REVIEW

Take-home naloxone to reduce heroin death

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ABSTRACT

Background This paper reviews the relevant literature related to the distribution of take-home naloxone.

Methods A Medline search was conducted on articles published between January 1990 and June 2004 to identify scientific literature relevant to this subject. Those publications were reviewed, and from them other literature was identified and reviewed.

Results The prevalence, pathophysiology and circumstances of heroin overdose, and also bystander response are included in this review. Naloxone peer distribution has been instituted to varying degrees in the United States, Italy, Spain, Germany and the United Kingdom.

Conclusion At this point the evidence supporting naloxone distribution is primarily anecdotal, although promising. Although the distribution of naloxone holds promise for further reducing heroin overdose mortality, problems remain. Naloxone alone may be insufficient in some cases to revive the victim, and cardiopulmonary resuscitation (CPR), especially rescue breathing, may also be needed. A second dose of naloxone might be necessary. Complications following resuscitation from overdose may infrequently need in-hospital care. Mortality from injecting without anyone else present will be unaffected by take-home naloxone. Take-home naloxone should be studied in a rigorous scientific manner.

KEYWORDS: Heroin, heroin-related death, naloxone, overdose, resuscitation.

INTRODUCTION

The distribution of the mu-receptor antagonist naloxone (brand name Narcan) to be given to victims of heroin overdose is a new and innovative approach to reducing heroin mortality. Because naloxone reverses respiratory depression, which is by far the most common cause of death after heroin overdose, its provision during heroin overdose can be life-saving.

This review summarizes the pertinent medical literature related to the distribution of take-home naloxone which is currently taking place in many countries around the world. The focus will be on evidence from the addiction medicine and emergency medicine literature

PREVALENCE OF HEROIN OVERDOSE

Overdose is a common occurrence amongst heroin users. In San Francisco, USA, 48% of young (median 22 years) injection drug user interviewees had already had at least one overdose (Ochoa *et al.* 2001). In London, UK, 38% of interviewees had overdosed at least once. In Russia, 59% of 763 users had overdosed (Sergeev *et al.* 2003). In Sydney, Australia, 68% had overdosed a median of three times (Darke, Ross & Hall 1996a).

Heroin overdose frequently results in death. In Albuquerque, USA, Goldstein & Herrera (1995) found a 34% mortality rate due to overdose in heroin addicts over a 22-year period. Hickman *et al.* (2003) found that more

London, UK, were due to opioid overdose. In Catalonia, Spain, a 10-year mortality rate of 30% was found, of which 30% were due to overdose (Sanchez-Carbonell & Seus 2000). In Rome, Italy, Davoli *et al.* (1993) found that 32% of deaths in intravenous drug-using males and 41% of deaths in intravenous drug-using females were due to overdose. Death rates have shown a steady increase in Italy from 1984 to 2000 (Preti, Miotto & De Coppi 2002), with a 13 times greater mortality rate from 1985 to 1998 in heroin injectors than in the general population (Quaglio *et al.* 2001).

The literature is contradictory in considering the relationship of the severity of an overdose to the dose of heroin. A correlation has been noted (Bertini *et al.* 1992). Huber *et al.* (1974) found a 10-fold (3.3–33.3 mg) variation in the amount of heroin per packet in a study in Atlanta, USA. Average street heroin purity and the range of heroin purity were found to be correlated with death rates (Darke *et al.* 1999). Other studies have not noted this finding (Kintz *et al.* 1989; Zador, Sunjic & Darke 1996). Heroin users do have difficulty in adjusting their dose. However, there are other very important factors, especially the tolerance of the individual to heroin and the concomitant use of other drugs.

PATHOPHYSIOLOGY OF HEROIN OVERDOSE

Although most deaths occur in individuals with a history of heroin addiction, most of these individuals commonly have reduced tolerance at the time of their deaths (Greene, Luke & Dupont 1973; Huber, Stivers & Howard 1974). Hair analysis in Verona, Italy, found that heroin overdose fatalities occurred mainly after a period of abstinence (Tagliaro *et al.* 1998). The period immediately following release from detention is especially dangerous (Darke *et al.* 1996a). Twenty-three per cent of overdose deaths in Glasgow, Scotland occurred within 2 weeks of release (Jones *et al.* 2002). It is also hypothesized that tolerance to respiratory depression may develop slower than tolerance to the euphoric effect, thus increasing the risk of overdose (White & Irvine 1999). Warner-Smith *et al.* (2001) have hypothesized that pre-existing pulmonary and hepatic dysfunction may lead to a higher risk of overdose mortality.

