Inspire or expire: a matter of life or death

Lemmen, M.A. van

PART II

Naloxone

CHAPTER 4

CHAPTER 4
Opioid overdose: limitations in naloxone reversal of respiratory depression and prevention of cardiac arrest

Maarten A. van Lemmen, Jeffry Florian, Zhihua Li, Monique van Velzen, Eveline van Dorp, Marieke Niesters, Elise Sarton, Erik Olofsen, Rutger van der Schrier, David G Strauss, Albert Dahan

Anesthesiology. 2023;139(3):342-53

Abstract

Opioids are effective painkillers 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 mu-opioid receptor and/or slow receptor dissociation kinetics are particularly resistant to the effects of naloxone. In this review, we will examine the pharmacology of naloxone, its safety and limitations in reversing opioid-induced respiratory depression under different circumstances, including its ability to prevent cardiac arrest.

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 non-selective, 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 ($t_{½}$ = 32 min), which can result in renarcotization (return of opioid effect) when antagonizing long-acting opioids, such as high-dose fentanyl.[4]

Naloxone was originally available for injection by intravenous, subcutaneous or intramuscular routes of administration. More recently, the US Food and Drug administration approved intramuscular autoinjectors and intranasal naloxone, including over-the-counter intranasal naloxone, for treatment of opioid overdose and opioid use disorder. In recent years knowledge on the pharmacokinetic and pharmacodynamic properties of naloxone has increased

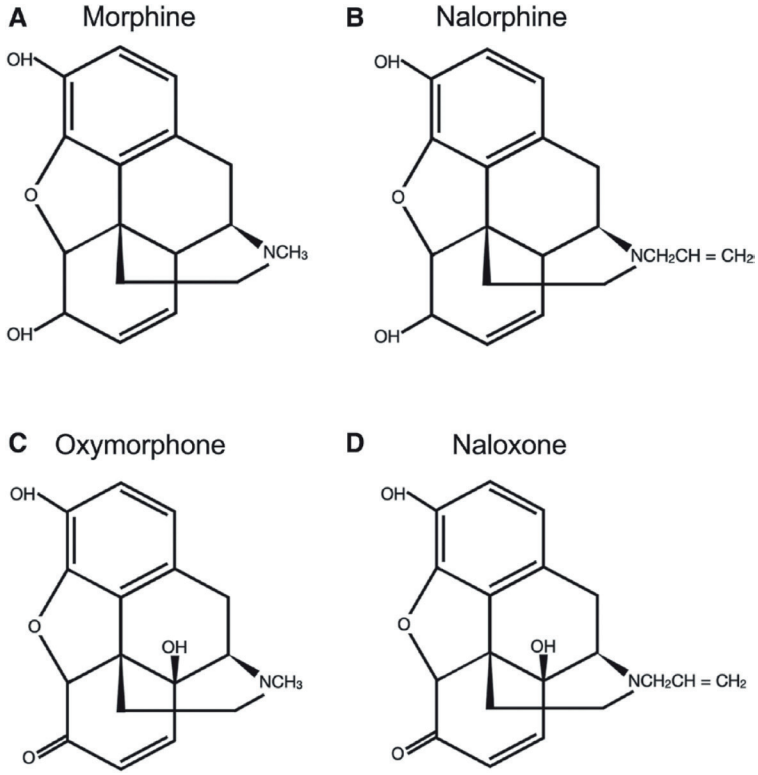

Figure 1. Chemical structures of four opioids, morphine (A), nalorphine (B), oxymorphone (C) and naloxone (D).

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 constant K_{ON} and K_{OFF}, respectively, with limitations in reversal when K_{OFF} values are low causing difficulty to dissociate the opioid from its receptor.[5, 6] Moreover, the effect is delayed following intramuscular and intranasal administration compared to the intravascular route. Additionally, naloxone has a reduced ability to reverse the deleterious non-opioid effect when opioids are combined with nonopioid centrally-acting depressants (co-intoxication) such as ethanol, benzodiazepines, α_2-agonists or antidepressants.[7, 8]

Opioids are highly effective painkillers, 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 cardio-respiratory 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, co-intoxication, comorbidities, timing of rescue, experience of rescuers, etc. 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 arrests 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 pharmacological intervention. The many deaths from opioids indicates 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 are 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

Oral naloxone has a low bioavailability (<5%), which increases to 25% following nasal administration and a variable albeit higher bioavailability after intramuscular administration.[3, 143,14] First pass elimination is high (>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 1.6-1.8 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/pharmacodynamic (PK/PD) data analysis is parameter $t½k_{e0}$ (= $ln2/k_{e0}$) 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 5-8 min for naloxone.[15, 16] This predicts a rapid onset as well as a rapid off-set of action. Although the duration of action may depend on the dose and the elimination half-life (30-45 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 high dose may precipitate withdrawal symptoms in chronic opioid users. Its affinity for the different opioid receptors varies with affinity constants (Ki) ~1.2 nM for the μ-opioid receptor and >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 focusses on naloxone reversal of μ-opioid agonistic effects. The magnitude and speed at which naloxone reverses an opioid overdose depends 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 (see Table 1): low affinity = Ki > 100 nM, which includes codeine (Ki 734 nM) and meperidine (450 nM); low-to-intermediate affinity = 1 < Ki < 100 nM, which include oxycodone (25.9 nM), methadone (3.38 nM), fentanyl (1.35 nM) and morphine (1.17 nM); and high affinity = Ki < 1 nM, which include 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/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}.[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}).[16, 20]

	Ki (nM)	K_{OFF} (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

Table 1. μ-Opioid receptor affinities (Ki) and receptor dissociation constants (K_{OFF}) of different opioids.[6,15,17-19]

