not observed in Scenario 2 due to carfentanil's ~1-h half-life.

DISCUSSION

Opioid exposure results in CNS and respiratory depression, where the extent of symptoms can vary (e.g., drowsiness to

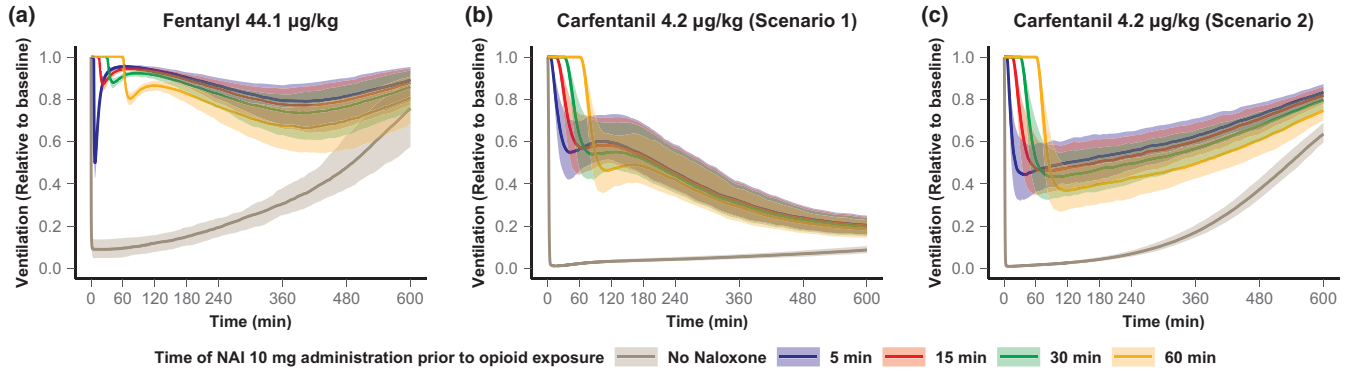

FIGURE 3 Ventilation time course for NAI 10 mg administration prior to fentanyl or carfentanil exposure. The solid lines and shaded areas are medians and 90% CIs of median, respectively from 200 simulation trials of 100 subjects per each simulation. Time represents the time since administration of NAI 10 mg.

TABLE 3 Maximum ventilation suppression and time following administration of NAI 10 mg prior to fentanyl or carfentanil exposure.

Opioid	Opioid dose (IV)	NAI dose	Time of naloxone administration prior to opioid exposure (min)	Maximum ventilation suppression[a] Median [90% CI]	Time to reach maximum ventilation suppression (min)[b] Median [90% CI]
Fentanyl	44.1 µg/kg	0	NA	0.09 [0.05–0.14]	9.9 [9–10.9]
		10 mg	5	0.49 [0.42–0.56]	2.6 [2.4–2.7]
			15	0.83 [0.8–0.86]	8.9 [7.7–10.1]
			30	0.84 [0.81–0.86]	12.7 [10.9–15.2]
			60	0.77 [0.73–0.8]	13.3 [11.5–15.2]
Carfentanil (Scenario 1)	4.2 µg/kg	0	NA	0.01 [0.01–0.01]	15.8 [15.59–16.3]
		10 mg	5	0.54 [0.42–0.69]	38.9 [32.5–46.43]
			15	0.55 [0.43–0.71]	54.05 [44.7–88.3]
			30	0.53 [0.41–0.68]	55.3 [45.98–78.1]
			60	0.46 [0.35–0.63]	50.65 [42.6–59.8]
Carfentanil (Scenario 2)	4.2 µg/kg	0	NA	0.01 [0.01–0.01]	10 [9.7–10.3]
		10 mg	5	0.42 [0.31–0.56]	29.35 [22–43.61]
			15	0.45 [0.34–0.57]	62.65 [46.58–83.67]
			30	0.42 [0.32–0.54]	65.2 [50.48–86.3]
			60	0.36 [0.26–0.48]	57.9 [45.2–59.8]

Note: Scenario 1: carfentanil $t_{1/2}$: ~5 h; Scenario 2: carfentanil $t_{1/2}$: ~1 h.

Abbreviation: NA, not applicable.

[a]Maximum ventilation suppression (relative to baseline).

[b]Time between opioid exposure and maximum ventilation suppression.

incapacitation, slow/shallow breathing to no respiration). The speed and severity of OIRD are affected by the opioid dose, type of opioid and its metabolites, route of opioid administration, and drug interactions. The use of high-potency opioids or large quantities of opioids has resulted in the need for higher doses of naloxone to reverse OIRD. The extent of naloxone's response is determined by a combination of naloxone and opioid PK and PD characteristics, including equilibrium rates during biophase distribution and receptor kinetics for naloxone and the opioid. The objective of this analysis was to evaluate the ability of 10 mg of naloxone administered IM via an auto-injector (NAI 10 mg) to reverse OIRD using PK–PD model-based simulations. The simulated clinical scenarios included different IV doses of four opioids representing a spectrum of activity in terms of agonist potential and potency. Intravenous administration of opioids results in 100% bioavailability and therefore

provides the highest possible systemic exposure compared with other routes of administration (i.e., worst case).

