Prolonged Bradycardia and Hypotension Following Guanfacine Extended Release Overdose

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To The Editor:

ATENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) is one of the most commonly diagnosed disorders of childhood. Currently, ADHD affects ~4–9% of the youth population (National Institutes of Health 2000).

There are many types of treatments for ADHD, which vary from behavioral therapy to medication. The most commonly prescribed medications for the treatment of ADHD are psychostimulants, derived from either amphetamine or methylphenidate (Wilens and Spencer 2000). However, other treatments include nonstimulant medications such as atomoxetine, clonidine (immediate and extended release), and guanfacine (immediate and extended release).

Guanfacine extended release is an α -agonist that is approved to treat ADHD in children and adolescents. Before receiving approval from the United States Food and Drug Administration (FDA) for use in ADHD, guanfacine was approved for use as an antihypertensive medication. In a placebo-controlled trial, guanfacine extended release was shown to be effective at reducing ADHD symptoms, while having mild to moderate adverse effects (somnolence, fatigue, and sedation) that generally subsided after the first 2 weeks of treatment (Sallee et al. 2009). Compared with guanfacine immediate release, guanfacine extended release has a longer duration of action and fewer fluctuations in concentration. As the use of guanfacine extended release in the treatment of ADHD is relatively new, there is not much information regarding intentional or accidental overdose. We present a case report of an accidental overdose of guanfacine extended release in a boy, which resulted in prolonged hypotension, bradycardia, and admission to the intensive care unit.

Case Report

The patient was an 8 years and 11 months old male with ADHD and a history of auditory hallucinations. His home medications include long-acting dexamethylphenidate 20 mg in the morning, short-acting dexamethylphenidate 5 mg at noon, guanfacine extended release 3 mg in the morning, and risperidone 0.25 mg in the evening. He and his parents reported good benefit from this pharmacological regimen.

The outpatient clinic staff were notified at 1:26 p.m. by the patient's school that he was accidentally given guanfacine extended release twice, once in the morning (as prescribed) and again at noon. The school stated that at the time of the second administration of guanfacine, the patient did not have any adverse reactions. However, the clinic staff asked the school personnel to contact the

local poison control center, monitor the patient's hydration, and monitor for increased fatigue and lowering of blood pressure. School personnel were also advised that if the patient's symptoms worsened, they were to take him to the nearest emergency department (ED). The patient's mother was also notified and made aware of this situation.

The patient came home from school at ~4:30 p.m. and was noted to have significant fatigue; he fell asleep easily but was difficult to arouse. The patient also seemed cold and had been perspiring since he came home. His mother took him to an urgent care center, where his pulse was recorded to be 56 beats per minute and his blood pressure was recorded to be 97/43 mm Hg. The patient's height was at the 99th percentile; therefore, this blood pressure was considered low for his age and height (National Heart, Lung, and Blood Institute 2004). He was transferred by ambulance to the hospital ED, and when examined by the physician on admission, his pulse was 50 beats per minute and his blood pressure was 93/34 mm Hg. He was alert, arousable, and answered questions appropriately, but would quickly fall asleep. His blood pressure later fell to the range of ~80/40 mm Hg, prompting an IV line to be placed and one fluid bolus administered. An electrocardiogram (ECG) was performed showing sinus bradycardia, but no prolonged QTc interval. After the fluid bolus, maintenance IV fluids were started, and 2 mg of naloxone was administered intravenously. This did not make a difference in his hemodynamics or somnolence. While asleep, his heart rate ranged from 40 to 50 beats per minute, and his respiratory rate ranged from 10 to 15 breaths per minute. The decision was made to transfer the patient to the intensive care unit (ICU).

In the ICU, the patient was on continuous telemetry with neurological examinations every 2 hours. Maintenance IV fluids were continued, and all home medications were withheld. The patient remained stable on room air overnight, with his heart rate in the 40–50 beats per minute range. The next morning (~18 hours since the ingestion) and throughout the day, his heart rate improved to the range of 50–60 beats per minute, the highest being 71 beats per minute. His blood pressure also improved and ranged from 87 to 100 mm Hg systolic, and from 31 to 53 mm Hg diastolic. He was transferred to a regular floor that afternoon for continued monitoring, where he stayed for 1 more day. Overnight on the floor, his heart rate stayed in the range of 50 beats per minute, and his blood pressure was 107–116/38–42 mm Hg. The next day he was discharged with a blood pressure of 114/52 mm Hg, pulse 62, and was breathing well on room air (~45 hours after ingestion).

Six days after he was discharged, his mother contacted the outpatient clinic, reporting that he was back to his normal behavior,

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and denying lethargy or bradycardia. At the next outpatient clinic visit, it was discussed that he was no longer taking risperidone, as he no longer had auditory hallucinations, but he was continued on guanfacine extended release 3 mg, long-acting dexamethylphenidate 20 mg, and dexamethylphenidate 5 mg.

Discussion

Medication errors occur commonly; 700,000 ED visits and 120,000 hospitalizations are caused by adverse drug events (ADEs) annually (Substance Abuse & Mental Health Services Administration 2013). In 2008, the most recent year for which we have national figures, >36,000 people died of drug overdoses in the United States, and >20,000 of these overdose deaths were from prescription drugs. This number has steadily increased over the last decade. Every day in the United States, 105 people die as a result of drug overdose, and another 6748 are treated in EDs for the misuse or abuse of drugs (Substance Abuse & Mental Health Services Administration 2013). Nearly 9 out of 10 poisoning deaths are caused by drugs (Paulozzi 2012).