Naloxone pharmacodynamics: 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 co-intoxication 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 – 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, complicates reversal and standard reversal doses of intravenous naloxone (≤0.4 mg) are associated with either no effect or with an increased likelihood of renarcotization.[6] A high naloxone dose (>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 > 90% lasts no longer than 30 min after 0.01 mg/kg naloxone bolus and about 1 hour after a ten- to fifteen-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]

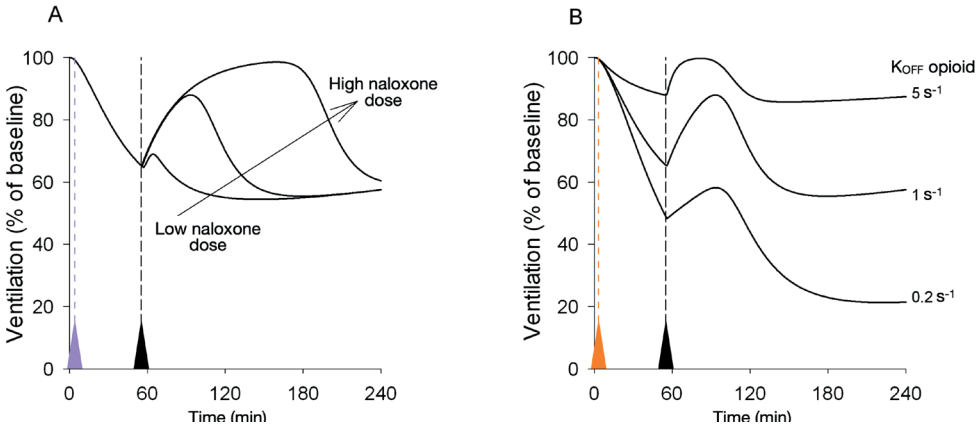

Figure 2. Effect of naloxone dose (A) and effect of different receptor dissociation rate constant (B) on opioid-induced respiratory depression. Purple and orange arrow, injection of the opioid; black arrow injection of a single naloxone dose. A. An increase of naloxone dose does cause a greater return of minute ventilation but the speed of reversal (Δventilation per time unit) does not change. B. The smaller the opioid KOFF, the increase in ventilation following a similar naloxone dose, is less. Note that at low KOFF 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).

(3) Opioids that dissociate slowly from the receptor ($K_{OFF} \leq 0.001\ s^{-1}$). 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 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.

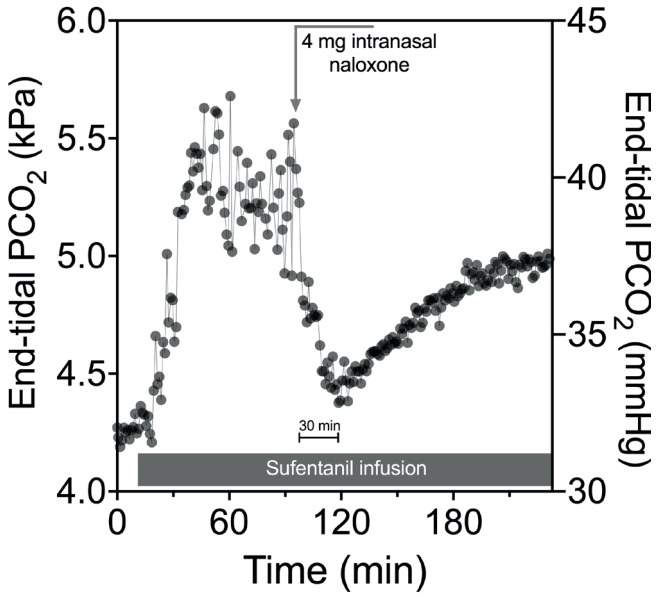

Figure 3. Reversal of sufentanil-induced respiratory depression by a single 4 mg intranasal naloxone dose. Maximal reversal occurs at 30 min. Each dot is a 1-min average of the measured end-tidal carbon dioxide partial pressure (pCO_2). Data from van Lemmen et al. (unpublished observation).

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 (2-4 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 following 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 following 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 > 40% of normal breathing volume (*i.e.* > 4-5 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 2-4 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 understand of the naloxone buprenorphine interaction.

(5) Reversal in the event of co-intoxication. In many individuals that overdosed on an opioid, posmortem examination revealed that intoxication was due to multiple drugs. We earlier demonstrated that oxycodone-induced respiratory depression is enhanced by co-administration of ethanol, or the antidepressants paroxetine or tianeptine.[30-32] Similar findings have been made for other centrally-acting depressants such as benzodiazepines.[7] While naloxone is unable to reverse the non-opioid 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 co-intoxication 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 below.

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]

