ANESTHESIOLOGY

Opioid Overdose: Limitations in Naloxone Reversal of Respiratory Depression and Prevention of Cardiac Arrest

Maarten van Lemmen, B.Sc., Jeffrey Florian, Ph.D., Zhihua Li, Ph.D., Monique van Velzen, Ph.D., Eveline van Dorp, M.D., Ph.D., Marieke Niesters, M.D., Ph.D., Elise Sarton, M.D., Ph.D., Erik Olofsen, Ph.D., Rutger van der Schrier, M.D., David G. Strauss, M.D., Ph.D., Albert Dahan, M.D., Ph.D.

ANESTHESIOLOGY 2023; 139:342–53

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ABSTRACT

Opioids are effective analgesics, but they can have harmful adverse effects, such as addiction and potentially fatal respiratory depression. Naloxone is currently the only available treatment for reversing the negative effects of opioids, including respiratory depression.

However, the effectiveness of naloxone, particularly after an opioid overdose, varies depending on the pharmacokinetics and the pharmacodynamics of the opioid that was overdosed. Long-acting opioids, and those with a high affinity at the μ-opioid receptor and/or slow receptor dissociation kinetics, are particularly resistant to the effects of naloxone. In this review, the authors examine the pharmacology of naloxone and its safety and limitations in reversing opioid-induced respiratory depression under different circumstances, including its ability to prevent cardiac arrest.

(ANESTHESIOLOGY 2023; 139:342–53)

Naloxone, a Narcotic Antagonist

Naloxone, *N*-allylnoroxymorphone (fig. 1), is currently the most important drug to reverse the effects of an opioid overdose. It was first synthesized in 1960 and further developed through the early 1970s in a successful effort to find a strong narcotic antagonist without negative side effects.[1] In contrast to the earlier antagonist nalorphine (*N*-allylmorphine), a derivative of morphine, naloxone was the first antagonist without any agonistic opioid activity.[2,3] Nalorphine and another early-developed opioid-receptor antagonist, nalbuphine, are partial antagonists and reverse the typical morphine effects at low dose but at high dose produce analgesia and other opioid side effects such as respiratory depression. Naloxone is a nonselective, competitive opioid antagonist at μ-, κ- and δ-opioid receptors but not at the atypical fourth opioid receptor, the nociceptin receptor.[2,3] As previously demonstrated and consistent with classical receptor theory, naloxone produces a rightward shift of the opioid dose-response curve.[4] In fact, 0.8 mg intravenous naloxone fully reversed 10 mg morphine-induced depression of the ventilatory response to inhaled carbon dioxide, a biomarker of opioid effect at the ventilatory control system.[4] However, naloxone has a relatively short half-life (32 min), which can result in renarcotization (return of opioid effect) when antagonizing long-acting opioids, such as high-dose fentanyl.[4]

Naloxon was originally available for injection by intravenous, subcutaneous or intramuscular routes of administration. More recently, the U.S. Food and Drug Administration (Silver Spring, Maryland) approved intramuscular autoinjectors and intranasal naloxone, including over-the-counter intranasal naloxone, for treatment of opioid overdose and

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Submitted for publication March 25, 2023. Accepted for publication May 9, 2023. Published online first on July 4, 2023.

Maarten van Lemmen, B.Sc.: Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

Jeffrey Florian, Ph.D.: Division of Applied Regulatory Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland.

Zhihua Li, Ph.D.: Division of Applied Regulatory Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland.

Monique van Velzen, Ph.D.: Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

Eveline van Dorp, M.D., Ph.D.: Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

Marieke Niesters, M.D., Ph.D.: Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

Elise Sarton, M.D., Ph.D.: Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

Erik Olofsen, Ph.D.: Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

Rutger van der Schrier, M.D.: Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

David G. Strauss, M.D., Ph.D.: Division of Applied Regulatory Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland.

