The Toxic Emergency - Is the Antidote Worse than the Disease?

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A 47 year-old man was found unconscious and cyanotic in his automobile by his family members. He had no history of suicide or drug abuse and it seemed impossible to his family that either of these were a factor. The patient does have a history of chronic back pain for which he uses a lidocaine patch and oxycodone sustained-release tablets. According to his family he has had increasing pain over the past several weeks and visited his physician two days ago.

The family lived near the hospital and drove the patient themselves rather than activating EMS. In the ED, his vitals signs were: blood pressure, 100/60 mm Hg; pulse, 100/min, respiratory rate, 4/min and shallow. A pulse oximeter revealed an oxygen saturation of 62% and a fingerstick glucose measurement was 120 mg/dL. After receiving supplemental oxygen by facemask his cyanosis resolved and his oxygen saturation rose to 98%. An intravenous line was inserted through which the patient received 0.4 mg of naloxone. Following this the patient awoke but was agitated and his blood pressure rose to 180/110 mm Hg. He complained of chest pain and dyspnea and his oxygen saturation declined to 85% over the next 10 minutes, though his level of consciousness remained normal and his respiratory rate rose to 24/min.

What is the brief differential diagnosis?

Certainly this case is consistent with either a cardiac or neurologic etiology, and these should be rapidly considered and assessed. The presence of the patient in an automobile, with the engine running or not (out of gas) should suggest carbon monoxide poisoning, though cyanosis would be highly uncommon. Methemoglobinemia is not supported by the patient's history and cyanosis due to the presence of methemoglobinemia should not improve with supplemental oxygen. The recent change in the patient's medication regimen is a red flag that a drug error may have occurred. Although lidocaine toxicity may produce altered mental status and respiratory depression, the lidocaine patch used properly results in negligible serum lidocaine concentrations. The response to naloxone essentially confirms the diagnosis of opioid toxicity, and the sympathomimetic state following naloxone suggests either opioid withdrawal or concomitant intoxication with a stimulant such as cocaine or amphetamine.

Is naloxone safe?

There is little question that naloxone is effective at doing what it is supposed to do…..reversing the effects of an opioid, such as oxycodone, heroin or methadone, at the opioid receptor in the brain. Naloxone is highly potent at binding the opioid receptor and has excellent penetration through the blood brain barrier [Oldendorf 1972]. However, efficacy must not be viewed in a vacuum, but rather in light of the entire clinical effect, which includes safety issues. That naloxone has been administered in massive doses (literally grams) to certain patients, such as those with spinal cord injury, with no perceptible significant adverse effect highlights the inherent safety of the drug. However, in patients who are dependent on the agonist effects of an opioid, naloxone may produce a withdrawal syndrome. It has been said that opioid withdrawal is not life-threatening or of major clinical significance, particularly when compared with the withdrawal syndrome from ethanol or benzodiazepines. Unsaid, however, is that this is predicated on the assumption that the opioid withdrawal syndrome develops over a period of

time (e.g., from lack of access to drug) rather than instantly. The administration of naloxone to an opioid tolerant person results in precipitous opioid withdrawal, the effects of which are indeed potentially life threatening.

Precipitated opioid withdrawal which is sometimes intentionally done in an attempt at detoxification (termed rapid opioid detoxification, or ultra-rapid opioid detoxification if performed under anesthesia) results in an exaggerated withdrawal response. [Kienbaum 2002] Delirium may develop. Massive catecholamine release from the autonomic nervous system results in hypertension, tachycardia, and cardiovascular sequelae such as pulmonary edema. In this setting, pulmonary edema may be functionally equivalent to "neurogenic" pulmonary edema, often described in patients with critical head trauma. Though typically mild and short lived, opioid-associated pulmonary edema may be life threatening, and it is highly associated with naloxone administration.[Buajordet 2004; Sterrett 2003; Sporer 2001]

In the substance abusing population, polysubstance misuse raises the risk profile of naloxone. That is, failure to awaken following naloxone in an opioid dependent patient may represent not a failure of naloxone but the presence of a concomitant substance, such as a benzodiazepine, tricyclic antidepressant or ethanol. Since vomiting is common in patients with precipitated (and natural) opioid withdrawal, the failure to awaken raises the concern for pulmonary aspiration. Furthermore, in patients with concomitant stimulant use, abrupt reversal of the sedative effect of an opioid may results in acute stimulant toxicity.

