Table 2

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Miller *et al* 1995 USA	In-hospital cardiac arrest, patients in arrest after initial ACLS steps, patients with poisoning, minors, pregnancy excluded, 62 patients included;Pilot study of 5 g MgSO4 administration and ACLS (n = 29) versus standard ACLS (n = 33)	Pilot study	Survival to discharge between two groups Resuscitation or return of spontaneous circulation	1 patient in each group survived 34% (3/33) in patients with ACLS and Magnesium versus 21% (6/29) only ACLS;p = 0.17	Not a randomised controlled, blinded study, pilot study In-hospital witnessed arrests, all rhythms included Small sample size
Fatovich *et al* 1997 Australia	All victims of out-of-hospital cardiac arrest eligible for inclusion, excluded if dead, not receiving CPR, resuscitated, arrest due to non-cardiac etiology; Prospective randomised double blind placebo controlled trial using high dose 5 g of MgSo4 (31 patients)and placebo936 patients)	Prospective randomised double blind placebo controlled trial	ROSC Survival to leave ED Survival to leave hospital	23%(Mg) and 22%(no Mg) 13% (Mg)vs 11%(no Mg) 1 patient (Mg)	Out-of-hospital arrests, magnesium administered only when in hospital, different rhythms included Low powered study, no mention of randomisation method
Thel *et al* 1997 USA	All patients greater than 18 yrs, in-patient in the hospital treated for cardiac arrest;Randomised double-blind study of 2 g magesium sulphate bolus followed by infusion of 2 g/24 hours (n = 76) versus placebo (n = 80) in hospital in-patients, excluded emergency, prehospital patients with cardiac arrest, diferent rhythms included, end points of ROSC, for at least 1 hour.	Randomised controlled double-blind study	Difference in ROSC 24 hr survival survival to discharge Karnofsky performance index	54% in those who had Magnesium, 60% no Magnesium,p = 0.44 43(Mg) vs 50%(no Mg) p = 0.41 21 vs 21% p = 0.98 Higher in Mg group	Hospital in-patients and witnessed cardiac arrests, emergency and prehospital excluded, all rhythms included Low powered study, no allocation concealment explained, at the time of arrest most patients were very ill, in ICU and with malignant diseases, time of administration not measured, low dose of magnesium given.
Allegra 2001 USA	All patients with non-traumatic cardiac arrest greater than 18 and had VF refractory to 3 electroshocks in prehospital set-up. Total of 116 patients, 58 Mg/58 placebo, enrolled between 1992 and 1996. 109 available for analysis.	Prospective double blind, placebo controlled multi-center prehospital clinical trial;58 received magnesium and 58 placebo	time to study drug administration ROSC Admission discharge	25.5 min for magnesium group, 30.4 for placebo group placebo 18.5 vs Mg 25.5%, P = 0.38 16.7 (placebo)vs 16.4%(Mg) P = 1.0 placebo 3.7% vs Mg 3.6%, P = 1.0	Time of administration of study drug greater than 25 mins, low dose of magnesium administered, low powered study. Study closed prematurely as it became difficult to enroll patients when Magnesium became class IIB agent in AHA guidelines for VF treatment
T B Hassan, C Jagger, D B Barnett 2002 UK	Patients in Cardiac Arrest with refractory or recurrent VF treated in the prehospital phase by the county emergency medical services and/or in the A&E department. 52 given Mg, 53 given placebo.	A randomised, double blind, placebo controlled trial	ROSC Patients alive to discharge Odds Ratio for ROSC in patients treated with Mg versus placebo	17%(Mg) and 13% (placebo) (CI-10% to +18%) 4%(Mg) and 2% (placebo) (CI −7% to +11%) 1.69 (0.54 to 5.30)	Possible that a type II error occurred, dose of magnesium given during CA may have been inadequate. Individual factors such as the incidence of bystander CPR, the response time to the first defibrillatory shock, protocol violations and even the aggressiveness of care provided in hospital both within the A&E department and particularly on the ICU can have major influences. Study population is small, response time could have been a significant factor in magnesium's seeming lack of efficacy in treating refractory VF in this study population

Thel MC, Armstrong AL, McNulty SE, *et al*. Randomized trial of magnesium in in-hospital cardiac arrest. *Lancet* 1997 Nov 1;**350**(9087):1272–6.
Allegra J, Lavery R, Cody R, *et al*. Magnesium sufate in the treatment of refractory venticular fibrillation in the prehospital setting. *Resuscitation* 2001 Jun;**49**(3): 245–9.
Hassan TB, Jagger C, Barnett DB. A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation. *Emergency Medicine Journal* 2002 Jan;**19**(1):57–62.

