Naloxone in opioid poisoning: walking the tightrope

S F J Clarke, P I Dargan, A L Jones

Acute opioid intoxication and overdose are common causes of presentation to emergency departments. Although naloxone, a pure opioid antagonist, has been available for many years, there is still confusion over the appropriate dose and route of administration. This article looks at the reasons for this uncertainty and undertakes a literature review from which a treatment algorithm is presented.

Although naloxone has been used as a specific antidote for opioid poisoning since the 1960s, there are variations in the recommended doses with the British National Formulary advising 0.8–2 mg boluses, repeated as necessary up to 10 mg for adults (10 µg/kg followed by 100 µg/kg boluses for children), and Poisonsindex suggesting 0.4–2 mg boluses. There is also wide variation in the route of administration.

There are a number of reasons for this. First, opioids exert their effect by binding to a series of receptors. Naloxone has antagonist activity at all of the receptor types and the amount needed to provide such an effect depends upon the number of receptors occupied. Recent evidence suggests that a dose of 13 µg/kg naloxone (approximately 1 mg in an 80 kg person) produces 50% receptor occupancy; however, this is also influenced by the dose of opioid ingested or injected. Unfortunately this is seldom known in clinical practice, and instances have been reported where over 20 times the recommended doses of naloxone have been needed to counteract massive opioid overdoses, and even more in body packers. Numerous case histories have revealed a 13-fold variation in rate of naloxone infusions given for prolonged overdoses.

Second, opioid antagonists can precipitate acute withdrawal symptoms (AWS) in chronic opioid users provoking an often violent reaction. In one early study on the use of naloxone to reverse morphine anaesthesia in non-opioid dependent, general surgical patients, acute withdrawal-like symptoms were observed to occur after the administration of 15 µg/kg naloxone. In another study, behavioural changes, sweating, and yawning were observed in 14 healthy volunteers given 2–4 mg/kg naloxone, and these effects often lasted for a number of hours after its administration.

Third, the pharmacodynamic actions of naloxone last for a briefer period than all but the most short acting opioids although the elimination half life of naloxone is similar to that of morphine (60–90 minutes) it is redistributed away from the brain more rapidly. Consequently, the patients may become renarcotised and suffer harm if they self discharge from medical care early. Clinicians are clearly walking a tightrope between precipitating AWS and avoiding renarcotisation.

Numerous case reports describing possible adverse effects of naloxone have been published. Pulmonary oedema has been reported but most instances have occurred in the postoperative period or in the presence of pre-existing cardiorespiratory disease, and in many of these reports it can be difficult to differentiate between the effect of naloxone and the effect of the underlying disease process or other drugs that have been ingested or administered. Many episodes of pulmonary oedema secondary to opioid toxicity have been published since it was first noted by William Osler in the 1880s and it has been suggested that naloxone simply reveals the opioid induced pulmonary oedema that had been masked by the respiratory depression.

Seizures and arrhythmias have also been noted, but could have been caused by hypoxia, the opioids themselves, their coingestants (most notably cocaine), or pre-existing disease. Interestingly, a number of episodes of severe hypertensive reactions have been reported following administration of naloxone to patients with pre-existing simple hypertension. In addition, one report showed a significant rise in serum catecholamine concentrations in a patient with a phaeochromocytoma following administration of naloxone without prior exposure to exogenous opioids. Currently, a great deal of research is being undertaken on the interaction of endogenous opioids and the autonomic nervous system and it would seem reasonable to postulate that the antagonistic action of naloxone may have an effect. Canine experiments have indicated that reducing hypoxia and hypercapnia lowers serum catecholamine concentrations. It has been proposed that hyperventilating patients prior to administration of naloxone would reduce the risk of sympathetic mediated adverse effects although this has not been verified in human.

In contrast with the above concerns, extremely high doses (up to 5.4 mg/kg boluses and 4 mg/kg/h infusions) of naloxone have been given to non-opioid dependent subjects without any reported adverse effects.

The aim of this review is to find evidence of the optimum dose and route for administration of naloxone.
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With one exception, all other serious complications became apparent within 20 minutes of arrival and treatment in the emergency department. The one exception was a case of...

Figure 1  Flowchart of treatment of opioid overdose.

60–90 minutes, it would seem logical to observe patients for signs of recurrent toxicity for at least 2 hours, although further studies are needed to validate this.
fatal pulmonary oedema, where the patient was found dead 7 hours after discharge (9 hours after ingestion of opioid). In this case, further opioid ingestion cannot be ruled out, and in any case it would seem that genuinely delayed adverse events are rare. Because it would be difficult to persuade opioid addicts to stay for 8 hours after they have had naloxone, it would be reasonable to discharge them if they fulfill Christensen’s criteria 2 hours after naloxone.

Research difficulties

The reasons for the dearth of randomised controlled clinical trials have been summarised recently by Whyte et al.29 Legal, political, and ethical difficulties, particularly in the context of obtaining consent allowing treatment, often hinder the recruitment of adequate numbers of patients. In addition, trials would have to be prohibitively large to achieve sufficient power when measuring outcomes that are rare.

It is difficult to eliminate confounding factors, such as the wide range of different opioids, co-ingestants, and adulterants that can be taken, the variety of routes by which they can be taken (orally, intravenously, subcutaneously, nasally, or by smoking), and the complex treatment regimes that are given. It is often difficult to determine what individual patients have taken because usually they do not know.

The external validity of the studies can be questioned because many are undertaken in regional poison centres whereas most patients are treated in general hospitals where there is limited access to specialised toxicological laboratory facilities. Similarly, it can be argued that patients who agree to participate in research are not representative of the whole population of opioid overdose patients.

Blinding of treatments is extremely difficult because patients are often in the emergency department for such a short period before they are discharged that the clinician who administers the treatment is usually the one who has to review the response to that treatment.

The research undertaken so far has relied heavily on observational studies, which have a number of well recognised limitations, such as difficulty in minimising confounding factors and retrospective data collection. Studies have often used different inclusion criteria in terms of degrees of sedation and respiratory rate as well as different thresholds for giving further doses of naloxone, which makes direct comparison of studies difficult.

Follow up of patients is difficult; Smith et al.24 managed to contact only 32% of the patients who had been discharged. Other studies compared the lists of patients discharged with ambulance service records and death certificates issued by the local coroners. They may have been lost to follow up if they had given misleading demographical details and after discharge were taken to another healthcare facility by private transport, or if they had died later and been given an alternative cause of death.

In spite of these difficulties, a number of conclusions can be drawn and further trials are needed to validate them clinically in the emergency department and thus help clinicians walk the tightrope between over and under treating these patients. Clinical judgement and meticulous observation are required to successfully manage opioid intoxicated patients.

CONCLUSIONS

Although the evidence base is sparse at present, the following algorithm has been devised to summarise the research in a way that is clinically useful. References have been included where relevant otherwise the recommendations are based on consensus derived from the clinical experience of Medical Toxicology Units in Europe, the USA, and Australia. Although recent studies have suggested that intranasal and nebulised naloxone may be useful alternatives to parenteral administration, the authors think that the evidence is not strong enough yet to add them to the algorithm; however, they could be easily included in the flowchart as further evidence becomes available.

Opioid overdose is a challenging condition that requires a difficult balancing act between over and under treatment with naloxone.

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