The Journal of Emergency Medicine, Vol. 57, No. 5, pp. 723–725, 2019

0736-4679/$ - see front matter

Case Presentations of the Harvard Affiliated Emergency Medicine Residencies

A COMMON ANTIDOTE FOR AN UNCOMMON INDICATION

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Dr. Nicole Nadeau: Today's case is that of a 26-month-old female who presented to our emergency department (ED) with somnolence. Per parental report, patient had been in her usual state of health up until that morning, when she emerged from the kitchen where she had been unsupervised briefly, shaking an object and imploring "more candy, more candy." On investigation parents discovered the object in the patient's hand to be a prescription bottle. Within 10 min the parents report that the patient began to be sleepy and kept "nodding off," prompting presentation to the ED. On arrival to the ED, the patient was afebrile, heart rate was 80 beats/min, blood pressure was 108/49 mm Hg, respiratory rate was 10 breaths/min, and oxygen saturation was 100% on room air.

Dr. Susan Wilcox: These vital signs would be relatively normal for an older child or adult. Can you comment on the expected vital signs for younger children?

Dr. Nadeau: This is an important point. At first glance the vital signs seem fairly unremarkable, until we remind ourselves of the appropriate references ranges for our toddler patients. In this case, the patient's heart rate was 50 beats/min below the more expected rate of approximately 130 and the respiratory rate of 10 breaths/min was quite reduced compared to a more appropriate rate of approximately 30.

Dr. Wilcox: Were there any key findings on the patient's physical examination?

The patient was somnolent and minimally arousable, responding only to painful stimuli. Head, ear, nose, throat, and neck examination showed no evident facial or cranial trauma, and revealed symmetric but miotic pupils. The cardiac examination revealed a regular bradycardia with no murmurs noted. The respiratory examination revealed bradypnea with otherwise unremarkable auscultation of the lungs. The abdomen was soft, without apparent tenderness or organomegaly. The extremities were unremarkable, without apparent injury. Examination of the skin showed no bruising or scarring. The neurologic examination was notable for the depressed mental status described previously, with symmetric facies and extremity movement with only with painful stimuli.

Dr. Margaret Samuels-Kalow: It sounds like this was a fairly concerning toxic ingestion. Which agents were you considering as being the most likely?

Dr. Nadeau: Yes, while the differential diagnosis of a toddler with depressed mental status is quite broad, we were fortunate to have history clearly identifying this as a toxic ingestion. While one must always worry about concomitant abuse or trauma in this situation, patient's examination was not suggestive of this.

Given patient's depressed mental status and bradycardia, we considered a β-blocker or calcium channel blocker ingestion. The cardinal signs of these ingestions in young children are somnolence, bradycardia, and hemodynamic instability. However, hypoglycemia often occurs in the setting of β-blocker ingestion and at times can assist in distinguishing between the two etiologies. The bradypnea and miotic pupils observed in our patient would be less consistent with these ingestions, however.

With the patient's physical examination, our initial concern was for an opioid ingestion, particularly given the increase in accidental opioid ingestions in the current epidemic. Opioids are a common cause of ingestions in the pediatric population and present similarly to adult patients, with somnolence, respiratory depression, and miotic pupils, as seen in our patient (1). Although opioids may cause some slowing of the heart rate, the prominent bradycardia observed would be less consistent with opioids, however. Clonidine, a centrally acting α-2 receptor agonist, could explain all of the effects seen in this child. Clonidine ingestions in children often present with somnolence quickly after ingestion, often with miosis, bradypnea, and bradycardia that can progress to hemodynamic collapse and respiratory insufficiency (2). Her parents were able to quickly confirm clonidine as the pill bottle in hand.

Dr. Samuels-Kalow: Given the noted somnolence, bradypnea, and bradycardia, what was the team's initial management strategy?

Dr. Nadeau: While the patient was maintaining her oxygenation and blood pressure, her bradypnea and bradycardia prompted concern for impending circulatory collapse and respiratory failure. We obtained i.v. access and prepared basic supportive measures, such as a bag mask for ventilation. While those interventions were ongoing, we administered intranasal naloxone 0.4 mg for treatment of presumed clonidine overdose.

Dr. Kathleen Wittels: How did the patient respond?

Dr. Nadeau: The patient had questionable effect from the first dose of 0.4 mg of intranasal naloxone so an additional 0.4 mg intranasally was repeated 3 min later. After the second dose, the patient had clear improvement in her vital signs, with return of heart rate and respiratory rate to age-appropriate values of 138 beats/min and 28 breaths/min, respectively. Her mental status also improved, with the patient opening her eyes and demonstrating purposeful movements. Unfortunately, similar to what we see with opiate ingestion, the half-life of naloxone is much shorter than that of clonidine, and the patient again became lethargic and obtunded with decreased respiratory effort approximately 15 min after its administration. The patient received a third dose of 0.4 mg intranasally and was then initiated on a naloxone i.v. infusion, with a sustained improvement in heart and respiratory rates as well as level of alertness, though not full normalization of her mental status or respiratory effort.

