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Cases from the Field

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Case presentation

Paramedics respond to the home of a 19 year-old female who is found by her mother unresponsive. She states that she saw her daughter 2 hours prior at dinner and the patient was normal at that time. Past medical history includes polycystic ovarian syndrome, chronic back and pelvic pain, and depression. The patient is taking Motrin (ibuprofen), Norco (hydrocodone/acetaminophen), Elavil (amitriptyline) and Paxil (paroxetine). She smokes tobacco, but is not known to use illicit drugs or engage in heavy alcohol use.

On evaluation, the patient is supine in bed with eyes closed, nonverbal and has minimal withdrawal to noxious stimuli. Her vital signs: RR 4 breaths per minute with shallow tidal volumes; HR 50; BP 90/60 mmHg; oxygen saturation 78%. Pupils are mid-sized and sluggish, skin is warm and dry. She has no aevidence of trauma or puncture wounds to the skin.

Paramedics initiate bag-mask ventilation at 12 breaths per minute with 100% oxygen, her heart rate increases to 70 and her oxygen saturation to 100%. Her blood pressure is now 100/60 mmHg and blood glucose level is 112 mg/dl.

What is the most likely etiology of this patients altered mental status?

This patient presents with acute altered mental status (AMS), for which there are many causes. The mnemonic AEIOUTIPS is often used to recall the common etiologies including: **A**lcohol, **E**pilepsy, **I**nsulin, **O**verdose, **U**remia, **T**rauma, **I**nfection, **P**sychiatric and **P**oisoning, **S**troke and **S**hock. This patient's history, as reported by her mother, as well as her medications and physical exam help to narrow the possible etiologies. There is no sign of trauma, no indication of recent illness, history of renal disease, known epilepsy or stigmata of recent seizure (e.g. tongue laceration or loss of urine). Her blood glucose is normal and her heart rate and blood pressure normalize once the hypoxia is corrected, so hypoglycemia and shock are not present. Her age, comorbidities, and presentation argue against stroke as a likely etiology. The most likely cause of acute AMS in this young female is toxic ingestion. Her predominant respiratory depression suggest opioid toxicity is at least one component, if not the sole etiology for her condition. There remains possibility for a mixed ingestion, particularly, although not suggested in this case, if intentional overdose is a concern. Her use of Amitriptyline and a selective serotonin reuptake inhibitor (SSRI) is important information to relay at transfer of care, because overdose of these medications require further emergency department management, beyond the scope of this discussion.

Patients with opioid toxicity present with altered level of consciousness and respiratory depression. The classic triad of the opioid toxidrome is depressed level of consciousness, respiratory depression and pupillary miosis (constriction). However, miosis is not a reliable finding. Some opiates such as morphine usually present with mid-sized or dilated pupils. Co-ingestions are possible, which can alter pupillary findings and, in some cases, pupillary constriction may be overcome by hypoxia-induced mydriasis (dilation). The most specific sign of opioid toxicity is respiratory depression, both slow rate <8 breaths per minute and reduced tidal volumes. Opioids exert these effects by binding to opioid receptors in the brain causing inhibition of neurotransmission in the central and peripheral nervous system.

Needle tracks are sometimes seen on physical exam, depending on the route of abuse. With potent ingestions, needles have been found still in the vein. However, in this case, the most likely route of ingestion is oral. The patient is taking the prescription opiate Norco, a combination of acetaminophen and hydrocodone.

What are the contributing factors and potential exposures that result in this toxidrome?

Rates of opioid prescriptions and opioid diversion and abuse have been rising in the United States (U.S.), such that opioid abuse is recognized as a major public health crisis. For example, prescriptions for hydrocodone increased by 73% and, accordingly, abuse more than doubled from 2004 to 2011. In 2014, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. Opioids reduce pain by binding to specific receptors in the brain, which both decrease patient's perception of pain and stimulate reward regions causing the euphoric effects. Patients develop an increased dependence and a tolerance for the medication over time, which can result in an increasingly higher amount of medication required to achieve pain control. Patients also develop a learned association between the drug and relief that can lead to inappropriate use and addiction. This combination of factors may lead patients to seek alternate sources of opioids, including illicit drug purchases.

FIGURE. Photo of four counterfeit Norco "M367" tablets obtained from patient 6 during the investigation of a counterfeit Norco poisoning outbreak — San Francisco Bay Area, California, 2016

Currently, there is a national epidemic of opioid overdose deaths and addictions. Opioid addiction can occur with both short- and long-term use. Although anyone is at risk, adolescence and depression, such as in this patient, increase the risk for addiction. Deaths from pharmaceutical opioids are on the rise with more than one third of the 44,000 opioid-related deaths in 2013 attributable to prescription opioids and heroin abuse causing 19%.