Intranasal naloxone in suspected opioid overdose

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Abstract
A short cut review was carried out to establish whether intransasal naloxone is effective in suspected opiate overdose. 596 papers were screened, of which eight presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. The clinical bottom line is that it is likely that intranasal Naloxone is a safe and effective first line prehospital intervention in reversing the effects of an Opioid overdose and helping to reduce the risk of needle stick injury. A large, well conducted trial into it's usage is however required to confirm this.

Three part question
In a [patient with a suspected opioid overdose] is the [intranasal administration of Naloxone] a safe and effective method of [reversing the effects of the overdose]

Clinical scenario
A 25 year old male is brought into the emergency department by ambulance with a history of respiratory arrest following a suspected Opioid overdose. One of the paramedics describes struggling and failing to achieve peripheral venous access,

Table 3

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Hussain *et al*, 1984, USA	Male rats approximately 240 g, anaesthetised with Phenobarbital, receiving 30 mcg radiolabelled naloxone either IN via micropipette (n = 3) or IV (n = 3)	Animal study, Controlled Trial	Bioavailability of naloxone based on plasma concentrations from arterial sampling Half life of Naloxone Time at which peak plasma levels occurred	Both methods show 100% bioavailability. Half life same IV and IN. Peak plasma levels of IN occurred within 3 mins	No mention of ethical approval, could be considered ethically unjustifiable. Results may not be reproducible in humans
Lorimer *et al*, 1992, Pakistan	30 patients, 22 male opiate dependent and 8 male controls. Each receiving 1 mg naloxone (1 mg/400 μL) via nasal spray.	Controlled Clinical Trial	Series of measurements from 0 to 30 mins of; Severity of withdrawal symptoms (Modified rating score) Pulse and BP Pupillary Response	No difference between groups at baseline, significant changes between groups and within group opiate dependent group from 1–30 mins. (P<0.01–<0.05) No statistically significant changes within or between groups. No change in control group. Opiate dependent group more constricted at baseline and had dilated significantly by 10 mins (P<0.01)	No mention of ethical approval; Small numbers
Lorimer *et al*, 1994, Pakistan	17 male opiate dependent patients. Given 1 mg IV Naloxone, being recommenced on Opium then given a further 1 mg Naloxone IM (n = 7) or IN (1 mg/400 μL) via nasal spray (n = 10)	Randomised Controlled Trial	Series of measurements from 0 to 180 mins of; Severity of withdrawal symptoms (Objective Opiate Withdrawal Scale) Vital Signs (Pulse/BP) Pupillary Response	Significant changes from baseline seen at 1 min IV, 5 min IN, 15 min IM. Significant increase in size seen at 5 min in IV and IN groups. No change seen in IM group No significant change seen after any route of administration	No mention of ethical approval; Small, unblinded study; Method of randomisation not stated; Inadequate basic data reporting
Kelly *et al.* 2002 Australia	6 patients with acute heroin OD treated in the Emergency Department with IN Naloxone 0.8 to 2 mg	Case Series	Time to return of adequate spontaneous respiration	All patients responded within 2 minutes	No mention of ethical approval; Very small numbers; Definition of acute heroin OD/ baseline obs. not stated; Concentration of Naloxone used and administrative instrument not stated; Dose of Naloxone not standardised; Clinical response not well defined
Barton *et al*, 2002, USA	30 patients presenting pre-hospital with Altered Mental Status (AMS) n = 11, Found Down (FD) n = 7 or Suspected Opiate OD) (OD) n = 12. Given 2 mg (1 mg/ml) IN Naloxone via atomizer, followed by IV rescue dose if required.	Case Series	Response to Naloxone by any route Response to IN Naloxone Need for and response to rescue IV Naloxone (given if no response to IN by the time a secure airway/IV) Number of IV attempts that could be avoided	37% (n = 11) 10 patients (91% of total responders) with average response rate of 3.4 min One patient responded to IV and not IN (has epistaxis) 91% of all Naloxone responders did so with IN alone. 64% of all patients did not require IV placement.	Small numbers, Uncontrolled; Response not clinically defined; Study population appear to be part of the population studied in the 2005 Barton E D. paper
Barton ED *et al* 2005 USA	95 Patients presenting pre-hospital with Altered Mental Status (AMS) n = 40, Found Down (FD) n = 20 or Suspected Opiate OD (OD) n = 38. (NB 3 patients listed in 2 categories) Given 2 mg (1 mg/ml) IN Naloxone via atomizer, followed by IV rescue dose if no response to IN by the time a secure airway/IV established.	Case Series	Response to Naloxone by any route (Response = "a significant improvement in consciousness") Response to IN Naloxone Need for further Naloxone following initial response to IN (due to recurrent somnolence) Time from initial patient contact to response Time from drug administration to response Nasal Abnormalities	52 patients 43 patients (83% of all Naloxone responders) 7 Patients 9.9 (+/− 4.4SD) Median 3.0 with IN, 2.8 (+/−7.6SD) Median 10 with IV 4.2 (+/−2.7SD) Median 3.0 with IN, 3.7 (+/−2.3SD) Median 3.0 with IV 5 of the 9 patients reported to have responded to IV and not IN	Small numbers; No baseline Obs; Clinical response not well defined; 4 of the 9 patients reported to have responded to IV and not IN, received the IN dose <4 mins after the IN dose, allowing limited time for the IN dose to take effect. Potential conflict of interest declared (one of authors is Vice President and Medical Director of company supplying the atomizer device)

Table 3 Continued.

