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Intranasal naloxone for the treatment of suspected heroin overdose

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ABSTRACT

Aims This paper reviews available literature regarding the effectiveness, safety and utility of intranasal (i.n.) naloxone for the treatment of heroin overdose. **Methods** Scientific literature in the form of published articles during the period January 1984 to August 2007 were identified by searching several databases including Medline, Cinahl and Embase for the following terms: naloxone, narcan, intranasal, nose. The data extracted included study design, patient selection, numbers, outcomes and adverse events. **Results** Reports of the pharmacological investigation and administration of i.n. naloxone for heroin overdose are included in this review. Treatment of heroin overdose by administration of i.n. naloxone has been introduced as first-line treatment in some jurisdictions in North America, and is currently under investigation in Australia. **Conclusion** Currently there is not enough evidence to support i.n. naloxone as first-line intervention by paramedics for treatment of heroin overdose in the pre-hospital setting. Further research is required to confirm its clinical effectiveness, safety and utility. If proved effective, the i.n. route may be useful for drug administration in community settings (including peer-based administration), as it reduces risk of needlestick injury in a population at higher risk of blood-borne viruses. Problematically, naloxone is not manufactured currently in an ideal form for i.n. administration.

Keywords Heroin, intranasal, naloxone, opioid, overdose, paramedic, resuscitation.

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INTRODUCTION

Administration of naloxone by the intranasal (i.n.) route to victims of suspected heroin overdose is a new and novel approach. Naloxone reverses the effects of heroin and, most importantly, respiratory depression, which is the most common cause of death after overdose.

Traditionally, naloxone has been administered via the intramuscular (i.m.) and intravenous (i.v.) routes in emergency situations by trained health professionals in hospital and community settings. Drug administration by these routes is problematic in a population at higher risk of blood-borne viruses (BBV).

Several promising reports of the effectiveness and utility of intranasal naloxone for the treatment of heroin overdose in emergency situations have been published recently. This review examines the available scientific literature regarding the use and practicality of i.n. naloxone for the treatment of heroin overdose, and also explores issues around the wider dissemination of its use in community settings by non-health-care providers.

METHODS

The Medline, Cochrane, Embase and Cinahl databases were searched using the following terms: 'naloxone.mp' or 'exp naloxone', 'narcan.mp.' or 'exp.Narcan' and 'exp administration, intranasal/or intranasal.mp' or 'nose.mp'. Fifteen papers were identified initially by Medline, of which seven were relevant [1–7]. Six reported findings from case series or clinical studies, and one was a brief review [1]. This short review [1] of the available literature in this field was performed to establish whether intranasal naloxone is effective in suspected opiate overdose. While this report outlined study findings, the authors did not elaborate on the safety, effectiveness and clinical importance of intranasal administration of

naloxone. We considered that a more detailed review of this topic was necessary and proceeded with our investigation.

No further papers were identified after review of the other databases; however, two further papers were found after assessment of references of identified papers: one a study in rats and the other a clinical study reported as an abstract at a scientific meeting [8,9].

Papers were deemed to be relevant if they discussed the effectiveness of naloxone by intranasal administration for opiate reversal. A total of eight papers were identified, as summarized in Table 1.

HEROIN USE AND OVERDOSE

Heroin is an opioid that is absorbed rapidly after all methods of administration: within 1 minute for intravenous [10], within 3–5 minutes for i.n. and i.m. [11] and within 5–10 minutes for subcutaneous administration [12]. Heroin usually produces euphoric effects, but in overdose toxic signs include abnormal mental status, substantial respiratory depression and miotic pupils [13].

Drug overdose is a leading cause of premature death for injecting drug users (IDUs) [14,15], and it has been estimated that 38–68% of users have overdosed at least once [16–18]. Overdose among IDUs typically involves heroin resulting in a mortality rate that is much higher than other groups in the community of the same age [15,19].

Death after heroin overdose results from loss of consciousness and respiratory suppression [20]. Fortunately, death rates after heroin overdose have been reported to be as low as 3% [21], and a minority of fatalities occur instantly after drug ingestion [13,22,23]. This delay offers a window for intervention.

