Toxicity from a Clonidine Suspension

Mariya F. Farooqi, PharmD^a, Steven A. Seifert, MD^{a,b}, Susan J. Kunkel, PharmD^a,
Mary I. Johnson, MD^c, Blaine E. Benson, PharmD^{a,d}

^aNew Mexico Poison and Drug Information Center and University of New Mexico College of Pharmacy, Albuquerque, NM

^bDepartment of Emergency Medicine, University of New Mexico School of Medicine, Albuquerque, NM

^cDepartment of Neurology, University of New Mexico School of Medicine, Albuquerque, NM

^dCollege of Pharmacy, University of New Mexico, Albuquerque, NM

ABSTRACT

Background: Clonidine is frequently prescribed to children. Clonidine overdose in children has resulted in major clinical effects and deaths.

Case Report: A 3.5-year-old male with a history of a seizure disorder and night terrors presented following difficulty walking, excessive sleeping, agitation when awake, and possible seizure activity. Chronic medications were valproic acid (VPA) and clonidine. On presentation, he alternated between poor responsiveness and agitation, with initial vitals: blood pressure, BP 144/76 mmHg; heart rate, 65 bpm; respiratory rate, 18 bpm; temperature 99.5°F; and pulse oximetry 96% on room air. VPA level was 35 µg/mL. A toxicology consult the next day noted a dry mouth, 2-mm pupils, intermittent gasping, and central nervous system (CNS) depression, with a diagnostic impression of clonidine overdose. The caregiver had been giving 1 mL (0.1 mg) qd of a pharmacy-compounded clonidine suspension by a provided syringe. The pharmacy procedure record agreed with the physicians order. The amount dispensed was a 30-day supply but the bottle was empty on day 19, leading us to suspect a possible accelerated dosing error. The concentration in the bottle thus could not be confirmed. The child slowly returned to his baseline state over 48 hours. A serum clonidine level drawn approximately 18 hours after his last dose later returned at 300 ng/mL (reference range = 0.5–4.5 ng/mL).

Case Discussion: Compounding and liquid dosing errors are common in children and may result in massive overdoses. There was an accelerated dosing error, but whether a compounding or suspension error or even an acute overdose occurred as well is unknown.

Conclusion: Particular care should be taken with medications that have low therapeutic indices, that are extemporaneously compounded, and are prepared as liquids, where medication errors are more likely.

INTRODUCTION

Clonidine is frequently prescribed to children for a variety of indications. Overdoses of clonidine in children can result in major clinical effects and death. We report a case of a massive overdose in a 3.5-year-old child receiving a compounded clonidine suspension.

CASE REPORT

A 19-kilogram, 3.5-year-old male with a history of a seizure disorder and developmental delay presented following an episode of suspected seizure activity. The primary caretaker reported that the child had apparently been behaving normally that morning until

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Corresponding author: Steven A. Seifert, MD, c/o New Mexico Poison Center, MSC09 5080, 1 University of New Mexico, Albuquerque, NM 87131-0001. *Email:* SSeifert@salud.unm.edu

noon, when he was experiencing difficulty walking and climbing steps. The patient slept for 4 hours, which was unusual for him, and was then brought for medical evaluation when it was noted that he was difficult to arouse. The patient's medications included valproic acid (VPA), 125 mg every morning and 250 mg at bedtime, prescribed for seizures, and clonidine 0.1 mg at bedtime, recently added for night terrors. The child presented to the emergency department (ED) approximately 12 hours after his last VPA dose and approximately 18 hours following his last clonidine dose.

On presentation, he was noted to be intermittently poorly responsive alternating with episodes of irritability and agitation, more so with stimulation, and with a Glasgow Coma Scale of 15. Initial vitals were a blood pressure of 144/76 mmHg, heart rate of 65 beats/min, respirations of 18 breaths/min, temperature of 99.5°F and room air oxygen saturation of 96% by pulse oximetry. Physical examination revealed warm, dry skin and normal muscle tone. Electrolytes, blood glucose, CXR, CBC, and lumbar puncture were unremarkable. VPA level was 35 µg/mL (therapeutic range 50–100 µg/mL). Serum ammonia was 2 mmol/L (nl = 15–45 mmol/L). He received a total of 2 mg of lorazepam for suspected seizure activity and 20 µg of fentanyl IV for additional sedation. His EEG indicated a lack of seizure activity but there were some delta and beta waves, suggesting drug effect. Urine toxicology was negative for propoxyphene, opiates, methadone, cocaine, barbiturates, and amphetamines.

