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Clinical Observations

Bupropion Overdose Presenting as Status Epilepticus in an Infant

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ABSTRACT

BACKGROUND: Bupropion is a monocyclic antidepressant in the aminoketone class, structurally related to amphetamines. The Food and Drug Administration withdrew this product from the market in 1986 after seizures were reported in bulimic patients. It was later reintroduced in 1989 when the incidence of seizures was shown to be dose-related in the immediate release preparation. Massive bupropion ingestion has been associated with status epilepticus and cardiogenic shock in adults. Seizures have been reported in children, but not status epilepticus. This report highlights a patient who presented with status epilepticus and developed cardiopulmonary arrest after bupropion ingestion. False-positive amphetamine diagnosis from urine drug screen on presentation was reported. **METHOD:** We review the presentation, clinical course, diagnostic studies, and outcome of this patient. We then review the literature regarding bupropion overdose in children. **RESULT:** Symptoms of bupropion toxicity and risk for seizures are dose-dependent and fatalities have been reported. Our patient developed status epilepticus and cardiopulmonary arrest and then progressed to have a hypoxic ischemic encephalopathy and refractory symptomatic partial seizures. **CONCLUSION:** Our report highlights the need to keep this medication away from children in order to prevent accidental overdose.

Keywords: status epilepticus, cardiogenic shock, hypotension, bupropion, toxicity, children

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Introduction

Bupropion is an atypical antidepressant that was originally approved by the Food and Drug Administration in the United States in 1985 for treatment of depression in adults but was withdrawn by the Food and Drug Administration in 1986 after an increased incidence of seizures was noted in bulimic patients.[1,2] It was reintroduced in 1989 when the incidence of seizures was shown to be dose-related, with an incidence of seizures similar to that of other antidepressants.[3]

Status epilepticus and cardiogenic shock after massive bupropion ingestion has been reported in adults.[4] Seizures have been reported after bupropion overdose in an infant and children,[5-7] but no cases of status epilepticus have been reported in children. Refractory hypotension and transient cardiac dysfunction in an infant from a massive bupropion overdose have been described.[5]

Our report illustrates the unique presentation of an infant with status epilepticus and cardiopulmonary arrest after accidental ingestion of bupropion. She initially exhibited a false-positive drug urine screen for amphetamines. A high frequency of false-positive amphetamine screens resulting from bupropion was recently reported.[8] We review the clinical presentation, hospital course, and diagnostic studies to educate other health care providers about this entity.

Patient Description

Our patient is a 15-month-old previously healthy girl who presented with new-onset seizures. The initial seizure was described as an episode of eye rolling with generalized jerking of all four extremities. She was initially evaluated by paramedics and was noted to be experiencing

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generalized tonic-clonic seizure activity for which she was transferred to a local emergency room and treated with two doses of intravenous lorazepam with transient cessation of seizure activity. She was lethargic and continued to have intermittent seizures consisting of jerking of the upper and lower extremities over the next few hours. Approximately 7-8 hours from presentation, she had worsening of the rhythmic jerking and was treated with a third dose of intravenous lorazepam (doses of lorazepam not documented in available records) and a loading dose of fosphenytoin (20 mg/kg).

She had no improvement in her mental status over the next several hours. Approximately 16-17 hours after initial presentation, she became apneic with pulseless cardiac arrest. Intubation and cardiopulmonary resuscitation were performed. She received three doses of epinephrine, lactate ringer bolus, and one dose of sodium bicarbonate. After 15-20 minutes, sinus rhythm was restored. She was transferred to the intensive care unit in our tertiary care hospital, where further history was obtained from her mother and grandmother, whose custody she was in at the time of seizure onset. They adamantly denied that the child had access to prescription medications or illicit substances.

The review of systems was significant for mild runny nose and cough, but no fever. Her medical history and birth history was unremarkable, including no history of seizures, meningitis, or head trauma. Family history was positive in the maternal uncle and maternal great-grandfather for seizures. There was no reported family history of psychiatric illnesses. Developmental history including gross motor, fine motor, language, and social skills were appropriated for age.

Her initial physical examination on arrival to our facility included a temperature of 34.4°C, blood pressure 74/52 mmHg, and heart rate 104. Dopamine drip and warming measures were started. She was intubated and had no respiratory effort. Neurological examination revealed bilateral dilated, nonreactive pupils, with gaze deviation to the left, no brainstem reflexes, and no withdraw to painful stimuli.

The laboratory results from the referring hospital showed evidence of metabolic acidosis before her cardiopulmonary arrest with a pH of 7.21, bicarbonate 19 mmol/dL, and base excess of negative 8.7 on an arterial blood gas. Urine drug screen was positive for amphetamines and was negative for barbiturates, benzodiazepine, cocaine, opiates, and cannabinoids. Blood chemistry and liver enzymes were normal. Complete blood count was remarkable for mild microcytic anemia but no leukocytosis.