Aside from death, other sequelae reported after heroin overdose include: neurological damage after prolonged hypoxia, rhabdomyolysis, pulmonary oedema and pulmonary aspiration [24]. Prompt reversal of heroin overdose limits the occurrence and/or severity of these events, and full recovery is possible if hypoxia is reversed before permanent organ damage results.

NALOXONE THERAPY

Naloxone is a pure opioid antagonist that challenges the mu, kappa and delta receptors of the central nervous system [25]. As such, it is an effective agent for reversing the acute effects of opioids such as heroin and exerts little or no pharmacological effect when administered to patients who have not consumed opioids [6,25]. Naloxone is effective rapidly, with onset of action within 1–2 minutes after i.v. administration [25]. Duration of

Table 1 Summary of investigations for intranasal naloxone.

Author (date)	*Patient group (n)*	*Intervention*	*Study type: (n)*	*Outcome*
Hussain *et al.* (1984) [8]	Male rats (6)	Controlled trial	Comparison: i.v. (3) versus i.n. (3)	Bioavailability
Loimer *et al.* (1992) [6]	Male adult (30), opiate-dependent	Controlled trial	Observational	Severity of withdrawal
Loimer *et al.* (1994) [7]	Male adult (17), opiate-dependent	Randomized controlled trial	Comparison: i.v. versus i.m. (7), i.v. versus i.n. (10)	Severity of withdrawal
Kelly & Koutsogiannis (2002) [5]	Adult (6), heroin overdose	Case series	Observational: i.n.	Response
Barton *et al.* (2002) [3]	Suspected heroin overdose (30)	Case series	Observational: i.n.	Response
Barton *et al.* (2005) [2]	Suspected heroin overdose (95)	Case series	Observational: i.n.	Response
Kelly *et al.* (2005) [4]	Suspected heroin overdose (155)	Randomized controlled trial	Comparison: i.m. (71) versus i.n. (84)	Response
Robertson *et al.* (2005) [9]	Suspected heroin overdose (154)	Observational, medical record review	Comparison: i.v. (104) versus i.n. (50)	Response

i.v.: intravenous; i.n.: intranasal; i.m.: intramuscular

effect usually persists in the range of 1–4 hours after i.v. administration, with an elimination half-life of 60–90 minutes [25].

Serious complications (seizure, pulmonary oedema, asystole, cardiac arrest) after naloxone administration are reportedly rare (0.3 and 1.6%) [26–28]. Signs of opioid withdrawal (confusion, headache, nausea or vomiting, aggressiveness, tachycardia, sweating and tremor) are more likely to occur [26–28].

Historically, the treatment of heroin overdose with naloxone occurred in the hospital environment, where naloxone was administered parenterally (i.m. and i.v.) after ambulance transfer of patients. Today, treatment of these patients often occurs in the pre-hospital setting with the administration of naloxone undertaken by paramedics [4,28,29]. More recently there have been trials of peer-administered naloxone for heroin overdose in community settings with reported success [30–36].

DIFFICULTIES WITH CURRENT MODE OF TREATMENT

While there is evidence of success with the parenteral (i.v., i.m.) administration of naloxone for heroin overdose, there are several recognized problems including venous access, BBV risk and technical competence.

A large proportion of heroin users inject intravenously [37–39]. It can be challenging for health professionals, including paramedics, to access patent peripheral veins in IDUs whose veins may be damaged after excessive use for illicit drug administration. Difficult and repeat cannulations are time-consuming, which may lead to treatment delays.

A degree of clinical expertise is required in the use of needles, syringes, vials and ampoules in order to administer naloxone using parenteral routes. Patients are often found in less than ideal environments, including alleyways, parks and public toilets [4,26] that can be dark and cramped, rendering injection and cannulation more difficult. Also, after heroin reversal patients are often restless and aggressive upon awakening [4,26]. Risk of needlestick injury to the health-care provider is increased in these situations. Given the increased prevalence of BBV, such as hepatitis B and C and HIV, in the IDU population [40,41] there is a risk of transmission of these viruses during needlestick injury. In addition, the safe disposal of used syringes and needles is a major issue. Regardless of the outcome of a needlestick injury, the affected person and kin are usually anxious until negative test results are obtained (which can take several months) [42]. HIV prophylactic medications taken during this time have significant and impeding iatrogenic side effects [43].