Almost all (99%) heroin overdose death is after intravenous use (Sporer 1999). Death from heroin overdose is caused primarily by respiratory depression leading to cardiac arrest. Death may occur very rapidly, as reported in about 17% of lethal cases (Greene *et al.* 1973). The discovery of a cadaver with the syringe still in the arm is not rare (Cami & Domingo-Salvany 1995). More commonly, *et al.* 1973; Sporer 1999). Others present may be less likely to recognize the danger of a less dramatic, slowly developing narcosis (McGregor *et al.* 1998).

Infrequent causes of delayed death from heroin overdose are non-cardiogenic pulmonary edema and aspiration pneumonia. Bertini *et al.* (1992) found a rate of non-cardiogenic pulmonary edema of 0.8% and the rate was 0.9% in the study by Sporer, Firestone & Isaacs (1996). The non-cardiogenic pulmonary edema is due probably to pulmonary vasoconstriction from hypoxemia. It does not occur from opioids not taken in over-dosage. It is usually evident within a short period after the overdose. A study in Switzerland found only one case (in 160) of delayed pulmonary edema after successful resuscitation with naloxone (Osterwalder 1995). Opioids are known to cause nausea and vomiting, even in therapeutic doses. Aspiration of gastric contents after heroin overdose can lead to serious aspiration pneumonia. This can be precipitated by a side effect of heroin itself, the effects of concomitant drug use, especially alcohol (Darke & Hall 2003) or from the rapid onset of withdrawal symptoms after the injection of naloxone. Aspiration pneumonia was found in only one of 124 heroin overdoses treated in an emergency department in El Paso, USA (Smith *et al.* 1992).

There were no survivors among 16 patients in asystolic arrest (without advance sign of death) in the study by Sporer *et al.* (1996). However, prompt provision of naloxone and advanced cardiac life support (ACLS) by ambulance personnel may still be life-saving. Bertini *et al.* (1992) reported successful resuscitation of five of seven patients in asystole, with only one of these later dying from post-anoxic encephalopathy.

CIRCUMSTANCES OF HEROIN OVERDOSE

The setting of the heroin overdose strongly influences the overdose outcome. Most overdoses occur with other people present (McGregor *et al.* 1998; Powis *et al.* 1999; Sporer 1999). The other person or people present are most commonly other intravenous heroin users (Strang *et al.* 1999).

Although most drug users inject with others, there are some areas that report high rates of injecting alone. If the heroin user is alone, a fatal outcome becomes more likely. Davidson *et al.* (2003) found that in 333 heroin-related deaths in San Francisco, USA, 68% were reportedly alone. Take-home naloxone will have little or no effect on reducing unwitnessed overdose mortality, as the overdose victim would not be in a condition to administer it to himself or herself. No cases of self-administration of

tation on the potential of take-home naloxone to reduce heroin mortality. It emphasizes the importance of educating heroin users on the dangers of using alone.

BYSTANDER RESPONSE

Heroin overdose death can nearly always be prevented by the prompt provision of professional emergency services. Ambulance personnel in developed countries can administer naloxone and provide respiratory support, if necessary, until the naloxone takes effect. Ambulance response times in developed countries in urban areas are usually just a few minutes.