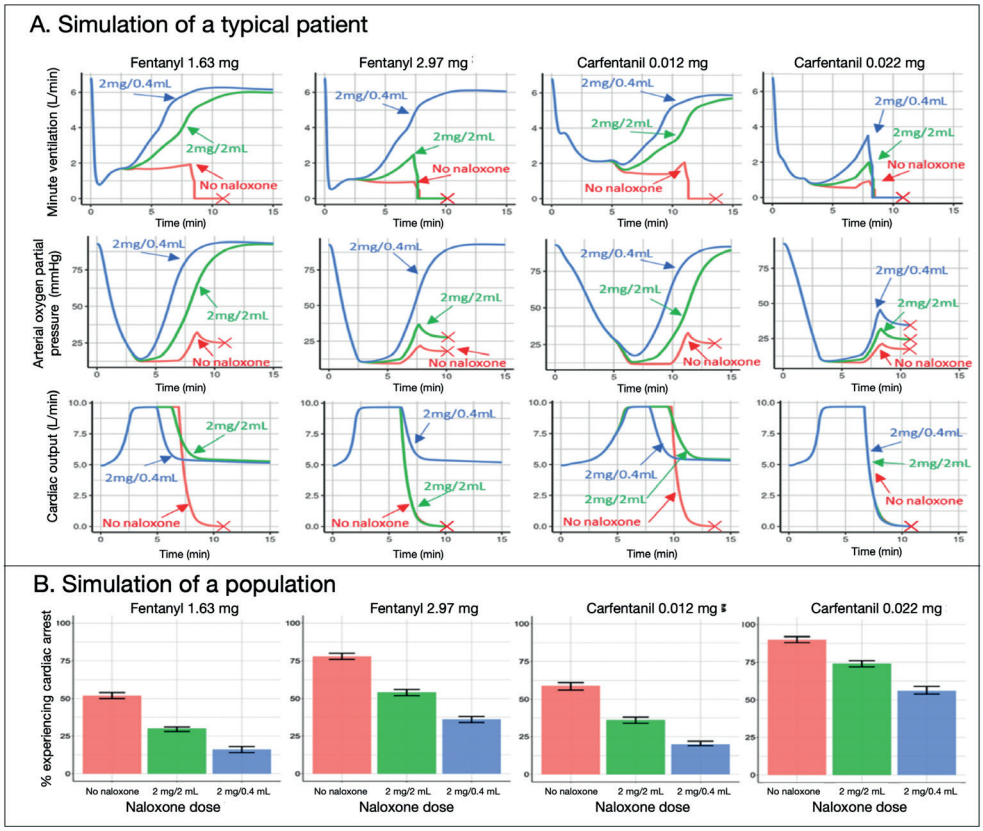

Figure 4. A. Simulations of the effect of intramuscular naloxone injection on minute ventilation (top row), arterial oxygen partial pressure (middle row) and cardiac output (bottom row). Two opioids (fentanyl and carfentanil) and two doses per opioid are simulated. No reversal is simulated (red lines, 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 panel A. Data from Mann et al. [6] Clin Pharmacol Ther 2022; 112: 1020-32 (with permission).

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 heroine-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 (increases) naloxone K_{OFF}-value. A similar observation, yet into the other direction has earlier been made for morphine-6-glucuronide that enhances H^3-naloxone affinity for the μ-opioid receptor by 20-40%.[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 (FiO_2 < 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 following 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 following 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 fentanyl, due to its slower association to the μ-opioid receptor (K_{ON}); (*ii*) reversal of respiratory depression by naloxone was more difficult following 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 following 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 30-40% more simulated patients following low-dose compared to high-dose carfentanil injection (0.012 mg versus 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-naïve individuals, it is generally without effect or side effects. Severinghaus and colleagues,[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/anxiety, hypertension abdominal pain, malaise and insomnia.[2, 3, 41] In extremely rare cases, abrupt reversal of opioid 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 following high-dose or rapidly injected naloxone. Vasoconstriction and an increase in blood pressure and the occurrence of tachy-arrhythmias 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 (psychological) 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 that 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 US 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 eight- to ten-fold longer half-life ($t_{½}$ = 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 hours 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 Ref. 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/antagonists, scrubber molecules and monoclonal antibodies against specific opioids (including antibodies that enhance opioid metabolism).[8, 54] Still, none of these strategies are at present 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 <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 only been studied 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 following 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.[32, 56-60] In case of opioid-induced muscle rigidity and/or vocal cord closure the respiratory stimulant might not work or worsen the clinical condition of the patient.[58] This is another reason why the combination of a non-opioid respiratory stimulant with naloxone is favorable, as the opioid antagonist is able to reduce muscle rigidity.[58] Still, also other non-opioid mechanism may be involved such as 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 pharmacological 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 later 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 2-3 min intervals.[61, 62] In 2021, the US Food and Drug Administration (FDA) approved a 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 following 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-naïve individuals and chronic opioid consumers using a pharmacokinetic/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.

References

1. Garfield E. The 1982 John Scott Award goes to Jack Fishman and Harold Blumberg for synthesis and investigation of naloxone. Essays of an Information Scientist. 1983;6:121-30.

2. Martin WR. Drugs five years later: naloxone. Annals of internal medicine. 1976;85(6):765-8.

3. van Dorp EL, Yassen A, Dahan A. Naloxone treatment in opioid addiction: the risks and benefits. Expert opinion on drug safety. 2007;6(2):125-32.

4. Kaufman RD, Gabathuler ML, Bellville JW. Potency, duration of action and pA2 in man of intravenous naloxone measured by reversal of morphine-depressed respiration. The Journal of Pharmacology and Experimental Therapeutics. 1981;219(1):156-62.

5. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. Anesthesiology. 2010;112(1):226-38.

6. Mann J, Samieegohar M, Chaturbedi A, Zirkle J, Han X, Ahmadi SF, et al. Development of a translational model to assess the impact of opioid overdose and naloxone dosing on respiratory depression and cardiac arrest. Clinical Pharmacology & Therapeutics. 2022;112(5):1020-32.

7. Boon M, van Dorp E, Broens S, Overdyk F. Combining opioids and benzodiazepines: effects on mortality and severe adverse respiratory events. Annals of Palliative Medicine. 2020;9(2):54257-557.

8. van der Schrier R, Dahan JD, Boon M, Sarton E, van Velzen M, Niesters M, et al. Advances in reversal strategies of opioid-induced respiratory toxicity. Anesthesiology. 2022;136(4):618-32.

