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Naloxone dosage for opioid reversal: current evidence and clinical implications

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***Abstract*:** Opioid-related mortality is a growing problem in the United States, and in 2015 there were over 33,000 opioid-related deaths. To combat this mortality trend, naloxone is increasingly being utilized in a pre-hospital setting by emergency personnel and prescribed to laypersons for out-of-hospital administration. With increased utilization of naloxone there has been a subsequent reduction in mortality following an opioid overdose. Reversal of opioid toxicity may precipitate an opioid-withdrawal syndrome. At the same time, there is a risk of inadequate response or re-narcotization after the administration of a single dose of naloxone in patients who have taken large doses or long-acting opioid formulations, as the duration of effect of naloxone is shorter than that of many opioid agonists. As out-of-hospital use of this medication is growing, so too is concern about effective but safe dosing.

Keywords: naloxone, opioid overdose, harm reduction, route of administrations

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Current context

Opioid overdoses have quadrupled in the past 15 years, and in 2015 there were over 33,000 opioid-related deaths in the United States.[1] Opioid overdose induces respiratory depression that can lead to hypoxia, hypercarbia and death. In an attempt to expedite treatment and improve outcomes following overdose, naloxone is increasingly being utilized in a pre-hospital setting by both emergency personnel and prescribed to laypersons for out-of-hospital administration.[2] Efficacy of reversal following naloxone administration by laypersons is high, having been reported at 75–100%,[3] and in general take-home naloxone programs are considered effective for reducing opioid-overdose mortality.[4]

Naloxone overall is a safe medication, and is not known to cause harm when administered in typical doses to opioid-naïve patients.[5–8] There is concern about the precipitation of opioid-withdrawal syndrome following its administration in the setting of prior opioid exposure. Despite the long-standing use of naloxone to reverse the symptoms of opioid overdose or toxicity, appropriate dosing remains controversial, with varying doses recommended over time and by medical specialty.[9] In a hospital setting, this medication is typically administered initially in a low dose, which is then titrated to optimize reversal of opioid-induced respiratory depression while attempting to minimize the risk of withdrawal.[10] In a non-medical setting, the ideal of gradually titrating naloxone to effect is not practical, thus a single standardized initial dose for out-of-hospital naloxone rescue has been sought. This review will evaluate the literature to address the question of optimal naloxone dosing to reverse opioid-induced respiratory depression while minimizing patient risk.

History

Naloxone was developed in the early 1960s as a novel opioid antagonist with fewer side effects than its predecessors.[11] Naloxone hydrochloride is a competitive mu-opioid receptor antagonist historically used only by trained clinical professionals for the reversal of opioid overdose in an emergency or inpatient setting. It is approved for administration by a variety of routes, including intravenous (IV), intramuscular (IM), subcutaneous (SQ) and intranasal (IN), but is also administered *via* inhalation following nebulization or endotracheal tube in intubated patients.[12–14] Formulations for many other routes of administration are currently under development, including sublingual and buccal.[15] Naloxone is not typically administered orally due

to extensive first-pass metabolism in the liver that renders much of the drug inactive, although efficacy has been reported for 1000–3000 mg doses and the duration of action has been reported to be 6–24 h.[16–18]

Naloxone is considered a safe medication. In 2015 the American Association of Poison Control Centers reported no fatalities due to naloxone other than buprenorphine/naloxone combinations.[12] Naloxone has no effect at standard doses in opioid-naïve or non-opioid-dependent patients in doses up to 1 mg/kg.[6,19–25] At high doses of 2 mg/kg IV or greater, patients experienced only behavioral symptoms such as dizziness, paresthesias, sweating, yawning, nausea, inertia and diminished cognitive performance without serious side effects.[26] Significant changes in systolic blood pressure and respiratory rate without a significant change in pulse were only observed in healthy volunteers when given naloxone at doses of 2–4 mg/kg.[27] Adams and colleagues also found that among patients who did experience possible naloxone-associated symptoms, there was no relationship to dose.[20] When naloxone is administered to patients who are opioid-dependent or acutely intoxicated with opioids, it can precipitate an acute withdrawal syndrome, the symptoms of which range from mild behavioral disturbances to reports of cardiovascular instability and pulmonary edema.[28–31] For this reason, the American Heart Association previously empirically recommended an initial dose of naloxone from 0.04 to 0.4 mg IV or IM, and newer guidelines recommend using the 'lowest effective dose' of naloxone to minimize risks of withdrawal, although, as discussed below, it is unclear if the occurrence of such life-threatening events is dose-dependent, while the growing number of opioid overdoses has resulted in the inclusion of non-healthcare provider naloxone administration in the 2015 guidelines at an initial dose of 0.4 mg IM or 2 mg IN.[32]

Provision of naloxone directly to people with opioid use disorder (OUD) was first proposed over 25 years ago.[33] Beginning in the late 1990s, numerous cities and countries developed programs for the distribution of naloxone kits to high-risk individuals, with some countries going so far as to reschedule naloxone to make it available over the counter.[34–36] Products recently approved by the United States Food and Drug Administration (FDA) for administration by non-medical bystanders include an intramuscular autoinjector, Evzio®, approved in April 2014, and a spray device for intranasal delivery, Narcan®, approved in November 2015.[37,38]

Recently the FDA has approved a newer version of Evzio® that delivers 2 mg of naloxone IM/SC, five times the initial dose administered by the original device.[39,40] The increase in dose followed growing numbers of opioid overdoses due to highly potent synthetic opioids, such as fentanyl, as well as reports of emergency medical services (EMS) use of naloxone in a pre-hospital environment revealing an increasing percentage of patients who require multiple doses of naloxone.[41,42] During this same time frame, the number of fatalities associated with more potent synthetic opioids such as fentanyl grew, calling into question the most effective dose of naloxone, particularly when delivered in a pre-hospital setting by individuals without training in or access to advanced life-support techniques.[41,43] As the number of naloxone products intended for use in such non-medical settings grows, so too does concern about appropriate dosing of this medication to ensure adequate reversal of life-threatening opioid overdoses while minimizing the risk of adverse events. Another concern is the lack of dosing information in special populations. Currently the product labels for naloxone autoinjectors and other pre-prepared products do not have altered dosing for children or pregnant women, although these doses are within the recommended range for pediatric resuscitation.[44] The common thought is that it is best to have effective-dose products available in the community that will work on the majority of the population.

Opioid withdrawal

People who inject drugs (PWID) may have a negative overall impression of naloxone due to its association with an acute withdrawal syndrome, which can present with symptoms such as agitation, drug craving, piloerection, vomiting, hypertension and tachycardia, but these are rarely life-threatening.[45] In addition, naloxone administration can result in violent patient behavior upon reversal of opioid-induced sedation.[46] Though rarely fatal, reports of life-threatening or lethal responses to naloxone administration exist; severe but rare reported side effects of opioid withdrawal include pulmonary edema, cardiac arrhythmias, profound hyper- or hypotension and cardiac arrest.[47]