Albert Dahan, M.D., Ph.D.: Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

 Anesthesiology 2023; 139:342–53. DOI: 10.1097/ALN.0000000000004622

<zdoi;10.1097/ALN.0000000000004622>

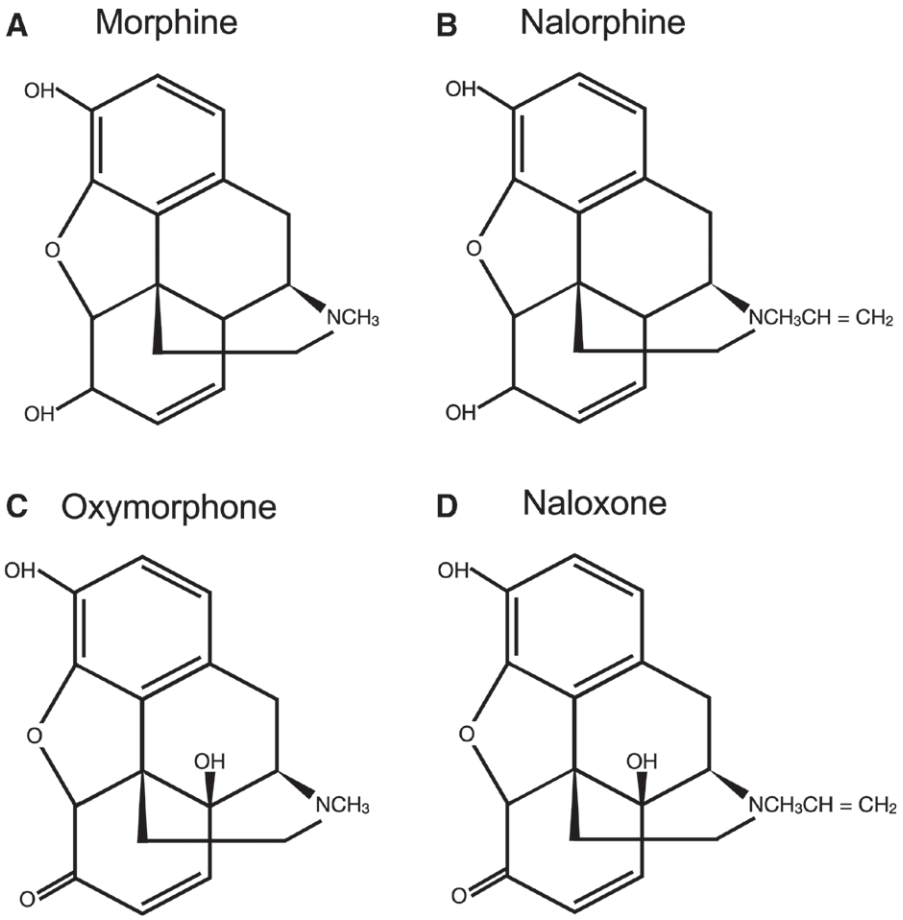

Fig. 1. Chemical structures of four opioids: morphine (*A*), nalorphine (*B*), oxymorphone (*C*), and naloxone (*D*).

opioid use disorder. In recent years, knowledge on the pharmacokinetic and pharmacodynamic properties of naloxone has increased, and various limitations in its practical use were identified. For example, there are a series of conditions in which the effectiveness of naloxone as an opioid reversal agent is limited. These are predominantly related to the findings that the speed and magnitude of opioid reversal is dictated by opioid receptor association and dissociation kinetics, defined by rate constants K_{ON} and K_{OFF}, respectively, with limitations in reversal when K_{OFF} values are low, causing difficulty in dissociating the opioid from its receptor.[5,6] Moreover, the effect is delayed after intramuscular and intranasal administration compared to the intravascular route. Additionally, naloxone has a reduced ability to reverse the deleterious nonopioid effect when opioids are combined with nonopioid centrally acting depressants (cointoxication) such as ethanol, benzodiazepines, α_2-agonists, or antidepressants.[7,8]

Opioids are highly effective analgesics, but their use is accompanied by undesirable side effects that include dependence and potentially lethal respiratory depression. These two side effects are a particularly lethal combination, which contributed to the current opioid crisis in the United States, Canada, and certain European countries, and are responsible for hundreds of daily opioid deaths.[9] When individuals overdose on a potent opioid, their breathing will initially become irregular, then cyclic, and after a period of gasping will become apneic. This is due to initial slowing and subsequent cessation of rhythmic respiratory activity from activation of μ-opioid receptors expressed on neurons within the respiratory networks of the brainstem.[10–12] Respiratory depression leads to asphyxia (a combination of hypoxia and hypercapnia), which may cause dysrhythmias, bradycardia, cardiac ischemia, and cardiorespiratory collapse, and when no rescue is initiated, will progress into an inevitable death. Depending on the condition of the patient, rescue may include cardiopulmonary resuscitation (chest compressions), artificial ventilation (mouth-to-mouth resuscitation, mask ventilation or intubation and assisted ventilation), and administration of opioid antagonists, most commonly naloxone. The success of rescue depends on many factors such as opioid dose, degree of opioid tolerance, the opioid

affinity at the opioid receptor, cointoxication, comorbidities, timing of rescue, and experience of rescuers, among others. In most cases, naloxone is administered to improve or restore spontaneous breathing and prevent the sequence leading to a circulatory arrest. Note that the pathophysiology, patient demographics, and management of an opioid-induced cardiac arrest differ from those of an ischemic arrest related to an atherosclerotic plaque rupture.[13] In the case of an opioid-induced cardiac arrest, effective chest compressions with return of circulation is pivotal to enable naloxone to reach the brainstem to dissociate the opioid from its receptor. However, there are suggestions that in the event of a cardiac arrest, use of naloxone during a standard resuscitation (including assisted ventilation) is of limited benefit, and standard resuscitation medication suffices for restoration of cardiac activity.[13] Still, this is debatable, since while circulation might resume, opioid receptor occupancy persists, and the subject remains at risk without any pharmacologic intervention. The many deaths from opioids indicate that rescue from respiratory depression is often ineffective or too late (or not initiated). Interestingly, survival after an opioid-related out-of-hospital cardiac arrest is greater than after an arrest from other causes, indicating that those that overdose on an opioid are more resilient and younger with less comorbidities than other populations experiencing a cardiac arrest, although misdiagnosis in some cases cannot be excluded.[13] Surprisingly, there is a lack of data on the effect of opioid overdose on brain function in individuals who survive an opioid-related cardiac arrest, as we suspect serious brain damage in a large proportion of overdose cases.

This review will examine the pharmacology of naloxone and its effectiveness and limitations in reversing opioid-induced respiratory depression under various conditions. We will also discuss its ability to prevent cardiac arrest and briefly mention potential naloxone alternatives.

Naloxone Pharmacokinetics and Pharmacodynamics

Oral naloxone has a low bioavailability (less than 5%), which increases to 25% after nasal administration and a variable albeit higher bioavailability after intramuscular administration.[3,14] First-pass elimination is high (greater than 95%). Given its poor absorption and high metabolic breakdown, naloxone is not suitable for sublingual or oral administration. Still, also for the other administration routes, relatively high doses are needed to rapidly reach effective central concentrations after administration. Naloxone is primarily metabolized in the liver, while about one third of the dose is excreted unchanged *via* the kidney. In the liver, naloxone is glucuronidated into the inactive compound naloxone-3-glucuronide and to a minor extent metabolized by *N*-dealkylation and 6-oxo group reduction.[3] As stated above, naloxone elimination half-life is short. In several studies in healthy young participants, we performed population pharmacokinetic model analyses of naloxone using two compartment models. Typical model parameter estimates were an elimination clearance of 3.5 l/min (in a 70-kg individual) and volume of distribution of 1.6 to 1.8 l/kg.[15,16] Similar elimination clearance estimates were later observed when studying high-dose naloxone (3.4 l/min) but with a somewhat greater volume of distribution (2.7 l/kg),[17] which may be explained by differences in naloxone sampling schemes. An important model parameter derived from pharmacokinetic or pharmacodynamic data analysis is parameter $t½k_{e0}$ (= $\ln 2/k_{e0}$) which is the arterial blood to effect-site equilibration half-life. Parameter $t½k_{e0}$ describes the hysteresis or the lag between changing drug concentrations and effect and is 5 to 8 min for naloxone.[15,16] This predicts a rapid onset as well as a rapid offset of action. Although the duration of action may depend on the dose and the elimination half-life (30 to 45 min), the onset of effect as concentrations are increasing and offset of effect as concentrations are decreasing depend on the pharmacodynamics, which is affected by access to the site of drug action and receptor kinetics.