It is estimated that 378 000–756 000 needlestick injuries occur annually in the United States [44]. One response to this issue has been the Needlestick Safety and Prevention Act introduced by the Occupational Safety and Health Administration in 2001 [45]. Passed as a response to the continued prevalence of infectious disease transmission via needlestick injury in the health-care work-place, this legislation outlined the responsibility of employers to identify, evaluate and implement safer medical devices with the aim of decreasing needlestick and sharps injuries. Strategies introduced in accordance with these responsibilities included the elimination of needle recapping and the use of safer needle devices, the use of sharps collection boxes, gloves and personal protective gear, as well as universal precautions. As a result of these strategies needlestick injuries have declined in the United States from an estimated 1 million exposures per year in 1996 to 385 000 per year in 2000 [46]. In spite of this apparent success, the incidence of needlestick injury is high.

INTRANASAL MEDICATION ADMINISTRATION

The administration of medication via non-parenteral routes is another means of reducing occupational hazard for health-care workers by reducing risk of needlestick injury. Intranasal medication administration has been investigated widely for a broad range of pharmacotherapies in emergency medicine, including fentanyl for pain relief [47], metoclopramide for nausea [48] and midazolam for seizure treatment [49]. A full list of medications studied for i.n. administration has been reported previously [2].

Nasal administration is attractive for several reasons. Drug administration is simple and convenient, without the requirement for needles. This reduces the risk of needlestick injuries to care-givers, and reduces discomfort to patients. Delivery of medication does not require sterile or technologically advanced equipment, and nasal passages are easily accessible.

The nose has an extensive absorptive surface with considerable blood flow. This allows rapid and thorough drug absorption via the bloodstream and cerebral spinal fluid [50,51]. Absorption rates and plasma concentrations are comparable for i.n. and i.v. administration [50].

Nasal absorption is dependent upon several variables, including drug formula, anatomy and physiology and medication characteristics that influence drug bioavailability (molecular size, pH, concentration/volume, formulation vehicle) [51]. It is recommended that less than 1 ml be administered into each nares to avoid excess volumes escaping the nasal passage [51]. Nasal mucosal

destruction and excess mucous and blood secretions can inhibit drug absorption and render the medication less effective [51].

Maximal surface area coverage of the nasal passages achieves optimal drug absorption. This is achieved by distribution between two nostrils and the use of atomized drug delivery systems. Compared with drops and spray methods, atomization of the drug for i.n. administration, using commercial equipment such as the mucosal atomization device (MAD®, Wolfe Tory Medical Inc., Salt Lake City, UT, USA), results in superior surface area coverage [51,52].

THE EVIDENCE REGARDING INTRANASAL NALOXONE

As a strategy to reduce BBV transmission, researchers have sought alternative routes for administration of naloxone, in particular non-invasive methods. Investigation of the oral [53] and conjunctival routes [54] have been unsuccessful. Hussain and colleagues were the first to report investigation of naloxone for i.n. administration [8] in comparison to i.v. administration. They found the i.n. route to have similar pharmacokinetics to the i.v. route with 100% bioavailability, a half-life duration of 40–45 minutes and peak plasma concentrations within 3 minutes [8].

Detection of opioid dependence has been demonstrated in two smaller studies after i.n. naloxone administration [6,7]. The first study, by Loimer *et al.* [6], involved 30 patients (22 opiate-dependent and eight controls). Opiate-dependent participants demonstrated a significant increase in withdrawal distress and pupillary dilation after 1 mg naloxone by i.n. administration, and the effect peaked at 10 minutes after treatment. No response of withdrawal was observed in control subjects.

