

The Role of Emergency Naloxone in Responding to Suspected Opioid Overdoses

Joseph V Pergolizzi Jr¹, Jo Ann LeQuang¹, Robert Taylor Jr¹, John Bisney^{1*}, Gregory P Hess^{2,3} and Michael Annabi⁴

¹NEMA Research Inc., Naples, Florida, USA

²Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania, USA

³Scientific Studies and Projects Group, Symphony Health, Conshohocken, Pennsylvania, USA

⁴Las Palmas Hospital, El Paso, Texas, USA

*Corresponding Author: John Bisney, NEMA Research Inc., Naples, Florida, USA.

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Abstract

Opioid overdose mortality is on the increase, in part because of the rise in use of illicit fentanyl as an adulterant in heroin and other street drugs. Emergency medical services often address suspected opioid overdose cases, which typically manifest as profound and potentially life-threatening respiratory distress. After restoring ventilation, intranasal administration of naloxone is recommended. Questions and concerns have arisen with the increase in opioid-associated deaths in that sometimes higher-than-recommended doses of naloxone are required to resuscitate overdose patients. Naloxone is effective in reversing opioid toxicity; it works quickly but its short half-life often expires before the opioids are out of the patient's system, leading to a phenomenon called "rebound toxicity." Many hospital systems require rescued patients to come to the hospital for a period of observation, but there is little evidence to guide whether this should occur and for how long and some overwhelmed hospital system allow for a "treat and release" approach if a resuscitated overdose patient refuses transport to the hospital. Naloxone is effective at reversing opioid toxicity and exhibits essentially no pharmacologic activity in the absence of opioids.

Keywords: Naloxone; Opioid; Mortality; Toxicity

Introduction

On average, 91 Americans die every day from an opioid overdose [1] and mortality-which reached 33,000 in 2015 [2]-continues to increase. It has been estimated that about 4% of the adult population of the U.S. misuses opioids [3]. Illicit fentanyl has emerged as a new public health concern in that heroin and other drugs are adulterated with cheap, potent, and dangerous fentanyl analogs [4]. On the street, heroin adulterated with illicit fentanyl is known as "gray death", and the Drug Enforcement Administration (DEA) has stated that it is driving the upward trend in opioid mortality [5]. Fentanyl is rarely disclosed to abusers or mid-level dealers, so individuals may ingest fentanyl unawares. As a result, heroin users presenting at the emergency department after naloxone administration to reverse opioid toxicity cannot adequately identify the presence of fentanyl, which in one study (n = 30) was found to be the case in 96.7% of "heroin overdose" patients [6]. Fentanyl is highly lipophilic and passes more readily to the brain than morphine and binds more strongly to the mu-opioid-receptors (MOR). A lethal dose of fentanyl can be miniscule and is but a fraction of the lethal dose of other opioids, such as heroin.

Emergency medical services (EMS) personnel must respond to the increasing numbers of suspected opioid overdose. Opioid overdose typically causes respiratory depression which may become so profound that it can result in potentially life-threatening hypoxemia and hypercapnia. Complicating emergency rescue is the fact that many opioid abusers are polysubstance abusers and have multiple drugs in their system.

Discussion

What is the Initial Response to Suspected Opioid Overdose?

Suspected opioid overdose typically manifests as an unresponsive patient who is not breathing or not breathing well, but these signs can also indicate sudden cardiac arrest and other conditions. When called to a possible overdose, the EMS personnel should assess the scene carefully. Drug paraphernalia, visible powder, or bystanders who attest to drug use by the victim all suggest drug abuse, but the absence of such things does not mean that no opioids were ingested. Of particular concern to EMS professionals is avoiding contact with highly potent illicit fentanyl analogs, so universal precautions (nitrile gloves, masks, eye protection) should be used [7]. Any residual powder or other suspicious substances on or near the patient should not make contact with bare skin of the EMS team.

According to the American Heart Association (AHA) 2015 guidelines on cardiac arrest in patients with known or suspected opioid overdose, standard resuscitative measures for achieving high-quality cardiopulmonary resuscitation (CPR) should take priority over naloxone administration in patients without a definite pulse [8]. After starting compressions, restoring ventilation to the patient must follow

quickly as the next step. In the event that rescue breathing is required, it should be noted that opioids, including fentanyl, are not exhaled. However, if there is powder or visible traces of substances on the patient's face, the rescue team should not touch them or, if necessary, only do so with gloved hands [7]. In some instances, field intubation may be required.

What is the Pharmacological Response to Suspected Opioid Overdose?