Receptor Kinetics

At effective doses, naloxone will reverse the opioid effects, and consequently will cause loss of analgesia and respiratory depression and at a high dose may precipitate withdrawal symptoms in chronic opioid users. Its affinity for the different opioid receptors varies with affinity constants (Ki) approximately 1.2 nM for the μ-opioid receptor and greater than 10 nM for the κ- and δ-opioid receptors; naloxone has no affinity for the nociception receptor.[3] Ki represents the drug concentration at which 50% of the receptors are occupied (in equilibrium). Since the opioid activation of the μ-receptor is most relevant to respiratory depression, the remainder of the discussion focuses on naloxone reversal of μ-opioid agonistic effects. The magnitude and speed at which naloxone reverses an opioid overdose depend on factors that are related to the opioid that requires reversal. These pharmacologic factors include the opioid pharmacokinetics, opioid dose, the opioid affinity for the μ-opioid receptor, and its potency at the receptor. So, naloxone effectiveness differs under varying conditions. For the discussion, it is important to know the values of μ-opioid receptor affinity constant Ki and rate constant K_{OFF} of some relevant opioids. Volpe *et al.*[18] separated clinically used opioids into three categories according to their μ-opioid receptor affinities (table 1): low affinity, Ki greater than 100 nM, which includes codeine (Ki 734 nM) and meperidine (450 nM); low-to-intermediate affinity, 1 less than Ki less than 100 nM, which includes oxycodone (25.9 nM), methadone (3.38 nM), fentanyl (1.35 nM), and morphine (1.17 nM); and high affinity, Ki less than 1 nM, which includes hydromorphone (0.37 nM), buprenorphine (0.22 nM), sufentanil (0.14 nM), and carfentanil (0.05 nM).[18,19] K_{OFF} is a model parameter determined from mechanism-based pharmacokinetic or

Table 1. μ-Opioid Receptor Affinities and Receptor Dissociation Constants of Different Opioids[6,15,17–19]

	Receptor Affinities (nM)	Receptor Dissociation Constants (s^{-1})
Codeine	734	
Meperidine	450	
Oxycodone	25.9	
Methadone	3.38	
Fentanyl	1.35	0.004
Morphine	1.17	0.002
Hydromorphone	0.37	
Buprenorphine	0.22	0.0002
Sufentanil	0.14	0.001
Carfentanil	0.05	0.00025
Naloxone	1.1	0.040

pharmacodynamic modeling studies. Relevant K_{OFF} values are naloxone 0.040 s^{-1}, fentanyl 0.004 s^{-1}, sufentanil 0.001 s^{-1}, and carfentanil 0.00025 s^{-1}.[6,20] It can generally be assumed that opioids with a high affinity for the μ-opioid receptor have low K_{OFF} values (0.001 s^{-1} or less).[16,20]

Naloxone Reversal Scenarios

We here give several specific naloxone reversal scenarios that depend on the circumstances that warrant reversal, such as (1) an opioid overdose in the perioperative setting, (2 and 3) the community setting in which fentanyl or a high-affinity opioid is overdosed, (4) the reversal of an opioid partial agonist, (5) reversal in case of a cointoxication with a tranquilizer, and (6) reversal in case of brain hypoxia. We refrain from discussing accidental exposure to fentanyl by skin contact or accidental inhalation of fentanyl powder,[21] or treatment of mass casualties from intentional release of aerosolized high-affinity opioids in the environment.[22]

(1) Perioperative (Moderate) Respiratory Depression

In clinical practice, particularly at the end of surgery, opioid concentrations at the receptor are often just above the threshold for neuronal depression with consequently an absence of respiratory rhythmic activity.[5] Hence, administration of multiple relatively low naloxone doses (40 to 120 μg), titrated to effect, are adequate to restore rhythmic breathing activity. An intravenous route in the clinical setting is preferred above other routes of administration, as perioperative patients all have an intravenous access line. Since respiratory effect occurs at a higher receptor occupancy than analgesia,[5] this approach will have a limited effect on pain relief up to intravenous naloxone doses of 0.4 mg. For example, intravenous naloxone doses of 0.2 to 0.4 mg fully and rapidly (within 4 min) reverse 0.15 mg/kg morphine-induced respiratory depression in healthy human volunteers.[15] This morphine dose is commonly used to prevent occurrence of postoperative pain.

