Narcan or Nar-can't: Tips and Tricks to Safely Reversing Opioid Toxicity

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ANNALS CASE

Your next patient is a 34-year-old man with a history of intravenous drug use who was brought in by emergency medical services. In the field, he had a respiratory rate of 5 breaths/min, decreased mental status, and pinpoint pupils, all of which significantly improved with out-of-hospital naloxone. He now has normal mental status and normal vital signs, and admits to intravenous fentanyl (or so he was told) use. After downing 3 hospital tuna salad sandwiches, he requests discharge.

Sound familiar? Well, it should. Drug overdose is now the leading cause of injury death in the United States, with frequency tripling from 1999 to 2014.[1] Illicit opioids contribute to the significant increase in opioid-associated deaths. The result: you have probably administered naloxone recently once, twice, or even dozens of times to reverse acute opioid overdoses. But what is the "standard" dose again? And how long do patients need to be observed? For something we do frequently, the lack of evidence-based dosing and observation times is troubling. Lucky for us, the recent publication by Scheuermeyer et al[2] examines the safety of an empiric emergency department (ED) protocol for the management of patients with presumed fentanyl intoxication. After primarily intravenous fentanyl use, the majority of patients were safely discharged after a 2-hour observation period.

NAR-CAN! BUT HOW MUCH?

Naloxone hydrochloride (Narcan) reverses opioid intoxication symptoms such as respiratory and central nervous system (CNS) depression. The typical ED starting dose seems to be 0.4 mg administered intravenously. Use of this dose, like all things in medicine, is well supported by multiple, large, randomized trials. Just kidding! It comes from the 1960s anesthesia literature as the dose needed to reverse excessive postoperative sedation in opioid-naive patients.[3] Decades later, changes in our patient population and the opioids they use have complicated naloxone dosing.

Common unknowns such as the opioid amount, type, and tolerance influence naloxone dose and time between doses. Unfortunately, a thin line separates improved respiratory rate and symptoms from acute iatrogenic withdrawal. Naloxone-induced opioid withdrawal is, to put it mildly, horrifically uncomfortable for patients. More important, it can also lead to bad outcomes by increasing circulating catecholamines, leading to hyperventilation, tachycardia, hypertension, acute respiratory distress syndrome, heart failure, and cardiac dysrhythmias![4-6] There is even evidence that ultrarapid opioid detoxification with naloxone is associated with death.[7]

Dosing Option 1: Sleeping Beauty Cocktail for Gentle Awakenings

Unfortunately, in patients with long-term opioid use, even the 0.4-mg typical starting dose can precipitate withdrawal symptoms.[8,9] This pathophysiology even extends to cancer patients with long-term opioid use for severe chronic pain. Clearly, no one wants to induce acute opioid withdrawal in a cancer patient. A gentler approach is needed whether the naloxone is given for diagnostic or therapeutic reasons. Dilute 0.4 mg of naloxone in 10 mL of normal saline solution to produce a solution of 0.04 mg/mL. Then administer it in 1-mL boluses, with the goal to improve the respiratory depression (respiratory rate >8 breaths/min). In patients receiving methadone, this gentler, "sleeping beauty" method of reversal can reverse respiratory and CNS depression, with a median dose requirement of just 0.08 mg.[10] The upsides: no angry, possibly aggressive patient with acute withdrawal (aka vomiting and

diarrhea-ing). And no risk of really bad patient outcomes associated with acute withdrawal! The downside is that these doses require more bedside vigilance to monitor for clinical efficacy.

Dosing Option 2: Waking the Giants

On the other hand, the synthetic opioids (eg, fentanyl, carfentanil) require increased amounts of naloxone for opioid reversal, and their prevalence is increasing. During periods of known fentanyl outbreaks, dosing as high as 12 mg of naloxone has been reported![11] Although it is universally acknowledged that patients may need escalating doses of naloxone to reverse the effects of opioid intoxication, there is no established best protocol. Some articles have suggested increasing the dose of naloxone every 2 to 3 minutes (from 0.5 to 2 mg, to 4 to 10 mg, and finally 15 mg).[12] Although unimproved CNS or respiratory depression after 2 naloxone doses may indicate other cause or cointoxicants, no response to a 15-mg dose of naloxone more definitively indicates another diagnosis. Anecdotally, some clinicians have doubled the dose of naloxone every 2 to 3 minutes (ie, 0.04 to 0.08 to 0.16 mg) until clinical response is achieved. More research needs to be conducted in this area, but, in summary, naloxone should be given in systematically increasing dosages up to 12 to 15 mg when synthetic opioid overdose is suspected.