Pulmonary edema

There are multiple reports of pulmonary edema associated with naloxone administration; however, opioid overdose itself can result in non-cardiogenic pulmonary edema (NCPE), which is observed in most fatal opioid overdoses, even those occurring before the widespread use of naloxone,[48,49] with a reported prevalence of 48% in hospitalized opioid overdose patients, although this number is likely an overestimation of the incidence of this condition overall due to an underestimated denominator that did not include patients who were not admitted to the hospital.[50] The incidence of such pulmonary edema has decreased in the past few decades, likely related to improvements in EMS treatment of opioid toxicity, including increased pre-hospital administration of naloxone.[48] Opioid-induced pulmonary edema is likely a form of neurogenic pulmonary edema, which results following neurologic injury involving both a hemodynamic and an inflammatory response to brain or cervical spinal insult, resulting in both vasoconstriction with subsequent increased pulmonary hydrostatic pressure as well as increased capillary permeability.[51] The tracheal edema fluid from patients who developed pulmonary edema following heroin use demonstrates evidence for such increased pulmonary capillary permeability.[52] The effects of this change in pulmonary function may merely be revealed by the reversal of opioid-induced respiratory depression following naloxone administration.[31]

Reports of naloxone-associated pulmonary edema following reversal of opioid-induced respiratory depression are diverse. This phenomenon has been observed among young and old patients and after a wide range of naloxone doses. In some cases, the patient had an underlying pulmonary condition prior to the opioid overdose.[53] However, the rapid development of pulmonary edema following naloxone administration to reverse the effects of opioid anesthesia in post-operative patients has been repeatedly described. In some cases the surgical procedure involved the administration of large volumes of IV fluids,[54,55] but others involve healthy young adults emerging from anesthesia after relatively minor surgical procedures.[56–58] The total doses of naloxone given prior to the development of pulmonary edema range from 0.08 mg to 0.4 mg, and include cases where naloxone was carefully titrated in small increments or given as a single bolus.[54–58] In most cases, the edema quickly resolved, particularly in response to furosemide and/or additional opioid.

Pulmonary edema is presumed to involve the release of catecholamines following naloxone reversal of opioid analgesia. In dogs, naloxone produced an increase in HR and MAP in all animals after fentanyl but produced an increase in catecholamines only in hypercapnic dogs.[59] In humans, most patients who receive naloxone do so because of respiratory depression and are likely to be hypercapnic, but overall the incidence of naloxone-induced pulmonary edema appears to be rare and primarily encountered within the peri-operative arena.

Severe cardiovascular events

Naloxone administration is generally associated with an increase in heart rate, cardiac output and arterial blood pressure in humans and in dogs,[60] and studies in the latter have shown increased coronary blood flow and myocardial oxygen consumption.[61,62] Initially, studies of the administration of high doses of naloxone to patients with OUD under general anesthesia for purposes of detoxification produced no significant changes in heart rate, mean arterial pressure, cardiac index, peripheral resistance or oxygen saturation.[63] However, later studies found that such treatment with naloxone is accompanied by a 30-fold and 3-fold increase in epinephrine and norepinephrine plasma concentrations respectively, and that this catecholamine surge is associated with significant increases in cardiac index, stroke volume index, heart rate, whole-body oxygen consumption and a systemic vascular resistance index decrease, all consistent with the effect of epinephrine.[64–66] In the post-operative period, Tigerstedt and Tammisto observed that when patients were given 0.08 mg naloxone after anesthesia with fentanyl, there were no significant differences between the naloxone and control groups in CO_2 output, O_2 uptake or cardiac index.[67] However when 0.16 mg of naloxone was similarly administered to patients 10 min after fentanyl-supplemented balanced anesthesia, there were significant increases in respiratory rate, minute volume, CO_2 output and O_2 uptake, as well as an increase in the cardiac index, thought to reflect a metabolic increase that may not be tolerated in all patients, thus careful titration was recommended.

Cardiovascular events following administration of naloxone after surgical anesthesia have included severe hypertension, atrial tachycardia and ventricular tachycardia or fibrillation in patients who underwent open heart surgery and were seen after

a wide range of doses (0.1–0.4 mg).[68,69] Such events have also been reported in response to naloxone in patients with underlying cardiac dysrhythmias[70] as well as during reversal of opioid overdose in PWID, particularly those who also use stimulant drugs such as cocaine or amphetamines.[71–74] Post-operative naloxone administration precipitated severe hypertension that led to re-bleeding of a cerebral aneurysm.[75] However, sudden death has also occurred following 0.2 mg of naloxone administration to healthy adults with no medical problems after uncomplicated orthopedic surgeries.[76]

In light of these risks, many authors have recommended the cautious use of naloxone in divided doses.[77] However, as some of these events occurred following doses >2 μg/kg, it is unclear what, if any, dose should be considered safe. Thus, the risk of under-dosing the antagonist to reverse opioid toxicity may not be balanced by the presumed avoidance of severe adverse effects if these may present at such small doses in susceptible individuals; however, even non-life-threatening withdrawal symptoms may adversely impact an opioid user's decision to administer naloxone to a peer.

Pharmacokinetics and pharmacodynamics

After IV administration, approximately 60–65% of naloxone is excreted through the kidney as conjugated metabolites.[18] Naloxone undergoes a rapid and extensive hepatic metabolism to conjugated (naloxone-3-glucuronide), n-dealkylated and reduced metabolites.[18,78–80] The serum half-life of naloxone is approximately 60 min, though individual variations range from 30–90 min, and the serum half-life of morphine is similar at 62 min (ranges from 20 to 120 min).[18,81,82] The volume of distribution and metabolic clearance following an IV bolus of naloxone are about 200 L and 2500 L/d, respectively.[18]

Naloxone transfers and equilibrates rapidly between the plasma and the brain, and has a blood effect-site equilibration half-life of 6.5 min,[83] comparable to that of fentanyl and its similarly lipid-soluble analogs and in contrast to the more hydrophilic morphine molecule.[84,85] In addition to simple diffusion, the transfer of both naloxone and fentanyl across the blood–brain barrier (BBB) also involves a saturable transporter in animal and *in vitro* models, and for low, therapeutic concentrations of fentanyl, this mechanism may produce a 2.5-fold increase in brain endothelium fentanyl levels over simple diffusion alone.[86,87] In animal studies, naloxone levels in the brain 5 min after an IV bolus are indeed higher than those in serum, but the levels decline in parallel following this initial peak, while in contrast brain levels of morphine decline very slowly, remaining near the initial concentration for 1 h despite a rapid decline in serum morphine concentration over this period.[81] This could account for the very short duration of morphine antagonism by naloxone despite overall similar serum pharmacokinetics, as the effects of morphine are delayed in onset but outlast those of naloxone likely due to the lower lipid solubility of morphine and its retention in the brain.[18,80,81]

One of the initial studies of parenteral naloxone dosing in a clinical setting found that all patients who had received high doses of IV morphine (up to 6 mg/kg) as the sole anesthetic for cardiac surgery experienced reversal of post-operative respiratory depression following 10 μg/kg of naloxone IV administered in divided doses of 5 μg/kg.[88] Additional studies in anesthetized patients have also reported 5 μg/kg IV to be an adequate dose to protect against or reverse opioid-induced respiratory depression measured as both respiratory rate and minute volume; however, this dose often needs to be repeated or followed by an infusion of naloxone to maintain this effect.[7,88,89]

Receptor antagonism

Just as different opioids vary in the degree and duration of respiratory depression they induce, so too do they differ in their ease of antagonism by naloxone.[90,91] In addition to its rapid elimination and blood–brain transfer, the receptor association/dissociation kinetics of naloxone are fast.[83,92] With regard to the potency of naloxone, 1.55 μg/kg is required to reduce the effect of a 12 mg morphine dose by half[93]; however, predicting an adequate dose in a clinical setting is challenging as effective antagonism of opioid toxicity depends upon the amount of opioid present and its potency, as well as its interactions with the opioid receptor.[94,95] The former are dependent not only upon the specific opioid and the dose administered, but also the route of administration and the patient's ability to clear the drug, further complicating accurate prediction of an effective dose of naloxone to adequately reverse opioid toxicity.[96,97] Moreover, an opioid's affinity for and kinetics of association and dissociation with the

opioid receptor also greatly impact its ease of reversal by naloxone.[90,83] A dose of 13 μg/kg (approximately 1 mg in an 80 kg individual) of naloxone will occupy 50% of available receptor sites in the human brain,[98] but as naloxone is a competitive antagonist at the mu-opioid receptor, this dose may be insufficient to reverse toxicity due to very large overdoses or compounds with a higher affinity for the mu-opioid receptor, in which case very few opioid binding sites remain unoccupied.