(2) Long-acting Potent Opioids with Low-to-intermediate Affinity for the μ-Opioid Receptor

In case of a fentanyl overdose in the community setting, an intravenous access line is unavailable and other routes of naloxone administration are used, such as intranasal or intramuscular routes. Fentanyl is a μ-opioid receptor with intermediate receptor affinity and K_{OFF} value of 0.004 s^{-1};[18] at high dose it becomes a rather long-acting drug due to its pharmacokinetic properties (*i.e.*, its context-sensitive half-time),[23,24] and due to the high receptor occupancy, higher doses of naloxone are required for a relatively rapid and long-lasting effect. In a modeling study, Moss *et al.*[25] demonstrated that 2 mg intramuscular naloxone displaced low-dose fentanyl from the μ-opioid receptor to 50% receptor occupancy after respectively 3 min (fentanyl concentration 25 ng/ml) and 10 min (50 ng/ml). At a higher fentanyl exposure (75 ng/ml), 2 mg intramuscular naloxone dose failed to displace fentanyl to 50% occupancy, and higher intramuscular doses were needed (5 mg and higher) to cause reversal to an opioid occupancy of 50% or less within 6 min. These later data indicate that the limiting factor for naloxone reversal of long-acting opioids with a low-to-intermediate affinity for the μ-opioid receptor is the opioid dose. Higher opioid dose or, more importantly, higher opioid concentrations in the brain complicate reversal, and standard reversal doses of intravenous naloxone (0.4 mg or less) are associated with either no effect or an increased likelihood of renarcotization.[6] A high naloxone dose (greater than 2 mg), repeated dosing, or a continuous infusion are then necessary for adequate reversal. One has to be aware that after a single high naloxone dose, renarcotization still might occur.[6,26] For example, simulations of naloxone receptor blockade (without an opioid present) indicate that μ-opioid receptor blockade greater than 90% lasts no longer than 30 min after 0.01 mg/kg naloxone bolus and about 1 h after a 10- to 15-fold higher dose.[26] When moderate- to high-affinity opioids are on board, the naloxone receptor blockade will be shorter due to the competition with the higher-affinity opioid at the receptor.[27]

(3) Opioids that Dissociate Slowly from the Receptor (K_{OFF} 0.001 s^{-1} or Less)

High-affinity opioids with slow receptor dissociation kinetics are used in clinical practice and often found in illegal substances. Again, also in this scenario, intranasal and intramuscular routes of naloxone administration are preferred due to lack of an intravenous access line. In case of respiratory depression from such opioids, receptor kinetics is the first limiting factor in naloxone's ability to reverse respiratory depression.[16,20] Opioids with low K_{OFF} values are more difficult to displace from the receptors than opioids with high K_{OFF} values, and the reversal rate is consequently

slower (fig. 2). For optimal management of overdose-related respiratory depression, it is theoretically relevant to know the overdosed opioid K_{OFF} value. However, for all practical purposes, it is best to assume slow receptor kinetics. This is particularly true since one can assume that the overdose is related to a high opioid dose with a prolonged duration of action, and the second limiting factor of naloxone effectiveness is its short duration of action. In case of any of these limiting events, high-dose naloxone or a continuous naloxone infusion is required for reversal. This was earlier demonstrated for buprenorphine, an opioid with high receptor affinity and a low K_{OFF} value.[16,28] A high intravenous naloxone dose (2 to 4 mg) was able to reverse respiratory depression but only when given as a continuous infusion. Since continuous intravenous naloxone infusions are only possible under controlled conditions, alternatives have been developed such as intranasal or intramuscular naloxone, or long-acting naloxone analogs. We recently tested 4 mg intranasal naloxone after high-dose sufentanil administration and observed effectiveness in reversal of opioid-induced respiratory depression (fig. 3; unpublished observation). Note that for high-affinity opioids, reversal with naloxone is possible, but the rate of reversal is relatively slow (peak effect after 25 min). Moreover, the rate or speed of reversal cannot be efficiently increased by increasing the naloxone dose (fig. 2A), although a higher dose will achieve greater reversal.[20] Additionally, the effect dissipates rapidly. In a binding study,[27] Kang *et al.* studied displacement of radioactive carfentanil by naloxone and showed more than 90% naloxone occupancy of the μ-opioid receptor at 5 min but only 50% occupation at 27 min after 0.035 mg/kg intravenous naloxone. A two-fold greater dose was needed to produce 50% occupation at 85 min. These data are relevant as they exemplify the rapid return of opioid effect after naloxone treatment. Still, full reversal of respiratory depression is not necessary to sustain or reinitiate gas exchange in the lungs. We estimate that more than 40% of normal breathing volume (*i.e.* more than 4 to 5 l/min, or μ-opioid receptor occupancy of 60% or less)[28] may be sufficient to enable sufficient oxygen uptake.[6] Supplemental oxygen will evidently further improve the patient condition.

(4) Reversal of μ-Opioid-receptor Partial Agonists

Apart from its slow receptor kinetics, buprenorphine is a partial agonist at the μ-opioid receptor.[16,29] Previously, we demonstrated that this complicates the effectiveness of naloxone in reversing respiratory depression. High doses of naloxone cause effective albeit slow reversal; at an intravenous naloxone infusion of 2 to 4 mg administered in 30 min, reversal is complete.[29] However, at higher naloxone doses, reversal decreased. This results in a bell-shaped or inverse U-shaped naloxone dose-response curve rather than the expected sigmoid E_{MAX} dose response with full reversal at increasing naloxone doses. The mechanism of the bell-shaped curve remains unknown, but possibly at high dose, the naloxone affinity for the receptor decreases causes loss of reversal effectiveness. Further studies are needed to improve our understanding of the naloxone–buprenorphine interaction.

(5) Reversal in the Event of Cointoxication

In many individuals that overdosed on an opioid, postmortem examination revealed that intoxication was due to multiple drugs. We earlier demonstrated that oxycodone-induced respiratory depression is enhanced by coadministration of ethanol, or the antidepressants paroxetine or