In a study of 17 opiate-dependent volunteers [7] the efficacy of i.n. naloxone was compared with alternative routes (i.m. and i.v.) by examination of the severity of withdrawal symptoms and pupillary responses. Subjects were divided randomly into two treatment groups: (i) i.v. versus i.m., seven subjects; or (ii) i.n. versus i.v., 10 subjects. Intranasal naloxone was shown to be as effective as the i.v. route, with similar responses for severity of withdrawal symptoms (peak response at 5 minutes) and pupillary reaction in opioid addicts. Response to naloxone administered by the i.m. route was delayed in comparison to both the i.n. and i.v. routes.

These two studies [6,7], performed in non-emergency settings, provided evidence that naloxone administered intranasally precipitated abstinence symptoms in opioid-dependent subjects. Naloxone was found to be absorbed rapidly from the nasal cavity, and the authors recommended its use in emergency medicine.

TREATING OPIOID OVERDOSE EMERGENCIES USING INTRANASAL NALOXONE

There is increasing evidence that the i.n. route may be useful for the administration of naloxone in cases of opioid overdose. Several case series [2,3,5,9] have reported use of i.n. naloxone for suspected opiate overdose in both pre-hospital and hospital settings. Its use was reported first by Barton *et al.* [3] for the management of heroin overdose in a pre-hospital setting in Denver, USA [3]. Using a formulation of 1 mg/ml/nostril, 30 patients were given i.n. naloxone by atomization. Eleven (36.7%) patients responded to naloxone therapy (i.v. or i.n.). An average response time of 3.4 minutes was observed, and the majority (10 of 11 patients) responded to i.n. naloxone alone; i.v. access was not required for seven (64%) patients. In that study, patients encountered by paramedics with altered mental status (AMS), 'found down' (FD) (e.g. collapsed at the roadside) or with suspected heroin overdose (OD) were initially administered 2 mg of naloxone using MAD®. Of these, one patient in the AMS group (9%, one of 11), no patient in the FD group (0%, none of seven) and 10 patients in the OD group (10 of 12, 83%) responded to naloxone.

A larger case series was reported by Barton *et al.* in 2005. That study included 95 patients who received naloxone for AMS, being FD or suspected heroin overdose in a 6-month period [2]. All patients received 2 mg naloxone i.n., followed by i.v. naloxone. Approximately half the study participants (52 of 95 patients) responded to naloxone, of whom 43 (83%) responded to i.n. naloxone alone. As described for the earlier study [3], patients with AMS, FD or OD were eligible for study inclusion. Consequently, naloxone was administered to a large proportion of non-opioid overdoses or alternate clinical conditions.

More recently a before-and-after case study of 154 patients [104 i.v. (before) and 50 i.n. (after)] was reported [9]. More patients in the intranasal group received a second dose of naloxone (18% i.v. versus 34% i.n., $P = 0.05$), and time to adequate clinical response was delayed for this group (13 versus 8 minutes, $P = 0.02$).

Use of i.n. naloxone in a hospital setting has been reported for patients who presented to an emergency department [5]. This was a small informal study of six patients with suspected heroin overdose who were administered i.n. naloxone by syringe drops using various doses (0.8–2 mg). Heroin reversal was achieved for all patients within 2 minutes. There was no comparative treatment option for these cases.

One prospective unblinded randomized study has examined the effectiveness and safety of i.n. naloxone in comparison to i.m. naloxone for the treatment of patients with suspected heroin overdose [4]. One hundred and

fifty-five unrousable patients with inadequate respirations were administered 2 mg naloxone by paramedics using either the i.m. (71) or i.n. (84) route [4]. In Australia at the time of the study, naloxone was available only in a preparation of 0.4 mg/ml, resulting in an i.n. volume of 5 ml (2 mg dose)—far in excess of expert recommendations for nasal administration (less than 1 ml per nostril) [51]. Patients who received i.n. naloxone were more likely to require a second dose (i.m. 13%, versus i.n. 26%). Adequate spontaneous ventilation was quicker in the i.m. group [5 minutes (95% confidence interval 4–6 minutes) versus 7 minutes (95% confidence interval 6–8 minutes), $P = 0.006$]; however, time to adequate conscious state was not significantly different between the two groups. Withdrawal symptoms were more common for the subjects who received i.m. naloxone [21% (i.m.) versus 12% (i.n.)].

