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

Ther Adv Drug Saf
2015, Vol. 6(1) 20–31
DOI: 10.1177/2042098614564776

Daniel P. Wermeling

***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

Correspondence to:
Daniel P. Wermeling, Pharm.D.
University of Kentucky College of Pharmacy, 789 South Limestone Street, Lexington, KY 40536, USA
dwermel@uky.edu

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

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

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 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.

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)
	n=726	*n*=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.

'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 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 cardiocirculatory 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

Table 5. Complications seen before or after naloxone administration (or patients may have never received naloxone) for acute intoxication with heroin or heroin mixtures ($n = 538$) [Osterwalder, 1996].

Event	Number reported	Percentage of 538	Resulting in death	Percentage of 538
Cardiocirculatory arrest	9	1.7	5	0.9
Delayed onset of consciousness and normal respiration	8	1.5		
Pulmonary edema	8	1.5	1	0.2
Aspiration	5	0.9		
Hyperthermia	4	0.7		
Generalized seizures	3	0.6	1*	0.2
Rhabdomyolysis	3	0.6		
Pneumonia	2	0.3	2	0.3
Hypoglycemia	2	0.3		
Hypothermia	2	0.3		

*Patient had asystole, hyperthermia (40°C) and hypoxemic encephalopathy before naloxone.

Table 6. Events seen after naloxone administration in the prehospital setting [Yealy *et al.* 1990].

Event	Number reported (percentage of 813)	Comment
Generalized tonic-clonic seizure	1 (0.1%)	Underlying seizure disorder
Vomiting	2 (0.2%)	One patient received ipecac
Significant hypertension*	1 (0.1%)	Total dose 1.2 mg
SBP increases > 30 mmHg	7 (0.9%)	Systolic blood pressure (SBP) between 100 and 160 mmHg
Significant hypotension**	2 (0.2%)	

No patient had ventricular tachycardia, fibrillation, or asystole; pulmonary edema was not assessed.
*If SBP increased by more than 30 mmHg and above 160 mmHg.
**If SBP decreased to less than 120 mmHg and dropped by 30 mmHg.

glucose over 80 mg/dl or who had no response to glucose administration. In some cases, naloxone was given prior to ascertainment of hypoglycemic status. Charts for 813 patients were eligible for review. Patients had a mean age of 42.4 ± 9.7 years and 59% were male. Most patients (800) received naloxone IV with initial doses of 0.4–0.8 mg and the mean dose was 0.9 mg (range 0.4–2.4 mg). The remaining 13 patients received naloxone by either the IM, SC, intra-tracheal or sublingual routes. Adverse events reported are as shown in Table 6.

The authors concluded that a protocol change to smaller doses of naloxone does not appear to be warranted.

Post-treatment recurrence of respiratory depression

A concern has been raised about prehospital administration of naloxone, as some patients are revived and then refuse further medical care, leaving against medical advice (AMA). Two publications report on the medical examiner records of overdose deaths [Vilke *et al.* 1999, 2003] over a 1-year and 5-year period, respectively. These studies each compare databases of patients who received naloxone for opioid overdose and then left AMA to the databases of the medical examiner for deaths within 12 hours of the naloxone treatment. In these two studies, there were no cross-reports found, indicating that patients who were treated with naloxone for overdose and then refused further medical treatment (leaving AMA), were not later found dead.

Safety profile after intranasal administration of naloxone injection

Of the reports describing the response to naloxone delivered nasally, only two studies described the adverse events seen in detail.

Table 7. Adverse events after naloxone 2 mg by intramuscular (IM) or intranasal (IN) routes [Kelly *et al.* 2005].

Event term	IM (n = 71)	IN (n = 84)
	n (%)	n (%)
Agitation and/or irritation	10 (14%)	2 (2.4%)
Nausea and/ orvomiting	4 (5.6%)	6 (7.1%)
Headache	2 (2.8%)	0 (0%)
Tremor	1 (1.4%)	1 (1.2%)
Sweating	0 (0%)	1 (1.2%)

Table 8. Adverse events after naloxone 2 mg by intramuscular (IM) or intranasal (IN) route [Kerr *et al.* 2009].