The respiratory depression induced by buprenorphine, a partial agonist with a notably high affinity for the mu-opioid receptor, is resistant to antagonism by typical doses of naloxone.[99,100] Gal tested the efficacy of several doses of naloxone to reverse the respiratory depression caused by a large (0.3 mg/kg) IV dose of buprenorphine.[101] They found that 1 mg IV had little effect, but 5 mg and 10 mg of naloxone both reversed the respiratory depression, though the larger dose did so to a greater degree. This effect was delayed and did not reach its maximum until 3 h after naloxone administration, which is in stark contrast to the very rapid (2–3 min) reversal of the respiratory effects of most other opioids.[102] Similarly, van Dorp and colleagues found that a 0.8 mg dose of naloxone had minimal effect on the respiratory depression induced by 0.2–0.4 mg of buprenorphine.[103] A 2 mg IV bolus of naloxone followed by a 2 h infusion of naloxone at 4 mg/h did adequately reverse the respiratory depression of a smaller dose of buprenorphine, while a 3 mg IV initial bolus was required prior to the infusion to reduce the respiratory effects of the larger buprenorphine dose. This response was delayed despite increasing the dose of naloxone to counteract the effects of the higher opioid dose and the improvement in respiration was not complete until 40–60 min after naloxone administration, regardless of the antagonist dose. Most interestingly, full reversal ±20% was achieved for all buprenorphine doses after a naloxone dose between 2 mg and 4 mg, while higher doses of naloxone than this demonstrated a reduced ability to antagonize the buprenorphine-induced respiratory depression, resulting in an inverse-U-shaped dose–response curve.

Naloxone more slowly antagonizes the respiratory depression induced by the morphine metabolite, morphine-6-glucuronide (M6G), than it does the respiratory effects of morphine, owing to the slower receptor association–dissociation kinetics of M6G.[104] However, the duration of naloxone reversal is longer for M6G than for morphine, likely impacted by naloxone's four-fold greater potency as an antagonist of the metabolite than the parent compound. In healthy volunteers, increasing the naloxone dose did not improve the speed of reversal of M6G-induced respiratory depression, but did increase the degree and duration of reversal. In contrast, alfentanil-induced reduction in respiratory response to a hypoxic challenge is rapidly reversed by a single IV dose of naloxone 6 μg/kg.[94]

The rapidity of reversal of opioid-induced respiratory depression is dependent upon these opioid agonist–receptor interactions for most opioids other than those with very fast receptor association–dissociation kinetics, such as fentanyl, and thus is not hastened by increasing the dose of the opioid antagonist.[104–106] Hence, the interactions between the opioid agonist and the mu-opioid receptor may be the greatest determinant of the speed of recovery from the respiratory effects of many opioids, which may not markedly accelerate with increasing doses of naloxone, but rather respond to a minimum effective dose, while for compounds like buprenorphine, higher doses of naloxone may even lose efficacy.

There has been a recent international increase in the number of opioid overdoses attributable to fentanyl.[43,107,108] Due to its high lipophilicity, fentanyl rapidly equilibrates between the plasma and the cerebrospinal fluid, leading to a fast onset of both analgesia and respiratory depression, while this same property results in extensive redistribution to less highly perfused tissues such that fentanyl is typically considered a very short-acting opioid when given IV; however, its duration of action is prolonged by large doses that progressively saturate these tissues, and delayed respiratory depression may even be seen.[109] A growing number of reports of opioid toxicity due to fentanyl or its derivatives such as carfentanil (100 times more potent than fentanyl) describe resistance to reversal with standard doses of naloxone.[110–112]

National EMS data from 2015 reveals that almost one-fifth of patients receiving naloxone from EMS required more than one administration, up from one-sixth of patients in 2012; in Massachusetts, almost one-third of all incidents treated with naloxone required multiple administrations, although the doses and routes through which they were administered are not clear.[41,113] Numerous

reports describe fentanyl overdoses initially unresponsive to IN naloxone and only transiently reversed with IV naloxone (if at all), requiring additional IV doses or continuous infusions to prevent recurrence of toxicity and respiratory depression.[110,112,114] There are similar case reports of controlled-release oxycodone overdose requiring massive doses of naloxone (over 100 mg in under 12 h) for reversal.[115] These reports may reflect the magnitude of over-dosing in these cases due to the compounds' high potency or dose as opposed to their intrinsic resistance to naloxone antagonism as is seen with buprenorphine. Remarkably, serum fentanyl levels in several patients hospitalized for such an overdose were up to three times greater than the highest therapeutic concentration for analgesia, and were almost four times greater than the maximum therapeutic level among those patients who died.[116] In those fatal cases, postmortem testing detected no norfentanyl, the primary metabolite of fentanyl, presumably because the patients died before metabolism could occur, thus it is unlikely that any dose of naloxone could have reversed the effects of such an immense overdose. As the number of deaths due to synthetic opioids such as fentanyl increased by over 72% from 2014 to 2015, such reports have prompted the FDA to re-evaluate recommended naloxone dosing out of concern for inadequate reversal of these potent opioids.[43,117]

Duration of effect

The duration of reversal of opioid-induced respiratory depression is brief and dependent upon the dose and potency of the opioid given, as well as the amount of naloxone administered. In healthy volunteers, a 0.4 mg IV dose of naloxone reversed the sedation induced by morphine 0.3–0.6 mg/kg within 2 min of administration, but the subjects began to feel the effects of the morphine again after 15–30 min and returned to the pre-naloxone level of sedation within 45 min.[118] Surgical patients receiving high-dose morphine required additional doses of IV naloxone anywhere from 30 min to 90 min after initial reversal.[88,89] There are reports that combining IV and IM administration of naloxone extends the duration of effect,[89,119] but the larger doses administered may precipitate opioid-withdrawal symptoms and may not confer a survival benefit following opioid overdose.[120]

Continuous IV infusions of naloxone best prevent recurrence of opioid-induced respiratory depression while minimizing the risk of opioid-withdrawal symptoms expected to follow a large bolus dose.[121–124] Under experimental conditions in healthy volunteers, it was found that 3.66 μg/kg of naloxone given as a bolus then infused at this rate for 10 h would reverse the respiratory and sedative effects of 2 mg/kg morphine in volunteers, though not to baseline levels; however, there was a high incidence of vomiting within the first 4 h of the infusion.[102] Based upon available pharmacokinetic data, Bradberry and Raebel recommended that opioid overdoses be treated with a 5 μg/kg loading dose of naloxone immediately followed by 2.5 μg/kg infused over 60 min, then continued as needed for 24–48 h or greater based upon the presenting level of unconsciousness or the involvement of methadone, a long-acting opioid.[121]

