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A 19-Year-Old Woman with a History of Depression and Fatal Cardiorespiratory Failure Following an Overdose of Prescribed Bupropion

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 19-year-old
Final Diagnosis: Poisoning by bupropion
Symptoms: Altered mental status • cardiogenic shock • seizure
Medication: —
Clinical Procedure: —
Specialty: Toxicology

Objective: Management of emergency care

Background: Bupropion is a norepinephrine/dopamine-reuptake inhibitor (NDRI) that has been reported to increase the risk of suicide attempts in some patients. This report is of a case of a 19-year-old woman with a history of depression who suffered fatal cardiorespiratory failure following an overdose of prescribed bupropion.

Case Report: A 19-year-old woman presented to the Emergency Department with an estimated bupropion overdose of 28.2 g and possible oxcarbazepine co-ingestion. This serum level was estimated based on the patient's history of medication reconciliation and number of pills remaining in the prescription bottle at presentation. The patient was unresponsive on arrival to the Emergency Department and was treated for intermittent seizures and shock. Despite aggressive medical interventions, her condition progressed to cardiogenic shock and eventually cardiac arrest, from which she could not be resuscitated. Several existing reports regarding bupropion overdose describe sinus tachycardia and seizures corrected by symptomatic treatment. This case may document the highest reported ingestion of bupropion recorded thus far in the literature and demonstrates the rapid onset of cardiac dysfunction and cardiogenic shock.

Conclusions: In the context of this case, we discuss the clinical manifestations of bupropion overdose and the rapid progression to cardiogenic shock. By examining the pathophysiology of overdose in an adolescent who consumed an extremely high dose of bupropion, we hope this information can be helpful to clinicians who are managing similarly challenging critical cases.

Keywords: Bupropion • Critical Care • Drug Overdose • Emergency Medicine • Psychiatry • Toxicology

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Background

Bupropion is a norepinephrine/dopamine-reuptake inhibitor (NDRI) that has been reported to increase the risk of suicide attempts in some patients [1]. This highly lipophilic drug undergoes extensive stereoselective metabolism into its major active metabolites, hydroxybupropion, threohydrobupropion, and erythryohydrobupropion, which reach even higher plasma concentrations than does bupropion. Bupropion is often prescribed in the primary care setting for depression, smoking cessation, anxiety disorders accompanying alcoholism, and bipolar disorder [2]. Although the toxic dose of bupropion has not been established, seizures can occur even at therapeutic doses of up to 450 mg/day and occur almost universally in overdoses of greater than 6 g. Although fatalities are rare, they usually involve overdoses of greater than 9 g. Doses range from 75 mg up to 522 mg for the once-daily form using intranasal insufflation or intravenous methods of administration. Notable adverse effects of bupropion use include insomnia, agitation, seizures, headache, dry mouth, and nausea. When neurological effects start to manifest, bupropion overdose should be considered and carefully managed to prevent cardiopulmonary arrest as a consequence of hypoxia and metabolic acidosis [3]. This report is of a case of a 19-year-old woman with a history of depression who suffered fatal cardiorespiratory failure following an overdose of prescribed bupropion.

Case Report

A 19-year-old woman presented to the Emergency Department (ED) after a reported bupropion and oxcarbazepine overdose. Her past medical history was significant for asthma, eating disorder, and mood disorder with depressive features.

The patient presented to the ED after being found unresponsive by Emergency Medical Services (EMS) approximately 60 min after an intentional ingestion, of which she had notified her family via text message. Her bottle of 150-mL XL bupropion HCl, which was refilled with 200 tablets 13 days prior, was found empty, and an oxcarbazepine bottle was found partially empty. The patient had 4 seizures during transport to the ED and was treated by EMS with intravenous midazolam, but remained unresponsive throughout transport to the hospital.

On arrival in the ED, the patient presented with hypertension (blood pressure 143/99 mmHg), tachycardia (pulse 169 beats/min), and mild hypothermia (temperature 36°C). She was unresponsive, with intermittent convulsions, non-reactive mydriasis, and warm, diaphoretic skin.

The patient's relevant laboratory findings are shown in **Table 1**.

Table 1. Laboratory findings.