Naloxone may be administered promptly thereafter. Intranasal administration is frequently used because it is a fast, simple, effective route and dispenses with the need for intravenous access, which can be difficult to achieve if the patient is restless, resistant, or seizing [9]. Intramuscular injection is also possible.

Naloxone competes with the opioid drug for the MOR in the body and can reverse the effects of opioids in moments. The FDA-recommended dose of naloxone is 0.4 mg, but naloxone dosing is empirical [10]. Naloxone has essentially no pharmacological activity in the absence of opioids, and it can rapidly reverse opioid toxicity so dose escalation is considered clinically prudent in the event that an initial dose does not resuscitate the patient [11]. It is recommended that 0.4 mg of naloxone be administered and then doses be increased in approximately 2 mg increments every one or two minutes until the patient responds or up to 15 mg or more based on clinical judgment. Recent reports indicate that in some cases, 20 mg of naloxone may be required in order to reverse profound toxicity [12]. Higher-than-routine doses of naloxone may be required because the patient has ingested substances, such as illicit fentanyl, which requires more naloxone (because fentanyl binds tightly to the MOR) or because the patient is opioid tolerant. In some cases, the patient may fail to respond for other reasons, such as anoxic brain injury, secondary organ failure, and the concomitant ingestion of other drugs that naloxone cannot reverse (such as benzodiazepines). More than 30% of opioid overdose deaths involve the concomitant use of benzodiazepines [13] described below in a subsequent section.

The goal of naloxone administration is to reverse respiratory depression which may or may not include the rousing the patient back to consciousness. In some cases, the naloxone will cause the patient to resume normal breathing and restore wakefulness. In other situations, the patient may resume breathing but require additional care. In the event that 15 or 20 mg of naloxone does not reverse respiratory depression, it is likely that the patient's condition is not due to opioid overdose and steps should be taken to address other underlying issues, such as ventricular tachyarrhythmia.

Naloxone is effective as a rescue agent for opioid toxicity. A retrospective study with follow-up interviews of 312 patients who received emergency naloxone from January to April 2016 in New Jersey found 99/312 (46%) received the first dose of naloxone from EMS personnel while the others (64%) received the first dose from a family member, bystander, or police [14]. Of these patients 233/312 (68%) improved with naloxone and 90% arrived at the hospital alive. In a retrospective chart review, 2,166 patients administered intra-nasal naloxone by first responders for suspected opioid overdose were evaluated. In this study, 9% required two doses of naloxone and 2% needed a third dose to reverse respiratory distress [15]. Similar findings were reported from a study of 793 overdose patients who received naloxone; naloxone was effective in 95% of patients, but 9% required more than one dose [16].

Despite the effectiveness of naloxone as a rescue agent for opioid toxicity, there remain some important questions about its use.

Is There a Dose Resistance with Naloxone?

Anecdotal reports among clinicians have speculated that there is some degree of resistance to naloxone emerging. Certainly, escalating doses of naloxone seem to be required of late in certain cases [17]. In a retrospective analysis of events that occurred in 53 hours in West Virginia in 2016, 20 opioid overdoses were reported in a single county, all of which resulted in EMS encounters. Eighty percent of patients were administered rescue naloxone, and of that group, 30% required multiple doses of naloxone [18].

Naloxone dosing has always been empirical-and it is likely that the effective dose of naloxone varies among patients and might include such things as the patient's opioid tolerance, the amount of opioid(s) ingested, the type of opioid(s) ingested, concomitant substances, patient size and weight, and underlying health conditions. In a study of prescription opioid patients who suffered respiratory depression associated with overdose (n = 307), the incidence of severe respiratory depression was 83.3% for those taking licit fentanyl compared to 3.6% for those taking codeine [19]. Thus, EMS teams may be more likely to be summoned to fentanyl overdose cases than more "routine:" opioid overdoses. Since fentanyl may require higher doses of naloxone to reverse, this may cause the impression that naloxone resistance is emerging.

In a study of EMS providers administering naloxone, the percentage of patients who required more than one dose of naloxone increased from 14.5% in 2012 to 18.2% in 2015, a 26% increase in four years [20]. The biggest increase in individuals needing multiple nal-

oxone doses occurred in patients in the age group 20 to 29 years. The requirement for multiple doses of naloxone may vary by geographic region, which, in turn, varies by the type of drugs used in that region [20].