Unfortunately, in many overdoses, bystanders fail to call for ambulance services. This failure is due primarily to fear of the police. In countries such as the United States, the same call to 911 for emergency medical assistance also notifies the police of the situation. Because the use of heroin is illegal and the victim or others present may be on parole or have outstanding warrants, this fear is rational and understandable. Police view the site of a heroin overdose as a crime scene and their presence may delay or interfere with emergency care for the victim. Davidson *et al.* (2002) reported that in San Francisco, USA, calling emergency services is often an option of last resort, and fear of the police frequently caused the failure of bystanders to call emergency services. Three-quarters of heroin user respondents in Multnomah County Oregon, USA, reported fear of police (Oxman *et al.* 2000). This problem has also been reported in Russia (Sergeev *et al.* 2003), Italy (Preti *et al.* 2002) and Australia (Darke, Ross & Hall 1996b; McGregor *et al.* 1998; Hargreaves *et al.* 2002). Another potential problem with the police, at least in the USA where naloxone requires a prescription, is that people found with naloxone can be cited and have the naloxone confiscated (Giuliano 2001). This problem would be solved if naloxone were made available over the counter. This fear of police is predictably country- or region-specific. For example, reluctance to call for emergency services due to fear of police was not found in Dublin, Ireland (Cullen, Bury & Langton 2000). In Western Australia, a protocol was implemented limiting police presence at overdose events (Hargreaves *et al.* 2002). An attempt to address this police problem has been training in how to report the overdose in such a way as to reduce the possibility of a police response. Reporting to the emergency operator that 'my friend is unconscious and not breathing' (Anonymous 2000) without saying the cause may reduce the possibility of problems from the police. Survey results in San Francisco, USA found that the availability of naloxone would not change the rate of calling emergency services (Seal *et al.* 2003). It is understood ing help in overdose emergencies, and is a major reason for providing take-home naloxone.

Untrained people present at overdoses try a variety of methods to attempt to aid the overdose victim. These include mouth-to-mouth resuscitation, heart massage, inflicting pain, walking the person around or injecting salt or milk or cocaine (Darke *et al.* 1996b). Some of these are helpful; many are of uncertain benefit, while some are almost certainly harmful. Painful or unpleasant stimuli may possibly stimulate enough respiration to prevent death. Injections of milk or salt water are of no benefit and are potentially harmful. Injection of cocaine could be lethal. In urban areas, overdose victims can be transported by private vehicle to emergency care. Other victims are taken to a public area to be discovered by bystanders or where emergency services can be summoned with less risk of police involvement.

The person most likely to be present at an overdose is another heroin user. A large proportion of heroin users have witnessed overdoses (Darke *et al.* 1996b). Most educational interventions and naloxone distribution programs are directed to this population.

NALOXONE: PHARMACOLOGICAL CONSIDERATIONS

Naloxone is a pure opioid antagonist (Physicians' Desk Reference 2001). Heroin is an opioid. The administration of naloxone is a simple procedure. It is important to make resuscitation as simple as possible, as others present at an overdose may themselves be intoxicated. Naloxone is commonly given by the intravenous (i.v.), intramuscular (i.m.) or subcutaneous (s.c.) routes. It can also be given through an endotracheal tube (ET). It is given uncommonly by sublingual or intralingual injection. It is not effective orally (p.o.). The onset of action of naloxone given i.v. is usually within 2 minutes. It is slightly slower if given s.c. or i.m. (Du Pont Pharma 2001). The effects last 45–90 minutes after i.v. injection (Sporer 1999). A study comparing the i.v. to s.c. routes found a slower average response time to a respiratory rate of 10 per minute after s.c. (5.5 minutes) than i.v. (3.8 minutes) (Wanger *et al.* 1998). However, the time required to obtain i.v. access more than made up for the difference, making s.c. a faster route to therapeutic response. The i.v. route for administration of take-home naloxone is not recommended for bystanders because of the delay associated with establishing i.v. access; i.m. administration is technically easier than s.c. and much easier than i.v. The i.m. route was preferred by most of the take-home naloxone distribution programs found in this literature review. Response to naloxone was 94% if given i.m. and a statis-

1996). The i.m. route is believed to have at least as fast absorption as s.c. It has a longer duration of action than the i.v. route (Du Pont Pharma 2001) and for this reason, patients who are being discharged after short periods of observation in the field (Vilke *et al.* 2003) are given an i.m. injection of naloxone prior to discharge, whether or not it be against medical advice. The longer duration of action is a definite advantage of the i.m. route.

The intranasal (i.n.) route by aerosol is gaining increasing interest. Because absorption is through the nasal mucosa, it requires exposure to the nasal mucosa and circulation. In one study (Barton *et al.* 2002) intranasal administration was affective even in patients 'found down' in overdose, but it was not effective in one patient who was noted to have a significant amount of epistaxis (bleeding from the nose). Naloxone may not be effective in patients with excessive mucus or other problems affecting access to mucus membranes (Barton *et al.* 2002). The intranasal route holds promise, because it eliminates the risks of needle exposures. Barton *et al.* (2002) found an average response time of 3.4 minutes after i.n. administration, with response in 10 of 11 overdose patients. Not surprisingly, the presence of epistaxis resulted in the lack of response. Naloxone nasal spray had been planned to be distributed in Britain (Abbasi 1998); however, no reports were found of naloxone nasal spray distribution in Britain having actually occurred. Intranasal administration of naloxone, in addition to i.m., is included in the take-home naloxone program in Baltimore, USA (Garza 2003).