Event term	IM (n = 89)	IN (n = 83)
	n (%)	n (%)
'Minor events'	17 (19.1%)	16 (19.3%)
Agitation and/or irritation	7 (7.9%)	5 (6.0%)
Nausea and/or vomiting	7 (7.9%)	7 (8.4%)
Headache	3 (3.3%)	4 (4.8%)
'Major event'		
Convulsion	1 (1.1%)	0 (0%)

Kelly and colleagues [Kelly *et al.* 2005] conducted a prospective, randomized trial comparing 2 mg IM naloxone with 2 mg/5 ml IN naloxone given by a mucosal atomizer. A total of 182 patients were enrolled, of whom 155 were evaluable. The patients averaged 28–30 years in age (range 13–57) and 72% were male. Patients who received IM naloxone responded faster than the IN group with respect to time until respirations >10/minute (6 minutes to response for IM *versus* 8 minutes to response for IN, $p = 0.006$). Time to Glasgow Coma Scale greater than 11 was not significantly different. In the IM group, 13% of patients needed 'rescue' naloxone, *versus* 26% in the IN group. Note the high volume (5 ml) used to deliver IN naloxone. The dilute naloxone solution is unable to be retained in the nasal cavity and likely was lost for possible absorption [Cosantino *et al.* 2007; Wermeling, 2012].

There were no major adverse events in either group. Adverse events (described as mild) are listed in Table 7.

In a follow up to the study by Kelly and colleagues, Kerr and coworkers [Kerr *et al.* 2009] compared safety and effectiveness of a specially prepared concentrated naloxone formulation (2 mg/ml) given via the IN *versus* IM routes in a randomized, controlled, open-label trial. A total of 172 patients suspected of heroin overdose were treated by emergency medical personnel and enrolled into the study: 83 received 1 mg/0.5 ml into each nostril (2 mg total) and 89 patients received 2 mg/ml IM. A total of 74% of the patients were male, and the average age was 31. The adverse events seen were similar between the two groups. The authors concluded that a low adverse event rate was observed in both arms, as shown in Table 8.

Discussion of significant adverse events

The summary of adverse event data from the previous studies suggests the following considerations. The dose and route of administration are significant factors with regard to the occurrence and intensity of adverse reactions [Cantwell *et al.* 2005]. IV administration can provide rapid and relatively higher exposure to naloxone in an emergency as compared with routes requiring drug absorption. Moreover, the IV route of administration results in rapid clearance of naloxone and may necessitate repeated dosing until the intoxicant is metabolized and eliminated. Routes of administration having an absorption phase, depending upon the dose, may provide a slower onset of revival that may be better tolerated during the recovery period. New products with an absorption phase adequate to reverse the overdose, but, not providing peak levels of naloxone similar to an IV dose, are likely to be successful in this new prehospital treatment context. A balance should be struck between rapidity of opioid reversal *versus* frequency and intensity of adverse reactions and opioid withdrawal symptoms.

The differences in IN response rates and adverse reactions across studies are likely due to the differences in formulation approaches of the relatively dilute naloxone solutions. Products designed for nasal delivery are typically formulated such that the dose is delivered in about 100–200 µl, a volume that can be retained in the nasal cavity [Costantino *et al.* 2007; Wermeling, 2012].

Withdrawal symptoms

Unlike withdrawal symptoms precipitated by withdrawal of other agents, opioid withdrawal is generally not life-threatening. Withdrawal symptoms induced by naloxone administration tend to dissipate in a period of 30–60 minutes due to the relatively short half-life of naloxone [Ngai *et al.* 1976; Dowling *et al.* 2008]. Due to naloxone's high metabolic clearance and the fact that most opioids have a longer persistence in the blood stream, the symptoms of withdrawal dissipate, and in about 15–20% of cases, administration of a repeat dose of naloxone may become necessary if overt toxicity such as central nervous system and respiratory depression recur [Boyer, 2012].

Seizures

Seizures are a well-known complication after severe cerebral hypoxia. Patients encountered by EMS personnel in the setting of opioid overdose may have been hypoxic for an unknown duration. The contribution by naloxone to a seizure is unclear.

