

Case report

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Bupropion overdose in adolescents: Three cases illuminating presentations and sequelae - A case series and review

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Abstract

Bupropion is a dopamine, norepinephrine, and serotonin reuptake inhibitor that is being prescribed more frequently as an antidepressant. It is also often used for a variety of other clinical indications. Limited information is available about the varied presentation of bupropion overdose, with few cases reported highlighting these presentations. There have recently been a rising number of calls to poison centers involving bupropion overdose in adolescents and young adults. This trend was acutely seen in October 2017 when three adolescents presented to a tertiary care University Children's Hospital in suburban New York following overdoses in attempted suicide. All three cases of bupropion overdose reviewed resulted in generalized tonic-clonic seizures and required intubation for at least three days, with one patient intubated for seven days. They experienced varying degrees of other symptoms including severe cardiotoxicity with vast prolongation of QTc, hallucinations, persistent tachycardia and tachypnea, loss of gag reflex, aspiration pneumonia, and agitation. One patient experienced significant neurologic findings mimicking the presentation of brain death, including absent doll's eye and corneal responses, fixed and dilated pupils, flaccid limbs with areflexia, and burst suppression pattern on EEG. These cases provided an opportunity to bolster the body of literature of varied clinical presentations of bupropion overdose.

Keywords: bupropion; depression; dopamine; suicide; overdose; norepinephrine

Introduction

Bupropion is being prescribed as an antidepressant in the child and adolescent population due to the widely held opinion that it has a more tolerable side effect profile than other antidepressants [1, 2]. In fact, among the newer antidepressants, bupropion has been said to have the lowest incidence of sexual dysfunction, weight gain and somnolence [3]. While bupropion is prescribed to children and adolescents off-label as an antidepressant, it is also available in their homes due to its multiple indications such as weight loss, smoking cessation, seasonal affective disorder, attention deficit/hyperactivity disorder (ADHD), neuropathic pain, and restless leg syndrome [2, 4]. There have recently been a rising number of suicide attempts by bupropion in adolescents and young adults [1]. Bupropion overdose can present with a broad variety and constellation of findings, including drug-induced seizures, cardiotoxicity, tachycardia, agitation, hallucinations, delusions, vomiting, tremor, hypertension, and brain death-mimicking symptoms, with approximately 20% of bupropion overdoses in adolescents resulting in major clinical outcomes [4-11].

Over the course of one month in 2017, three cases of adolescents overdosing on bupropion in attempted suicide presented to the same Children's Hospital, adding to the existing literature and allowing for an opportunity to review the danger of bupropion overdose.

Case reports

Case one

15-year-old female with a history of depression, suicidal ideation, and ADHD, admitted after a suicide attempt with 10 grams of Wellbutrin XR and 11 mg of clonidine.

On the day of admission the patient was found by a family member with a depressed level of arousal and a suicide note that detailed the amount of pills taken. On arrival to the emergency department, she was hypotensive, with dilated pupils that were minimally reactive. She became agitated requiring restraints and had two witnessed generalized

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tonic-clonic seizures, for which she received doses of lorazepam intravenously. However, the convulsions continued with persistent tachycardia and tachypnea, requiring endotracheal intubation. The patient was found to have severe pulmonary edema requiring diuretics, as well as a prolonged QTc interval. She had elevated creatine kinase levels. She developed a fever and was treated for aspiration pneumonia.

Her subsequent course was marked by steady improvement, and she was extubated in three days, with resolution of her prolonged QTc, downward trend of creatine kinase level, and no further seizure activity noted.

Case two

18-year-old female with history of anxiety and depression, admitted after an intentional overdose on 27 grams of Wellbutrin.

On the day of admission, she was found in the morning by a stranger, on the ground, disoriented but awake and responding appropriately, when she admitted to having made a suicide attempt. She was taken to the hospital, where she subsequently lost consciousness and had several generalized tonic-clonic seizures, each lasting a few minutes, which responded to intravenous lorazepam. However, due to depressed arousal and respiratory compromise, she was intubated and activated charcoal was given.

On day two of hospitalization, her exam was notable for hypotension and significant neurological findings including absent doll's eye and corneal responses, fixed and dilated pupils, and flaccid limbs with areflexia. She had periodic myoclonic jerks and burst suppression tracing on EEG.

Subsequent course was marked by steady improvement, with myoclonic jerk and EEG burst suppression improving on hospitalization day three and four, pupillary response and response to simple commands improving on day six, and extubation on day seven.

Case three

17-year-old female with history of depression and one prior suicide attempt, admitted after overdosing on Wellbutrin SR and Seroquel. The exact number of pills taken is unknown, but the patient was found with two empty bottles of Wellbutrin SR 200mg tablets with a 20 pill capacity (4 grams total), and Seroquel 100mg tablets with a 45 pill capacity (4.5 grams total).

On the day of admission, she was found in the evening by her mother. The patient was brought to the hospital where her mental status worsened as she became more confused, her gag reflex was absent, and she required intubation. Her electrocardiogram showed a prolonged QTc interval of greater than 550ms. She had one generalized tonic-clonic seizure that responded to intravenous lorazepam.