After the long-acting opioid buprenorphine was administered to healthy volunteers, an infusion of naloxone was required to sustain a reduction in buprenorphine-induced respiratory depression; once the infusion ended, ventilation rapidly declined, reaching pre-infusion values within an hour, though still remaining twice what was observed among patients treated with placebo instead of naloxone.[103] Kinetic modeling suggests that to reverse the respiratory effects of buprenorphine, an infusion of naloxone 4 mg/70 kg/h is necessary to avoid recurrence of respiratory depression, as this dose produces almost complete reversal of the drug's respiratory effects; doses greater than this may actually be less effective for buprenorphine reversal, though there is as yet no clear explanation for this bell-shaped response curve to naloxone.[83]

Clinically, naloxone has been administered as an infusion of 4–5 μg/kg/h following initial 1.5 μg/kg boluses to maintain respiration in post-surgical patients whose intra-operative anesthetic consisted of high-dose fentanyl (100 μg/kg) or sufentanil (20 μg/kg) without precipitating withdrawal symptoms beyond nausea, vomiting and headache.[122] To prevent more serious withdrawal symptoms, the authors recommended that a single IV bolus dose of naloxone should not exceed 1.5 μg/kg at 'an appropriate interval', yet all of the 20 patients required at least two such boluses and on average 4–7 boluses depending upon which opioid they had been administered, while the overall frequency of headache, nausea and vomiting did not differ from that reported in a study of patients after a similar anesthetic who did not receive post-operative naloxone. In a larger study

of naloxone infusion following high-dose fentanyl (mean dose 127 μg/kg) anesthesia by Takahasi and colleagues, naloxone was initially given as 50 μg boluses IV repeated at 2 min intervals until the patients fulfilled extubation criteria, which totaled on average 3.4 ± 2.6 μg/kg and did not precipitate any adverse symptoms.[123] At this point an infusion of naloxone was begun at an hourly rate equal to the sum of the bolus doses. This rate was adjusted up or down depending upon the patient's ability to maintain spontaneous respiration, the development of acute sympathomimetic or psychomimetic symptoms, or increased pain, the latter of which was the most common reason for dose adjustments. The total administered dose of naloxone, which needed to be infused for 10.8 ± 6.7 h after surgery, was 26.9 ± 23.2 μg/kg/h. The amount of naloxone required before the patients met extubation criteria was greater in this study than in the previously described report, likely due to the larger dose of fentanyl used by Takahashi, yet among their patients Takahashi and colleagues found no correlation between fentanyl and naloxone in terms of doses given nor plasma concentrations, reflecting the large variation in the balance of opioid and naloxone between individuals. Also important to note was the one patient who was excluded from the study after failing to adequately increase respiration after 600 μg of naloxone. Among the included patients, the mean plasma naloxone level at extubation and 3 h later was approximately 6 ± 4 ng/ml; previous pharmacokinetic studies have shown that 5 min after injection with 0.4 mg of naloxone the plasma concentration is 4.3 ± 0.3 ng/ml.[81] Rawal and colleagues administered epidural morphine to patients after abdominal surgery followed by naloxone bolus then infusion of either 0.4 mg and 10 μg/kg/h or 0.2 mg and 5 μg/kg/h or saline placebo.[124] None of their patients complained of pain after the bolus injection and visual analog scale scores were similar among both groups receiving naloxone, though were significantly higher than the placebo group at multiple time points, and the duration of analgesia from the epidural morphine was significantly shorter in the high-dose naloxone group compared to the placebo group. There were no major adverse effects noted, with an overall very low rate of nausea, vomiting and pruritis among all groups without significant differences. There was a marked improvement in respiratory rate in the groups receiving naloxone compared to placebo. At these doses, the average concentration of naloxone at 5 h was 3.68 ng/ml and 5.07 ng/ml for the 5 μg/kg/h and 10 μg/kg/h groups, respectively.[124]

Goldfrank and colleagues devised a dosing nomogram for the administration of a continuous naloxone infusion for the treatment of opioid overdose to overcome the short duration of effect of naloxone.[96] The authors discovered a large amount of variability after an IV bolus of naloxone (0.8 mg or 2 mg) in the beta rate constant of elimination among the seven patients sampled to develop the nomogram. They concluded that initial bolus dosing should be determined clinically to avoid over-dosing the patient with naloxone and precipitating withdrawal, but that once this value is determined, an infusion equal to two-thirds this initial dose per hour should suffice to prevent recurrence of respiratory and neurologic depression.

Route

Naloxone IM is frequently used by emergency response teams and emergency department providers to rapidly administer naloxone when IV access is not readily available and in an attempt to prolong the activity of naloxone.[125–127] Naloxone has similarly been made available for layperson IM administration in cases of opioid overdose *via* standard syringes and needles or a prefilled autoinjector.[128] The latter device reduces the risk of needlestick *via* an automatically retracting needle and results in a 15% greater maximum concentration than delivery *via* a standard needle and syringe.[129]

The intranasal (IN) administration of naloxone to reverse opioid overdose has been increasingly utilized due to ease of administration by laypersons as well as improved safety for EMS personnel through avoidance of potential needlestick injuries when treating a patient population at high risk for blood-borne illnesses.[128] The absorption of medications may be reduced by abundant nasal secretions or blood as well as prior use of vasoconstrictors such as decongestants or cocaine.[130–133] Like IM injection, IN administration allows drug delivery without the establishment of IV access, which can be particularly challenging in PWID. Naloxone given *via* both routes may provoke less severe withdrawal symptoms than when an equal dose is administered IV.[134] However, the pharmacokinetics of the two routes differ substantially.

In a study of the population pharmacokinetics of IN naloxone in healthy volunteers, Dowling and colleagues found that 0.8–2 mg of a standard 0.4 mg/ml concentration of naloxone has poor bioavailabilty of 4% (*versus* 35% for IM).[135] Compared to IM injection of 0.8 mg, IN delivery of 2 mg of naloxone resulted in more rapid time to peak concentration by about 5 min, but naloxone was only measurable in the blood for an hour *versus* up to 4 h following IM administration. This study was limited by the small number of participants and the large volume of liquid (5 ml) administered IN to achieve the highest dose, likely resulting in a large portion of the dose pooling in the nasopharynx before being swallowed; naloxone levels were only measurable in two out of six subjects after IN administration. In contrast, following administration of 0.2 ml per nostril of a 20 mg/ml or 40 mg/ml dose, the bioavailability of IN naloxone was found to be approximately 25%, although the time to maximal concentration for these larger doses was 2–3 times greater than that reported by Dowling and colleagues.[136] When 2–8 mg of naloxone was administered IN in a low volume *via* an FDA-approved device, plasma naloxone concentration rose faster, reached a higher maximum (C_{max}) and remained elevated longer than after a typical 0.4 mg IM dose.[137] However, a 2 mg dose of IM naloxone *via* autoinjector results in a C_{max} nearly twice that of the same dose given IN.[138,139]

Naloxone use and efficacy

Use by non-medical personnel (Table 1)

The implementation of programs to distribute naloxone kits to opioid users for peer administration, typically in conjunction with education about appropriate bystander response following an opioid overdose, has been associated with a decrease in the number of opioid-related deaths, particularly among high-risk groups.[140–143] In a rural county in North Carolina, for example, where overdose deaths are most commonly due to prescription opioid analgesics rather than heroin, the overdose death rate fell from 46.6 per 100,000 to 29.0 per 100,000 in the year following the introduction of an overdose-prevention program that included the distribution of naloxone to community members among other interventions such as patient and physician education about opioid use.[144] Numerous communities are also training non-medical first-responders such as police and firefighters to administer naloxone in cases of suspected overdose.[142,145] However, due to inconsistencies in study design, aims and reporting, as well as limitations in follow-up, it is difficult to evaluate the effects of such programs in aggregate.