The population naloxone PK model in this analysis is a two-compartment model with three transit absorption compartments and linear first-order elimination from the central compartment. A two-compartment model has been reported in the literature for naloxone after IV administration.[13] In the current analysis, the CL/F of naloxone following IM/SC administration using NAI was 3.26 L/min while the published reported clearance of naloxone following IV administration was 3.45 L/min.[13] The estimates of the apparent total volume of distribution (Vd/F) was ~486 L, which is larger than the total Vd following IV administration reported in the literature (i.e., 114 L).[13] The difference in clearance and volumes of distribution between the current analysis and literature may be explained by the different routes of administration (IM vs. IV) and the bioavailability of IM naloxone. In one published study, the bioavailability of IM naloxone was reported as 35–36% compared with IV.[20] With consideration of the bioavailability of IM administration using NAI, the estimated CL is slightly smaller, and the volume of distribution is larger, but overall, the difference is not considered significant. During model development, body weight was identified as a significant covariate on CL/F, but the impact of body weight on CL/F and thereby the area under the naloxone plasma concentration–time curve (AUC) was determined as not clinically significant. Therefore, in the model simulations, body weight in the virtual population was fixed at 70 kg. A consideration to note, while a dose-linear naloxone population PK model was considered adequate to represent the clinical data in this analysis, a more-than-dose-proportional increase in C_{max} was observed in the NAI 10 mg clinical study (i.e., dose-normalized geometric mean ratio [90% CI] for C_{max} of 1.21 [1.07, 1.37] for 10 mg and 2 mg). Adjusting the naloxone population PK model to account for this may result in even faster recovery to defined rescue ventilation thresholds.[23]

Mechanistic PK–PD models of the effect of opioids (buprenorphine, morphine, and fentanyl) on ventilation, the PD end point, were constructed and validated. Binding kinetic models for ventilation were used for buprenorphine and morphine, and a fractional E_{max} model was used for fentanyl according to the literature.[13–15] The E_{max} model for fentanyl was selected because it was already developed and validated on fentanyl-induced respiratory depression as reported in the literature.[15] Also, receptor binding assay results show that fentanyl has rapid equilibrium (within 10 min) and dissociation ($t_{1/2}$ ~ 6.8 min), with complete dissociation by 1 h.[22] Per the literature, the binding receptor kinetics of fentanyl would be faster than morphine, and the order of difficulty for naloxone reversal would be buprenorphine > morphine > fentanyl.[14] This was also demonstrated in the current modeling analysis. To account for the competitive binding of naloxone and fentanyl at the same MOP receptor, a competitive ligand binding model[24] was used.

There is limited published human PK and PD data on carfentanil. Therefore, the same PK model structure as fentanyl (two-compartmental PK model) was used with the assumption that the PK behaviors (similar distribution) are the same between fentanyl and carfentanil as carfentanil is a fentanyl analog with similar lipophilicity. The carfentanil PK parameters in humans were extrapolated with an interspecies allometric scaling method using reported IV data in the same species (mouse and rabbit) for both carfentanil and fentanyl. This approach led to the prediction of two different sets of carfentanil PK parameters (CL and V) in humans. In Scenario 1, the carfentanil half-life was estimated to be ~5 h, consistent with a carfentanil human case report.[25] In Scenario 2, the carfentanil half-life was estimated to be ~1 h, consistent with a paper that reported human PK data up to 90 min post-opioid exposure.[26] Overall, the simulation outcomes in Scenario 1 illustrated the naloxone reversal effect of OIRD in the presence of carfentanil with a longer duration of action (due to a longer half-life). In Scenario 2, the short carfentanil half-life and smaller V1 (central compartment volume) resulted in the simulation outcomes representing a worst-case scenario around its maximum concentration (observed as a sharp decline in ventilation), but a rapid reversal of carfentanil-induced-respiratory depression by NAI 10 mg due to carfentanil's short half-life even with its slow dissociation kinetics.

In the first two simulation scenarios, naloxone was immediately administered IM/SC (representative of proper NAI use) once ventilation dropped below the predefined threshold following IV administration of the opioid. After naloxone administration following exposure to high opioid doses, ventilation continued to drop briefly due to the time necessary for naloxone to be absorbed from the injection site and cross the blood–brain barrier (biophase distribution). Severe acute hypoxemia and subsequent naloxone resistance were not evaluated because there was no delay in administering naloxone and the model did not presume a delay in providing naloxone treatment.