The patient was extubated in three days. Following extubation, the patient experienced episodes of hallucinations and emotional instability, however the patient continued to improve, with resolution of her

prolonged QTc interval and hallucinations. She did not have additional seizures. Trans-thoracic echocardiogram performed also demonstrated normal findings.

Results

These cases highlight the vast majority of the symptoms that have thus far been recorded in the literature in cases of bupropion overdose. All three of these cases resulted in generalized tonic-clonic seizures, and they all required intubation, ranging from three to seven days. The patients also all experienced varying degrees of hallucinations and agitation, persistent tachycardia and tachypnea, and loss of gag reflex complicated by aspiration pneumonia. Of the differences, two of the patients experienced severe cardiotoxicity with vast prolongation of QTc. One experienced significant neurologic findings resulting in absent doll's eye and corneal responses, fixed and dilated pupils, flaccid limbs with areflexia, and an EEG with a burst suppression pattern, mimicking the presentation of brain death. Despite the differing symptoms and degrees of severity, all three of the patients recovered completely and were transferred to inpatient psychiatric units.

Discussion

Bupropion is an atypical antidepressant medication that inhibits dopamine, norepinephrine, and serotonin reuptake in the brain [3]. In addition, its acute administration has been shown to reduce firing of dopamine and norepinephrine neurons in the brainstem, along with inhibiting firing rates of norepinephrine neurons in the locus ceruleus [3]. It is hepatically metabolized into active metabolites and renally cleared. It exhibits linear kinetics and the approximate elimination half-lives of its metabolites are 20 (\pm 5) hours for hydroxybupropion, 33 (\pm 10) hours for erythrohydrobupropion, and 37 (\pm 17) hours for threo hydrobupropion [12].

Prior studies have explored many of the side effects of bupropion, and the fact that bupropion is an antidepressant that, when ingested in overdose by adolescents, can have serious outcomes and hospitalizations has recently been reported by various studies [1]. The most universally reported major side effect of bupropion overdose is drug-induced seizures. Multiple case studies have demonstrated this point [5, 7]. This adverse effect was seen in all three cases highlighted above, as they all resulted in generalized tonic-clonic seizures. The mechanism for these seizures is largely unknown, but bupropion has been demonstrated to lower the seizure threshold, making it contraindicated in patients with seizure disorders [13]. In addition, as is seen in our three patients, there have also been reports of seizures after bupropion overdoses in patients with no prior history of these disorders [13, 14]. A 2013 report with data from 37 toxicology centers identified bupropion, followed by anticholinergic agents, as being the most common source of drug-induced seizures in the pediatric population [15].

Other more potentially life-threatening side effects have been noted in multiple case reports. One such study reviewed 2253 ingestions of bupropion in overdose compared with 1496 ingestions of tricyclic antidepressants reported

to a regional poison center. This study demonstrated a greater incidence of hallucinations, delusions, vomiting, tremor, tachycardia, and hypertension, in addition to single seizures, in the bupropion group than was found in the TCA group. Other such case studies have corroborated the side effects of tachycardia and cardiotoxicity, agitation, hallucinations, non-epileptic myoclonus, and seizures in adolescents and young adults ingesting bupropion in overdose [5-7, 9, 11]. These findings were also seen in our patients in varying degrees. Cardiotoxicity is a potentially life-threatening side effect of bupropion overdose, and can remain refractory to medical management, requiring venoarterial extracorporeal membrane oxygenation (VA-ECMO) [16]. There has been evidence of QRS segment widening and QT prolongation, which are thought to occur secondarily to changes in gap junctions between myocytes [3]. Two of our patients experienced such severe cardiotoxicity, resulting in QT prolongation.

Few cases have been reported where ingestion of bupropion in overdose resulted in a coma. One such case report stated that a 51-year-old woman who ingested 27g of bupropion in overdose resulted in a coma associated with EEG-burst-suppression and brief tonic seizures following her overdose from which she awoke three days later [8]. Similarly, another case report found a 13-year-old girl who suffered a bupropion overdose resulted in a coma associated with absent brainstem reflexes, EEG-burst-suppression and a normal CT scan [10]. A third case report presented along with the above case and cited from the American College of Physicians Colorado Chapter Annual Meeting in 2008, found a man who had been declared brain dead but was discovered to have regained some brainstem and cerebral functioning during the process of sterilization for organ harvest, and was able to return to baseline with no neurologic sequelae [4, 10]. These are symptoms similar to those found in one of our patients. The fact that this patient not only ingested the largest dosage of bupropion, but that she also solely ingested bupropion, highlights the gravity of its presentation.

Conclusion

Because of the multiple indications for bupropion use and an increase in its prescribing, it is important to recognize the various presentations of patients who overdose on bupropion so that they can be accurately diagnosed and treated. The presentation may mimic status epilepticus, cardiotoxicity, brain death, and/or intoxication with other psychoactive agents. Brain death in particular should not be declared until the drug has been fully eliminated from the patient's system, as this can result in a devastating error. In addition, the dangerousness of overdose should be considered when prescribing the medication to both adolescents and to adults with children in the home. This report is limited by the small number of cases in the series, as well as the ingestion of other psychotropic medication in two of the cases.

Conflicts of interest

Authors declare no conflicts of interest.

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