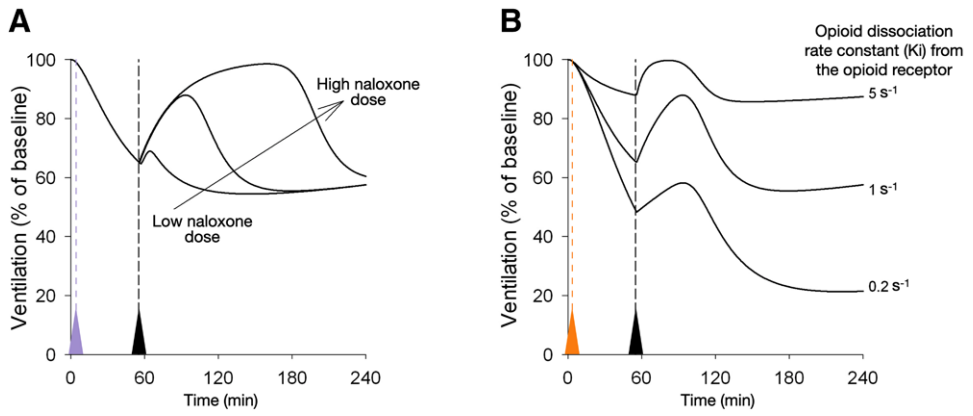

Fig. 2. Effect of naloxone dose (*A*) and effect of different receptor dissociation rate constant (*B*) on opioid-induced respiratory depression. *Purple and orange arrows*, Injection of the opioid; *black arrow*, injection of a single naloxone dose. *A*, An increase of naloxone dose does cause a greater return of minute ventilation but the speed of reversal, (Δ ventilation per time unit) does not change. *B*, The smaller the opioid K_{OFF}, the increase in ventilation after a similar naloxone dose is less. Note that at low K_{OFF} values, the degree of respiratory depression increases (at a similar opioid dose). Data from Martini *et al.*[20] Exp Rev Clin Pharmacol 2011; 4:719–28 (with permission).

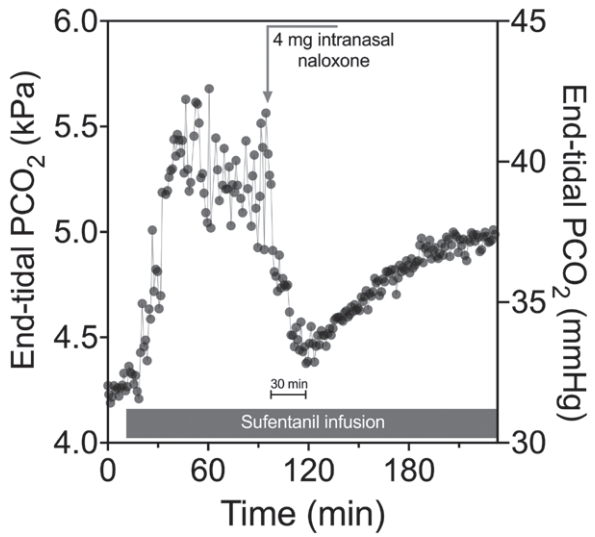

Fig. 3. Reversal of sufentanil-induced respiratory depression by a single 4 mg intranasal naloxone dose. Maximal reversal occurs at 30 min. Each dot is a 1-min average of the measured end-tidal carbon dioxide partial pressure. Data from van Lemmen *et al.* (unpublished observation, Maarten van Lemmen, Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands, written communication, June 1, 2023).

tianeptine.[30–32] Similar findings have been made for other centrally acting depressants such as benzodiazepines.[7] While naloxone is unable to reverse the nonopioid component of intoxication, it can reverse the opioid effect, while the nonopioid effect on the ventilatory control system remains. The nonopioid may similarly be a potent respiratory depressant (*e.g.*, tranquilizers such as the benzodiazepine etizolam or the α_2-agonist xylazine).[33] This will again make reversal difficult with just naloxone. A potential alternative would be to combine naloxone with a nonopioid or agnostic respiratory stimulant or, in case of a benzodiazepine cointoxication, with the benzodiazepine receptor antagonist flumazenil.[34] For example, in rats intoxicated with high-dose fentanyl and diazepam, combining low-dose naloxone (1 mg/kg) with the nicotine acetylcholine receptor agonist varenicline was able to successfully prevent occurrence of lethal apneas.[35] We will further discuss agnostic respiratory stimulants in the section "Naloxone Alternatives: Agnostic Respiratory Stimulants".

The inability to reverse the opioid effect when given in conjunction with gabapentinoids is exemplified is two rodent studies. These studies examined the effect of naloxone effectiveness in reversing opioid effect when combined with pregabalin or gabapentin.[36,37] In one study in mice, naloxone (5 mg/kg) pretreatment did not reduce the significant potentiation produced by coadministration of morphine and pregabalin on pain relief from visceral pain.[36] In a recent study in rats,[37] naloxone at a dose of 0.0056 mg/kg fully reversed heroin-induced respiratory depression. However, after pretreatment with either pregabalin or gabapentin, the dose was less effective, and a dose of 0.1 mg/kg was needed for full reversal, despite no effect of the gabapentinoids on the respiratory depression induced by heroin. Since the gabapentinoids were devoid of respiratory depressant effect, these data suggest that the gabapentinoids affect (increase) the naloxone K_{OFF} value. A similar observation yet in the other direction has earlier been made for morphine-6-glucuronide that enhances H^3-naloxone affinity for the μ-opioid receptor by 20 to 40%.[14,38]

(6) Naloxone Effect under Hypoxic Conditions

A recent study in awake and sedated rats showed that reversal by intravenous naloxone (2 mg/kg) of 0.3 mg/kg fentanyl-induced apnea was dependent on the oxygen concentration of the inhaled gas.[39] At low inspired oxygen fractions (fractional inspired oxygen tension less than 10%), the apnea was irreversible in 90% of animals, while during room air breathing the return to regular breathing occurred in all animals. Probably the central depressant effects of hypoxia prevent reversal of respiratory rhythmic neuronal activity. These observations have evident clinical implications as any antidote, naloxone as well as agnostic respiratory stimulants, will be ineffective in case of severe hypoxia. This highlights the importance of ventilatory support in addition to naloxone administration in the case of a rescue attempt of an overdose victim.