Of particular interest is the veterinary agent carfentanil which sometimes is used to adulterate street heroin [21]. Carfentanil is an extraordinarily potent opioid used to sedate large animals, such as elephants. There is limited information about human toxicity with carfentanil, and indeed with other emerging fentanyl analogs. A report from the literature describes a veterinarian who had intended on using a dart containing 1.5 mg of carfentanil and 50 mg xylazine hydrochloride to sedate an elk but was inadvertently splashed in the eye with the dart contents before it could be used. He was rendered unconscious and his companions then quickly administered 100 mg of naloxone (another opioid antagonist)-which had also been intended to use on the elk-in the field and rushed to the emergency department where he was discharged in good condition after 24 hours [22]. However, carfentanil is so toxic at such low doses that it has been considered as a potential agent for a “weapon of mass destruction” [23]. The authors were not able to find specific mortality rates attributable to carfentanil.

Are The “Right” Patients Getting Naloxone?

In cases of opioid overdose, naloxone must be quickly administered at an effective dose. However, EMS personnel may be at times unsure about whether to administer naloxone, in particular when it is not clear if the patient’s condition is attributable to an opioid overdose or some other cause. Since drug users may wish to minimize their contact with authorities, companions of an overdose patient may either disappear before EMS arrival or, if present, fail to be forthcoming with relevant details. Thus, it typically falls to the EMS team to determine if opioid overdose is suspected and, if that is the case, to restore proper respiration and administer naloxone. There may be no other sources of information other than the patient-who is unresponsive.

In a retrospective study of 124 individuals who died following attempted resuscitation by EMS providers, naloxone had been administered to 66.1% of them. Those least-likely to receive emergency naloxone were women (odds ratio [OR] 2.9, 95% confidence interval [CI], 1.2 to 7.0, $p = 0.02$), patients without signs of drug abuse (OR 3.3, 95% CI, 1.2 to 9.2, $p = 0.02$), and individuals over the age of 50 (OR 4.8, 95% CI, 1.2 to 17.4, $p = 0.01$) [24].

Data from 229 suspected overdose cases over six months were analyzed and it was determined that heroin was taken in 43% of those cases, prescription opioids (without heroin) in 37%, and 20% of cases defied categorization. Overall, heroin overdose patients were younger than those taking prescription opioids (median age 33 vs. 41 years, $p < 0.05$), more likely to be male (80% vs. 61%, $p < 0.01$), fewer required intubation (8% vs. 22%, $p < 0.01$) and more were likely to be administered naloxone by EMS personnel (72% vs. 51%, $p < 0.01$) [25].

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Thus, risk factors may emerge regarding those who might need but fail to get naloxone: those who did not require intubation, older individuals, and women. In the case of patients who did not require intubation, naloxone may not have been administered because the respiratory depression was not severe enough or the patient resumed normal respiration unaided. It is likely that older people and females did not get naloxone as frequently, because clinicians may have considered them less likely to be opioid abusers. While young men are the “typical opioid abusers”, opioid abuse are also prevalent among geriatric patients and women. More than 5 million Americans over age 50 are estimated to require some form of substance abuse rehabilitation in 2020 [26]. Many geriatric opioid abusers are individuals who have persisted with opioid misuse from their younger years [27]. In addition, older individuals may have health concerns, including but not limited to cancer, that result in an opioid prescription [28]. Healthcare providers often miss signs of addiction in women patients [29]. While more men than women die of opioid overdose, the mortality rate for women has increased by 400% from 1999 to 2010 while it increased 237% in the same time period for men [30]. Yet women are clearly at risk for substance abuse, as they are at greater risk for certain forms of mental health disorders (depression and anxiety among them) [31] and have a higher prevalence of adverse childhood experiences than men [32]. Women report painful symptoms more frequently than men and certain painful conditions are more prevalent among females, such as dysmenorrhea, endometriosis, fibromyalgia, and migraine, along with pain associated with gender-based violence [33-35]. For these reasons, EMS professionals should not discount the possibility of opioid overdose in females.

Do Patients Require Observation After Naloxone Administration?

Some overdose patients will be resuscitated successfully after naloxone and be conscious of their surroundings and able to discuss care with the EMS personnel. Such individuals sometimes decline further care and refuse transport to the hospital. In a systematic review of the literature (8 studies, $n = 5,433$), among those patients who were reversed from opioid toxicity but refused hospital observation, there were 4 deaths (0.07%), resulting in a number-needed-to-transport of 1361 [36]. There are few studies to provide guidance on the value of post-resuscitation hospital treatment for such patients.

Patients who emerge from respiratory depression with naloxone may experience abrupt withdrawal symptoms or be agitated, confused, upset, or even combative. Others emerge aware of their surroundings and the situation and with few adverse effects.