9. Okie S. A flood of opioids, a rising tide of deaths. New England Journal of Medicine. 2010;363(21):1981-5.

10. Varga AG, Reid BT, Kieffer BL, Levitt ES. Differential impact of two critical respiratory centres in opioid-induced respiratory depression in awake mice. The Journal of physiology. 2020;598(1):189-205.

11. Palkovic B, Callison JJ, Marchenko V, Stuth EA, Zuperku EJ, Stucke AG. Dose-dependent respiratory depression by remifentanil in the rabbit parabrachial nucleus/Kölliker-Fuse complex and preBötzinger complex. Anesthesiology. 2021;135(4):649.

12. Baertsch NA, Bush NE, Burgraff NJ, Ramirez J-M. Dual mechanisms of opioid-induced respiratory depression in the inspiratory rhythm-generating network. Elife. 2021;10:e67523.

13. Dezfulian C, Orkin AM, Maron BA, Elmer J, Girotra S, Gladwin MT, et al. Opioid-associated out-of-hospital cardiac arrest: distinctive clinical features and implications for health care and public responses: a scientific statement from the American Heart Association. Circulation. 2021;143(16):e836-e70.

14. Dowling J, Isbister GK, Kirkpatrick CM, Naidoo D, Graudins A. Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. Therapeutic drug monitoring. 2008;30(4):490-6.

15. Olofsen E, van Dorp E, Teppema L, Aarts L, Smith TW, Dahan A, et al. Naloxone reversal of morphine-and morphine-6-glucuronide-induced respiratory depression in healthy volunteers: a mechanism-based pharmacokinetic–pharmacodynamic modeling study. Anesthesiology. 2010;112(6):1417-27.

16. Yassen A, Olofsen E, van Dorp E, Sarton E, Teppema L, Danhof M, et al. Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: a study in healthy volunteers. Clinical pharmacokinetics. 2007;46:965-80.

17. Papathanasiou T, Springborg AD, Kongstad KT, Staerk D, Møller K, Taylor BK, et al. High-dose naloxone, an experimental tool uncovering latent sensitisation: pharmacokinetics in humans. British Journal of Anaesthesia. 2019;123(2):e204-e14.

18. Volpe DA, Tobin GAM, Mellon RD, Katki AG, Parker RJ, Colatsky T, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. Regulatory Toxicology and Pharmacology. 2011;59(3):385-90.

19. Frost JJ, Wagner Jr HN, Dannals RF, Ravert HT, Links JM, Wilson AA, et al. Imaging opiate receptors in the human brain by positron tomography. Journal of computer assisted tomography. 1985;9(2):231-6.

20. Martini C, Olofsen E, Yassen A, Aarts L, Dahan A. Pharmacokinetic–pharmacodynamic modeling in acute and chronic pain: an overview of the recent literature. Expert review of clinical pharmacology. 2011;4(6):719-28.

21. Moss MJ, Warrick BJ, Nelson LS, McKay CA, Dubé P-A, Gosselin S, et al. ACMT and AACT position statement: preventing occupational fentanyl and fentanyl analog exposure to emergency responders. Journal of Medical Toxicology. 2017;13:347-51.

22. Wax PM, Becker CE, Curry SC. Unexpected “gas” casualties in Moscow: a medical toxicology perspective. Annals of emergency medicine. 2003;41(5):700-5.

23. Iizuka T, Nishimura R. Context-sensitive half-time of fentanyl in dogs. Journal of Veterinary

Medical Science. 2015;77(5):615-7.

24. Dahan A, Niesters M, Smith T, Overdyk F, Barash P, Cullen B, et al. Opioids. Clinical anesthesia: Wolters Kluwer, Philadelphia; 2017. p. 505-26.

25. Moss RB, Pryor MM, Baillie R, Kudrycki K, Friedrich C, Reed M, et al. Higher naloxone dosing in a quantitative systems pharmacology model that predicts naloxone-fentanyl competition at the opioid mu receptor level. PLoS One. 2020;15(6):e0234683.

26. Trøstheim M, Eikemo M, Haaker J, Frost JJ, Leknes S. Opioid antagonism in humans: a primer on optimal dose and timing for central mu-opioid receptor blockade. Neuropsychopharmacology. 2023;48(2):299-307.

27. Kang Y, O'Conor KA, Kelleher AC, Ramsey J, Bakhoda A, Eisenberg SM, et al. Naloxone's dose-dependent displacement of [11C] carfentanil and duration of receptor occupancy in the rat brain. Scientific reports. 2022;12(1):6429.

28. Olofsen E, Algera MH, Moss L, Dobbins RL, Groeneveld GJ, van Velzen M, et al. Modeling buprenorphine reduction of fentanyl-induced respiratory depression. JCI insight. 2022;7(9):e156973.

29. van Dorp E, Yassen A, Sarton E, Romberg R, Olofsen E, Teppema L, et al. Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology. 2006;105(1):51-7.

30. van der Schrier R, Roozekrans M, Olofsen E, Aarts L, van Velzen M, de Jong M, et al. Influence of ethanol on oxycodone-induced respiratory depression. Anesthesiology. 2017;126(3):534-42.

31. Florian J, van der Schrier R, Gershuny V, Davis MC, Wang C, Han X, et al. Effect of paroxetine or quetiapine combined with oxycodone vs oxycodone alone on ventilation during hypercapnia: a randomized clinical trial. Jama. 2022;328(14):1405-14.

32. Algera H, van der Schrier R, Cavalla D, van Velzen M, Roozekrans M, McMorn A, et al. Respiratory effects of the atypical tricyclic antidepressant tianeptine in human models of opioid-induced respiratory depression. Anesthesiology. 2022;137(4):446-58.