Naloxone Ability to Prevent Cardiac Arrest

Cardiac arrest may occur after an opioid overdose due to apnea- or hypoventilation-induced asphyxia complicated by cardiac dysrhythmias. Mann *et al.*[6] were the first to develop an *in silico* simulation of the ability of naloxone to prevent occurrence of a cardiac arrest after potent opioid overdoses. In fact, their model is the first to simulate the opioid overdosing with fentanyl and its congeners in the community setting. The model they developed has multiple parts and incorporates opioid and antagonist pharmacokinetics, μ-opioid receptor kinetics, opioid and antagonist mechanism-based respiratory pharmacodynamics, and circulatory physiology. They describe the effects of low- and high-dose intravenous fentanyl (1.63 and 2.97 mg) and carfentanil (0.012 mg and 0.022 mg) on a series of relevant parameters, including ventilation, arterial Po_2 and cardiac output, brain blood flow, and brain tissue Po_2. Next, they determined the effect of no reversal and naloxone reversal by an intramuscular injection of 2 mg naloxone in 0.4 ml and 2 mg in 2 ml solvent on these parameters. Naloxone was given when ventilation decreased to 40% of estimated baseline level. Their results are summarized as follows (fig. 4):[6] (i) respiratory depression induced by the full μ-opioid receptor agonist carfentanil develops slower compared to

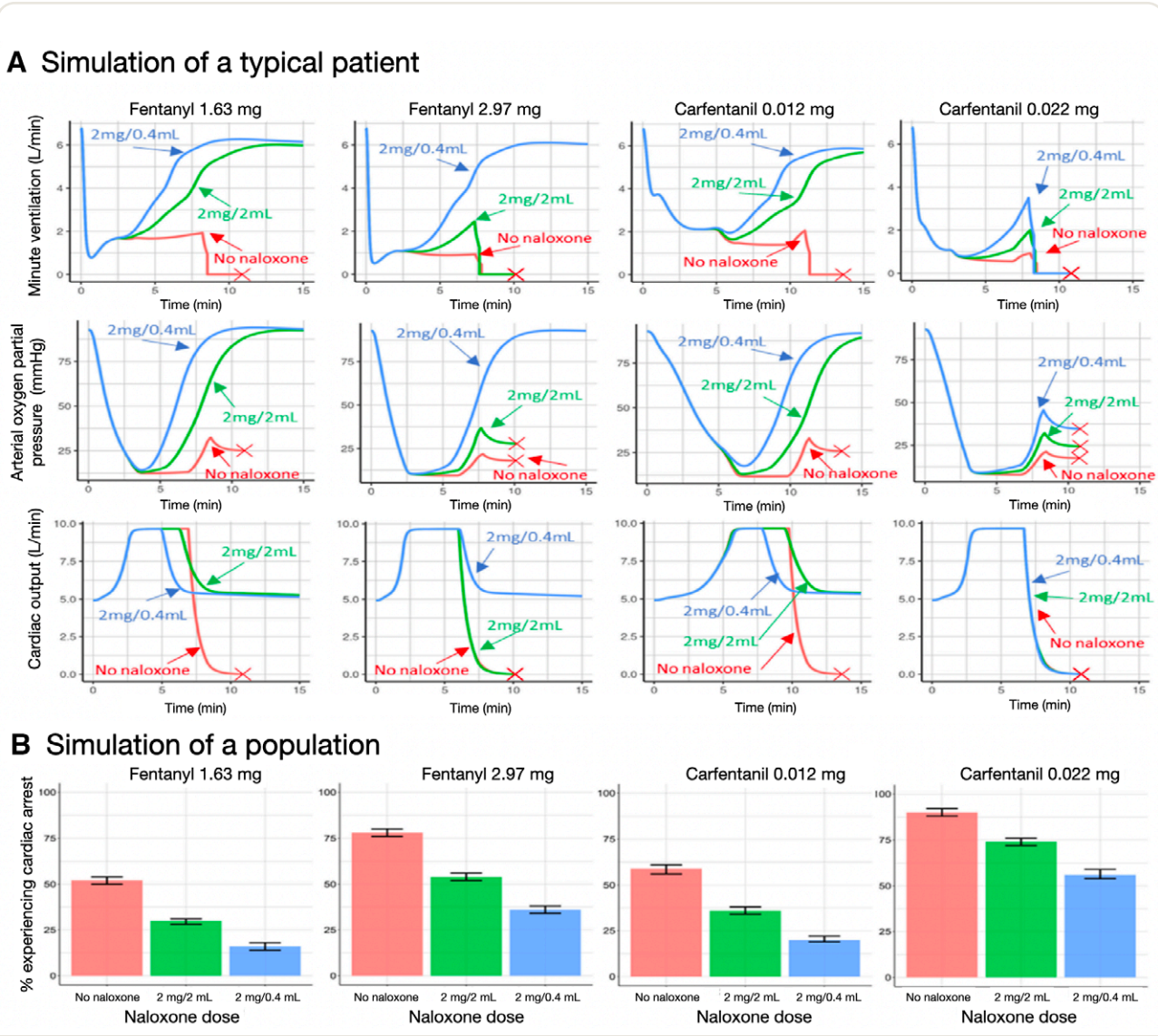

Fig. 4. (*A*) Simulations of the effect of intramuscular naloxone injection on minute ventilation (*top row*), arterial oxygen partial pressure (*middle row*), and cardiac output (*bottom row*). Two opioids (fentanyl and carfentanil) and two doses per opioid are simulated. No reversal is simulated (*red lines*, no naloxone) and two intramuscular naloxone strategies: *green lines*, 2 mg naloxone in 2 ml solution, and *blue lines*, 2 mg naloxone in 0.4 ml solution. The *red* × indicates the simulated patient's death. (*B*) Population simulations of the percentage of simulated individuals that experienced cardiac arrest under the simulated conditions given in *A*. Data from Mann *et al.*[6] Clin Pharmacol Ther 2022; 112:1020–32 (with permission).

fentanyl, due to its slower association to the μ-opioid receptor (K_{ON}); (ii) reversal of respiratory depression by naloxone was more difficult after carfentanil administration compared to fentanyl, due to its slower dissociation from the μ-opioid receptor (K_{OFF}); (iii) the greater naloxone concentration (2 mg/0.4 ml) was a more effective reversal agent than the lesser concentrated naloxone (2 mg/2 ml), related to the higher plasma concentrations reached with the former; (iv) high-dose carfentanil was lethal under both naloxone scenarios with cardiac arrest occurring in almost 90% of virtual patients after no naloxone and 74% and 59% after 2 mg/2 ml and 2 mg/0.4 ml naloxone, respectively (fig. 4B). Equivalent values for high-dose fentanyl were 75% (no reversal), 52% (2 mg/2 ml naloxone) and 36% (2 mg/0.4 ml naloxone).