Additionally, new routes of administration have made naloxone administration much easier, especially when venous access is unavailable or difficult to obtain.

Nebulized Naloxone

Nebulized naloxone (2 mg in 3 mL normal saline solution administered through a standard face mask) has been touted as an effective method to administer the appropriate dose of naloxone for a gentler awakening. The purported benefit is its exemplary titratability, or should we say self-titratability. Nebulized naloxone is gradually inhaled, in contrast to a single, rapid intravenous bolus. Once CNS depression improves enough, the patient can (and likely will) remove the face mask. All without the risk for precipitating withdrawal! It sounds brilliant and elegant in principle, but studies so far have shown contradicting outcomes, ranging from no improvement over placebo[13] to a reduced need for supplementation of oxygen and improvement in Glasgow Coma Scale score.[14] As such, if a clinically suspected opioid overdose is not responding to nebulized naloxone, intravenous naloxone should be given. Based on clinical experience, the practical downsides are that this treatment applies only to a very limited patient population, a patient with enough opioid-induced CNS or respiratory depression to warrant reversal, but not so much that he or she requires more immediate reversal. Additionally, these patients still need close monitoring to ensure that clinical symptoms improve…and someone needs to help keep the face mask in place.

Intranasal Naloxone

Intranasal naloxone, although more extensively studied in the out-of-hospital setting, can be useful in ED patients with difficult intravenous access who need immediate reversal. Typical administration is 1 mL of a solution of 1 mg/mL per naris, for a total dose of 2 mg. Out-of-hospital studies show an 83% response rate[15] and response rates similar to that of intravenous naloxone.[16] However, the similar rates of response observed in these studies could be related to the delay in obtaining intravenous access.[6] Potential downsides include difficult titration and unpredictable absorption, but data in rats describe a 100% bioavailability and half-life similar to that of intravenous naloxone.[17]

SO THE NAR-CAN WORKED…NOW WHAT?

Unfortunately, and perhaps predictably, there is no simple answer because many variables, including the duration of effect, the specific potency and type of opioid consumed, the administration route, coingestants, and the patient's underlying opioid tolerance (to name just a few), complicate the opioid's duration.

In one study of healthy patients sedated by opioids, a 0.4-mg dose of intravenous naloxone reversed the effects within 2 minutes. However, symptoms started to return after 15 to 30 minutes and completely returned within 45 minutes.[18] According to this information, it may be reasonable to discharge a patient without recurrence of symptoms after 1 hour of observation if you know that the opioid was short acting and pure. Studies have supported the safety of discharging patients after 1 hour of observation in the ED after use of heroin.[19] However, real life is never so straightforward.

One argument for prolonged observation is that adulteration of street drugs may prolong the opioid intoxication. Street heroin may include fentanyl, diphenhydramine, codeine, morphine, phenobarbital, and diazepam.[20] In addition, novel synthetic opioids (such as U-47700) have unpredictable or unknown pharmacokinetics.[21] Studies have shown recurrence of symptoms from opioid toxicity, requiring repeated reversal from naloxone up to 187 minutes after initial naloxone administration.[12] There are also regional variations in adulterants, making it difficult to

generalize one specific study result to all recreational drug users.

Route of Administration

The route of administration can change the duration of action. Different routes include nasal insufflation ("snorting"), smoking, and injection into the vein, into muscle, or underneath the skin ("skin popping"). Intravenous administration leads to an acute pharmacologic peak, whereas other routes result in more delayed effects or even unpredictable kinetics. Oral doses produce lower amounts of euphoria and the first-pass metabolism decreases bioavailability.[20] Opioids and anticholinergic medications are known to delay gut motility and absorption.

Currently, there is no clear answer to the question of ED length of observation. Factors that would increase index of suspicion for recrudescence of opioid intoxication include concern for adulterants, oral ingestion of medications, or use of long-acting opioids.

IS TESTING HELPFUL?

Screens for drugs of abuse will not add much to ED patient management. Naloxone administration is based solely on clinical presentation. Additionally, most standard screens for drugs of abuse test for morphine and its derivatives, but results will be negative with synthetic opioids such as methadone, fentanyl, or hydromorphone. If you think it's an opioid overdose, just treat!

BOTTOM LINE

Naloxone administration is nuanced. Start low and titrate to your patient's clinical symptoms.

Consider other methods of naloxone administration if an intravenous route is unavailable.

Safe observation time depends on the specific patient population.

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