American Heart Association guidelines recommend that victims of opioid-induced respiratory depression treated with naloxone by non-medical observers should access advanced healthcare systems.[12] Bystanders of PWID frequently report not calling EMS when witnessing an opioid overdose.[146–148,152,154,157] It is thus imperative that naloxone be available and administered in adequate dosage to reverse most opioid-induced respiratory depression. The manufacturer recommended initial dose is 2 mg or 4 mg IN or 0.4 mg or 2 mg IM/SC to be repeated after 2–3 min if needed; however, there is no consensus nor recommendation to guide which of the available doses should be selected in a given case of opioid overdose.[47,166] However, as the half-life of naloxone after IV administration is approximately 1 h and the duration of effect is 45–180 min, there is a risk of recurrence of respiratory depression or inadequate response following reversal with naloxone when treating the effects of long-acting, high-dose or potent synthetic opioids.[18,81,119,167–169] Although there has been a surge in the number of heroin-overdose deaths in recent years with heroin-related deaths outnumbering deaths due to opioid analgesics as of 2015, there are still a large number of the latter and it may be difficult to differentiate respiratory depression due to a short-acting agent such as heroin from that caused by a longer-acting prescription medication or by a highly potent synthetic opioid like fentanyl and its derivatives.[170] In addition, 79% of patients experience acute morbidity from non-fatal opioid overdose.[171] There is no literature evaluating long-term morbidity associated with non-fatal opioid overdose.

Pre-hospital use by EMS (Table 2)

Route. Despite the poor bioavailability of standard concentration (0.4–1 mg/ml) IN naloxone, there are numerous reports of its clinical efficacy being equal to or surpassing that of IV administration.[134,172–174] Barton and colleagues evaluated the pre-hospital administration of IN followed by IV naloxone to patients suspected of opioid overdose.[175] Among 52 patients that responded to either IV or IN naloxone, 83% responded to an

Table 1. Administration of naloxone in a community setting by non-medical personnel.

Study	Dose and route	Naloxone administrations and reversal success rate	Withdrawal symptoms	Recurrence of respiratory depression	Location; other
Dettmer and colleagues[34]	0.4 mg × 2 for IM (Berlin); 0.8 mg for IM (Jersey)	Berlin: 29 administrations: 76% were given 0.4 mg, 14% got 0.2 mg and 10% were given 0.8 mg; 48% IM, 45% IV, 7% SQ. All 29 recovered. Jersey: 5 instances, all fully recovered	34% sudden withdrawal; no other side effects Jersey: no adverse consequences other than withdrawal symptoms	N/R	Berlin, Germany and Jersey; Pilot
Seal and colleagues[146]	0.4 mg × 2 for IM	Administered in 15/20 OD cases; 100% survival	'No evident adverse consequences'	'No evident adverse consequences' (N/R)	San Francisco, CA; CPR provided to 80% of witnessed ODs; EMS called by the participants in 2 cases (and by other bystanders in an additional 4 cases)
Galea and colleagues[147]	0.4 mg × 2 for IM	Administered in 10/17 ODs, 100% survival rate in those 10	N/R	N/R	New York, NY; 83% said they would want naloxone administered if they were overdosing; EMS called by 82% Among the 7 OD cases where naloxone was not given, 5 lived, 1 died and 1 outcome was unknown
Maxwell and colleagues[140]	10 ml of 0.4 mg/ml; IM	319; only one unsuccessful revival (polysubstance OD), one required 5 sequential doses before effect achieved. The authors conclude that 0.4–0.8 mg IM is sufficient in almost all cases.	1 vomiting, 1 seizures (history of benzodiazepine use) 'the opiate reversal symptoms are mild and abate within 40–60 minutes'	None	Chicago, IL; dose repeated in 5 cases (though within 2 min of initial administration in 4 cases); trend of increasing heroin deaths annually reversed after initiation of the naloxone program
Piper and colleagues[148]	1 mg/ml × 2 for IM	82 administrations, 83% of which survived (17% unknown outcome)	N/R	N/R	New York, NY; 50 of 71 participants administered naloxone when witnessing an OD; 86% of the participants said they would want naloxone administered if they were overdosing.
Strang and colleagues[149]	NR	Naloxone used in 12 instances (2 were ambulance) out of 18 experienced/witnessed ODs; all successful reversal	No severe adverse events but did precipitate withdrawal in unreported percentage; 4 annoyed/angry	NR	England
Doe-simkins and colleagues[150]	2 mg/2 ml mucosal atomization device	74 successful reversals (100%)	2/74 (3%)	2/74 (3%)	Boston, MA; first 15 months after program implemented August 2006; EMS involvement reported in 58% of ODs

(Continued)

Table 1. (Continued)

Study	Dose and route	Naloxone administrations and reversal success rate	Withdrawal symptoms	Recurrence of respiratory depression	Location; other
Tobin and colleagues[151]	0.4 mg/ml × 10 ml for IM (50% given 1 ml, 19% 2 ml and 31% 3 ml or more; >55% received ⩾2 ml)	19 administrations; N/R success	N/R	N/R	Baltimore; MD; among participants who witnessed an OD both before and after training, 65% called EMS before training *versus* 49% after; after training 44% administered naloxone: 74% gave 1 dose; 21% gave 2; 5% gave 3 or more injections
Enteen and colleagues[152]	0.4 mg × 2 for IM	Naloxone used in 399 events with 83% reversed by bystanders; 89% reversal rate after bystander and/or EMS naloxone administration. Six deaths, 4 of which occurred in victims given naloxone, 3 of whom had been unconscious for unknown time prior to naloxone administration.	Seizures (<1%), vomiting (13%), anger or discomfort (9%)	N/R	San Francisco, CA; 2003–2009; naloxone used in an OD by 11% of all participants; EMS called in 29% of OD events
McAuley and colleagues[153]	1 × 0.4 mg syringe	Two administrations and both survived	NR	NR	Scotland
Wagner and colleagues[154]	0.4 mg/ml × 2 for IM	Administered in 28/35 observed ODs (80%); 74% of OD victims recovered at the scene and/or hospital (14% outcome unknown, 11% died), but not specified if these were the patients to whom naloxone was administered	Not specified if adverse events were associated with naloxone administration: 14.7% angry, 2.9% vomited, 0 seizures	N/R	Los Angeles, CA; 60% called EMS
Bennett and colleagues[155]	NR	Administered for 249 ODs, 96% 'okay'; 2 deaths (1 involved benzodiazepines and the other cocaine in addition to opioids) and 3.2% unknown outcome	NR	NR	Pittsburgh and Allegheny County, PA; 2005–2008; EMS called in 10% of the 249 cases of naloxone administration *versus* 33% prior to naloxone training
Bennett and Holloway[156]	1 × 0.4 mg	28 uses; 27 recoveries (96%) and 1 fatality	NR	NR	Wales; 85% called EMS; take-home users and EMS both noted often needing to use more than one 0.4 mg dose
Lankenau and colleagues[157]	NR	Of 30 witnessed ODs, 29 survived and 1 outcome unknown; 17 naloxone administrations, 100% of which survived	NR	NR	Los Angeles, CA; EMS called for 13 events (7 by naloxone program participant); naloxone was titrated to minimize withdrawal in several cases
Leece and colleagues[158]	2 × 1 ml (0.4 mg) vials; IM	17 administrations, 100% successful	NR	NR	Toronto, ON
Walley and colleagues[159]	2 × 2 mg/2 ml with atomizer for IN	92 rescues	NR	NR	Massachusetts; 2008–2010; heroin reported in 90% of the ODs, methadone in only 4.8%