Computed tomography scan of the head obtained after arrival at the outside facility approximately 1 hour after seizure onset revealed no hemorrhage, edema, mass, or midline shift. Electrocardiogram showed sinus tachycardia that was appreciated on telemetry tracing.

She arrived to our facility after the cardiopulmonary arrest and approximately 22 hours from seizure onset; significant laboratory abnormalities included a blood gas revealing mild lactic acidosis (2.75 mmol/L), pH 7.08, bicarbonate 15 mmol/dL, and base excess of negative 11. Liver function tests revealed an elevated aspartate aminotransferase of 1169 unit/L and alanine aminotransferase of 242 unit/L. Urine drug screen was negative. Lumbar puncture was completed on arrival, and she had 2 white blood cells/F, 193 red blood cells/G, glucose 98 mg/dL, and protein 21 mg/dL.

A five hour electroencephalograph was obtained, within an hour of arrival, and was abnormal with status epilepticus noted for the first 105 minutes, then for the next 3.25 hours intermittent background suppression, and biposterior epileptiform discharges over the left and right parietal, temporal, and occipital head regions. (No further seizures.)

She was treated with two doses of intravenous lorazepam (0.2 mg/kg/dose), one loading dose of levetiracetam (40 mg/kg), and one dose of intravenous fosphenytoin (20 mg/kg) with no improvement in clinical or electrographic seizure activity. However, after one loading dose of intravenous phenobarbital (20 mg/kg), clinical and electrographic seizure activity stopped.

She was treated with supportive care and started on maintenance levetiracetam (40 mg/kg/day given bid), fosphenytoin (8 mg/kg/day), and phenobarbital (5 mg/kg/day) all given intravenously. Over the next 24 hours, spontaneous eye opening, corneal reflex, and gag reflex were appreciated. She also had irregular respiratory effort. She continued to have gaze deviation, no tracking, and minimal movement of all four extremities to noxious stimuli. Echocardiography was performed 22 hours after seizure onset and it revealed normal anatomy, ventricular size, and systolic function.

Magnetic resonance imaging of the brain and brainstem performed 48 hours after cardiopulmonary arrest showed findings consistent with severe hypoxic ischemic encephalopathy with areas of restricted diffusion involving bilateral occipital lobes, bilateral superior aspect of the lentiform nuclei, and caudate nucleus. (Figure).

Over next few weeks, she showed clinical signs of global hypoxic ischemic encephalopathy, including cortical blindness and spastic quadriparesis. Tracheostomy and gastric tube placement were required. She developed symptomatic, refractory partial epilepsy and is currently taking multiple medications.

Although the family adamantly denied that she took any medications, confirmatory laboratory testing of her serum was submitted on arrival to our facility. High-power liquid chromatography detected bupropion.

Discussion

Our patient presented after experiencing multiple seizures followed by cardiopulmonary arrest requiring cardiopulmonary resuscitation. Afterwards she was noted to be in status epilepticus (i.e., electroencephalographic and subtle clinical seizures) that was responsive to phenobarbital treatment. The initial clinical presentation of acute onset seizures in a previously developmentally normal and healthy infant with a positive urine drug screen for amphetamines and a negative computed tomography could be explained by amphetamine ingestion. However, the status epilepticus and cardiopulmonary arrest, followed by significant hypotension, were not as easy to explain, especially given the repeat urine drug screen was negative for amphetamine. Further diagnostic studies including cerebrospinal studies were negative for central nervous system infection. The rest of the laboratory studies showed lactic acidosis, metabolic acidosis, and elevated liver function test, all a consequence of the cardiopulmonary arrest. The etiology of the arrest did not become completely clear until chromatography confirmed bupropion ingestion.

Bupropion is an atypical monocyclic antidepressant commonly prescribed in the United States for the treatment of major depressive disorder, seasonal affective disorder, adult attention deficit hyperactivity disorder, and smoking cessation. All forms of bupropion combined totaled 20,745,363 prescriptions in the United States in 2008.[9] The amino-ketone structure of bupropion is metabolized in the liver by the cytochrome P450 isoenzyme CYP2B6 to the active metabolites R,R-hydroxybupropion, S,S-hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, which are responsible for the pharmacological activity of bupropion.[10] Different formulations are available for bupropion including immediate, sustained, and extended-release. It has a plasma half-life of 10 hours, but longer half-lives have been reported for the metabolites.[6]

Bupropion, erythrohydrobupropion, and threohydrobupropion have chemical structures similar to amphetamine, which may result in cross-reactivity with antibodies used in urine drug screen immunoassays.[8-10] Three reports demonstrated false-positive amphetamine urine drug screens associated with bupropion. A recent study evaluating the incidence of false-positive amphetamine screening associated with therapeutic use of bupropion showed that bupropion appeared to be the most frequent cause of false-positive urine drug screens for amphetamines