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Washington University Emergency Medicine Journal Club
Intranasal Naloxone in the Treatment of Opiate Overdose

Vignette

It's a typical busy shift in TCC. Your attending is busy dealing with a 75 year old with transient hypotension and syncope that was upgraded to a level 1 trauma due to his forehead abrasion when a car pulls up to the trauma bay, dumps out a 24 year old male who is apneic, and drives away. As you get him into a room, you notice the pinpoint pupils, track marks covering all his extremities, and the burned spoon that falls out of his pocket. You order naloxone but unfortunately no one is able to insert a peripheral IV.

Using your expert ultrasound skills, you place a 22 gauge IV in his thumb and revive him. You spot your attending as you leave the room and let him know about your nice save. Instead of the "great job!" that you are expecting, he just asks "well why didn't you use a different route to administer the narcan?" Feeling discouraged, you make your way back to EM1 and spot Dr. Halcomb and Dr. Mullins in the hall. You go to ask them their opinion about giving narcan by a different route but notice that they are having a lively conversation about the Krebs cycle. Deciding you don't want any part of that, you go back to Dr. Cohn's office to do your own literature search.

PICO Question
Population: Adult patients with acute opiate overdose with respiratory depression and/or altered mental status
Intervention: Intranasal naloxone
Comparison: Intravenous, intramuscular, or subcutaneous naloxone
Outcome: Time from first contact or drug administration to significantly increased respiratory rate or improved mentation, need for rescue dose of naloxone, healthcare cost, duration of emergency department (ED) incidence of needlestick injury by providers.

Search Strategy

After quickly searching Google and pulling up a variety of entertaining pictures about heroin intoxication, you decide that Pubmed might be more useful. You enter a number of search terms including "narcan," "naloxone," "opiate," "heroin," "intranasal," "intramuscular," and "subcutaneous." You eventually simplify your search, entering "intranasal naloxone," (http://tinyurl.com/nztrfdb) resulting in 46 articles. You scan these and come up with the following 4 articles.

Article 1: Robertson TM, Hendey GW, Stroh G, Shalit M. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. Prehosp Emerg Care. 2009 Oct-Dec;13(4):512-5. Answer Key.

Article 2: Merlin MA, Saybolt M, Kapitanyan R, Alter SM, Jeges J, Liu J, Calabrese S, Rynn KO, Perritt R, Pryor PW 2nd. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. Am J Emerg Med. 2010 Mar;28(3): 296-303. Answer Key.

Article 3: Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Aust. 2005 Jan 3;182(1):24-7. Answer Key.

Article 4: Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009 Dec;104(12):2067-74. Answer Key.

Bottom Line

Opiate overdose remains a significant health problem in the US and elsewhere, with increasing overall rates of overdose and death related to overdose observed (Hall 1999, Preti 2002, Shah 2008, Bryant 2004). Naloxone remains the second most commonly administered antidote in the US (Wiegand 2012). While naloxone is typically administered either by intravenous (IV) or intramuscular (IM) injection, other potential routes of administration have been proposed, including nebulization (Baumann 2013, Tataris 2013), endotracheal injection (Tandberg 1982), and subcutaneous (SQ) injection (Wanger 1998). High rates of needlestick injuries have led some to propose avoiding IV, IM, and SQ naloxone administration, with many favoring intranasal (IN) administration as first-line treatment in the management of opiate overdose.

In addition to reducing the risk of percutaneous needlesticks among healthcare workers, IN naloxone administration has other potential benefits over other routes. Theoretically, naloxone should have 100% bioavailability through the nasal mucosa with a similar onset of action and similar half-life to IV administration. While rat studies have demonstrated such pharmacodynamics, a single human volunteer study showed poor bioavailability (4% vs. 35%) for the IN vs. the IV route (Dowling 2008); however, this study used a more dilute solution of naloxone than typically recommended (2 mg in 5 mL) and did not address the impact of IN naloxone in actual opiate overdose.