Dr. Samuels-Kalow: We all associate naloxone use with opioid overdose; is its use well-established in clonidine ingestion?

Dr. Nadeau: Interestingly, clonidine overdose is not listed as an on or off-label indication for naloxone in multiple commonly used pharmacologic resources (3,4). Our state Poison Control Center, however, agreed with naloxone administration for this patient and recommended the use of repeat boluses and initiation of an infusion.

Dr. Wittels: Is there literature to support its use?

Dr. Nadeau: Review of the literature shows that the use of naloxone in clonidine overdose was first suggested as far back as 1981, on the basis of animal studies showing the reversal of clonidine-associated hypotension and two clinical cases in which empiric use demonstrated benefit (3).

The same review of the literature also shows that naloxone use in clonidine ingestion has been a point of debate in the 4 decades since this first recommendation was made (5–8). There are individual case reports in the literature of the same evident and immediate improvement in bradycardia, respiratory effort, and mental status that we appreciated in our patient (5,9,10). Further, small case series show promising responses in up to 50%–80% of patients, with one case series attributing avoidance of mechanical ventilation in four out of five children to the use naloxone (11–13). Dosing of naloxone in these cases involved 0.05–0.1 mg/kg boluses followed by subsequent infusions (11). Critics, however, point to an inconsistent response across the literature, with other case reports and small case series showing no response or low rates of response (8,14–17). One larger retrospective chart review of 80 patients is cited as showing only a 16% rate of response, though this series was notable for highly variable naloxone dosing (18).

One important recent addition to the literature specifically addresses the importance of dosing in observed response. A case series from 2018 specifically evaluated using higher doses of naloxone in pediatric clonidine ingestions. Forty of 51 patients had reversal of somnolence and 7 of 11 had reversal of hypotension. These authors emphasize the importance of appropriate dosing and unequivocally support the use and efficacy of naloxone in clonidine overdose (19).

Dr. Samuels-Kalow: I am curious about the variability of response. What dosing would you recommend if one were to utilize naloxone for this indication?

Dr. Nadeau: For pediatric clonidine ingestions, naloxone dosing of 0.1 mg/kg up to 2 mg per dose, repeated every 1–2 min, has been suggested previously

(8). This is consistent with the dosing utilized in earlier case series in which higher rates of response were seen (11,13). Authors of the recent article supporting high-dose clonidine recommend markedly more elevated doses of up to 6–10 mg (19). Given these recommendations, clinicians may consider higher initial doses or may at least want to consider rapid repeat dosing up to 10 mg total prior to determining lack of efficacy (19).

Dr. Wilcox: What is the mechanism of action thought to be? Are there any potential negative effects?

Dr. Nadeau: The mechanism of action is incompletely understood but appears fairly complex. A simplified version suggests that in addition to clonidine causing direct α-2 agonism, it also has a role in triggering endogenous opioids that modulate the body's sympathetic response, as well as the central nervous system. Naloxone's effect is thought to be in counteracting these endogenous opioids, thus allowing it to both reverse central nervous system depression and increase vascular tone (20).

Regarding possible adverse effects of naloxone use with clonidine ingestion, marked hypertension has been the only potential negative effect cited. The etiology of this, however, is debated, as clonidine itself can cause a paradoxical hypertension in some patients in overdose. Additionally, there are no reports of any clinical sequelae surrounding this hypertension. In the case series of 51 pediatric patients with clonidine ingestion receiving doses as high as 6–10 mg of naloxone, there were no adverse events (19).

Dr. Wittels: What was the patient's course?

Dr. Nadeau: The patient was admitted to the pediatric intensive care unit for observation. Patient remained stable on the naloxone infusion, but overnight was placed briefly on non-invasive positive pressure ventilation out of concern for observed periodic breathing, though she never had any episodes of associated desaturations. By the following morning, the patient had a fully normalized mental status and began self-discontinuing her respiratory support and leads. The naloxone infusion was discontinued and patient was observed with ongoing normal mental status, respiratory effort, and vital signs. She was subsequently discharged to home with her parents following a social work consult for support and education regarding safe medication storage in the home.

Dr. Wilcox: What were the final teaching points for the case?

Dr. Nadeau: This patient's clear and immediate response to our naloxone administration and my subsequent review of the most recent literature surrounding naloxone and clonidine ingestion has reinforced its utility in clinical practice, specifically for its ability to prevent the morbidity of endotracheal intubation. The option to administer naloxone intranasally if necessary is also a substantial additional benefit in young patients, in whom i.v. access can be challenging and time-consuming. Dosing is of particular importance with naloxone for clonidine ingestion. While this patient responded quickly to a low dose of 0.8 mg, clinicians should rapidly escalate doses to as high as 10 mg prior to determining lack of efficacy, while of course otherwise providing cardiopulmonary support as needed.

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