Lab finding	Value	Reference range
CO2 (mEq/L)10	10	22-30
Anion Gap	30	5-16
Sodium (mg/dl)	142	137-145
Potassium (mg/dl)	3.5	3.5-5.3
Chloride (mg/dl)	102	98-107
Blood urea nitrogen (mg/dl)	11	7-17
Creatinine (mg/dl)	0.75	0.00-1.11
AST (U/L)	29	(14-36)
ALT (U/L)	22	(11-66)
Serum phosphate (mg/dl)	7.7	2.5-4.5
Calcium (mg/dl)	9.3	8.8-10.5
White blood cell count (K/uL)	12.5	3.7-4.1
Hemoglobin (g/dL)	9.7	11.5-15.0
Platelet count (K/uL)	665	140-400
Arterial blood gas		
pH	7.27	7.35-7.45
PaCO2 (mmol/L)	44	35-45
HCO3- (mmol/L)	19.3	23-28
Base excess (mmol/L)	-7.9	-2.4-2.3

The patient's chest X-ray showed no acute pathology, and her electrocardiogram (ECG) was notable for a normal sinus rhythm with QT prolongation (541 ms) and a left bundle branch block.

Management of the patient included rapid-sequence intubation, without induction or paralysis, as she was completely unresponsive. Activated charcoal and whole-bowel irrigation were initiated via an orogastric tube. The patient became hypotensive, requiring multiple vasopressor supports with norepinephrine (0.25 mcg/kg/min) and phenylephrine (0.5 mcg/kg/min). The inpatient toxicology service was consulted and recommended administration of intravenous lipid emulsion (Intralipid), seizure control with propofol, vasopressor support as needed, and bicarbonate boluses for QRS widening or ventricular dysrhythmias. The patient was admitted to the Intensive Care Unit (ICU), where she received multiple bicarbonate and magnesium boluses for QRS widening on ECG and QTc prolongation, respectively, as well as 2 additional boluses of Intralipid. An urgent echocardiogram showed an ejection fraction of 10% to 20%, with global left and right ventricle

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hypokinesis. On examination, the patient had persistent hypotension and widening QRS on ECG despite correction of electrolytes, Intralipid, and bicarbonate boluses.

The patient was emergently transferred via helicopter to another care facility with capabilities for veno-arterial extracorporeal membrane oxygenation (VA-ECMO). En route, she received multiple vasopressor supports, including epinephrine 0.5 mcg/kg/min, norepinephrine 1 mcg/kg/min, neo-synephrine 2 mcg/kg/min, vasopressin 0.04 u/min, and dopamine 10 mcg/min. The latter was discontinued shortly after arrival at the helipad because of worsening hypotension.

Upon arrival at the helipad at the new facility, she went into a ventricular fibrillation cardiac arrest. Resuscitative efforts, including cardiopulmonary resuscitation, defibrillation (twice), and multiple boluses of epinephrine and calcium chloride, achieved brief periods of return of spontaneous circulation, which could not be maintained despite increasing inotropic and vasopressor support. Serial point-of-care cardiac ultrasounds showed a progressive decline in cardiac function, and the patient reverted to a pulseless electrical activity cardiac arrest. The patient was pronounced dead after prolonged, aggressive resuscitation efforts failed to achieve a return of spontaneous circulation.

Discussion

This case highlights the rare development of cardiogenic shock with no recovery, despite aggressive goal-directed treatment. Bupropion has been shown to delay rectifier potassium current, disrupt cardiac coupling via gap junctions, and block voltage-gated sodium channels, resulting in QT prolongation and QRS widening [4,5]. Oxcarbazepine is known to suppress action potential firing by blocking voltage-gated sodium channels and potassium currents [6]. Bupropion can also induce the release of catecholamines, leading to autonomic depletion and resulting in profound hypotension and bradycardia [7].

One study reported that only 3 (2.6%) of 116 patients with bupropion overdose developed seizures, supraventricular tachycardia, and conduction delays but recovered within 2 to 4 days following ingestion. Life-threatening arrhythmias were not observed in any patients. The data suggest that less than 0.5% of reported bupropion overdoses result in death [8]. The most commonly reported symptom of cardiovascular toxicity is sinus tachycardia, seen in 40% of cases [9]. In another study of 69 adult bupropion overdoses, a dose-dependent relationship was correlated with seizure activity. Every patient who ingested more than 60 tablets of bupropion experienced generalized tonic-clonic seizures [10]. The severity of seizures following bupropion overdose is associated with peak serum and cerebral concentrations, which are 10 to 25 times higher than the plasma concentration [11-13]. Although serum bupropion concentrations were not obtained in our patient, and pill counts can be a generally poor estimate of the actual ingested dose, the estimated ingestion of 28.2 g seems consistent with the subsequent presentation and complications.