Table 1. (Continued)

Study	Dose and route	Naloxone administrations and reversal success rate	Withdrawal symptoms	Recurrence of respiratory depression	Location; other
Doe-simkins and colleagues[160]	2 × 2 mg/2 ml for IN	599; 97% successful; 54% used 1 dose, 46% used 2 or more doses	NR	NR	Massachusetts; 2006–2010; EMS was called in fewer than one-quarter of ODs
Morgan and Smith[161]	NR	375 reported administrations since 2009 with 5 fatalities; 160 administrations between 2013–2014 with 2 fatalities (1.3%) and 8 outcomes unknown	NR	NR	Wales: 2013–2014; EMS contacted in 59% of naloxone administrations; beginning one year after the implementation of take-home naloxone program, the incidence of heroin/morphine deaths began to decline after rising steadily in the preceding 5 years; however, there continue to be an increasing number of fatalities due to methadone/buprenorphine
Oluwajenyo Banjo and colleagues[162]	0.4 mg IM × 2	85 total reversals reported but records only available for 64 pre-EMS reversals 48% required one ampule, 36% required 2 and one case required 3 ampules	Mild withdrawal in 28%, Severe withdrawal in 8%, aggression displayed in 14%	NR	94% of ODs involved heroin, 19% involved fentanyl; only 39% called EMS
Rando and colleagues[142]	2 mg IN × 1 and call EMS	Naloxone administered to 67 individuals; 77.6% survival (11% lost to follow-up, 10.5% died)	NR	NR	Lorain County, OH; 2011–2014; police officers trained to administer naloxone Quarterly number of opioid OD deaths decreased by 4.1 individuals per quarter in contrast to pre-program quarterly increase by 1.5 deaths
Rowe and colleagues[163]	2 × IM or IN kits (dose NR)	Out of 702 administrations there were 10 deaths (1.4%) (in 6 cases the participant knew it was 'too late' but administered naloxone anyway)	NR	NR	San Francisco, CA; 2010–2013; data obtained only from participants returning from refill rather than active data collection; >90% reported using heroin; EMS was called in 27.4% cases
Chronister and colleagues[164]	0.4 mg IM × 2	30 administrations, 100% successful 40% of ODs responded within 2 min, another 40% within 2–5 min	Four treated individuals were reportedly angry due to withdrawal; no other issues	NR	Sydney, Australia; two-thirds who witnessed an OD called EMS
Madah-Amiri and colleagues[165]	0.8 ml IN (divided as 0.4 ml in each nostril) *via* atomizer and repeat × 1; given 2 ml of 1 mg/ml	277 administrations of which 265 survived (96%; remaining unknown or missing) Doses titrated and 24% of participants reported using all the doses available: 73% used 2 doses or less while 27% used the whole 2 ml and one used 4 ml	In 27% of administrations, no adverse symptoms were reported, while after given naloxone, 27% were confused, 11% were angry, 7% were nauseous, 1% vomited, 5% were tired, 3% 'shock' and 8% had other adverse symptoms	NR	Norway; 2014–2015; 66% called EMS for OD; 84% of naloxone uses were for heroin OD

EMS, emergency medical services; NR, not reported, OD, overdose.

Table 2. Naloxone administered by EMS or in the emergency department.

Study	Dose; route	Reversals; outcomes	Adverse events	Recurrence of respiratory depression	Misc.
Yealy and colleagues[178]	0.4–0.8 mg initial dose (mean total dose 0.9 ± 0.6 mg; range 0.4–2.4 mg); 800 IV, 7 ET, 4 SL, 1 IM, 1 SQ	813 patients administered naloxone by paramedics; 7.4% improved within 5 min	No ventricular tachycardia, ventricular fibrillation or asystole, 1 patient had a generalized tonic-clonic seizure after 0.8 mg IV (had underlying seizure disorder and no response to naloxone); 2 patients vomited after 0.8 mg IV (1 had received ipecac before naloxone); 1 patient became hypertensive without improvement in level of consciousness and 7 others had 30 mmHg increase in systolic blood pressure but returned to <160 mmHg; 2 patients became hypotensive after 0.8 mg IV	NR	Pittsburgh, PA; excluded patients without palpable pulse at the time of naloxone administration
Bertini and colleagues[179]	Altered respiratory arrest mean dose 0.8 mg IV (range 0.4–2 mg) Cardipulmonary arrest mean dose 1.2 mg (range 0.4–2.8 mg)	52 patients in respiratory arrest, of whom 77% recovered spontaneous breathing following pre-hospital naloxone administration; all 52 survived; 4 of 7 patients in cardiopulmonary arrest with asystole survived after resuscitation with naloxone IV and advanced life support	NR	NR	Florence, Italy; 1984–1987
Smith and colleagues[180]	91 patients given 2 mg or 4 mg IV; 96 given 2 mg IM and 87 patients received both IM and IV	124 patients administered naloxone: 107 not admitted, 5 died in the ED	No delayed onset pulmonary edema; 3 patients developed NCPE within 20 min of arrival in ED	None (no deaths within 5 days of hospital visit)	El Paso, TX; June–November 1989
Osterwalder[181]	NR	Detailed evaluation of 169 intoxications, of whom 142 received naloxone	1 death due to delayed pulmonary edema (incidence of 0.6%)	No readmissions for coma or pulmonary edema within 24 h but 1 death with symptoms of pulmonary edema over 8 h after treatment	St Gallen, Switzerland; compared ED records over 2 years (1991–1992) to forensic fatality records

Table 2. (Continued)

Study	Dose; route	Reversals; outcomes	Adverse events	Recurrence of respiratory depression	Misc.
Seidler and colleagues[182]	0.4–0.8 mg initially, repeated as indicated	308 opioid overdoses identified by EMS and 83 ED admissions for overdose; on average required 2.1 ampules pre-hospital per overdose; after pre-hospital treatment, 63% required no additional naloxone	Naloxone precipitated agitation in 4 cyanotic, comatose patients; 1 pediatric patient had signs of pulmonary edema on chest x-ray	25% of cases required additional naloxone after transport to ED, up to 4 h after admission; no subjects were re-treated for or died due to overdose in the next 48 h	Vienna, Austria; data from 4 EDs September–December 1993 compared to forensic fatality data; 90% of opioid overdoses diagnosed as heroin overdose; almost one-third of cases refused transport to the ED and of those transported, nearly one-quarter left within 3 h
Sporer and colleagues[183]	487 received IM, 122 received IV 58% given 2 mg, 3–4 mg used for 28%, >4 mg in 7%	726 presumed opioid ODs; 94% of the 609 patients not in cardiac arrest or dead responded to naloxone administration by EMS; average response interval of 4.6–5.2 min; similar response to IM and IV (94% IM, 90% IV)	Four admitted with NCPE; 42 patients (7%) required restraints for agitation after receiving naloxone No hypotension	Two admitted with persistent respiratory depression, 2 with persistent altered mental status	San Francisco, CA; retrospective review of 1993
Watson and colleagues[184]	Most frequently received 2 mg (0.2–4 mg range); similar doses before initial response among those patients who did and those who did not have recurrence of toxicity	Half of 84 patients with opioid toxicity treated with naloxone responded	Withdrawal in 5 patients	31% (13 of 42 cases) recurrence among responders, occurred within 3–120 min after the initial response. Recurrence was more common in patients exposed to long-acting opioids and was not associated with presence of CNS depressants such as ethanol. Six of those who developed recurrence received additional naloxone	Kansas City, MO; retrospective case-control study from 1987–1995 in the ED
Vilke and colleagues[185]	2 mg IV/IM or 4 mg ET and repeat if no response	1714 total patients administered naloxone; 317 were then released AMA; 1 dose administered to 18.6%, 2 doses to 78.6%, 3 to 2.8% 69.5% of single doses were IV, 30.5% IM	NR	None of these were identified as deceased due to morphine by the ME within the next 12 h.	San Diego, CA; ME cases from 1996 Only looked at ME deaths due to morphine so would miss deaths due to opioids w/o morphine as a metabolite

