

Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access

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Abstract: Opioid overdose and mortality have increased at an alarming rate prompting new public health initiatives to reduce drug poisoning. One initiative is to expand access to the opioid antidote naloxone. Naloxone has a long history of safe and effective use by organized healthcare systems and providers in the treatment of opioid overdose by paramedics/emergency medicine technicians, emergency medicine physicians and anesthesiologists. The safety of naloxone in a prehospital setting administered by nonhealthcare professionals has not been formally established but will likely parallel medically supervised experiences. Naloxone dose and route of administration can produce variable intensity of potential adverse reactions and opioid withdrawal symptoms: intravenous administration and higher doses produce more adverse events and more severe withdrawal symptoms in those individuals who are opioid dependent. More serious adverse reactions after naloxone administration occur rarely and may be confounded by the effects of other co-intoxicants and the effects of prolonged hypoxia. One component of the new opioid harm reduction initiative is to expand naloxone access to high-risk individuals (addicts, abusers, or patients taking high-dose or extended-release opioids for pain) and their close family or household contacts. Patients or their close contacts receive a naloxone prescription to have the medication on their person or in the home for use during an emergency. Contacts are trained on overdose recognition, rescue breathing and administration of naloxone by intramuscular injection or nasal spraying of the injection prior to the arrival of emergency medical personnel. The safety profile of naloxone in traditional medical use must be considered in this new context of outpatient prescribing, dispensing and treatment of overdose prior to paramedic arrival. New naloxone delivery products are being developed for this prehospital application of naloxone in treatment of opioid overdose and prevention of opioid-induced mortality.

Keywords: antidote, drug-delivery systems, naloxone, opioid, overdose

Introduction

Drug-induced deaths have reached a public health crisis level for unintentional mortality; overdose deaths now exceed automobile accidents as a preventable cause of death in the United States [Mack, 2013]. Opioids, as a class of medications, are responsible for the majority of deaths with over 16,500 US deaths (out of roughly 40,000 drug overdose deaths) recorded by the US Centers for Disease Control for 2010. The United Kingdom reported 1496 opioid related deaths out of 2597 people who died from a drug overdose [Lancet, 2013].

Public policy to reduce opioid mortality has taken a number of directions [SAHMSA, 2013]. Medical, public health, and legislative efforts have attempted to address the licit and illicit access and use of opioids that lead to adverse consequences [Hewlett and Wermeling, 2013]. Opioid use policy reforms and strategies have been proposed and implemented including: closer attention to opioid prescribing guidelines, use of prescription drug monitoring programs to identify improper prescribers, increased medical and interprofessional education, increased law enforcement, and medication take-back to return

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unused medication to law enforcement for destruction. In spite of these public policy efforts the adverse consequences of societal exposure to opioids continue.

An additional harm-reduction strategy, although not widely adopted and validated yet as a potential standard of care, has been implemented in some locations around the world. The evolving practice is to treat opioid overdose prehospital by prescribing naloxone, the opioid antidote, to an individual or family with one or more residents at risk of opioid overdose [Goodman and Gilman, 2001; Doe-Simkins *et al.* 2009; Wheeler *et al.* 2012; Sporer and Kral, 2007; Walley *et al.* 2013a, 2013b]. Naloxone is a competitive antagonist to opioids in the central nervous system and has been approved as a prescription medication in the US since 1971. It is generally devoid of activity unless opioids are present in a person. A recent publication provides an excellent overview for the management of opioid analgesic overdose and the use of naloxone [Boyer, 2012].

The newly evolving practice is intended to move the continuum of care forward before the arrival of emergency medical services (EMS) at the scene [SAMHSA, 2013]. In overdose situations the person will be unconscious, hypoxic, perhaps apneic, and unable to save themselves, yet time is of the essence in this medical emergency. Therefore, individuals in close contact with a person at risk of overdose must recognize overdose and understand what to do if overdose is suspected. First responders are commonly close family contacts or police officers. Expanding access to naloxone to bystanders is also important because: (1) basic-level emergency medical technician (EMT) services in some locales will not stock naloxone injection on the ambulance and are not permitted to administer an injection; (2) an ambulance is not called due to fear of being arrested by police authorities likely to respond to the scene; and (3) emergency response time in rural areas can be long. A five-step process is recommended for the first responder encountering a suspected opioid overdose.