33. Montero F, Bourgois P, Friedman J. Potency-enhancing synthetics in the drug overdose epidemic: xylazine ("tranq"), fentanyl, methamphetamine, and the displacement of heroin in Philadelphia and Tijuana. Journal of illicit economies and development. 2022;4(2):204.

34. Geller E, Crome P, Schaller M, Marchant B, Ectors M, Scollo-Lavizzari G. Risks and benefits of therapy with flumazenil (Anexate®) in mixed drug intoxications. European neurology. 1991;31(4):241-50.

35. Ren J, Ding X, Greer JJ. Countering opioid-induced respiratory depression in male rats with nicotinic acetylcholine receptor partial agonists varenicline and ABT 594. Anesthesiology. 2020;132(5):1197-211.

36. Meymandi M-S, Sepehri G. Gabapentin action and interaction on the antinociceptive effect of morphine on visceral pain in mice. European journal of anaesthesiology. 2008;25(2):129-34.

37. Flynn SM, France CP. Effects of gabapentinoids on heroin-induced ventilatory depression and reversal by naloxone. ACS Pharmacology & Translational Science. 2023;6(4):519-25.

38. Abbott FV, Palmour RM. Morphine-6-glucuronide: analgesic effects and receptor binding profile in rats. Life sciences. 1988;43(21):1685-95.

39. Haouzi P, Guck D, McCann M, Sternick M, Sonobe T, Tubbs N. Severe hypoxemia prevents spontaneous and naloxone-induced breathing recovery after fentanyl overdose in awake and sedated rats. Anesthesiology. 2020;132(5):1138-50.

40. Kagawa S, Stafford MJ, Waggener TB, Severinghaus JW. No effect of naloxone on hypoxia-induced ventilatory depression in adults. Journal of Applied Physiology. 1982;52(4):1030-4.

41. Isoardi KZ, Parker L, Harris K, Rashford S, Isbister GK. Acute opioid withdrawal following intramuscular administration of naloxone 1.6 mg: a prospective out-of-hospital series. Annals of Emergency Medicine. 2022;80(2):120-6.

42. Maloney LM, Alptunaer T, Coleman G, Ismael S, McKenna PJ, Marshall RT, et al. Prehospital naloxone and emergency department adverse events: a dose-dependent relationship. The Journal of Emergency Medicine. 2020;59(6):872-83.

43. Farkas A, Lynch MJ, Westover R, Giles J, Siripong N, Nalatwad A, et al. Pulmonary complications of opioid overdose treated with naloxone. Annals of emergency medicine. 2020;75(1):39-48.

44. Kummer RL, Kempainen RR, Olives TD, Leatherman JW, Prekker ME. Naloxone-associated pulmonary edema following recreational opioid overdose. The American Journal of Emergency Medicine. 2022;53:41-3.

45. Al-Azzawi M, Alshami A, Douedi S, Al-Taei M, Alsaoudi G, Costanzo E. Naloxone-induced acute pulmonary edema is dose-dependent: a case series. The American Journal of Case Reports. 2021;22:e929412-1.

46. Elkattawy S, Alyacoub R, Ejikeme C, Noori MAM, Remolina C. Naloxone induced pulmonary edema. Journal of Community Hospital Internal Medicine Perspectives. 2021;11(1):139-42.

47. France CP, Ahern GP, Averick S, Disney A, Enright HA, Esmaeli-Azad B, et al. Countermeasures for preventing and treating opioid overdose. Clinical Pharmacology & Therapeutics. 2021;109(3):578-90.

48. Federal Register : Determination That REVEX (Nalmefene Hydrochloride Injection), 0.1 Milligram Base/Milliliter and 1.0 Milligram Base/Milliliter, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness [March 24, 2023]. Available from: https://www.federalregister.gov/documents/2017/11/03/2017-23952/determination-that-revex-nalmefene-hydrochloride-injection-01-milligram-basemilliliter-and-10.

49. Keating GM. Nalmefene: a review of its use in the treatment of alcohol dependence. CNS drugs. 2013;27(9):761-72.

50. Yazdi K, Fuchs-Leitner I, Gerstgrasser NW. Nalmefene in the treatment of internet pornography addiction–A case report and review of literature. Journal of Addiction Medicine. 2020;14(4):348-51.

51. Yeung DT, Bough KJ, Harper JR, Platoff GE. National institutes of health (NIH) executive meeting summary: Developing medical countermeasures to rescue opioid-induced respiratory depression (a trans-agency scientific meeting)—August 6/7, 2019. Journal of Medical Toxicology. 2020;16:87-105.

52. Krieter P, Gyaw S, Crystal R, Skolnick P. Fighting fire with fire: development of intranasal nalmefene to treat synthetic opioid overdose. The Journal of pharmacology and experimental therapeutics. 2019;371(2):409-15.

53. Zhang T, Li M, Han X, Nie G, Zheng A. Effect of different absorption enhancers on the nasal absorption of nalmefene hydrochloride. AAPS PharmSciTech. 2022;23(5):143.

54. Lin M, Eubanks LM, Karadkhelkar NM, Blake S, Janda KD. Catalytic antibody blunts carfentanil-induced respiratory depression. ACS Pharmacology & Translational Science. 2023;6(5):802-11.

55. Raleigh MD, Accetturo C, Pravetoni M. Combining a candidate vaccine for opioid use disorders with extended-release naltrexone increases protection against oxycodone-induced behavioral effects and toxicity. The Journal of Pharmacology and Experimental Therapeutics. 2020;374(3):392-403.

56. Torralva R, Janowsky A. Noradrenergic mechanisms in fentanyl-mediated rapid death explain failure of naloxone in the opioid crisis. The Journal of pharmacology and experimental therapeutics. 2019;371(2):453-75.