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Kelly *et al*, 2005, Australia	155 patients with suspected opiate OD who were un-rousable with RR<10. Randomised to receive 2 mg Naloxone IM (n=71) or IN (0.4 mg/ml) via atomizer (n=84) pre-hospital.	Randomised Controlled Trial.	Time to regain RR>10 Patients with spontaneous resps at 8 min Patients with GCS >11 at 8 min Patients requiring rescue Naloxone Patients in IN group requiring additional therapy. Adverse events	Faster in IM group (mean 6 min vs. 8 min, P=0.006) Greater in IM group (82% vs. 63%, P=0.0163) No statistical difference between groups. (72% IM vs. 57%IN, P=0.0829) No statistical difference between groups. (13%IM vs. 26%IN, P=0.0558) 26% More agitation/irritation in IM group (13% vs. 2%, P=0.0278)	Unblinded study; Adequate sample size not achieved; Statistics not based on intention to treat (3 patients excluded because of technical problems with nasal administration); GCS used in non-trauma patients
Robertson *et al*, 2005, USA	154 patients with suspected narcotic overdose in the pre-hospital setting. 104 given IV and 50 IN Naloxone.	Retrospective Case Note Review (before and after introduction of IN Naloxone into pre-hospital protocols) (poster presentation)	Time from medication administration to Clinical Response (defined as increase in RR or GCS>6) Time from patient contact to Clinical Response Patients requiring rescue doses by same route Clinical Response (Defined as increase in RR or GCS>6)	Significantly longer in IN group (8.1 vs. 12.9 min, P=0.02) No significant difference in response times (20.3 IV vs. 20.7 min IN, P=0.9) No statistical difference (18% IV vs 34% IN, P=0.05.) NB. 3 patients in IN group required IM or IV rescue IV group 56%, IN Group 66%	Small study; No mention of ethical approval; Patient baseline obs not verified. Dose/Concentration of Naloxone and administrative instrument not verified. GCS of 6 and un-quantified rise in RR not clinically useful endpoints.

IN, intranasal; IV, intravenous

sustaining a needle stick injury in the process. The paramedic describes proceeding to administer a total of 800 mcg of Naloxone intramuscularly to which the patient's response has been slow. You wonder whether the administration of Naloxone intranasally, would have been effective in both reversing the effects of the overdose and eliminating the need to use needles in the prehospital environment in a patient at high risk of having both limited peripheral venous access and potentially contractible blood-borne viruses.

Search strategy

Medline 1966-11/2005 using Ovid Interface.

Embase 1980 to 2005 Week 53 using Ovid Interface.

Search details

[(exp ADMINISTRATION, INTRANASAL OR Intranasal$.mp. OR exp NOSE OR exp NASAL MUCOSA OR exp NASAL CAVITY OR Nasal.mp. OR Pernasal$.mp. OR Transnasal$.mp. or exp MUCOUS MEMBRANE or Transmucosal$.mp.) AND (Naloxone.mp. OR exp NALOXONE OR Narcan.mp. OR Nalone.mp OR Naloxon.mp OR Narcotic Antagonist$.mp. OR exp NARCOTIC ANTAGONISTS OR Opioid Antagonist$.mp. OR Opioid Receptor Antagonist$.mp. OR Opiate Antagonist$.mp. OR Opiate Receptor Antagonist$.mp.)] LIMIT to English Language.

Plus Google Search for Intranasal Naloxone.

Search outcome

280 papers were identified on Medline of which five were relevant and 416 papers were identified on Embase of which an additional 2 were relevant. One further relevant paper/poster presentation was identified on a Google Search.

Comments

The evidence from the above papers is weak and there are conflicting results regarding the efficacy of intranasal compared to iontravenous and intramuscular routes of Naloxone administration. It does seem, however, that intranasal Naloxone is safe and has significant efficacy in reversing the effects of an opioid overdose.

The intranasal route of administration may be a potentially useful first line intervention in managing Opioid OD in the community, as it reduces the need for needles to be used in an often hostile prehospital environment, in patients who are often poor candidates for peripheral venous cannulation and at increased risk of carrying blood-borne pathogens. The option of being able to administer rescue intravenous or intramuscular Naloxone, would however need to remain in place.