A summary effect size cannot be calculated because the outcomes and study designs used in these investigations are too diverse.

LIMITATIONS OF EVIDENCE

Research in this field has not been extensive. Several competing issues challenge robust study designs for research conducted in emergency settings. Recently, Clarke *et al.* [55] highlighted the difficulties in conducting randomized controlled clinical trials investigating naloxone for opioid poisoning. First, the majority of patients who receive naloxone in the pre-hospital setting are unconscious and are therefore incapable of providing informed consent for participation. Research has shown that the processes for obtaining exemption of informed consent from human research committees are both costly and timely [56]. Secondly, the nature of illness demands swift administration of life-saving health-care measures, including respiratory support and drug administration. Treatment by different modes in combination, that would be required for a blinded study, would not be efficient or safe. Thirdly, the majority of reporting required for data collection is reliant upon accurate and precise documentation by paramedics. Data collected in this format may be inaccurate and biased. Finally, serious adverse outcomes are rare after naloxone therapy [57]. For randomized controlled trials where the outcome of interest is rare, prohibitively large numbers are required to achieve sufficient power.

Despite this, a recent report [1] has suggested that while the evidence regarding i.n. naloxone compared to i.v. and i.m. routes is weak and conflicting, it appears that it is safe and has significant efficacy in reversing opiate overdose. There have been no reports of any serious adverse events during i.n. naloxone administration.

THE CURRENT PLACE OF INTRANASAL NALOXONE IN TREATMENT

Treatment of heroin overdose by paramedics has proved to be safe and effective [13,29,58,59]. In some regions, administration of naloxone using the i.n. route by paramedics for suspected heroin overdose has been introduced [2,9], but to our knowledge its use is not widespread. At this stage, universal introduction in paramedic protocols may be limited by the absence of strong evidence that i.n. naloxone is superior to or equally effective as injectable forms. Further research is needed to investigate alternative naloxone preparations (absorption, concentration, dosage) that confirm effectiveness, adverse event profiling and clinical utility.

Compounding the lack of confirmatory evidence, administration by devices currently available are not simple to use. Available solutions are manufactured and stored in vials. The medication is extracted using a needle and syringe. This level of complexity may be too advanced for use by non-health-care trained personnel. Also, current formulations of naloxone are not ideal for nasal administration. As mentioned previously, volume should not exceed 1 ml per nostril [51]. In Australia, naloxone is available either as a prefilled Min-I-Jet syringe (CSL Ltd., Victoria, Australia) (0.8 mg/2 ml, 2 mg/5 ml) or ampoule (400 µg/1 ml). Neither preparation is suitable for nasal administration.

THE POTENTIAL FUTURE PLACE OF INTRANASAL NALOXONE

Reversal of heroin overdose could be expedited with bystander response in the form of peer-administered naloxone. Many heroin users have witnessed overdose by others [60,61]. The introduction of programmes for peer-administered naloxone, along with appropriate first aid training (heroin overdose prevention, recognition of signs and symptoms and management strategies), has been introduced successfully in some areas [31,34,62,63]. There is considerable debate in the literature regarding the efficacy and safety of peer-administered naloxone. Opponents to such programmes have raised concerns, including that heroin users may perceive such programmes as support and acceptance that drug use is condoned, that drug users may engage in more risky behaviour if the antidote is accessible, the short half-life of naloxone and concerns of re-sedation, shelf life and stability of naloxone, polydrug use, solitary heroin use, administration by intoxicated peers and undermining of other preventative strategies, including calling for an ambulance [33,35,64–68]. There are also medico–legal impedients in that the drug is most likely to be administered by a third party, compromising the patient and prescriber [35,67]. Treatment of acute life-

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