Cardiac arrest

The package insert for naloxone [IMS, 2001] states that abrupt reversal of narcotic depression with naloxone may result in: tachycardia, increased blood pressure, seizures and cardiac arrest. In the context of hypoxia (as in after a narcotic overdose), seizures and cardiac arrest can occur. Likewise, in the overdose setting, co-consumed drugs may be contributory, such as cocaine [Shah *et al.* 2007].

Tachycardia

Buajordet and colleagues [Buajordet *et al.* 2004] reported tachycardia in the range of 80–180 bpm. None of these patients were hospitalized, probably due to resolution of the tachycardia before termination of observation by EMS personnel. Tachycardia is also listed as one symptom of opioid withdrawal [Hospira, 2006].

Pulmonary edema

Pulmonary edema was not reported by Buajordet and colleagues, but it was reported by Osterwalder.

In addition, it has been reported after postoperative narcotic reversal (package inserts). The mechanism for pulmonary edema is unclear. Pulmonary edema can be observed as a terminal event of a severe opioid overdose. In postoperative patients, there are questions as to the contributing factor of pre-existing cardiac disease in the patients or concomitant administration of potentially cardiotoxic drugs. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone is similar to neurogenic pulmonary edema, i.e. a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures. An additional theory is that the airway may be partially or mostly obstructed and creating negative pulmonary pressure edema [Boyer, 2012].

Practical considerations for expanding access to naloxone

Naloxone is a prescription injection-based medication that has traditionally been administered by paramedics, emergency medicine physicians and anesthesiologists in organized healthcare settings. A new practice of expanding access to naloxone for non-medical first responders is in development, with 24 states having legislation authorizing this medical practice akin to state legislation authorizing epinephrine auto-injector prescribing and third-party drug administration for treatment of suspected anaphylaxis or severe asthma. Expanding access to naloxone requires consideration for the prescribing, dispensing and counseling to patient contacts and families regarding overdose recognition, rescue breathing, calling for EMS and administering naloxone. In general, organized healthcare at this time does not have systems in place to support prescribing and dispensing naloxone and counseling at-risk families on opioid overdose prevention and treatment.

Physicians and prescribers in primary care and in substance abuse treatment may be unaware of the potential to use naloxone, albeit in an off-label manner of nasal spraying of the injection, or an approved auto-injector, to prevent opioid overdose related mortality and morbidity in the outpatient setting. A significant educational programming activity is necessary to broaden knowledge in the general medical community [Walley *et al.* 2013a, 2013b]. Prescribers have no standard of care for opioid overdose prevention in households.

Pharmacy systems traditionally stock naloxone in a hospital or surgical setting; certainly not in a community outpatient retail pharmacy setting [Bailey

and Wermeling, 2014]. Initially, the outpatient pharmacy of a hospital system is the most likely location in which a naloxone prescription can be filled. A retail pharmacy could stock naloxone if prescribers were to approach the pharmacist-in-charge. Pharmacy systems also lack outpatient billing and reimbursement programs for naloxone as they do for most other medications. The Center for Medicare Services, Medicaid in most states and private insurers do not have naloxone on their formulary or have a computer code for a pharmacy to complete an electronic prescription and reimbursement transaction. The nasal administration device, not being a medication, is also not likely covered by drug-related insurance. Therefore, transactions are not likely covered by insurance; patients would have to pay cash. It is likely that drug distribution methods and healthcare finance will evolve to provide greater access to naloxone from retail pharmacies and at discharge from a hospital or emergency room. New FDA-approved naloxone products would likely have labeling and reimbursement systems in place facilitating greater access.

Many US states have created legislation that is permissive of lay person naloxone administration to an overdose patient [Hewlett and Wermeling, 2013; Davis *et al.* 2013]. The notion is akin to state laws passed enabling a physician to write an epinephrine injection prescription for a patient with anaphylaxis or severe allergic reaction risks. The scenario requires the prescriber to write a prescription for the patient but likely requires a third party, a so-called Good Samaritan, to administer the medication during the emergency. The legal context is similar in that an opioid overdose patient is likely unconscious and unable to save themselves. Therefore, the prescriber needs a legal carve-out to write an unusual prescription and to provide immunity to the Good Samaritan. Other legal options allow for third-party prescribing so that the concerned parent or spouse may be able to acquire naloxone for access in the home. Many states have adopted the necessary legislation and others are moving through the public debate and legislative process. Model language is available for professional and legislator consideration [Davis *et al.* 2013].