In the first simulation scenario, NAI 10 mg administration resulted in a faster return to 40% and 70% ventilation thresholds for all opioids and doses compared with NAI 2 mg. Similarly, a higher percentage of subjects recovered back to the 70% ventilation rescue threshold for the two highest opioid doses after NAI 10 mg administration compared with NAI 2 mg. Overall

with the lowest buprenorphine, morphine, and fentanyl doses, smaller percentages of subjects reached the defined ventilation threshold requiring naloxone administration, and little or no differences in the percentage of subjects that recovered back to the thresholds were observed for NAI 10 mg and NAI 2 mg. Therefore, subsequent simulation scenarios were conducted using only the highest opioid doses.

In the second simulation scenario, administration of a second NAI 10 mg at 60 min post-opioid exposure resulted in further ventilation recovery with a higher percentage of subjects reaching the defined thresholds with faster rescue times. For long-acting opioids with slow unbinding kinetics (e.g., buprenorphine, carfentanil [Scenario 1]), there is likely a risk of renarcotization even with two NAI 10 mg because of naloxone's short half-life resulting in a shorter duration of action than that of the opioid. However, these simulations demonstrated a significant duration of response after the administration of a single NAI 10 mg and a longer delay of renarcotization after a second NAI 10 mg was administered 60 min post-opioid exposure. The carfentanil PK–PD simulation results obtained in these first two simulation scenarios are comparable to study results evaluating carfentanil-induced respiratory depression in non-human primates, their recovery using a human equivalent of 10 mg of naloxone, and the potential of renarcotization (animal data, unpublished).

In the last simulation scenario, NAI 10 mg administration at each timepoint prior to opioid exposure reduced the initial respiratory depressive-effect of fentanyl or carfentanil. Naloxone is slightly less effective in reducing OIRD when administered 5 or 60 min prior to fentanyl exposure, since at the time of fentanyl administration naloxone is still being absorbed or has already begun to be cleared, respectively. Prophylactic administration of naloxone before carfentanil exposure prevented profound respiratory depression; however, in the simulation with a carfentanil half-life of 5 h, the mitigating effects of naloxone were limited and increased respiratory depression is predicted after ~2 h post-opioid exposure.

The development of these mechanistic opioid-naloxone PK–PD models provides a framework to evaluate other aspects of opioid-naloxone interactions and will facilitate the development of other models exploring different routes of administration (for opioid and/or naloxone). Future modeling studies could investigate the impact of biological factors such as chemoreceptors that influence the ventilation response to changes in oxygen and CO_2 levels (e.g., hypoxic environments), opioid metabolites that may impact the duration or extent of respiratory depression, or genotypic variations of enzymes that influence opioid metabolism. Known drug interactions (e.g., benzodiazepine-opioid or alcohol-opioid) that may influence respiration could also be evaluated in future modeling. As described in Reference [23], the FDA developed a PK–PD naloxone–opioid model that included different physiological conditions, rescue end points, naloxone administration timing, route of opioid administration, and the basis of the carfentanil PK model. They conducted independent simulations using their model. The FDA's analysis further supports the data presented in this aricle and the clinical efficacy of NAI 10 mg and illustrates that the use of PK–PD modeling to evaluate the antagonistic effects of drug dosing schemes is beneficial, especially when clinical studies are unethical.[23]

Overall, the PK–PD model-based simulation results provided evidence that NAI 10 mg can reverse respiratory depression caused by exposure to high-potency opioids, even at doses surpassing lethal levels; NAI 10 mg reduces the risk of renarcotization by these opioids; and if used prophylactically, NAI 10 mg could help prevent profound OIRD caused by high-potency opioids.

AUTHOR CONTRIBUTIONS

T.E.Y., B.G., and C.K. wrote the manuscript; T.E.Y., J.Z., J.K., S.M.L., L.I., B.G., and C.K. designed the research; T.E.Y., F.D.B., and S.M.L. performed the research; T.E.Y., F.D.B., and S.M.L. analyzed the data.

ACKNOWLEDGMENTS

The authors would like to thank the U.S. Department of Defense for funding this study and providing editorial support. Portions of this article were presented as a poster at ACoP13 in Aurora, CO, October 2022.

FUNDING INFORMATION

Funding to support the creation of the models, simulations, and associated analyses was received from the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND). The views expressed in this article reflect the views of the authors and do not necessarily reflect the position of the Department of the Army, Department of Defense (DoD), or the US Government. References to non-federal entities do not constitute or imply DoD or Army endorsement of any company or organization.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yang TE, Del Bene F, Lavezzi SM, et al. Mechanistic pharmacokinetic–pharmacodynamic modeling and simulations of naloxone auto-injector 10 mg reversal of opioid-induced respiratory depression. *CPT Pharmacometrics Syst Pharmacol*. 2024;13:1722-1733. doi:10.1002/psp4.13215