1. Check for signs of opioid overdose (unconscious and unarousable, slow or absent breathing, pale, clammy skin, slow or no heart beat).
2. Call EMS to access immediate medical attention.
3. Administer naloxone.

4. Rescue breathe if patient not breathing.
5. Stay with the person and monitor their response until emergency medical assistance arrives. After 5 minutes, repeat the naloxone dose if person is not awakening or breathing well enough (10 or more breaths per minute). A repeat dose may be needed 30–90 minutes later if sedation and respiratory depression recur.

A challenge for expanding access to naloxone is that the medication is currently available only as an injection for intravenous (IV), intramuscular (IM), or subcutaneous (SC) injection [IMS, 2001; Hospira, 2006; Martindale Pharma, 2014; Kaleo, 2014]. Some harm reduction programs include the training of first responders on use of an injection; however, there has been concern about the potential for accidental needlestick injury and transmission of hepatitis or HIV infection. Some patients will be undergoing acute opioid withdrawal and will be agitated as they are being revived with naloxone, thus increasing the risk of an injury to the provider [Doe-Simkins *et al.* 2009]. Medical directors supervising paramedics in many large cities have adopted the practice of spraying naloxone injection into the nasal cavity as a needle-free means of administering naloxone, thus reducing the risk of needle stick injury [Barton *et al.* 2002]. Therefore, an unmet medical need is to have more user-friendly, needle-free naloxone delivery systems available for medical professionals, first-responders and at-home family member use.

Consideration of alternative naloxone drug-delivery systems is quite complex. The epidemiology of the condition itself must be understood. Conditions of use in various scenarios must be considered. The ability of the person to use the delivery system (e.g. human factors or ergonomics) is critical under the circumstances of an overdose. And of course, the medication, naloxone in this case, must be adaptable and safe and effective for the clinical condition.

Epidemiology of opioid overdose

The Hindu parable regarding blind men examining and trying to describe an elephant may well be relevant in attempting to understand the opioid overdose phenomenon. Overdoses occur as therapeutic misadventures, or adverse effects, from the licit use of medications for pain management or

opioid maintenance. Other overdoses occur from nonmedical use of prescription opioids or illicit use of heroin [Osterwalder, 1996; Shah *et al.* 2007; Warner *et al.* 2011; Rosen *et al.* 2013]. Regardless, medical and public health officials will be able to determine root causes of opioid use in their communities and region and can adopt strategies appropriate for their circumstances.

The Centers for Disease Control and Prevention provide some overall descriptive statistics for those who have died in the US from overdose [Mack, 2013]. Most deaths were unintentional, but there was a significant note that 13% of drug overdoses were suicidal drug poisoning attempts. Considering age as a risk factor, middle-aged men carry the highest rate of drug-induced mortality. More deaths occur in non-Hispanic white males but highest rates occur in US ethnic minorities. The rate of rise of deaths in children and adolescents is becoming of great concern [Bond *et al.* 2012; Bailey *et al.* 2009].

An additional factor to consider is the rural *versus* urban nature of opioid overdose [Rosen *et al.* 2013; Wunsch *et al.* 2009; Havens *et al.* 2007]. Large metropolitan areas with high population density typically report heroin as the opioid most commonly associated with adverse outcomes. Rural Appalachian states typically report prescription medications implicated in most overdoses. Methadone and hydrocodone/oxycodone account for the majority of opioid-related deaths in Kentucky and West Virginia. These two states represent only 2% of the US population (about 6 million citizens) but account for 10% of deaths nationally. In Kentucky, the largest number of deaths occurs in the more urban centers of Louisville and Northern Kentucky, yet the highest rates occur in rural poverty-stricken counties, exacerbating a declining vitality [Bunn and Slavova, 2012].

Certain overdose risk factors are associated with a call for EMS [Boyer, 2012; Mack, 2013; Toblin *et al.* 2010; Wunsch *et al.* 2009; Warner *et al.* 2011]:

- injection of opioid;
- combining opioids with other central nervous system depressants;
- opioid doses greater than 100 mg/day of morphine or equivalent;
- loss of opioid tolerance after detoxification or incarceration and resuming opioid use;
- comorbid mental health, central nervous system, renal, hepatic or pulmonary diseases;

- young people experimenting with opioids;
- accidental ingestion.