These simulations depict the sequence of events that lead to cardiac arrest and exemplify that the success of a naloxone intervention is dependent on opioid receptor kinetics, opioid dose and naloxone dose and concentration. With respect to opioid dose, naloxone was effective in 30 to 40% more simulated patients after low-dose compared to high-dose carfentanil injection (0.012 mg *vs.* 0.022 mg).[6]

Additionally, the model predicts that a large proportion of simulated individuals will survive but will have sustained low levels of brain oxygen concentration, which may result in brain damage or other deleterious effects not explicitly represented in the model. What remains to study is to determine the influence of timing of the naloxone intervention on the success of rescue and prevention of brain damage and, equally important, to go beyond the current simulations and determine the influence of resuscitation on rescue after cardiac arrest occurred.

Naloxone Safety

Naloxone is a safe drug in the sense that when administered to healthy awake and opioid-naive individuals, it is generally without effect or side effects. Kagawa *et al.*,[40] for example, administered 10 mg intravenous naloxone to healthy volunteers during moderate hypoxia and detected no deleterious effects. In the event of an opioid overdose, naloxone may have adverse effects, albeit clinical data indicate that serious events are rare.[3,41–46] In case of individuals with an opioid use disorder, withdrawal symptoms may become apparent after naloxone administration; symptoms include tachycardia, mild agitation or anxiety, hypertension abdominal pain, malaise, and insomnia.[2,3,41] In extremely rare cases, abrupt reversal of opioid-induced respiratory depression by naloxone has been followed by seizures, pulmonary edema, cardiac dysrhythmias, hypertension, and cardiac arrest.[3,42–45] While a direct dose and effect relationship has not been established, the cardiopulmonary complications may be secondary to a sudden release of catecholamines after high-dose or rapidly injected naloxone. Vasoconstriction and an increase in blood pressure and the occurrence of tachyarrhythmias may be the basis of these complications, with pulmonary edema arising from a rapid fluid shift or from inspiration against a closed glottis (negative pressure pulmonary edema).[3,46] Complications may be enhanced when the patient is in a circulatory unstable condition such as low blood pressure from opioid-induced vasodilation or in case of a high vasomotor tone from (psychologic) stress, agitated delirium and/or pain.[3] In the event of complications, it is crucial to treat the different symptoms and reduce the elevated sympathetic activity with an α_2-adrenergic receptor agonist.[3] In individuals who received naloxone rescue medication in a community setting, agitation and aggression may be dangerous for those providing care such as police, ambulance personnel, and bystanders, and in some cases requires chemical sedation.[41] Finally, it is important to realize that sudden nausea and vomiting may occur upon naloxone administration with a risk of aspiration.[43]

Naloxone Alternative: Nalmefene

Nalmefene is an opioid receptor antagonist that was earlier available in the United States for treatment of an opioid overdose,[47] and was not withdrawn from the market for reasons of safety or effectiveness, but because of commercial reasons.[48] The oral formulation is still available for treatment of alcohol dependence and other forms of addiction.[49,50] Nalmefene remains an attractive naloxone alternative as it has high affinity for the μ-opioid receptor, is 10 times more potent than naloxone, and has an 8- to 10-fold longer half-life (8 to 11 h) than naloxone, reducing the likelihood of renarcotization from even long-acting opioids.[47,51] Recently, intranasal nalmefene was developed and studied for treatment of an opioid overdose.[51–53] Intranasal mucosal uptake of nalmefene, however, is relatively slow.[53] In rats, adding a mucosal absorption enhancer speeds uptake with peak concentrations at about 1 min after administration.[53] Such values make clinical use attractive, particularly since it stays active much longer than naloxone. In human volunteers, 3 mg intranasal nalmefene combined with a mucosal absorption enhancer reduced the time to the maximal plasma concentration from 2 h to about 30 min,[53] Further studies should evaluate the effectiveness of intranasal nalmefene in rapidly reversing opioid-induced respiratory depression.

Naloxone Alternatives: Agnostic Respiratory Stimulants

Since naloxone is not effective in a variety of overdose conditions, so-called agnostic respiratory stimulants are being developed. These stimulants allow reversal of respiratory depression without any interaction with the underlying cause of respiratory depression. We recently discussed a series of old and new nonopioid stimulants (see van der Schrier[8] and references cited therein). Respiratory stimulants with promising results in animal or human studies include nicotinic acetylcholine receptor agonists, ampakines, potassium channel blockers, partial opioid receptor agonists or antagonists, scrubber molecules, and monoclonal antibodies against specific opioids (including antibodies that enhance opioid metabolism).[8,54] Still, none of these strategies is currently sufficiently scrutinized to allow definite conclusions regarding effectiveness and safety. For example, it remains unknown whether these strategies are able to overcome severe respiratory depression (*e.g.*, ventilation less than 40% of baseline, gasping, or apnea) and are able to prevent cardiac arrest. In fact, we contend that most strategies share some of the naloxone drawbacks, and reversal might be difficult as we predict that under conditions of cardiorespiratory collapse, insufficient drug will reach the brainstem. Stimulants with a site of action outside the brain compartment might have an advantage (such as potassium channel blockers that act at the carotid bodies), or there might be an advantage of combining any of these stimulants with naloxone to target two independent mechanisms with a possible better outcome than either treatment alone. The combinations of any of these stimulants with naloxone has been studied only sparsely. We gave an example above of the combination of low-dose naloxone and the nicotinic

acetylcholine receptor partial agonist, varenicline.[35] These two drugs act within the brainstem at different sites, opioid- and nonopioid-related, to reinitiate rhythmogenesis after a potentially lethal apnea. Such therapy evidently only works provided presence of circulation. Just one other study investigated treatment combined with an opioid receptor antagonist. In individuals with an opioid use disorder, the combination of a vaccine against oxycodone with prolonged-release naltrexone was more efficacious than either treatment alone in the prevention of oxycodone-induced respiratory depression.[55] Evidently, such therapy cannot produce rapid onset reversal of respiratory depression.