EMS systems may require that patients who are suspected of overdosing on opioids be transported to the emergency department for observation and possible treatment, including those who respond well to naloxone. However, some already overburdened hospital systems have re-evaluated this guidance, in particular because many overdose patients do not appear to suffer adverse outcomes without a hospital stay. The concept of reversing opioid toxicity without bringing the patient back to the hospital has been termed “treat and release”. While there is some evidence that suggests the mortality rate in the “treat and release” population is low, there are no studies to confirm that this is a sound clinical policy. The exact duration of the clinically appropriate post-naloxone observation is not clear from the literature and there are likely large variations among patients. In some hospital systems, patients must be taken to the hospital, but only for a brief period of observation of about an hour [37].

The 2016 World Health Organization Recommendations for Community Management of Opioid Overdose recommends that “after successful resuscitation following the administration of naloxone, the affected person should have their level of consciousness and breathing closely observed until they have fully recovered” [38]. However, full recovery is defined as asymptomatic and at baseline mental status two hours after the last dose of naloxone, depending on the agent, route of ingestion, and amount. Accurate knowledge of the patient’s baseline mental status may be very difficult to determine unless a reliable history or historian is available [36,39].

What is Rebound Toxicity?

The half-life of naloxone is much shorter than the half-life of opioids. The result is that while naloxone may reverse opioid intoxication quickly, its effects subside and the patient may again experience the psychoactive and other effects of the opioid. Intranasal naloxone achieves $t_{50\%}$ in 8 minutes and t_{max} in 20 minutes [40]. The half-life of opioids varies by agent but is typically stated in hours. Thus, there may be a window of up to six hours wherein a patient is vulnerable to rebound toxicity [41]. Some have suggested patients should be observed following resuscitation for at least six hours because of rebound toxicity.

In a study of 3,875 opioid overdose patients who refused transport to a hospital following naloxone rescue, three patients died of rebound toxicity (0.07%). Such low mortality rates are often used to support the “treat and release” strategy to manage the burgeoning number of opioid overdose patients who flood the emergency systems in certain areas of the country.

What About Patients Who Take Multiple Drugs?

Polydrug abuse is common among addicts and polypharmacy is common among many patients with serious or comorbid medical conditions. Naloxone reverses opioid toxicity but it has no effect on benzodiazepine overdose or other forms of drug toxicity. If the patient has taken multiple drugs but suffers respiratory depression caused by an opioid, naloxone can reverse the toxicity and help to restore respiration, but the patient may still suffer from other (but possibly less lethal) effects of other drugs. Of particular concern in this area is benzodiazepine toxicity, which cannot be reversed with naloxone. Indeed, reversing benzodiazepine overdose is extremely challenging as there is only one known effective agent (flumazenil), whose use is widely contraindicated. Flumazenil should only be administered by trained clinicians familiar with its appropriate indications.

Flumazenil is a competitive benzodiazepine receptor antagonist that can be used for benzodiazepine overdose but it is contradicted for use in patients who have benzodiazepine tolerance (built up with long-term benzodiazepine use), those with certain cardiac conditions (prolonged QRS complex on ECG or certain arrhythmias), and those with a history of seizures. Because of its contraindications, flumazenil is not recommended for routine use or for use with patients who have an overdose of unknown drugs or polysubstance abuse. The recommended dose is 0.2 mg administered over 15 seconds or, more conservatively, 0.1 mg over one minute, to a maximum of 1 mg or desired effect. It should be noted that flumazenil is effective at reversing central nervous system (CNS) depression associated with benzodiazepine overdose, but it is much less effective at reversing respiratory depression.

Conclusion

The public health crisis of opioid abuse has been exacerbated by the increase in illicit fentanyl that increasingly is found in street heroin and other drugs. As a result, EMS professionals are likely to encounter increased numbers of suspected opioid overdose patients. The main sign of opioid overdose is potentially life-threatening respiratory depression. Patients should first receive adequate ventilation and then be administered naloxone. Although the standard recommended dose of naloxone is 0.4 mg, higher doses may be needed in some cases. EMS personnel should administer naloxone at increasingly higher doses in 2 mg increments up to 15 to 20 mg or until the patient responds. Many hospital systems require rescued overdose patients to be transported to the hospital for observation, although there is little evidence that this improves mortality. Rebound toxicity may occur as the half-life of naloxone is much shorter than most opioids, so patients may be vulnerable after rescue.

The main danger to an opioid overdose victim is receiving too little naloxone too late. EMS professionals must consider polypharmacy when treating suspected overdose patients, which might, in the case of concurrent benzodiazepine use, require in hospital administration of flumazenil. For suspected opioid overdoses, intranasal naloxone is recommended because of its ease of administration. Naloxone may also be administered intramuscularly or intravenously, although these latter two routes of administration may be more difficult in an emergency situation. Naloxone is effective when properly administered and it has no pharmacologic activity in the absence of opioids. EMS professionals may be able to rescue overdose patients with prompt naloxone interventions.

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