Therefore, understanding the high-frequency characteristics of opioid overdose is very important in the design of prevention strategies including provision of naloxone to those at highest risk [Hasegawa, *et al.* 2014].

Medical use of the opioid antidote, naloxone

Efficacy of naloxone injection

Naloxone is approved for use in the United States by IV, IM, or SC routes of administration [IMS, 2001; Hospira, 2006; Kaleo, 2014]. It is suggested that the onset of action of the IV route will be faster, so is preferred in emergency situations. However, obtaining IV access in the prehospital setting, especially among injection drug abusers, can be time-consuming and difficult [Sporer *et al.* 1996; Barton *et al.* 2002]. A series of studies, beyond the scope of this paper, describe comparative EMS clinical studies of various naloxone doses and routes of administration, including off-label administration of naloxone injection as an intranasal (IN) spray [Barton *et al.* 2005; Belz *et al.* 2005; Osterwalder 1996; Robertson *et al.* 2009; Wanger *et al.* 1998; Kelly *et al.* 2005; Kerr *et al.* 2008, 2009; Merlin *et al.* 2010; Yealy *et al.* 1990]. Times to drug administration and revival show comparable efficacy of the tested dosing methods. Small differences in efficacy relative to percent revived (according to predefined criteria) are apparent but perhaps not clinically relevant. Some patients required a repeat dose to achieve a satisfactory clinical outcome. Several studies also provide comparative safety data for examination.

Naloxone safety profile after parenteral use

One approved US package insert [IMS, 2001] states that, in the absence of narcotics, naloxone exhibits essentially no pharmacologic activity. Similarly, the naloxone package insert by Hospira, Inc. [Hospira, 2006] states that a small study including volunteers receiving 24 mg/70 kg did not demonstrate toxicity.

Adverse events listed in the approved US package inserts after the use of naloxone for reversal of narcotic depression are provided in Table 1.

After awakening from unconsciousness the overdose victim may experience a relatively short

Table 1. Adverse effects after naloxone in reversal of opioid depression.

System organ class
MEDRA preferred term
Cardiac disorders
Cardiac arrest
Tachycardia
Ventricular fibrillation
Ventricular tachycardia
Gastrointestinal disorders
Nausea
Vomiting
Investigations
Blood pressure increased
Nervous system disorders
Convulsion
Tremor
Psychiatric disorders
Withdrawal syndrome
Respiratory, thoracic and mediastinal disorders
Pulmonary edema
Skin and subcutaneous tissue disorders
Hyperhidrosis

period of withdrawal. Unlike alcohol, opioid withdrawal symptoms are generally not life-threatening, but can make the patient physically uncomfortable. Symptoms of opioid withdrawal, as derived from the Hospira [Hospira, 2006] package insert, are included in Table 2.

In addition, when used in the postoperative setting, the following events are listed in Table 3. The most relevant adverse outcomes encountered with naloxone injection are those reported for opioid reversal in patients who have developed physical dependence to an opioid. The following authors have published in this area and are briefly summarized.

Belz and colleagues [Belz *et al.* 2006] reported a retrospective case series review of patients treated in 2004 by EMS responders. A total of 164 patients aged 14–86 years were treated with naloxone by IV (primarily), IM, or IN routes. They reported naloxone associated ‘violence’ described as agitation/combativeness (15%) and vomiting in 4% of the cases.

Buajordet and colleagues [Buajordet *et al.* 2004] conducted a prospective study to assess adverse events after naloxone treatment for episodes of

Table 2. Opioid acute withdrawal syndrome symptoms.

System organ class
MEDRA preferred term
Cardiac disorders
Tachycardia
Gastrointestinal disorders
Diarrhea
Nausea
Vomiting
General disorders and administration site conditions
Asthenia
Chills
Pain
Pyrexia
Investigations
Blood pressure increased
Nervous system disorders
Tremor
Psychiatric disorders
Nervousness
Restlessness
Respiratory, thoracic and mediastinal disorders
Rhinorrhea
Sneezing
Yawning
Skin and subcutaneous tissue disorders
Hyperhidrosis
Piloerection

suspected acute opioid overdose. This study included 1192 episodes treated with naloxone. The patients had a mean age of 32.6 years and 77% were male. Naloxone was administered by an initial IM dose of 0.4–0.8 mg (depending on body size) plus an immediate IV dose of 0.4 mg. The paramedic investigators recorded adverse reactions on a reporting chart containing predefined events. Adverse events were reported in 538 of the 1192 episodes (45%). In the 538 episodes which had adverse events, there were 726 adverse events reported (Table 4).

