Abstract:
Medication error is the most common medical error and disproportionately affects pediatric patients. Physicians have a responsibility to understand root causes for medication error and common prevention strategies. Further research in this field is imperative to prevent medication errors resulting in adverse patient events. This article uses a case of potential clonidine toxicity that presented to the emergency department to illustrate and review these concepts. Given that clonidine is being prescribed to both pediatric and adult patients for expanding clinical indications, children are at higher risk for potential overdose. Therefore, a brief review of clonidine toxicity and its management is also provided.

Keywords:
clonidine toxicity; medication error

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Clonidine Overdose: A Review of Pharmacology and Medication Error

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A 2-year-old girl with a complicated medical history arrived to the emergency department (ED) for an evaluation. She had recently been transferred to a rehabilitation hospital after a lengthy admission in the intensive care unit for management of *Streptococcal pneumoniae* bacteremia, hemolytic uremic syndrome, and multisystem organ failure which resulted in severe neurologic deficits. During that admission, tracheostomy and gastrostomy tubes were placed, and she was discharged on several medications, which included scheduled morphine, lorazepam, and clonidine.

On the morning of her presentation to the ED, staff at the rehabilitation hospital called 911 after realizing the patient had inadvertently received a 10-fold increase in her prescribed dose of clonidine. She was asymptomatic and had been in her usual state of health prior to this event. Staff contacted the regional poison control center, and per their recommendations, the patient received a 1-time dose of activated charcoal via her gastrostomy tube. An ambulance brought her to the ED for further evaluation.

On initial evaluation in the ED, she was afebrile with a heart rate of 130 and a blood pressure of 100/60 mmHg. She was oxygenating well on room air via her tracheostomy and breathing 25 times per minute. Her pupils were equal and reactive without obvious miosis or mydriasis. The remainder of her examination

was notable for altered mental status and for the presence of her baseline hypertonicity and hyperreflexia.

A comprehensive metabolic panel, complete blood count, urinalysis, acetaminophen, ethanol, and salicylate levels were all unremarkable. A urine toxicology screen was negative. A screening electrocardiogram showed normal sinus rhythm with a normal QRS duration and QT interval. Poison Control recommended observation for a minimum of 6 to 8 hours, with supportive care and doses of naloxone if she developed vital sign abnormalities. She was admitted to the step-down intensive care unit for observation. The patient's mental status improved throughout her hospital stay without further intervention, and she was ultimately discharged back to the rehabilitation hospital to resume physical, occupational, and speech therapy.

THE PATHOPHYSIOLOGY OF CLONIDINE TOXICITY

Clonidine is an α-2 receptor agonist that also acts on imidazoline-1 receptors. It is prescribed as an antihypertensive agent primarily for adult patients. In the pediatric population, it is more commonly used to treat attention-deficit/hyperactivity disorder and, as in our patient, withdrawal syndromes. The most common routes of delivery are transdermal (patch) and oral (tablet or compounded suspension). It reaches peak concentrations 2-4 hours postingestion.[1] Most adverse effects in cases of overdose manifest 30 minutes to 2 hours after ingestion.[2]

Clonidine toxicity manifests as neurologic depression, miosis, respiratory depression, bradycardia, hypotension, and hypothermia. The mechanism of action is believed to include several receptors but primarily involves α-2 receptor activation leading to inhibition of norepinephrine at the neuronal synapse, which leads to a decrease in sympathetic tone. A transient, early hypertension has been described in case reports[3] and is thought to relate to baseline sympathetic tone and catecholamine release, although the mechanism is not fully understood.[1]

Mainstays of treatment, as with many cases of toxicity, focus on supportive care. Airway protection with endotracheal intubation should be pursued in cases of severe neurologic or respiratory depression. From a cardiovascular standpoint, atropine may be useful for hemodynamically significant bradycardia. Hypotension should be treated with intravenous fluid support and, in refractory cases, with vasopressive agents. Although there is no antidote for clonidine, naloxone has been used in both adult and pediatric patients with variable response.[3] In one retrospective cohort study of 51 patients, 40 showed improvement with high-dose naloxone.[4] Naloxone dosing for opioid toxicity is 0.1 mg/kg up to a maximum of 2 mg IV; many of these patients received repeat doses as high as 10 mg before demonstrating improvement in their neurologic status and hemodynamics.[4] Other case reports describe no improvement with bolus doses of naloxone.[5] Ultimately, poisoned pediatric patients seem to recover with good supportive care after an observation period of 12 to 24 hours.[1]