During the night in the pediatric unit, his oxygen saturation decreased to a low of 84%. He was placed on 0.5 L/min of oxygen by nasal cannula. He was noted to be having episodes of sinus bradycardia, with a low of 60 beats/min. Due to the concern that he might be having ongoing seizure activity, he was loaded with intravenous VPA and repeat level was within therapeutic range. The neurologist's opinion was that, because his behavior was not similar to previous seizures and the EEG did not show seizure activity, these were not seizures.

When the toxicology service examined the patient the next day, heart rate was 90 beats/min, blood pressure 144/76 mmHg, and respirations 22 breaths/min. He had not been hypotensive at any point during medical observation. He was not directly responsive, and had a very dry mouth, 2-mm pupils, exhibited intermittent gasping, and marked CNS depression. The clinical impression was clonidine overdose.

Upon further questioning, the grandmother revealed that the child had been taking clonidine (0.1 mg/mL) as a suspension prepared at a compounding pharmacy. She stated that after shaking the bottle, she gave 1 mL of the suspension to her grandchild using a syringe provided by the pharmacy.

The compounding procedure for this particular prescription was requested from the pharmacy along with a copy of the physician's call-in order for the prescription. Upon review by members of the toxicology service, the written record of the compounding pharmacy's procedure was found to be in agreement with the physician's order. The pharmacy, in its compounding activities, had two pharmacists independently verify the identity and amount of medications being transferred between compounding

and dispensing operations. However, although the amount dispensed was for a 30-day supply, the bottle was empty on day 19.

The child slowly returned to his baseline state and was discharged 3 days after presentation. A serum clonidine level drawn at presentation, approximately 18 hours after his last dose, later returned at 300 ng/mL (reference range 0.5–4.5 ng/mL, Medtox Scientific, HPLC). The bottle and dispensing syringe were not available for inspection or for chemical analysis.

DISCUSSION

Clonidine is an alpha-2-adrenergic agonist antihypertensive medication. In the pediatric population, clonidine is commonly prescribed for attention deficit-hyperactivity disorder, autism, and anxiety. Due to its sedative properties, it is frequently prescribed for sleep disorders in children with neurobehavioral disorders. In a mail survey sent to pediatricians, it was found that clonidine was the second-most-often prescribed medication for treating sleep disturbances in children, with first-generation antihistamines the only medication class prescribed more frequently for this indication [1]. Of 222 pediatricians, 79% reported prescribing alpha-2-adrenergic agonists primarily for school-age children, as they felt more comfortable with this agent than with other sleep aids. However, to date there are no short- or long-term efficacy and safety studies with clonidine in children to support this prescribing pattern [1].

There are 4 reports of fatality from single-substance, acute clonidine ingestion; of these, 2 were in children [2,3]. According to 2006 American Association Poison Control Center data, a total of 3,250 cases with single-substance clonidine exposure were reported, with an overwhelming majority (78%) being unintentional exposures. Of the single-substance exposures, 1,365 cases (42%) involved children less < 6 years of age. In this series there were no deaths, but 94 cases—both adult and pediatric—resulted in a major outcome, defined as exhibiting life-threatening symptoms or resulting in significant residual disability [4]. Of note, there has been a decrease in the number of exposures in children < 6 years of age reported to US poison centers between 2004 and 2006, from 1,888 per year to 1,068 per year [4,5].

In our patient, the reported level of 300 ng/mL is > 4 times the highest previously reported pediatric level [6] and likely does not represent the peak level, since it was drawn approximately 18 hours after the last dose. It seems likely that his caregivers missed the initial symptoms and signs of toxicity which, because of tolerance, insidious onset, and lay observers, were only noticed when he had a significant decrease in his level of consciousness. On presentation his initial bradycardia and mild hypertension was not appreciated by the admitting service. Although there was a history of somnolence and the patient was intermittently somnolent after arrival, he also had episodes of agitation that may also have confused the diagnosis. Other signs of clonidine toxicity, such as dry mouth and miosis (mediated by alpha-2-adrenoreceptors located in the salivary glands and the nucleus coeruleus [7]), were also not appreciated initially, although this

presentation was entirely consistent with clonidine toxicity. Classic signs, such as somnolence and respiratory depression, may have been more pronounced at night when he was unstimulated. Our patient returned to baseline status at approximately 48 hours, consistent with other cases of clonidine overdose, despite the very high serum level [6,8–10].