57. Haouzi P, Tubbs N. Effects of fentanyl overdose-induced muscle rigidity and dexmedetomidine on respiratory mechanics and pulmonary gas exchange in sedated rats. Journal of Applied Physiology. 2022;132(6):1407-22.

58. Algera MH, Cotten JF, van Velzen M, Niesters M, Boon M, Shoham DS, et al. Respiratory effects of thyrotropin-releasing hormone and its analogue taltirelin on opioid-induced respiratory depression. British Journal of Anaesthesia. 2022;129(1):e4-e6.

59. Bennett JA, Abrams JT, Van Riper DF, Horrow JC. Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. Anesthesiology. 1997;87(5):1070-4.

60. Miner NB, Schutzer WE, Zarnegarnia Y, Janowsky A, Torralva R. Fentanyl causes naloxone-resistant vocal cord closure: a platform for testing opioid overdose treatments. Drug and alcohol dependence. 2021;227:108974.

61. Adapt Pharma Inc., NARCAN® (naloxone hydro-

chloride) nasal spray [December 24, 2022]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208411lbl.pdf.

62. US Food and Drug Administration. Drug approval

package: KLOXXADOTM [January 5, 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/212045Orig1s000TOC.cfm.

63. US Food and Drug Administration. FDA approves

higher dosage of naloxone nasal spray to treat opioid

overdose [December 24, 2022]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-higher-dosage-naloxone-nasal-spray-treat-opioid-overdose.

64. Disney A, Olson KM, Shafer AM, Moore SC, Anand JP, Traynor JR, et al. Opioid antagonists from the orvinol series as potential reversal agents for opioid overdose. ACS Chemical Neuroscience. 2022;13(21):3108-17.

65. Jimenez Jr VM, Castaneda G, France CP. Methocinnamox reverses and prevents fentanyl-induced ventilatory depression in rats. The Journal of Pharmacology and Experimental Therapeutics. 2021;377(1):29-38.

66. Kassick AJ, Wu M, Luengas D, Ebqa'ai M, Tharika Nirmani L, Tomycz N, et al. Covalently loaded naloxone nanoparticles as a long-acting medical countermeasure to opioid poisoning. ACS Pharmacology & Translational Science. 2021;4(5):1654-64.

CHAPTER 4.1

CHAPTER 4.1
Naloxone for Opioid Overdose: comment

Bonnie L. Milas, Albert J. Varon

Anesthesiology. 2024;140(4):857

To the Editor:

As ASA members spearheading the REVIVEme.com initiative, we appreciate the thorough review of naloxone's pharmacokinetics and dynamics by Lemmen *et al.*[1] and the focus it brings to our Journal's readers. It is clear that further study of opioid overdose reversal of respiratory depression and prevention of cardiac arrest is warranted, and novel μ-receptor antagonists or combinations with agnostic respiratory stimulants represent promising developments.

There are three crucial takeaway points from the information presented in the review that require emphasis. First, because the K_{off} value for naloxone is greater than that of fentanyl, sufentanil, and carfentanil, one needs to be aware that a minimum of 4 mg naloxone should be given, that repeated doses may be needed to reverse respiratory depression, and that renarcotization can occur. Rescuers should always be instructed not to leave a victim unattended after giving naloxone even if breathing and consciousness are restored. It should be noted that the illicit drug supply in the United States predominantly contains fentanyl, not sufentanil, and a much lower percentage contains carfentanil.

Second, naloxone reversal of opioid-induced apnea becomes irreversible at low inspired oxygen fractions but can return to regular breathing at room air concentrations of oxygen. However, full reversal of respiratory depression is not needed to sustain or reinitiate gas exchange, because the authors suggest that only 60% or less of μ-receptor occupancy is adequate to allow for sufficient oxygen uptake. Ventilatory support (rescue breathing) is crucial in a naloxone rescue attempt of a hypoventilating or apneic overdose victim. It provides the conditions for naloxone to fully restore normal breathing and protects the brain from potential irreversible injury.

Last, survival after an opioid-related out-of-hospital cardiac arrest is greater than after arrest from other causes, therefore attempts at resuscitation should be undertaken. As indicated above, ventilation plays a critical role in resuscitation and is the standard of care per the American Heart Association algorithm in a primary respiratory arrest regardless of the underlying cause. If the pulse is eventually lost, then chest compressions should be instituted. According to data from the U.S. transplant registry, the single greatest percentage increase in mechanism leading to organ donation during the past 25 yr is drug overdose. The heart may be resuscitated, but the brain is not tolerant of anoxia. The relationship of the opioid crisis to irreversible brain injury or death due to overdose cannot be overstated.

There is a multitude of variables in the success of rescue from opioid overdose that cannot be controlled as in clinical studies, such as the drug, dose, tolerance, combined intoxication, patient's comorbidities, timing of rescue, or experience of the rescuers. As opposed to a simulated model, an actual opioid overdose victim is a vast unknown entity. All that can be identified on the scene are signs of likely drug overdose, breathing adequacy or absence, and pulse presence or absence. That is all that any rescuer has to act upon.

Calling 911, naloxone, rescue breathing, and chest compressions as indicated are the mainstays of overdose resuscitation. Naloxone 4mg nasal spray is user friendly and proven safe; basic life support is a skill any layperson can learn. It is not the medication that ultimately limits survival, instead it is the conditions on the scene, which includes our personal biases and the willingness to be an immediate responder to an overdose victim.