The incidence of unintentional poisonings from ADHD drugs has also increased over the past decade, based on data from hospitalizations alone (Levine et al. 2013). The incidence of medication overdose errors not requiring hospitalization is unknown.

Guanfacine extended release was approved by the FDA for treating ADHD in 2009. It was originally approved for treatment of hypertension because of its selective stimulation of α_2 adrenoceptors in the brainstem, resulting in reduced sympathetic outflow, producing a decrease in vasomotor tone and heart rate. The immediate release format has long been used off-label as an adjunct treatment for ADHD. The exact mechanism of its benefit in ADHD is not known. It has been proposed that postsynaptic α_2 agonist stimulation regulates subcortical activity in the prefrontal cortex, thus improving attention and impulsivity. The product information provides a warning of possible bradycardia and hypotension, which typically is asymptomatic.

Guanfacine immediate release has a half-life of ~17 hours, with a range from 10 to 30 hours, whereas the extended release format reportedly has a half-life of 14 hours in children (Lexicomp 2013). The time to peak concentration for guanfacine extended release is ~5 hours, and the half-life is 14–16 hours (Lexicomp 2013). The recommended dosing guideline for the treatment of ADHD is 1 mg once daily, and can be titrated up in increments of no more than 1 mg per week as tolerated (Lexicomp 2013). Whereas benefits for ADHD symptoms are seen soon after oral ingestion, the antihypertensive effect peaks at 8–12 hours postadministration, and lasts 24 hours. Our patient demonstrated symptoms 4 hours after ingestion of the incorrect dose, and cardiovascular effects ~10 hours after ingestion when in the ED. He received general supportive care but did not require vasopressor agents, and had an uneventful recovery.

Guanfacine overdose in the pediatric age group is uncommon. Minns et al. reported a case of a 16-year-old female who received 25 mg of guanfacine and had a similar hospital course (Minns et al. 2010). This would be estimated at 6–12 times a typical adult dose. Van Dyke et al. described an accidental overdose of 4 mg ingested by a 2-year-old male, estimated to be 35 times the usual adult dose (Van Dyke et al. 1990). Our case is of interest for four reasons. First, the child received a single dose of guanfacine extended release at breakfast and a single extra dose ~4 hours later. This would not be considered a significant overdose, and he was managed with close observation by the parent. As symptoms worsened, he was taken to

receive medical care, admitted to intensive care, and remained symptomatic overnight until the next morning. This marked response to a relatively small overdose emphasizes the need for medical involvement for any overdose of this α_2 adrenergic agent.

The second reason relates to the pharmacodynamic response seen in this patient. His cardiovascular response and behavior were similar to those caused by other ingestions of proportionately much greater amounts. In addition, despite receiving the extended release format of this medication, his response was very much like that seen with immediate release overdose. The persistence of hypotension beyond 24 hours and well beyond the expected half-life has also been reported in other cases, and suggests that monitoring should continue for some time after ingestion.

The third reason also relates to management via other options besides observation. In our patient, IV fluids were administered as part of the hemodynamic support. Previous studies have documented patients who have overdosed receiving a pressor agent, such as dopamine or dobutamine. Our patient did not need these agents, but did receive naloxone 2 mg. There are other studies in which young children have received naloxone for a guanfacine or clonidine overdose, and in some cases it was beneficial for the patient. In one study, a 2-year-old received naloxone for a guanfacine overdose because of the symptoms of bradycardia, hypotension, and drowsiness, and an 11-month-old received naloxone in addition to activated charcoal and was intubated, because this patient had miosis and drowsiness, and was in a coma (McGrath and Klein-Schwartz 2002). In another study, a 4-year-old male developed symptoms after taking 2 mg of guanfacine extended release. He received two doses of 0.1 mg/kg naloxone intravenously, and then was started on an IV infusion of naloxone because of hypotension, drowsiness, and bradycardia; this intervention was determined to be beneficial (Tsze and Dayan 2012). However, in our case, it did not make a difference in the hemodynamics or somnolence symptoms our patient presented.

The final reason relates to the potential interaction between guanfacine extended-release and the patient's other home medications (dexamethylphenidate and risperidone). There have been reports of increased irritability, agitation, and hyperactivity upon switching ADHD management from risperidone to methylphenidate (examples include a 6-year-old male, a 6-year-old female, and a 15-year-old female, all with ADHD, and either oppositional defiant disorder or borderline intellectual functioning). It is known that methylphenidate can increase blood pressure via sympathomimetic activity, whereas guanfacine can decrease blood pressure via sympatholytic activity. It is also known that both guanfacine and risperidone are synergistic, which can lead to central nervous system depression. However, there are currently no documented interactions among guanfacine, methylphenidate, and risperidone, and although some sources state that the effects of all three medications together can be minimal, it is still important to closely monitor therapy.

The addition of extended-release α adrenergic agents to the roster of approved medications for treatment of ADHD increases the number of drugs available for mistaken use. Clinicians should be aware of the potential risks associated with misuse of these agents, and counsel patients and families accordingly.

Acknowledgments

The authors thank Marcel J Casavant, MD, FACEP, FACMT and Amy Reed (Doctor of Pharmacy candidate) for their comments on management of guanfacine overdose.

Disclosures

Dr. Walton receives support from Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau. Dr. Coury receives research support from Autism Speaks, HRSA/Maternal and Child Health Bureau, SynapDx, and Neuren Pharmaceuticals for activities unrelated to this case report. The other authors have nothing to disclose.

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