One problem with efficacy was highlighted in patients who didn't respond to intranasal Naloxone due to nasal abnormality (epistaxis/trauma/deformity/mucous). Other nasal pathology and prior use of intranasal drugs such as Cocaine could therefore potentially also lead to treatment failure.

At present Naloxone remains unlicenced for IN use and is not available in the UK at a concentration greater than 0.4 mg/ml.

► CLINICAL BOTTOM LINE

It is likely that intranasal Naloxone is a safe and effective first line prehospital intervention in reversing the effects of an Opioid overdose and helping to reduce the risk of needle stick injury. A large, well conducted trial into it's usage is however required.

Hussain A, Kimura R, Huang C-H, *et al*. Nasal Absorption of Naloxone and Buprenorphine in Rats *International Journal of Pharmaceutics* 1984;**21**(2):233–237.

Loimer N, Hofmann P, Chaudhry H R. Nasal Administration of Naloxone for Detection of Opiate Dependence. *Journal of Psychiatric Research* 1992 Jan;**26**(1):39–43.

Loimer N, Hofmann P, Chaudhry H R. Nasal Administration of Naloxone is as Effective as the Intravenous Route in Opiate Addicts. *International Journal of the Addictions* 1994 Apr;**29**(6):819–27.

Kelly A M, Koutsogiannis Z. Intranasal Naloxone for Life Threatening Opioid Overdose. *Emergency Medicine Journal* 2002;**19**(4);375.

Barton E D, Ramos J, Colwell C, *et al*. Intranasal Administration of Naloxone by Paramedics. *Prehospital Emergency Care* 2002 Jan–Mar;**6**(1):54–8.

Barton E D, Colwell C B, Wolff T, *et al*. Efficacy of Intranasal Naloxone as a Needleless Alternative for Treatment of Opioid Overdose in the Prehospital Setting. *Journal of Emergency Medicine* **29**(3);265–271.

Kelly A M, Kerr D, Dietze P, *et al*. Randomised Trial of Intranasal versus Intramuscular Naloxone in Prehospital Treatment For Suspected Opioid Overdose. *Medical Journal of Australia* 2005 Jan;**182**(1):24–7.

Robertson T M, Hendey G W, Stroh G, *et al*. Versus Intravenous Naloxone for Prehospital Narcotic Overdose. *Academic Emergency Medicine* 2005 May;**12**(5) suppl 1:166–167.

Table 4

Author, date, and, country	Patient group	Study type (level of evidence)	Outcomes	Key result	Study weakness
Holdgate A & Pollock T, 2004, UK.	448 patients taken from 5 prospective, double-blind, randomised control trials. Adults aged 16–79 who were diagnosed with acute renal/uretertic colic were randomised to receive either IV NSAID or IV Opiate. Patients in whom calculi could not be diagnosed; those who had already taken analgesics; those who passed the offending stone; and those with common CI's to NSAID's were excluded.	Meta-analysis Study 1: (Lehtonen at al, 1983) Indometacin Vs Pethidine Study 2: (Jonsson *et al*, 1987) Indomethacin Vs Oxycone/Papaverine Study 3: (Curry and Kelly, 1995) Tenoxicam Vs Pethidine Study 4: (Al-Sahlawi and Tawfik, 1996) Indomethacin Vs Aspirin Vs Pethidine Study 5: (Cordell *et al*, 1996) Ketorolac Vs Meperidine	Effectiveness (based on pain relief scores and/or reduction of Pain intensity scores 20–30 min after dministration of 1st dose of drug)	Study 1: Ind = Peth Study2: Ind=Oxy/Pap Study3: Ten = Peth Study 4: Ind > Asp (P=0.05), Peth > Asp (P=0.01), Ind = Peth Study 5: Ket > Mep (P<0.001) Study 1: Ind 21% Peth 26% Study 2: Ind 54% Oxy/Pap 73% Study 3: Ten 18% Peth 17% Study 4: Ind 4% Asp 26% Peth 0% Study 5: Ket 64% Mep 89% (p=0.04) Study 1: Ind 27% Peth 55% Study 2: Ind 60% Peth 73% Study 3: Ten 0% Peth 18% Study 4: Ind 4% Asp 0%, Peth 0% Study 5: Ket 37% Mep 55% (p=0.07)	Randomisation details were unclear in Studies 1, 2, and 4. Only Study 5 performed intention-to-treat analysis (NSAID was still more efficacious than Opiate at 30 min, P<0.001). Studies 1–4 lack statistical analysis of the differences in additional analgesia requirement & adverse effects between the various groups of drugs