References

1. van Lemmen M, Florian J, Li Z, van Velzen M, van Dorp E, Niesters M, et al. Opioid overdose: limitations in naloxone reversal of respiratory depression and prevention of cardiac arrest. Anesthesiology. 2023;139(3):342-53.

CHAPTER 4.2

CHAPTER 4.2
Naloxone for Opioid Overdose: comment

Gavin G. Pattullo

Anesthesiology. 2024;140(4):856

To the Editor:

As clinicians, we often question why some patients respond to naloxone and others do not when opioid-induced ventilatory impairment is suspected. This inexplicability is disconcerting, given the toll of opioid-induced ventilatory impairment–related deaths. Our search for greater understanding, as recently provided in this Journal by van Lemmen et al.,[1] is paramount.

As minute ventilation falls under the influence of an opioid, the PaO_2 will decline, and the Paco2 will rise.[2] This relationship may be estimated in a perfect circumstance (without any contribution from shunt, for example) by the alveolar gas equation.[3] A patient affected by opioid-induced ventilatory impairment breathing room air may present with an arterial oxygen saturation of 60% and a $PaCO_2$ 100 mmHg estimated by the alveolar gas equation.[4] Observational studies in human respiratory failure patients note aberrations of consciousness at $PaCO_2$ 90 mmHg and above and a loss of consciousness at 120 to 130 mmHg.[5, 6] Central to hypercarbia-induced sedation or loss of consciousness seems to be the presence of a resulting acidosis of the cerebrospinal fluid (CSF).[7] The lowering of CSF pH from a rise in $PaCO_2$ was shown to have a time constant (63% of change) of 12 min.[8] Thus, $PaCO_2$ must likely be consistently elevated before the CSF pH lowers and consciousness is depressed.[9] $PaCO_2$ likely needs to be consistently normalized on the corollary for consciousness to return.[6]

Depression of consciousness from sustained hypercarbia may explain the failure of response to naloxone in some patients. Naloxone perhaps is antagonizing the direct sedative effects of the opioid without correcting the depression of consciousness from hypercarbia. Research to date on opioid-induced ventilatory impairment does not seem to adequately clarify the role of direct opioid-induced sedation versus the consciousness-depressant effect of hypercarbia.10 Many clinicians have cared for patients who did not respond to naloxone as predicted. Two examples are known opioid use disorder presenting late to the emergency department unconscious or the postoperative ward patient administered opioids who was similarly detected to be unconscious after a time delay. Typically, these patients regain consciousness after several hours in intensive care with sustained invasive positive pressure (hyper)ventilation. This normalizes the $PaCO_2$ for an extended period; we can suspect CSF pH with it. Often nonresponse to naloxone is initially ascribed to the coadministration of other sedative medications. Later, on further enquiry or rational thinking, it transpires that the only substance exposed to excessively was an opioid.

The learned opinion of van Lemmen et al. on the possible role of hypercarbia would aid our

understanding of the pathogenesis of naloxone nonresponders.

References

1. van Lemmen M, Florian J, Li Z, van Velzen M, van Dorp E, Niesters M, et al. Opioid overdose: limitations in naloxone reversal of respiratory depression and prevention of cardiac arrest. Anesthesiology. 2023;139(3):342-53.

2. Pattinson KT. Opioids and the control of respiration. British journal of anaesthesia. 2008;100(6):747-58.

3. Lumb AB. Distribution of pulmonary ventilation and perfusion. Nunn's applied respiratory physiology. 2010:119-44.

4. Lumb A. Nunn's Applied Respiratory Physiology. 6th edition ed2005.

5. Westlake EK. Respiratory failure and carbon dioxide narcosis. Postgraduate medical journal. 1958;34(387):2.

6. Sieker HO, Hickam JB. Carbon dioxide intoxication: the clinical syndrome, its etiology and management with particular reference to the use of mechanical respirators. Medicine. 1956;35(4):389-424.

7. Eisele JH, Eger EI, Muallem M. Narcotic properties of carbon dioxide in the dog. Anesthesiology. 1967;28(5):856-65.

8. Bradley R, Semple S, Spencer G. Rate of change of carbon dioxide tension in arterial blood, jugular venous blood and cisternal cerebrospinal fluid on carbon dioxide administration. The Journal of Physiology. 1965;179(3):442.

9. Semple S. Respiration and the cerebrospinal fluid. British Journal of Anaesthesia. 1965;37(4):262-7.

10. Pattullo GG. Clinical implications of opioid-induced ventilatory impairment. Anaesthesia and Intensive Care. 2022;50(1-2):52-67.

CHAPTER 4.3

CHAPTER 4.3
Naloxone for Opioid Overdose: reply

Maarten A. van Lemmen, Jeffry Florian, Zhihua Li, Monique van Velzen, Eveline van Dorp, Marieke Niesters, Elise Sarton, Erik Olofsen, Rutger van der Schrier, David G Strauss, Albert Dahan

Anesthesiology. 2024;140(4):857-859

In Reply:

We thank Dr. Pattullo[1] and Drs. Milas and Varon[2] for their interest and careful reading of our article on the use of naloxone in the reversal of an opioid overdose as might occur in the community setting in the United States.[3] Individuals that overdose are commonly found in a state of unconsciousness, and these overdose victims, as recently discussed in the general media,[4] are often positive for fentanyl as well as for other substances (e.g., methamphetamine, xylazine, cannabis, or gabapentin), that affect not only breathing but also the level of consciousness. Because illicit drugs often predominantly contain fentanyl, use of naloxone (4 to 8 mg given intranasally or 5 mg given intramuscularly) can rapidly restore rhythmic breathing activity, assuming that there is still cardiac activity. Otherwise, naloxone administration should always be combined with cardiorespiratory resuscitation.