From 2013 to 2017, there were 30 026 cases coded as "suspected suicide" related to adolescent exposure to SSRIs or bupropion. Bupropion was associated with only 11.7% of the attempted suicides and was implicated in all 8 deaths recorded in the study [14]. As evidenced in this report, physicians should be aware of the prevalence of bupropion abuse and should screen for any risk of seizures prior to administration to avoid cardiotoxic and neurotoxic adverse effects. Oxcarbazepine has also been implicated in causing seizures in young patients [15]. According to our patient's limited medical history, it is possible that she may have also suffered from bulimia. Frequent vomiting and laxative use in bulimic patients can cause dehydration and intermittent hypokalemia, which increases the risk of QT prolongation. Drugs that prolong the QT interval should be avoided, and renally excreted drugs like bupropion should be used with caution because their impaired elimination can increase the risk of seizures [16].

This patient's laboratory tests showed signs of an anion gap metabolic acidosis. Metabolic acidosis and hyperphosphatemia are known to share a pathogenic relationship, especially in the case of kidney disease. Of note, the patient presented with hyperphosphatemia, which is inconsistent with the electrolyte findings of hypophosphatemia seen in other bupropion overdose reports [17]. Bupropion overdose has been reported to cause metabolic acidosis and reduced cardiac contractility unresponsive to inotropic support due to lack of responsiveness from beta adrenergic receptors in the damaged myocardium [18]. Severe metabolic acidosis following seizures, especially generalized tonic-clonic seizures and status epilepticus, is a classic finding due to muscle hypoxia following convulsions. This patient's seizure activity following bupropion overdose may therefore explain her electrolyte abnormalities [19]. Other possible explanations for transient hyperphosphatemia in this patient include severe dehydration episodes with possible intravascular volume depletion or nephrotic syndrome with normal renal function [20].

In bupropion overdose, patient management is largely supportive as there is no antidote. When patients ingest a considerable amount, they should be admitted to the ICU, with continuous cardiac monitoring for the development of arrhythmias, seizures, and hypoxia [17]. Monitoring of blood and CSF concentrations of bupropion and its metabolite hydroxybupropion can be useful to predict toxicity symptoms and determine appropriate therapy. Intralipid can be administered to reduce myocardial depression following drug toxicity by providing

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an additional substrate for the cardiotoxic drug. Formal protocols exist for lipid emulsion therapy for toxicity due to local anesthetics such as bupivacaine, but there is currently no FDA-approved indication for lipid emulsion therapy in non-local anesthetic poisoning [21]. Intralipid has been used in critical care settings for life-threatening bupropion toxicity after other agents have failed or after return of spontaneous circulation but may not be a universally effective treatment for bupropion toxicity [22]. Furthermore, the use of lipid infusion in conjunction with plasmapheresis for treatment of acute bupropion toxicity has been shown to promote stabilization by the elimination of bupropion complexed to lipids and proteins. However, few cases of plasmapheresis have been reported owing to the difficulty in timely delivery of this therapy upon ED admission [23]. Interestingly, lipid emulsion therapy did not have a beneficial clinical effect on our patient despite administration before severe cardiac deterioration [24]. Although our patient died before receiving VA-ECMO therapy, she may have benefited from plasmapheresis and early ECMO. These therapies have been shown to increase survival in young adult patients with severe cardiovascular collapse due to beta blockers, calcium channel blockers, antiarrhythmics, and antidepressants [25-27].

Other strategies for removing bupropion after an overdose include administering activated charcoal and performing whole-bowel irrigation to remove the drug from the system before absorption. Activated charcoal can bind lipophilic bupropion in the gastrointestinal tract [28]. Whole-bowel irrigation to prevent medication absorption should be considered for a large ingestion of sustained-release tablets, although it is frequently performed incorrectly, and the efficacy of this treatment for bupropion specifically has not been proven and there are several known complications, including abdominal distention, hypotension, and vomiting [29].

Our patient's echocardiogram showed global hypokinesis. This finding can be explained by bupropion's inhibitory effects on the myocardial action potential, which reduces the mechanical activity of the ventricles. A similar case highlighted a bupropion overdose of 12 g that resulted in combined right and left ventricular hypokinesia without ventricular dilatation. Similar to our patient, the ejection fraction for this patient was severely reduced and estimated to be between 12% and 17%. Dobutamine (30 µg/kg/min) was immediately administered and norepinephrine was gradually stopped, resulting in the restoration of normal cardiac output [30]. However, our patient failed to respond appropriately to lipid emulsion therapy and vasopressors, indicating the severity and rapid progression of her cardiovascular collapse.

Conclusions

In the context of this case, we discuss the clinical manifestations of bupropion overdose and the rapid progression to cardiogenic shock by examining the pathophysiology of overdose in an adolescent who consumed large amounts of bupropion. This case report further highlights the importance of exercising caution when prescribing bupropion and other antidepressants to adolescent patients, especially patients with eating disorders. We hope this information can inform clinicians on how to manage these challenging cases.

Statement

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Conflict of Interest

None.

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