How can the safety of naloxone be improved?

Crucial in the understanding of opioid poisoning is that if naloxone disappeared today, no additional acutely opioid-poisoned persons would likely die unnecessarily. Opioids produce nearly all of their clinical morbidity by reducing the sensitivity of the brain's respiratory center to hypercarbia. This slows the patient's respiratory depth and rate. Simply by providing ventilatory support and supplemental oxygen, death should be readily preventable. Bag-valve-mask ventilation is generally sufficient to provide the requisite minutes for naloxone to become effective. Interestingly, the degree of catecholamine release is related to the degree of hypercarbia at the time of naloxone administration, suggesting that simply ventilating someone prior to naloxone administration may improve its safety.[Mills 1990]

The administration of naloxone remains desirable for several reasons. Since there is no practical diagnostic test for opioid poisoning, an appropriate response to naloxone serves in a diagnostic role. Even if the diagnosis of opioid poisoning is certain, prolonged BVM ventilation is labor intensive role and endotracheal intubation for mechanical ventilation is sometimes overkill. Thus naloxone plays a key role in the clinical management of patient who are likely to be opioid poisoned.

Naloxone's safety can be enhanced through titrated administration in divided doses to reach a total dose rather than in empiric bolus fashion. The typical dose of 0.4 mg or 2 mg that is often suggested is probably unnecessarily large and the onset too rapid. A preferred method is to administer naloxone in 40-50 μg (0.04 – 0.05 mg) aliquots; most patients respond appropriately, albeit more slowly. In concept, giving the drug slowly in small doses mimics the natural

withdrawal process and avoids precipitated withdrawal. The anesthesiology literature supports the effectiveness of this regimen, admittedly in a different patient population than is cared for in the emergency department. Notwithstanding this, the clinical pharmacology of naloxone supports this use with the caveat that it may take longer to reach the desired clinical endpoint. Patients who require prolonged naloxone administration may receive a continuous infusion at approximately 2/3 of the dose hourly that was required for initial reversal of sedation. The endpoint of naloxone administration is spontaneous ventilation, not withdrawal!

Clinical relevance of clinical pharmacology?
In an effort to avoid the risk of intravenous catheter placement, naloxone may be administered by alternative (e.g., subcutaneous) routes. Although subcutaneous administration intuitively seems like it would allow more rapid reversal than starting an intravenous line for administration, when all delays are considered, the use of naloxone via the subcutaneous route and the intravenous route are comparable. [Wanger 1998] An advantage of the subcutaneous route is the minimalization of precipitated opioid withdrawal due to the slow drug absorption phase, but this comes at the expense of easy titratability which may lead to a greater likelihood of over-reversal. Other routes, such as intranasal or nebulized, seem too difficult to titrate, and while they may be effective, their safety is largely unstudied.

Also of importance is the offset of clinical effect of naloxone. When administered intravenously, naloxone's effect is expected to persist for approximately 40 minutes. Administered subcutaneously, its effects may persist slightly longer due to prolonged absorption. Since many opioids, particularly methadone, have clinical duration far in excess of that of naloxone, observation for at least several hours seems warranted after reversal with this agent.

Case conclusion:
At the last physician visit methadone was added to the patient's medications regimen. Although the patient was aware of this addition, he was not aware of the potential drug interaction of taking two opioids, and that the oxycodone was intended to be discontinued. Thus the additive effect of the opioids

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