Patients treated with naloxone at home must still receive emergency medical care [Boyer, 2012]. Outpatient naloxone administration has simply provided a window of time in which a critically ill patient can breathe for themselves until expert care can be provided. Moreover, many intoxications involve more than one intoxicant, including acetaminophen, ethanol, and other central nervous system depressants which will also require medical treatment [Jones *et al.* 2014]. There are potential downstream complications even if the person survives the opioid overdose that requires treatment or prevention. Lastly, an overdose survivor may be open to discuss long-term treatment options if this is relevant to their case.

The public in general is aware of the opioid overdose epidemic but has not been educated on a public response. Success in overdose prevention will likely be dependent upon public awareness messages akin to those for use of automatic electronic defibrillators in public places and the consideration that harm reduction with naloxone is similar to community efforts to vaccinate against influenza. At risk families should contact their physician to discuss a prescription for at-home naloxone. New delivery systems can facilitate greater access to and administration of naloxone at the moment of need. A new auto-injector naloxone delivery system has just been approved by the FDA and now available in US pharmacies [Kaleo, 2014].

Development of alternative naloxone delivery systems

Expanded access to naloxone for home use has occurred by prescribing IM naloxone or by off-label use of naloxone injection by combining a prefilled syringe with a mucosal atomization device for IN spraying [Doe-Simkins *et al.* 2009; Barton *et al.* 2002; Kelly *et al.* 2005; Kerr *et al.* 2009]. The widening of this practice suggests there is an unmet medical need for lay-friendly naloxone administration. Moreover, expanded access to naloxone is under development as a public policy much in the way that epinephrine auto-injectors have become more widely available to patients and families with members at risk for anaphylaxis or severe allergic attacks. In general providing access to naloxone parallels the epinephrine practice. In the following we give examples of recently approved or products in late stage development.

Patient-friendly injection-based devices have entered the market

Martindale Pharma has developed a syringe that permits the rescuer to administer a 0.4 mg dose of naloxone by IM injection (Europe only). The device can provide more than one dose of medication as needed.

Kaleo has developed a 'smart' computerized auto-injector for naloxone administration. The device speaks to the rescuer moving through the steps to prepare and administer a 0.4 mg naloxone SC or IM injection. The needle is automatically withdrawn into the device to prevent an accidental needle-stick.

Both products administer the lowest approved dose of naloxone injection (0.4 mg). A repeat dose is available for inadequate initial response or for recurrence of sedation and respiratory depression.

Nasal spray products in development

Lightlake, Inc. and AntiOp, Inc. are developing naloxone nasal sprays. The AntiOp nasal spray is a unit dose, disposable and ready-to-use naloxone nasal spray product. Naloxone nasal sprays are formulated in a drug concentration resulting in a volume appropriate for retention in the nasal cavity. A needle-free system may be more desirable for paramedics and first responders and does not create hazardous waste.

Nasal spray and auto-injector products will have an absorption phase similar to the IM, SC and IN spray of the injection. Efficacy rates and adverse effect profiles will likely be parallel to the experiences from approved naloxone injection products.

Conclusion

Opioid overdose remains a significant public health concern. Pain patients, addicts and those who have entered opioid addiction treatment programs will continue to have significant risk factors for overdose. New strategies are needed to reduce overdose mortality including greater access to naloxone. Our healthcare systems, prescribers, pharmacists, patients and their families will need education on overdose recognition and treatment including naloxone. New products on the horizon can facilitate access to this life-saving medication.

Funding

This work was supported in part by a grant from the National Institute on Drug Abuse, National Institute of Health (grant number NIDA DA 4R42DA030001-05).

Conflict of interest statement

Dr Daniel Wermeling is the CEO and owner of AntiOp, Inc., a company developing a unit-dose, disposable naloxone nasal spray.

References

Bailey, A. and Wermeling, D. (2014) Naloxone for opioid overdose prevention: pharmacists role in community based practice settings. *Ann Pharmacother* 48: 601–606.