(Continued)

Table 2. (Continued)

Study	Dose; route	Reversals; outcomes	Adverse events	Recurrence of respiratory depression	Misc.
Christenson and colleagues[186]	Mean total dose 0.9 mg (±0.5) Dose change from 0.4 mg IV to 0.8 mg SQ (patients may have received either)	578 patients enrolled who received naloxone; only 573 analyzed; 90% administered pre-hospital, 23% in the ED	84 patients had adverse events (including repeat naloxone for hypoventilation) from the OD or treatment; 1 (0.2%) sustained tachycardia	52 (9%) repeat naloxone for hypoventilation No deaths within 24 h	Vancouver, BC; prospective cohort in the ED
Vilke and colleagues[187]	2 mg IV/IM or 4 mg ET and repeat if no response	8366 patients, 998 of whom refused additional medical care 1 dose given to 260 (26.1%; 69% IV, 30% IM), 2 doses to 714 (71.5%), 3 doses to 24 (2.4%); of those receiving 2 doses, 77% got IV then IM, 5.6% IM then IV, 6.6% IM both times and 10.4% IV both times	NR	None died within 12 h of naloxone administration due to morphine as the cause or contributing to the cause of death Unclear if repeat dosing due to response then recurrent toxicity or multiple doses to achieve initial response)	San Diego, CA; ME records over 5 years Only looked at ME deaths due to morphine so would miss deaths due to opioids w/o morphine as a metabolite
Buajordet and colleagues[127]	Initial 0.4–0.8 mg IM depending upon body size combined with 0.4 mg IV; repeat IV dose up to maximum 1.6 mg if no response (max. 2.4 mg) For severe poisoning, 0.2–2.8 mg (mean 1.2 mg), for moderate poisoning 0.4–1.6 mg (mean 0.8 mg) and mild 0.4–1.2 mg (mean 0.6 mg)	1192 episodes of naloxone administration by EMS for opioid toxicity: 183 (15%) resulted in referral to clinic or hospital and in 43 (23%) cases this was due to inadequate response to naloxone (others were due to problems unrelated to reversal)	Adverse events in 538 of 1192; more common in cases of severe poisoning, which were 87% of all episodes, than mild to moderate (49 *versus* 22%). All observed within 10 min of naloxone administration Serious events in 0.3% of the episodes. Confusion (32% of all reported adverse events), headache (22%), nausea/vomiting (9%), aggressiveness (8%), tachycardia 80–180 bpm (6%), seizures (4%), tremor (1%), sweating (3%), miscellaneous (9%). Three adverse events led to hospitalization: confusion with HA and vision changes, nausea/vomiting and confusion/tremor/'feeling bad'	NR	Oslo, Norway; prospective observational study over 1 year Most patients were cyanotic and hypoxic before naloxone treatment (may explain high incidence of HA and seizures)

Table 2. (Continued)

Study	Dose; route	Reversals; outcomes	Adverse events	Recurrence of respiratory depression	Misc.
Cantwell and colleagues[188]	Studied patient factors that predict chosen dose of IM naloxone Standard dose is 1.6 mg IM	7985 non-fatal heroin-overdose patients treated with naloxone by EMS; 86% were administered the standard dose, while 4% were given less than and 10% received more than the standard dose	NR	NR	Melbourne, Australia; 1998–2001; higher level of consciousness and RR get less than standard dose; those who received more than standard dose were more likely to have used alcohol in addition to heroin
Boyd and colleagues[189]	0.4 mg/ml; median dose 0.4 mg (24th and 75th quartiles 0.32 and 0.60)	145 OD cases, 71 patients given naloxone for presumed OD then not taken to the ED; 92% presumed Of those transported to the ED, 52 got naloxone among whom 47 responded; 51% had GCS of 15 and no respiratory distress after pre-hospital naloxone	NR	No life-threatening events in the subsequent 12 h after naloxone among the 71 not transported; 12 of the patients transported to the ED were given naloxone due to recurrent respiratory depression. Seven of these patients required >1 dose or an infusion of naloxone.	Helsinki, Finland; opioid overdose: 'witnessed using heroin or circumstantial evidence of drug use' Excluded cardiac arrest, but included all GCS <8 even if RR within normal limits Compared with ME and cardiac arrest registry
Rudolph and colleagues[125]	0.8 mg IV then ± 0.4 mg IM/SQ	2241 (0.13%) identified patients were treated for opioid OD and released on scene	NR	Three out of 2241 (0.13%) died from presumed rebound toxicity	Copenhagen, Denmark; 1994–2003; unable to identify the patients in 1517 cases so the outcomes are unknown
Wampler and colleagues[126]	2 mg IM then 2 mg IV infusion; attempt to get patient consent for additional 2 mg IM	592 patients given naloxone but not transported to the hospital (552 refused; 40 died during CPR in the field after presenting in cardiac arrest)	NR	None seen in the ME's office within 2 days; 9 died w/in 30 days but shortest time between date of service and date of death was 4 days	San Antonio, TX; 20 months in 2007–2009
Knowlton and colleagues[190]	0.4–2 mg IN (most common, used in 40%), IV (27%) or IM (22%) then repeated until respiration adequate; mean dosage 1.3 mg (range 0.02–2.4 mg)	1297 administrations: 62% of patient improved, 23% had no change and 0.2% worsened	NR	NR	Baltimore, MD; 13 months from 2008 to 2009; EMS records review; 91% of treated patients were transported to the ED

(Continued)

Table 2. (Continued)

Study	Dose; route	Reversals; outcomes	Adverse events	Recurrence of respiratory depression	Misc.
Levine and colleagues[191]	0.8–2 mg IM or IN and repeated if needed	205 individuals treated with naloxone by EMS and refused transport	NR	One patient died within 24 h due to heroin, 2 within 30 days (unknown and not opioid related), no additional deaths at 6 months	Los Angeles, CA; 1.5 years retrospective Names compared to coroner's w/in 24 h, 30 days or 6 months
Studies of route					
Wanger and colleagues[192]	0.4 mg IV *versus* 0.8 mg SQ	222 patients, 83 IV and 139 SQ Similar time to onset from EMS arrival for both routes: SQ administration is faster than IV by about 1.5 min; however, IV onset is faster by approximately 1.5 min 36/74 (35%) patients in the IV group and 18/122 (15%) patients in the SQ group required ⩾2 doses; 16 of the SQ patients received the second dose IV	One IV patient admitted to ED with diagnosis of 'vomiting' EMS reported generally less aggressive behavior after SQ reversal	Mean ED stay was 3.3 h for the IV group and 3.5 h for the SQ group	Vancouver, BC; evaluated 12–233 k period during protocol change from IV to SQ naloxone; SQ preferred by EMS due to less blood and perceived lower risk of needlestick injury as well as more gradual reversal
Robertson and colleagues[173]	2 mg IN *versus* unspecified dose IV	154 (104 IV, 50 IN); response in 56% of IV and 66% of IN; more patients in the IN group received 2 doses of naloxone (34% *versus* 18%) Slower time to response after IN *versus* IV administration (12.9 *versus* 8.1 min) but the same total time from patient contact	NR	NR	Central California; retrospective EMS records review; 17 months 2003–2004
Sabzghabaee and colleagues[172]	0.4 mg in 2 ml IN or 0.4 mg IV, repeated by same route as indicated	100 patients, 50 randomized to each group Significantly longer mean time to response in IN group *versus* the IV group (2.56 *versus* 1.48 min); IN resulted in significantly higher GCS but no significant difference in RR or arterial O_2 saturation *versus* IV	Agitation in 12 patients after IV, none after IN Significant increase in HR after IV but not IN naloxone	NR	Isfahan, Iran; treated in the Department of Poisoning Emergencies