It is unknown whether this overdose occurred solely as a result of accelerated dosing and/or also included a compounding error. Accelerated dosing may have occurred from the use of an incorrect dispensing instrument, dosing instruction, misinterpretation of directions, or other dosing error. The caregiver's history of dosing, however, and insistence that this 3-year-old developmentally delayed patient could not have self-dosed, as well as the lack of symptoms and signs for over 2 weeks during dosing, suggests that the amount of medication in each dose may have been progressively increasing if an incorrect suspending agent was used, and/or the bottle not shaken thoroughly with each dose. However, a full 30-mL bottle would contain only 3 mg of clonidine. Even if the entire contents of the bottle had been ingested all at once, based on the volume of distribution and case reports [11,12], we would have only expected a peak level of approximately 3.5 ng/mL (reference range = 0.5–4.5 ng/mL). A dose of at least 10 times that would have been required to achieve a level of 300 ng/mL, a circumstance more likely to result from a compounding error [13]. Although we were unable to detect an error in the pharmacy records and unable to directly measure the contents of the bottle, it seems likely that in addition to the accelerated dosing, there was also a compounding error. It is also possible that there was an acute large ingestion by the child that was not known to the caretaker.

Correlation between specific clinical effects and serum clonidine levels has not been well described. In a case report of a 1,000-fold clonidine overdose in a 5-year-old, in which a substitution of "milligrams" for "micrograms" in the compounding resulted in a three-order-of-magnitude dosing error, the clonidine level was 64 ng/mL, obtained 17 hours postingestion [6]. That patient became limp and unresponsive at home, was obtunded on arrival, but developed agitation with stimulation, had respiratory depression (respiratory rate 5–8 /min) with apneic episodes, a sinus bradycardia (heart rate 47 bpm), and an elevated blood pressure (133–137/96–103 mmHg). Pupils were 2 mm and the mouth and mucous membranes were dry. That child was discharged at 42 hours. In a series of 6,042 symptomatic children following clonidine exposure, the most common symptoms were lethargy (80%), bradycardia (17%), hypotension (15%), and respiratory depression (5%) [5]. However, clonidine toxicity may present with a number of atypical effects, including tachypnea and agitation. Hypertension may be present early in the course and hypotension may not develop [6,14].

This case highlights the danger of prescribing medications that require extemporaneous compounding—especially that include liquid formulations—and medications that have low therapeutic indices, such as clonidine, in children. First, extemporaneous compounding is associated with a significant risk of dose error, and

Table 1: Pitfalls of Prescribing Compounded and Liquid Preparations

Compounding	
Calculation errors	
Incorrect compounding procedure	
Inadequate counseling regarding dosing	
Failure to provide an appropriate dosing instrument	
Prescriber	
Prescribing drugs with a narrow therapeutic index	
Inadequate counseling regarding dosing and proper use	
Difficulty monitoring drug levels	
Patient	
Inappropriate use of measuring device	
Inappropriate measuring devices (e.g., using tableware spoon)	
Failure to appreciate medication risks with improper dosing	
Not shaking a liquid preparation before use	

compounding is more likely to result in order-of-magnitude dosing errors [13,15]. Second, liquids are also subject to unique dose-error scenarios, such as the substitution of droppersful for drops or tablespoons for teaspoons [13]. Finally, clonidine has a low therapeutic index (Table 1). Symptoms and signs of toxicity have been reported with doses as low as 0.1 mg [8] and significant toxicity (coma, respiratory depression, or hypotension) has been reported with doses at or above 0.2 mg [9,10].

If compounded preparations, liquids, and/or low therapeutic index medications are prescribed for children, certain precautions may help to reduce the incidence or potential severity of overdoses. Counseling caretakers on the correct method of administration, training on the use of dispensing devices, warning about the possibility of dose errors and to be alert for new prescriptions that appear to be different in appearance or taste from previously prescribed medicine, and carefully considering a drug's indications and risk-to-benefit ratio may all help to reduce the incidence and severity of overdoses [13,14].

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