Bailey, J., Campagna, E. and Dart, R. (2009) The under recognized toll of prescription opioid abuse on young children. *Ann Emerg Med* 53: 419–424.

Barton, E., Colwell, C., Wolfe, T., Fosnocht, D., Gravitz, C., Bryan, T. *et al.* (2005) Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. *J Emerg Med* 29: 265–271.

Barton, E., Ramos, J., Colwell, C., Benson, J., Baily, J. and Dunn, W. (2002) Intranasal administration of naloxone by paramedics. *Prehosp Emerg Care* 6: 54–58.

Belz, D., Lieb, J., Rea, T. and Eisenberg, M. (2006) Naloxone use in a tiered-response emergency medical services system. *Prehosp Emerg Care* 10: 468–471.

Bond, G., Woodward, R. and Ho, M. (2012) The growing impact of pediatric pharmaceutical poisoning. *J Pediatr* 160: 265–270.

Boyer, E. (2012) Management of opioid analgesic overdose. *N Engl J Med* 367: 146–155.

Buajordet, I., Næss, A., Jacobsen, D. and Brørs, O. (2004) Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *Eur J Emerg Med* 11: 19–23.

Bunn, T. and Slavova, S. (2012) *Drug overdose morbidity and mortality in Kentucky, 2000–2010*. Kentucky Injury and Prevention Center.

Cantwell, K., Dietze, P. and Flander, L. (2005). The relationship between naloxone dose and key patient variables in the treatment of non-fatal heroin overdose in the pre-hospital setting. *Resuscitation* 65: 315–319.

Costantino, H., Illum, L., Brandt, G., Johnson, P. and Quay, S. (2007) Intranasal delivery: physicochemical and therapeutic aspects. *Int J Pharm* 337: 1–24.

Davis, C., Webb, D. and Burris, S. (2013) Changing Law from Barrier to Facilitator of Opioid OVerdose Prevention. *J Law Med Ethics* 41(Suppl. 1): 33–36.

Doe-Simkins, M., Walley, A., Epstein, A. and Moyer, P. (2009) Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose. *Am J Public Health* 99: 788–791.

Dowling, J., Isbister, G., Kirkpatrick, C., Naidoo, D. and Graudins, A. (2008) Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. *Ther Drug Monit* 30: 490–496.

Goodman, L. and Gilman, A. (2001) *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*, 10th edn. New York: McGraw-Hill.

Hasegawa, K., Brown, D., Tsugawa, Y and Camargo, C. (2014) Epidemiology of emergency department visits for opioid overdose: A population-based study. *Mayo Clin Proc* 89: 461–471.

Havens, J., Walker, R. and Leukefeld, C. (2007) Prevalence of opioid analgesic injection among rural nonmedical opioid analgesic users. *Drug Alcohol Depend* 87: 98–102.

Hewlett, L. and Wermeling, D. (2013) Survey of naloxone legal status in opioid overdose prevention. *J Opioid Mgmt* 9: 369–377.

Hospira (2006) *Naloxone hydrochloride injection solution prescribing information*. Hospira, Inc.

IMS (2001) *Naloxone hydrochloride injection prescribing information*. International Medication Systems, Limited.

Jones, C., Paulozzi, L. and Mack, K. (2014) Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse – related emergency department visits and drug-related deaths – United States, 2010. *CDC MMWR* 63(40): 881–885.

Kaleo (2014) *Evzio™ prescribing information*. Kaleo, Inc.

Kelly, A., Kerr, D., Dietze, P., Patrick, I., Walker, T. and Koutsogiannis, Z. (2005) Randomised trial of intranasal *versus* intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust* 182: 24–27.

Kerr, D., Dietze, P. and Kelly, A. (2008) Intranasal naloxone for the treatment of suspected heroin overdose. *Addiction* 103: 379–386.

Kerr, D., Kelly, A., Dietze, P., Jolley, D. and Barger, B. (2009) Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction* 104: 2067–2074.

Lancet (2013) Editorial: The lethal burden of drug overdose. *Lancet* 382: 833.

Mack, K. (2013) Drug-induced deaths – United States, 1999–2010. *MMWR* 62(03): 161–163.