AMA, against medical advice; ED, emergency department; EMS, emergency medical services; GCS, Glasgow Coma Scale; HR, heart rate; NR, not reported; OD, overdose; RR, respiratory rate; HA, headache.

initial 2 mg IN dose. Sixteen percent of these patients required additional IV naloxone, while a single IN dose resulted in sufficient and sustained improvement in 84% of responders, and no patients in either group reported severe withdrawal reactions. The patients who responded to IV naloxone but failed to respond to IN naloxone were noted by the paramedics to have epistaxis, nasal mucus, trauma or septal abnormalities. Contrary to what would be expected based upon the pharmacokinetics described above, in a prospective, randomized trial of 2 mg (0.4 mg/ml) naloxone delivered either IN or IM to 155 patients suspected of opioid overdose in a pre-hospital setting, the patients who received IM naloxone responded faster and were more likely to achieve the primary outcome of more than 10 respirations per minute within 8 min (82% *versus* 63%).[176] There were no major adverse events in either group, but the patients who received IM naloxone experienced more minor adverse events, most notably a 13% rate of agitation/irritation *versus* 2% in the IN group. IN naloxone alone was sufficient to reverse opioid toxicity in 74% of patients that received it. A follow-up study employed a similar design but utilized a more concentrated 2 mg/ml formulation of naloxone.[177] Of the 172 patients enrolled in the randomized, controlled trial, 75% responded within 10 min of 2 mg naloxone administration and the response rate was similar between both the IM and IN groups; however, more patients in the IN group required further rescue naloxone treatment. The rates of minor adverse events were similar among both groups (19% overall; 6% IN *versus* 8% IM agitation, 8% nausea/vomiting in both and 4.8% *versus* 3.3% HA). The approximately 75–85% response rate following a 2 mg IM or IN dose of naloxone raises concern about the remaining 15–25% of patients who do not respond within 8–10 min, particularly when treated by laypersons without extensive training in additional resuscitation maneuvers.

Recurrence of respiratory depression. It has been well described that the agonist effects of many commonly used opioids far outlast the duration of effect of a single IV bolus dose of naloxone.[118] As naloxone is increasingly being used in community and pre-hospital settings, questions have arisen regarding the duration of effect following naloxone reversal of opioid overdose.[120,193]

A recent review of studies examining the need for hospital evaluation and the duration of observation following naloxone administration for heroin overdose found that of 5443 patients treated for opioid overdose with naloxone in a pre-hospital setting, there were four deaths, which suggests that the doses currently administered are of adequate magnitude and duration to counter most opioid overdoses following initial treatment, though this may consist of repeated doses.[120] Unfortunately, the route of administration was not recorded in all cases, although three of the four patients who died received a combination of IV and IM naloxone in an attempt to extend the duration of its effect. Among the 1069 overdoses attributed solely to heroin, which has a shorter duration of effect than most prescription opioids, there were no deaths. The majority of the data included in the analysis was obtained prior to the recent increase in deaths attributable to fentanyl, and the authors note that for respiratory depression due to long-acting opioids, it may not be reasonable to discharge patients once they are fully alert following naloxone administration.[43] Boyd and colleagues evaluated deaths among 71 patients with a diagnosis of heroin overdose who were administered naloxone by varying routes (IV, IM/SC and IV plus IM/SC in similar proportions) and subsequently not transported to the hospital.[189] After pre-hospital care, all had a Glasgow Coma Scale of 14 or 15 and demonstrated no hypoventilation. No deaths or life-threatening events were recorded among this group in the 12 h after treatment. However, among the 52 heroin-overdose patients who were given naloxone and then transported to the hospital, 12 patients were administered additional naloxone in the ED due to respiratory depression with signs of recurrent opioid toxicity, and 9 of these patients received more than one dose of naloxone due to recurring respiratory depression. Among all 123 patients given naloxone, over 70% were administered ⩽0.4 mg, 29.3% received 0.4–0.8 mg, and the median dose among those not transported to the hospital was 0.4 mg.

Conclusion

The administration of naloxone presents a challenge of balancing opposing outcomes, namely the reversal of opioid toxicity while avoiding opioid-withdrawal syndrome, as routine occurrence of the latter may reduce the willingness of PWID to administer the reversal agent when witnessing an overdose.[194] Current evidence suggests that in the hands of trained medical personnel in an environment replete with additional life-support equipment, favoring the avoidance of withdrawal

by utilizing a small initial dose of naloxone is safe. In this setting, the most expeditious route of administration (i.e. IM) may at times be necessary, but in general IV dosing is most reliably efficacious, titratable and predictable. However, in the hands of laypeople without adequate training or equipment to provide prolonged respiratory support, the risk of under-dosing naloxone far outweighs the potential risks of precipitating opioid withdrawal. In such cases, the risk of inadequate reversal of opioid toxicity is far greater than the risk posed by over-antagonizing respiratory depression to the point of precipitating opioid withdrawal, as the latter is unpleasant but rarely life-threatening, while untreated opioid overdose is frequently fatal, particularly as the incidence of overdose due to potent synthetic opioids rises. It is conceivable that naloxone and fentanyl share a transporter for cellular influx that becomes saturated by a high plasma concentration of fentanyl, preventing rapid influx of naloxone across the BBB regardless of dose,[195] or simply that recent reports of fentanyl and carfentanil toxicity resistant to naloxone reversal reflect a magnitude of over-dosing that results in an effect-site opioid concentration far exceeding that with which current standard doses of naloxone can compete for binding at the mu-opioid receptor. Unfortunately, there are no studies of naloxone kinetics in the setting of supra-therapeutic fentanyl doses, nor are there controlled trials to direct appropriate initial dosing of naloxone based upon the opioid and dose to which the patient was exposed, and such knowledge may be difficult to apply in cases of layperson naloxone administration. Real-world data from take-home naloxone programs remains limited by an incomplete denominator that fails to account for the fate of every naloxone dose dispensed. Fortunately, in addition to providing naloxone to individuals at risk of opioid overdose, all of the take-home naloxone programs noted herein include training in appropriate overdose response measures, including basic resuscitation and use of EMS in addition to the administration of naloxone, which may also help to mitigate the mortality associated with the rising trend of opioid misuse.

With these concerns in mind, the FDA Anesthetic and Analgesic Product Advisory Committee met in October 2016. During this meeting, the Committee recommended by a small majority to the FDA to increase the minimum standard naloxone exposure to be achieved by products intended for use in the community setting. Currently, the FDA is still considering these recommendations and no formal recommendation has been made regarding a minimal naloxone dose for layperson administration. In addition, this committee voted against creating separate dosing standards for adults and children, arguing that simplicity of administration outweighs the possibility of adverse effects from over-dosing of naloxone given its long history of safety. For a full review please see the FDA website at www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm.

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