Naloxone restores breathing activity by displacing fentanyl from the μ-opioid receptor. Consciousness may or may not be regained, which depends on many other factors. One problem is brain hypoxia that may result from the opioid overdose.[5] In such cases, hypoxia may cause brain damage, which may impair the rapid return of consciousness. Another problem is cointoxication with tranquilizers that depress consciousness. It is frequently difficult or even impossible to determine the composition of the substances that were abused. The overdose victim and responder often have no idea what adulterants were added to the drug of abuse. Still, high-dose naloxone will often be able to restore the ventilatory component of the overdose sequelae, irrespective of the arousal state, assuming that the upper airway is patent.

Dr. Pattullo introduces the role of hypercapnia, particularly the effect of acidosis of the cerebrospinal fluid on naloxone ability to reverse opioid-induced respiratory depression. We recently studied the effect of hypercapnia on consciousness and cardiorespiratory function in rats and humans.[6] Acutely induced hypercapnia causing severe arterial acidosis was detrimental at concentrations of more than 12% in humans, causing a state of dissociation, while the animal data indicated that levels of more than 20% reduce consciousness and increase the likelihood of mortality. Upon an opioid overdose and in contrast to opioid use in the postoperative setting, the rapid transition of the opioid to the brain compartment can silence respiratory neurons (causing apnea) before any accumulation of arterial carbon dioxide. Hence, in the acute setting, the use of naloxone can be lifesaving by restoring rhythmic breathing activity if the dose is sufficient and cardiac output is still present. When the opioid overdose causes hypoventilation for longer periods of time, hypercapnia will occur, and this may impair consciousness. However, we are not aware of data that suggest that naloxone is

unable to restore breathing activity during long-term hypercapnia, particularly in the absence of hypoxia. At moderate short-term hypercapnia, naloxone is able to reverse morphine- and even buprenorphine-induced respiratory depression.[7, 8] In this respect, hypoxia may be more important than hypercapnia because hypoxia may impair the naloxone activity, as shown by Haouzi et al.[5] A nonresponse to naloxone may be related to the naloxone dose, the presence of adulterants (e.g., tranquilizers), brain hypoxia, possibly hypothermia, and/or low cardiac output; cerebral spinal fluid acidosis may play a role as well. Cerebral spinal fluid acidosis may occur when respiratory depression has lasted for longer periods of time. This is not an unrealistic scenario and many overdose victims are found hours after the overdose occurred in a state of severe hypoventilation, hypoxia, hypercapnia, and hypothermic with low cardiac output. We argue that it is still appropriate to treat these individuals with naloxone, initiate cardiorespiratory resuscitation, and arrange transport to a hospital for further treatment.

Drs. Milas and Varon give an excellent summary of our article and highlight the importance of rapid action when encountering an overdose victim. They stress the importance of adequate naloxone dosing combined with immediate cardiorespiratory resuscitation. As discussed by us, we agree whole heartedly. We thank Drs. Milas and Vernon for their support of our work.

The naloxone dose and route of administration has not been fully defined, and most studies rely on pharmacokinetic data combined with modeling the effect of naloxone on the cardiorespiratory system.[9] We believe that such studies are important and enable the design of human studies that are safe but give sufficient data to provide dosing advice for rescue of overdose victims in the community setting. We are currently studying the effect of intranasal and intramuscular naloxone on high doses of fentanyl administered in healthy volunteers and individuals with an opioid use disorder (https://www.isrctn.com ISRCTN21068708). Other studies are evaluating agnostic respiratory stimulants, which may have a future role in improving outcomes after opioid overdoses (https://clinicaltrialregister.nl id NL9692; https://www.isrctn.com ISRCTN63027076; https://www.isrctn.com ISRCTN16683564).

References

1. Pattullo GG. Naloxone for opioid overdose: Comment. Anesthesiology. 2024;140(4):856.

2. Milas BL, Varon AJ. Naloxone for opioid overdose: Comment. Anesthesiology (Philadelphia). 2024.

3. van Lemmen M, Florian J, Li Z, van Velzen M, van Dorp E, Niesters M, et al. Opioid overdose: limitations in naloxone reversal of respiratory depression and prevention of cardiac arrest. Anesthesiology. 2023;139(3):342-53.

4. Hoffman J. A monster': Super meth and other drugs push crisis beyond opioid. New York Times November. 2023;13.

5. Haouzi P, Guck D, McCann M, Sternick M, Sonobe T, Tubbs N. Severe hypoxemia prevents spontaneous and naloxone-induced breathing recovery after fentanyl overdose in awake and sedated rats. Anesthesiology. 2020;132(5):1138-50.

6. van der Schrier R, van Velzen M, Roozekrans M, Sarton E, Olofsen E, Niesters M, et al. Carbon dioxide tolerability and toxicity in rat and man: A translational study. Frontiers in Toxicology. 2022;4:1001709.

7. Olofsen E, van Dorp E, Teppema L, Aarts L, Smith TW, Dahan A, et al. Naloxone reversal of morphine-and morphine-6-glucuronide-induced respiratory depression in healthy volunteers: a mechanism-based pharmacokinetic–pharmacodynamic modeling study. Anesthesiology. 2010;112(6):1417-27.

8. van Dorp E, Yassen A, Sarton E, Romberg R, Olofsen E, Teppema L, et al. Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology. 2006;105(1):51-7.

9. Mann J, Samieegohar M, Chaturbedi A, Zirkle J, Han X, Ahmadi SF, et al. Development of a translational model to assess the impact of opioid overdose and naloxone dosing on respiratory depression and cardiac arrest. Clinical Pharmacology & Therapeutics. 2022;112(5):1020-32.