One disadvantage of agnostic stimulants has not received any attention as yet. Many of the synthetic opioids can produce significant muscle rigidity (the wooden cage syndrome) and/or vocal cord closure impairing gas exchange due to a sharp reduction in tidal volume.[56–60] In case of opioid-induced muscle rigidity and/or vocal cord closure, the respiratory stimulant might not work or might worsen the clinical condition of the patient.[58] This is another reason why the combination of a nonopioid respiratory stimulant with naloxone is favorable, as the opioid antagonist is able to reduce muscle rigidity.[58] Still, other nonopioid mechanisms may also be involved such as those related to opioid-induced adrenergic and cholinergic receptor–mediated respiratory failure.[56] Our experience, however, is that at the appropriate dose, naloxone is able to rapidly overcome potentially lethal muscle rigidity from synthetic opioids. Miner *et al.*,[60] however, showed that fentanyl-induced vocal cord closure is resistant to reversal by naloxone, suggesting that muscle rigidity and vocal cord closure have a different underlying mechanism and require distinct treatments.

Given the above, we encourage further studies on the combination of an agnostic respiratory stimulant with naloxone under conditions of acute respiratory depression, mimicking an overdose from synthetic opioids.

Conclusions and Future Perspectives

Theoretically, naloxone is well-suited to antagonize the opioid effect at the μ-opioid receptor in the event of a potentially lethal respiratory depression; it has high affinity for the opioid receptor but lacks intrinsic activity at the receptor. However, its effectiveness is limited and determined by a variety of factors that interact in a complex fashion and remain poorly studied. Factors that that limit a rapid and full reversal may be divided into factors that relate to the opioid that has been overdosed and to the pharmacologic properties of naloxone. These factors include the opioid dose, the opioid affinity for the μ-opioid receptor (determined by Ki and K_{OFF}), the naloxone dose, its duration of action, the naloxone route of administration, and the timing of reversal. The latter factor is particularly relevant as a late attempt to rescue the patient may be complicated by a cardiac arrest. Given that most of these limitations remain unknown under real-life conditions, the optimal naloxone rescue dose remains uncertain, and current guidelines are based on simulation studies or retrospective case series. For example, the package insert of the 2 and 4 mg naloxone nasal spray (in 0.1 ml) advises a single spray into one nostril and additional doses if the patient does not respond at 2- to 3-min intervals.[61,62] In 2021, the U.S. Food and Drug Administration approved an 8 mg naloxone nasal spray to treat opioid overdose.[63] Recent pharmacokinetic modeling studies indeed suggest that an initial dose of 8 mg intranasal naloxone has superior pharmacodynamic effects compared to all other administration regimens (unpublished observation). However, the utility of staggered naloxone administration after such a schedule has not been evaluated outside of controlled settings. Recognizing that typical clinical studies in overdose patients are not feasible, we advocate for robust and well-controlled pharmacokinetic and pharmacodynamic evaluations in relevant patient populations to allow development of well-informed guidelines for treatment of an opioid overdose in the community. To address this issue, we are currently studying the effect of multiple 4 mg intranasal naloxone doses on high-dose fentanyl- and sufentanil-induced respiratory depression in opioid-naive individuals and chronic opioid consumers using a pharmacokinetic or pharmacodynamic modeling approach. Importantly, irrespective of the results of studies on single intoxications, one needs to be aware that proper reversal of polysubstance abuse and overdoses requires a different approach that might involve the combination of naloxone with an agnostic respiratory stimulant. While we are aware that new μ-opioid receptor antagonists that overcome the narrow treatment window of naloxone are being developed, human studies that determine effectiveness and safety under the conditions discussed above are still lacking. Discussion of such compounds (*e.g.*, antagonists derived from orvinol, methocinnamox, naloxone nanoparticles) is therefore still preliminary.[27,64–66] For now, naloxone remains the mainstay of treatment and should be administered in combination with appropriate supportive and resuscitation measures.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

In the last 36 months, Dr. Dahan received consultancy fees from Enalare Therapeutics Inc. (Princeton, New Jersey), Trevena Inc. (Chesterbroom, New Jersey), Cessation Therapeutics Inc. (Chapel Hill, North Carolina), and Takeda Pharmaceuticals International AG (Switzerland) and awards or grants from the U.S. Food and Drug Administration (Silver Spring, Maryland), the Netherlands Organization for Health Research and Development (ZonMW, The Hague, The Netherlands) in the framework of GGG (Good Use of

Medication; project No. 848120001), and from the Dutch Research Council (NWO, The Hague, The Netherlands) in the framework of the Nederlandse Wetenschaps Agenda-Onderzoek op Routes door Consortia (NWA-ORC) Call for research project TAPTOE, Tackling and preventing the opioid epidemic (NWA.1160.18.300). Dr. Dahan holds Enalare stock options. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Dahan: Department of Anesthesiology, Anesthesia & Pain Research Unit, Leiden University Medical Center, H5-022, 2300 RC Leiden, The Netherlands. a.dahan@lumc.nl.

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