Buajordet and colleagues reported that adverse events were significantly more often seen in cases of ‘severe poisoning’ than in cases with mild to moderate poisoning (49% *versus* 22% of cases). Severe poisoning cases included those with life-threatening complications (e.g. respiratory arrest) or cyanosis. Adverse events led to hospitalization in three episodes (0.3%). Events leading to hospitalization included one patient with confusion, headache and vision disorder; one patient with nausea and vomiting; and one patient with confusion, tremor and

Table 3. Adverse events associated with naloxone in postoperative patients.

System organ class
MEDRA preferred term
Cardiac disorders
Cardiac arrest*
Cardiac failure*
Cardiovascular disorder
Tachycardia*
Ventricular fibrillation*
Ventricular tachycardia*
Gastrointestinal disorders
Nausea
Vomiting
General disorders and administration site conditions
Injection site reaction
Investigations
Blood pressure increased
Nervous system disorders
Convulsion
Grand mal convulsion
Paraesthesia
Tremor
Psychiatric disorders
Agitation
Hallucination
Respiratory, thoracic and mediastinal disorders
Dyspnea*
Hypoxia
Pulmonary edema*
Respiratory depression
Skin and subcutaneous tissue disorders
Hyperhidrosis
Surgical and medical procedures
Reversal of opiate activity
Vascular disorders
Flushing
Hot Flashes
Hypotension*
Hypertension*

*Sometimes resulting in death, coma and encephalopathy as sequelae.

‘feeling bad’. The authors concluded that serious complications after naloxone were rare.

Osterwalder [Osterwalder, 1996] conducted a prospective study of 485 patients admitted to the hospital (538 times) for acute intoxication with heroin or heroin mixtures. Of these, 453 received naloxone either IV, IM, or IV plus IM (the

Table 4. Events reported after IM plus IV naloxone treatment for suspected opioid overdose [Buajordet *et al.* 2004].

Event	Number of events (%)	Number of events [% of total treatments]
	<i>n</i> =726	<i>n</i> =1192
Confusion*	235 (32)	235 (20)
Headache*	157 (22)	157 (13)
Nausea/vomiting*	66 (9)	66 (6)
Aggressiveness*	62 (8)	62 (5)
Tachycardia*	47 (6)	47 (4)
Shivering	33 (5)	33 (3)
Seizures*	27 (4)	27 (4)
Sweating	24 (3)	24 (2)
Tremor	9 (1)	9 (1)
Miscellaneous	66 (9)	66 (6)

* These events were predefined/listed in the reporting chart used by paramedics.

majority of patients). Dosing was not specified by protocol, but the median IV dose given was 0.2 mg naloxone (range 0.1–2.8 mg); the median IM dose was 0.2 mg (range 0.1–0.9 mg). Patients averaged 24 years old (range 15–47 years).

A total of 30 patients had 46 ‘complications’ (Table 5). Eight patients died: five due to cardio-circulatory arrest, two due to pneumonia, and one due to pulmonary edema. Another patient died after generalized convulsions, having had prenaloxone asystole in the emergency room, along with hyperthermia and hypoxemic encephalopathy.

Osterwalder concluded that naloxone may cause life-threatening complications in over 1% of heroin-overdosed patients, and suggested that lower naloxone doses should be used. In addition, he suggested that using a bag/valve/mask device to hyperventilate patients for 2–5 minutes before initiating treatment with an opioid antagonist may be beneficial. His conclusion can be contrasted with the retrospective study by Yealy and colleagues described next.

Yealy and colleagues [Yealy *et al.* 1990] performed a retrospective review of prehospital records to investigate the safety of naloxone administered by paramedics in the prehospital setting over a 1-year period. Patients eligible for treatment with naloxone under this EMS treatment protocol were patients with an acutely depressed level of consciousness with blood

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