Naloxone is available in the USA in 1 ml and 10 ml vials in strengths of 0.4 mg and 1 mg/ml. Because it comes in different strengths and different-sized containers, there is a concern about possible confusion (Giuliano 2001). It has a shelf-life of 18 months to 2 years (Lenton & Hargreaves 2000). It is uncertain how much potency is lost beyond this period.

Although it adds to the cost, in order to simplify administration prefilled syringes with naloxone have been proposed (Darke 1999), and are currently being distributed in New Mexico, USA. Analogously, epinephrine prescribed for take-home emergency use is also dispensed in prefilled syringes.

The dosage of take-home naloxone to be administered to a heroin overdose victim has been a somewhat difficult issue. A large dose will resuscitate the victim more reliably, but at the expense of causing more intensely unpleasant withdrawal symptoms, leading possibly to dangerous immediate use of more heroin. A less than effective dose will prolong the hypopnea leading to further injury and possible death. Titration of the dose is most often recommended in a medical setting, but may be asking too much of lay people who will be under stress

Although recipients of take-home naloxone are generally advised to summon emergency services in addition to administering naloxone, it is recognized that this will not always occur. One criticism of take-home naloxone is that a patient may be resuscitated successfully with naloxone but have a delayed recurrence of respiratory depression. Recipients of take-home naloxone are instructed to give additional doses if needed. This is because of the shorter half-life of naloxone than of heroin, resulting in the recurrence of respiratory depression. Watson *et al.* (1998) found recurrence of opioid symptoms in two of 10 patients after an initial response to naloxone in a hospital emergency department setting. However, this may be an over-rated concern for heroin (but not for longer-acting opioid agonists). In New South Wales, where overdose victims are treated *in situ*, only 0.004% of overdose fatalities occurred in patients who had received any naloxone (Darke, Mattick & Degenhardt 2003). Clarke & Dargan (2002) reviewed the literature and concluded that a well patient can be discharged after 1 hour. Vilke *et al.* (2003) found no subsequent related deaths in patients treated in the field by ambulance personnel with naloxone who refused transport to a hospital.

Although naloxone will reliably reverse the lethal effects of heroin, there can be a lethal delay between the administration of naloxone and when it takes effect. Because of this, naloxone distribution programs often include training in adult cardiopulmonary resuscitation (CPR) along with the provision of naloxone and injection equipment (Abbasi 1998). In a partially conscious patient, the placement into the recovery position (lying on the left side with the right hip and right knee flexed) to help maintain the airway and prevent aspiration, may be all that is required initially. A patient who has apnea or hypopnea will need respiratory support which can be provided by rescue breathing (mouth-to-mouth). Patients in cardiac arrest will need closed heart massage. Successful training of 'drug misusers' in CPR has been demonstrated (Dettmer, Saunders & Strang 2001; Graham *et al.* 2001). Dietze, Cantwell & Burgess (2002) reported a significantly lower rate of hospitalization in heroin overdoses who had received bystander CPR.

Naloxone is an extremely safe drug. Its profile is remarkably safe (Goldfrank *et al.* 1998). The only contraindication to its use is hypersensitivity (American Heart Association 1994). Naloxone has 'essentially no pharmacologic activity' in the absence of opioids or opioid agonists (Physicians' Desk Reference 2001). Multiple doses of 90 mg daily, nine times the maximum recommended dose for opioid intoxication, produced no behavioral or physiological changes (Du Pont Pharma 2001). It has essentially no agonist properties or abuse potential. One mg of naloxone will completely antagonize 25 mg of

immediate withdrawal syndrome in individuals who are physically dependent on opioids, its use can rarely be followed by brief withdrawal seizures. Administration of naloxone to 813 patients by paramedics in Pittsburgh, USA, was followed by one patient having a seizure (Yealy *et al.* 1990). Abrupt opioid withdrawal precipitated by naloxone can result in an angry or agitated patient. Sporer *et al.* (1996) found that 7% required restraints. Resuscitated victims may not believe that the unpleasant withdrawal symptoms are a consequence of saving his or her life. Because of these concerns, it is recommended that naloxone be given in the lowest effective dose. However, unpleasant withdrawal symptoms may be unavoidable in the treatment of severe hypopnea (Haddad, Shannon & Winchester 1998).