Martindale Pharma (2014) Prenoxad injection. http://www.martindalepharma.co.uk/news/martindale-pharma-launches-prenoxad-injection-for-the-emergency-treatment-of-opioid-overdose/ (accessed 1 November 2014).

Merlin, M., Saybolt, M., Kapitanyan, R., Alter, S., Jeges, J., Lui, J. *et al.* (2010) Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. *Am J Emerg Med* 28: 296–303.

Ngai, S., Berkowitz, B., Yang, J., Hempstead, J. and Spector, S. (1976) Pharmacokinetics of naloxone in rats and in man: basis for its potency and short duration of action. *Anesthesiology* 44: 398–401.

Osterwalder, J. (1996) Naloxone - for intoxications with intravenous heroin and heroin mixtures – harmless of hazardous? A prospective clinical study. *Clin Toxicol* 34: 409–416.

Robertson, T., Hendey, G., Stroh, G. and Shalit, M. (2009) Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehosp Emerg Care* 13: 512–515.

Rosen, L., Khan, D. and Warner, M. (2013) Trends and geographic patterns in drug-poisoning death rates in the US, 1999–2009. *Am J Prev Med* 45: e19–e25.

Shah, N., Lathrop, S., Reichard, R. and Landen, M. (2007) Unintentional drug overdose death trends in New Mexico, USA, 1990–2005: combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction* 103: 126–136.

Sporer, K., Firestone, J. and Isaacs, S. (1996) Out-of-hospital treatment of opioid overdoses in an urban setting. *Acad Emerg Med* 3: 660–667.

Sporer, K. and Kral, A. (2007) Prescription naloxone: a novel approach to heroin overdose prevention. *Ann Emerg Med* 49: 172–177.

SAMHSA (2013) *SAMHSA Opioid Overdose Prevention Toolkit*. Rockville, MD: Substance Abuse and Mental Health Administration.

Toblin, R., Paulozzi, L., Logan, J., Hall, A. and Kaplan, J. (2010) Mental illness and psychotropic use among prescription drug overdose deaths: a medical examiner chart review. *J Clin Psychiatry* 71: 491–496.

Vilke, G., Buchanan, J., Dunford, J. and Chan, T. (1999) Are heroin overdose deaths related to patient release after prehospital treatment with naloxone? *Prehosp Emerg Care* 3: 183–186.

Vilke, G., Sloane, C., Smith, A. and Chan, T. (2003) Assessment for deaths in out-of-hospital heroin overdose patients treated with naloxone who refuse transport. *Acad Emerg Med* 10: 893–896.

Walley, A., Doe-Simkins, M., Quinn, E., Pierce, C., Xuan, Z. and Ozonoff, A. (2013a) Opioid overdose prevention with intranasal naloxone among people who take methadone. *J Sub Abuse Treat* 44: 241–247.

Walley, A., Xuan, Z., Hackman, H., Quinn, E., Doe-Simkins, M., Sorensen, A. *et al.* (2013b) Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* 346: f174.

Wanger, K., Brough, L., Macmillan, I., Goulding, J., MacPhail, I. and Christenson, J. (1998) Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose. *Acad Emerg Med* 5: 293–299.

Warner, M., Chen, L., Makuc, D., Anderson, R. and Miniño, A. (2011) *Drug poisoning deaths in the*

United States, 1980–2008. NCHS data brief, no. 81. Hyattsville, MD: National Center for Health Statistics.

Wermeling, D. (2012) A response to the opioid overdose epidemic: naloxone nasal spray. *Drug Del Trans Res* 3: 63–74.

Wheeler, E., Davidson, P. and Jones, T. (2012) Community-based opioid overdose prevention programs providing naloxone – United States, 2010. *MMWR* 61(06): 101–105.

Wunsch, M., Nakamoto, K., Behonick, G. and Massello, W. (2009) Opioid deaths in rural Virginia: A description of the high prevalence of accidental fatalities involving prescribed medications. *Am J Addict* 18: 5–14.

Yealy, D., Paris, P., Kaplan, R., Heller, M. and Marini, S. (1990) The safety of prehospital naloxone administration by paramedics. *Ann Emerg Med* 19: 902–905.