MEDICATION ERROR

A fundamental understanding of toxicology, including both toxidrome recognition and treatment, is imperative for any emergency medicine physician. However, our patient's ED presentation stemmed from a medication error, and physicians should also have a thorough understanding of this patient safety topic. In 1999, the Institute of Medicine released its landmark report, *To Err is Human*" shedding light on the 40 000 to 98 000 deaths attributable to medical error each year.[6] Of those deaths, 7000 were due to medication error. Medication error is by far the most common medical error, affecting approximately 1.5 million people per year.[7] One study reported that 20% of adverse event injuries stemmed from medication injury. Adverse medication events are divided into unpreventable (an adverse drug reaction) and preventable events (an error related to the ordering, dispensing, or delivery of a medication.)[7,8]

Pediatric patients are certainly not immune from medication error. According to one study, researchers identified 784 errors in a sample of 3312 medication orders (11 978 total doses).[9] Clinicians realized most of these errors before they reached patients, but the authors point out that this further complicates an already complex process. Physicians write medication orders (prescribing), pharmacists prepare the medication (dispensing), and nurses deliver the medication (administration). This is a perfect example of the Institute for Healthcare Improvement's Swiss cheese model: despite many layers to prevent harm, occasionally, the holes in the slices of cheese align to allow an error to pass through to the patient.[10]

In fact, certain factors place pediatric patients at higher risk for medication error than their adult counterparts. Weight-based dosing requires several calculations; calculations are a frequent source of error, with dosing errors by a factor of 10 a common occurence.[11] Different dosing strategies (ie, dosing

per kilogram vs by body surface area) and multiple available drug concentrations introduce even greater complexity. Medications are typically stored in vials containing an adult dose, requiring a pharmacist to measure out the appropriate pediatric dose. Other medications are not readily available as a suspension, and the process of compounding introduces opportunities for error.[12] Children may not be able to verbalize effects from an incorrect dose and also have immature hepatic and renal systems, making them more susceptible to a medication's effects. Lastly, more research about appropriate dosing and safe drug regimens is needed for pediatric patients as the vast majority of pharmaceutical trials have been performed using adult subjects.[13,14]

Although understanding the magnitude and gravity of the problem is important, PEM providers should also be aware of effective prevention strategies. Two of the most common solutions include computerized physician order entry (CPOE) and clinical decision support (CDS); both help to limit prescribing errors. CPOE is an electronic method of entering patient orders, which includes prescribing of medications. CDS encompasses the flags within an electronic medical record (EMR) that notify the provider of allergies, drug interactions, and appropriate dosing ranges. These systems have reduced medication error, especially errors related to transcription of physician handwriting.[15] However, these systems remain imperfect. For example, some institutions cap weight-based calculations for dosing at a maximum amount, whereas others do not. This may lead to patients receiving inappropriately high doses of medications, especially in today's obesity epidemic. Providers can also click past alerts about inappropriate dosing or potential allergies or medication interactions.

Medication reconciliation is another patient safety process that has been integrated into the EMR. Reconciliation of a patient's current medications upon admission is believed to reduce medication error, although studies of its role in preventing error are lacking. A more studied, non-EMR strategy to prevent medication error involves incorporation of in-unit pharmacists, especially on rounds. One study found that the presence of an in-unit pharmacist may have prevented more than 80% of medication errors.[16] However, there are cost and space considerations to implementing this particular strategy. Careful storage of "look alike sound alike" medications, patient bracelet scanning to prevent administration of medications to the wrong patient, and the use of electronic pumps to deliver medications are all other examples of error prevention techniques.[15] In a systematic review of different strategies to prevent medication error, the authors summarize these issues while calling for standardized research investigating prescription error, dispensing error, and administration error. They also highlight the need for research on medication administration in ambulatory community settings.[17]

The American Academy of Pediatrics (AAP) published its own recommendations for medication error prevention in 2003. In summary, the AAP recommends that there be an adequate number of staff with appropriate pediatric training, the use of a drug formulary, presence of standardized equipment and measurements, computerized checks and balances, medication reconciliation, and error reporting systems. The AAP also promotes creation of a safe work environment and development of a culture of safety and improvement. They specifically mention the importance of quality improvement science as we move forward, providing care for children that is safe, equitable, efficient, effective, timely, and patient centered.[8,18]

SUMMARY

Our patient luckily did not suffer any health consequences as a result of the unintentional clonidine overdose. However, this case serves as an example of a serious medication error, one that could easily cause significant morbidity. Clonidine is a potentially dangerous medication that is becoming more commonly used in pediatric care, especially for medically complex patients. Although ubiquitous strategies like CPOE and CDS are useful, we encourage emergency physicians to pursue further quality and process improvement work to prevent medication error in their own institutions. Further research is also needed to understand the complex factors that lead to medication error, especially in different settings—academic and community hospitals, intensive care units, outpatient settings, inpatient units, and emergency departments. Given that the high volume and acuity in the pediatric ED often create an environment prone to error, participation in quality improvement and patient safety activities by pediatric emergency medicine physicians will be critical as we strive toward providing care that achieves the 6 pillars of health care quality set forth by the National Academy of Science, Engineering and Medicine.

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