Opponents of the distribution of take-home naloxone (Ashworth & Kidd 2001; Mountain 2001) quote the study by Osterwalder (1996), which reported severe adverse reactions after naloxone administration in six of 453 patients. In the Osterwalder study, an episode of asystole occurred in a patient in severe respiratory acidosis. An episode of pulmonary edema could be explained by the toxicity of the heroin. Three convulsions could be explained by cerebral hypoxia or the withdrawal syndrome. An episode of violent behavior can be explained by the intensely unpleasant experience of sudden opioid withdrawal. Thus, none of the adverse effects reported by Osterwalder can be attributed reliably to naloxone toxicity. Hoffman & Goldfrank (1995) concluded after a review of the literature that the complications attributed to naloxone are erroneous or, at most, extremely rare.

Concern over the cost of naloxone has been raised (Darke & Hall 1997). Because a death rate of only about 3% per overdose was found in Australia (Darke *et al.* 2003), it is likely that many uses of naloxone will not have been necessary to prevent mortality. However, naloxone also has the benefit of preventing hypoxic brain injury by reducing respiratory depression. Even if 30 or even 300 doses must be distributed to prevent one death, the cost per life saved would still be much less than other life-saving interventions undertaken commonly in developed countries.

NALOXONE USE IN MIXED OVERDOSES

Many studies have found that often one or more other drugs were present in fatal overdoses (Darke *et al.* 1997). Central nervous depressants, especially ethanol and benzodiazepines, have additive effects to the central nervous depressant effects of heroin. Beswick, Best & Burn (2002) found that this combination was present in eight of 11 witnessed overdose fatalities. Darke *et al.* (1997) found overdoses in Sydney, Australia with a significant inverse correlation between blood alcohol and blood morphine concentrations. A study of heroin deaths in Maryland, USA, found that concomitant use of ethanol was a clear risk factor (Levine, Green & Smialek 1994). There is no contraindication to the use of naloxone in the presence of ethanol and/or benzodiazepines. Lethal overdoses of ethanol alone or benzodiazepines alone are relatively rare. Naloxone would be expected to prevent death from opioid respiratory insufficiency, even in the presence of other central nervous system (CNS) depressants, although it would not be effective for respiratory distress due to severe alcohol poisoning alone.

The concomitant use of cocaine is more problematic. Coffin *et al.* (2003) found in 7451 accidental overdose deaths in New York City, USA that this combination of opioids and cocaine was the most frequently observed drug combination. O'Driscoll *et al.* (2001) also found that this combination was particularly lethal in Seattle, USA. Because of cocaine's stimulant properties, its administration is sometimes used by bystanders in an ill-advised attempt to treat an overdose victim (Beswick *et al.* 2002). Concomitant cocaine use could also increase impulsive use of opioids or other respiratory depressants.

NALOXONE DISTRIBUTION

Narcan distribution, along with training in overdose management, has resulted in treating 60 overdoses in Barcelona, Spain (Trujols 2001). In 2001 New Mexico began providing naloxone to drug users in efforts to reduce overdose death (Shah, Lathrop & Landen 2003). A naloxone distribution program in Chicago, USA, involves two physician volunteers who provide naloxone prescriptions (Bigg 2002). Chicago Recovery Alliance (2004) has reported that as of 1 January 2004, over 200 lives had been saved by naloxone. Naloxone was distributed to injection drug users in Torino, Italy leading to successful resuscitations (Seal *et al.* 2003). Dettmer *et al.* (2001) reported 29 administrations by 22 individuals who had been trained in its use in Berlin, Germany. Ninety per cent of the usages of naloxone were judged to be appropriate with the remainder being of uncertain benefit or pointless.

Naloxone can also be administered as part of the medical attention provided at safer injection facilities (SIFs). SIFs also have the advantage of reducing HIV and hepatitis C transmission by providing sterile injecting equipment. SIFs have been in operation in 26 European cities and Sydney, Australia (Wood *et al.* 2003). The dispensing of take-home naloxone at discharge from emergency services, either with or against medical advice, to heroin

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