Increasing criminal activity and production of increasingly potent synthetic opioids has fueled the rise in opioid abuse. In California, there have been multiple recent deaths linked to fentanyl-contaminated counterfeit Norco. Also known as "China White," this illicit form of fentanyl was first discovered in the bodies of two overdose victims in Orange County in 1979. It is a synthetic opioid analgesic that has 100 times the potency of morphine. It is back on the rise in California and local production was discovered in April 2016 in a warehouse in Orange County.

There are many natural and synthetic opioid antagonists that can result in opioid toxicity. The more common pharmaceutical and illicit opioids are included in the table below, along with their potency relative to morphine, time of onset, duration of action, and ability for detection on urine drug screening in the emergency department.

What are the implications for field management?

The predominate cause of morbidity and mortality in opioid overdose is respiratory depression. Therefore, the initial management should focus on establishing a patent airway and assisting ventilations when indicated. The patient's respiratory rate of 4, along with hypoxia and bradycardia, is a clear indication for immediate bag mask ventilation. Naloxone (Narcan) is the reversal agent and should be administered to all patients with suspected opioid toxicity with respiratory depression. The initial dose of 0.8-2mg may be administered to adults and 0.1 mg/kg (2 mg maximum single dose) for children by intranasal, intramuscular or intravenous routes. However, patients who ingest potent synthetic opioids may require higher doses and frequent repeat doses of naloxone.

Patients may not be aware that they have ingested these opioids, believing that they have purchased Norco or other pharmaceutical opioids. Providers should maintain a high degree of suspicion for opioid toxicity in patients with stigmata of opioid abuse including past medical history, medications available to the patient, presence of track marks, and exam findings consistent with the opioid toxidrome.

Naloxone has an onset of 2 minutes when given IV and 5 minutes by other routes so it is important to provide respiratory support to the patient until their condition improves. Even if the patient responds, he/she should be monitored closely for deterioration because the duration of action is short compared to most opioids (approximately 1 hour), but may be shorter depending on the severity of the ingestion. In the table above

Pharmacology of Common Opioid Agonists

Opioid	Potency	Onset (min)	Duration (hrs)*	Urine Drug Screen +
Morphine	Reference	30-45	3-4	Yes
Codeine	0.1x	45-60	4-6	Yes
Hydrocodone	1x	45-60	4-6	Variable
Oxycodone	1.5x	45-60	4-6	Variable
Methadone	4x	60-90	6-12	Variable
Hydromorphone	5x	30	2-3	Variable
Fentanyl	100x	10-20	1-2	Variable
Heroin (IV)	2x	1-2	1-2	Yes

*For normal dosage. Duration will be longer at higher doses.

shows the duration of action of common opioids, many which exceed the duration of naloxone even at normal/low doses (shaded in dark gray). At higher doses, even short acting opiates such as fentanyl can have prolonged duration. This implies that, when the naloxone wears off, the effects of the opioid can recur resulting in respiratory depression hours after the naloxone was given.

What is the appropriate disposition for the patient and potential challenges?

Given the duration of action of the ingested opioid will be longer than that of naloxone, the patient cannot be safely left on scene. All patients with opioid toxicity requiring naloxone reversal must be transported to the emergency department for observation and additional treatment as indicated. If the patient is alert after treatment and refusing transport, the first step should be to engage the patient in a discussion about the risks, hopefully with the help of friends or family when available. Online medical control personnel can also help communicate with the patient. Patient communication and verbal de-escalation is often sufficient to allow safe transport of the patient to the hospital. However, if the patient continues to refuse despite other efforts, law enforcement should be involved for crew safety. The patient with opioid toxicity does not have capacity to refuse care; their initial presentation of altered mental status is only temporarily improved by the initial field treatment.

Case conclusion

Paramedics recognize opioid toxicity and continue to ventilate the patient while an IV is established. They administer naloxone 2mg IV. The patient's respiratory rate improves to 10 breaths per minute, but she remains lethargic requiring frequent stimulation. The paramedics discuss with online medical control and administer a second dose of naloxone 2mg IV, after which the patient further improves. She states she took Norco for her pain, which she recently bought on the street. She denies suicidal intent and refuses transport to the hospital, "I'm fine". With the help of the patient's mother, the paramedics explain to the patient the seriousness of her condition and the risk of respiratory arrest should she stay at home without additional medical care. En route to the hospital she becomes unresponsive and bradypneic, requiring assisted ventilations and a third dose of naloxone 2mg IV is administered.

Take Home Points

- Opioid poisonings and overdose are on the rise.
- Recognition of a clinical situation consistent with opioid poisoning or overdose is critical to prevent adverse outcomes including death.
- Naloxone is an effective antidote but may not last long enough in a patient's system to prevent additional complications from the ingestion/overdose.
- Patients often do not recognize the danger they face from opioids, therefore all patients with recognized opioid poisoning/overdose require transport to the emergency department for further evaluation and management.

References

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