Robertson 2009, Merlin 2010

Two retrospective chart reviews were identified assessing the utility of IN versus IV naloxone in the prehospital setting. The study by Robertson demonstrated similar rates of clinical response (66% and 56% in the IN and IV groups, respectively) and similar mean time from patient contact to clinical response (20.3 vs. 20.7 minutes in the IN and IV groups, respectively). The study by Merlin demonstrated similar median increases in respiratory rate (RR) (4 vs. 6 breaths/minute) and Glasgow Coma Scale (GCS) (3 vs. 4) between the IN and IV groups.

Unfortunately, these studies suffered from several major methodological flaws. These were both retrospective chart reviews using prehospital records. Neither study reported on appropriate chart review methods, including abstractor training, use of standardized abstraction forms, blinding of abstractors to the study hypothesis, or assessment of interrater reliability. Additionally, there was no standardized or independent method used to assess outcomes such as respiratory rate, time elapsed, or the need for additional doses of naloxone, and no interrater reliability was assessed for these measurements. The study by Merlin assessed changes in RR and GCS over the course of the EMS encounter, but did not assess the duration of time over which these changes occurred. While the study results suggest that IN naloxone is as effective as IV naloxone, the poor methodological quality of the studies brings this conclusion into question.

Kelly 2005, Kerr 2009

Two randomized controlled trials were also identified, assessing IN versus IM naloxone in acute opiate overdose in the state of Victoria, Australia. The two studies were conducted by the same group, 4 years apart. In the first study, the IM group required less time from naloxone administration to achieve a respiratory rate of 10 breaths per minute than the IN group (mean 6 minutes vs. 8 minutes, $p = 0.006$), and was more likely to achieve a respiratory rate of 10 or more by 8 minutes after naloxone administration (82% vs. 63%, $p = 0.0163$). The IN group did have a lower rate of agitation/irritation (2% vs. 13%), and there was no statistically significant difference in the rates of minor adverse events. There was no difference in the need for rescue naloxone. The second study demonstrated similar rates of adequate response within 10 minutes of initial naloxone administration between the IN group and IM group (72.3% vs. 77.5%), as well as similar mean response times (8.0 minutes vs. 7.9 minutes). More patients in the IN group required rescue naloxone (18.1%) compared to the IM group (4.5%). There was no difference between the two groups with respect to minor adverse events, hospitalization rates, agitation/ violence, nausea/vomiting, or headache.

While these studies were randomized, the providers, patients, and outcome assessors were not blinded to treatment group; no sham or placebo treatments were given. As in the previous two studies, there was no standardized, objective, independent means of measuring time or respiratory rate, or of determining the need for rescue naloxone. The difference in outcomes between these two studies

was addressed by the authors, who conceded that the first study used a diluted solution of naloxone in the IN group, administering 5 mL via atomizer instead of the standard 1 mL in order to deliver 2 mg of naloxone (Wolfe 2004). As previously stated, this may lead to decreased bioavailability, likely due to the inability of the nasal mucosa to absorb such a large volume leading to a significant amount of medication being swallowed.

Consensus

Given the similar rates of minor adverse events in these four studies, and the low rate of major adverse events (one seizure in a patient receiving IM naloxone in the Kerr study), all three routes seem reasonably safe. Despite all of the authors' reported concerns over needlestick injury in healthcare workers administering IV and IM naloxone, there were no reported needlestick injuries in any of the studies. The current evidence suggests that IN naloxone is both safe and effective, though may require a rescue dose of naloxone be administered in many cases. The consensus among our group was that few would use IN naloxone as first-line therapy for opiate overdose, but that it would be viable alternative in certain circumstances (e.g. patients with difficult IV access, patients requiring extraction from vehicles).

In addition to healthcare provider administered IN naloxone, peer distribution of IN naloxone has been studies in the US (Doe-Simkins 2009). A survey of Australian heron users revealed strong support for the practice, and some groups have pushed for further research in this area (Lenton 2000, Lenton 2009) as well as the UK (Wright 2006). Potential problems with peer distribution include the medico-legal risk of prescribing medications that will most likely be administered to people other than those for whom they were prescribed, the cost of distributing a sufficient supply of naloxone to have significant impact on overdose morbidity and mortality, and failure of bystanders to contact EMS after administering naloxone, potentially leading to increased morbidity and mortality in cases of naloxone failure or overdose recrudescence (Darke 1997). Further research to address these concerns will likely be necessary before widespread implementation.