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Journal of Clinical Toxicology

Case Report

Massive Bupropion and Oxcarbazepine Overdose

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ABSTRACT

Context: To describe a case of massive bupropion overdose leading to cardiac toxicity and seizures in an adolescent suicide.

Case: A 19 year old female presented to the emergency department with an estimated bupropion overdose of 28.2 grams with possible oxcarbazepine consumption. The patient was unresponsive and was treated for intermittent seizures and cardiogenic shock but could not be resuscitated and died within 48 hours.

Discussion: Several existing reports regarding bupropion overdose describe sinus tachycardia and seizures corrected by symptomatic treatment. However, to our knowledge, this case documents the highest ingestion of bupropion recorded thus far in literature and demonstrates the rapid onset of cardiac dysfunction.

Keywords: Bupropion overdose; Oxcarbazepine; Cardiogenic shock; Seizures

INTRODUCTION

Bupropion is an anti-depressant of the aminoketone class that inhibits the reuptake of dopamine and norepinephrine. The drug is prescribed for depression, smoking cessation, anxiety disorders accompanying alcoholism, and bipolar disorder. Bupropion reaches peak plasma values within three hours of ingestion and has a half-life of 21 hours, with metabolite formation taking up to 40 hours. It is absorbed orally with 85% protein binding while first pass metabolism occurs in the liver *via* CYP2B6 [1]. In a bupropion overdose, the onset of neurological and cardiac symptoms can be delayed up to 8 hours with immediate release, 14 hours with sustained release, or 24 hours with extended release formulations [2]. Bupropion has a narrow therapeutic index with a maximum daily dose of 450 mg due to the drug's seizure-inducing effects at daily doses of 600 mg or higher. Oxcarbazepine is an anti-epileptic prodrug that exerts its effects by blocking voltage-gated sodium channels and decreasing action potential firing. Oxcarbazepine does not have many cases of reported toxicity, as it does not produce an epoxide metabolite. In this report, we highlight an overdose due to an unknown amount of oxcarbazepine and 28.2 g of bupropion resulting in seizures, cardiotoxicity, cardiogenic shock and ultimately death.

CASE REPORT

A 19-year-old female presented to the ED (Emergency Department) for a bupropion and oxcarbazepine overdose. The patient had intentionally overdosed and 60 minutes later was found prone and unresponsive by EMS (Emergency Medical Services). Her 150 ml XL bupropion HCl bottle which was refilled with 200 tablets 13 days prior was found empty, and her oxcarbazepine bottle was partially empty. The patient had four seizures during transport to the ED and had a Glasgow Coma Score (GCS) of three, with no withdrawal to pain in any extremity throughout the transport. The patient's medical history was significant for asthma, eating disorder, and mood disorder with depressive features.

In the ED, the patient presented with hypertension (BP 143/99 mmHg), tachycardia (pulse 169 beats/min), and mild hypothermia (temperature 36°C). On exam, she appeared obtunded with intermittent convulsions, had non-reactive mydriasis, and warm, diaphoretic skin. She was intubated for severe AMS (Altered Mental Status). Her relevant labs included decreased CO_2 (10 mEq/L), increased anion gap, increased serum/plasma (30 mEq/L), and hyperphosphatemia (7.7 mg/dL). Patient's CBC showed elevated WBC (12.5 K/uL), decreased Hgb (9.7 g/dL), increased RDW of RBC (25.6%), and

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Received: July 03, 2020; **Accepted**: July 17, 2020; **Published**: July 24, 2020

Citation: Sathe A, Thiemann A, Toulouie S, Durant E (2020) Massive Bupropion and Oxcarbazepine Overdose. J ClinToxicol. 10:448. DOI: 10.35248/2161-0495.20.10.448

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elevated platelet count (665 K/uL). Arterial blood gas analysis showed decreased corrected arterial blood pH (7.27), increased PaO_2 (98 mmHg), decreased HCO_3- (19.3 mmol/L), and low base excess (-7.9 mmol/L). No illicit drugs such as stimulants, hallucinogens, or narcotics were detected in the urine drug screen.

Over the next three hours, the patient's severe hypotension improved and blood pressure normalized. However, the patient remained tachycardic. Sodium Chloride 0.9% IV Bolus was given for dehydration in order to achieve hemodynamic stability. Etomidate (20 mg) was administered for sedation and induction of anesthesia. Fentanyl (PF) Inj 50 mcg and Propofol 1000 mg/100 mL IV premix were administered for anesthesia. RocuroniumInj 29.9 mg was administered as a paralytic for rapid sequence intubation. Norepinephrine in normal saline 4 mg/250 mL (16 mcg/mL) IV solution was given for hypotension. LorazepamInj 2 mg was given for seizures. Magnesium Sulfate in 5% Dextrose Injection 1 g/100 mL IV premix was given for prevention of recurrent seizures and treatment of cardiac arrhythmias. Naloxone Inj 2 mg was given to reverse any possible opioid depression. After consulting with a toxicologist, two doses of Intralipid were given to reduce myocardial depression. Oral suspension of 25 g of activated charcoal was administered to prevent absorption of bupropion and oxcarbazepine into the bloodstream. Lastly, COLYTE Oral Solution was given to prep the patient for whole bowel irrigation.

The patient's chest x-ray showed no acute pathology and her electrocardiogram (ECG) showed normal sinus rhythm with QT prolongation (541 ms) and a Left Bundle Branch Block. Toxicology recommended to considerVeno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO). The patient was admitted to the ICU. A repeat ECG showed QT prolongation and 2 amps of Bicarbonate IVP and 2 additional bolus of Intralipid were administered. On urgent echocardiogram, she appeared to have an Ejection Fraction (EF) of 10%-20%, global left and right ventricle hypokinesis, and mild mitral regurgitation.

Due to her deteriorating status, the patient began air transportation for further management on VA-ECMO at another care facility. Upon arrival at the helipad at the new facility, the patient went into Ventricular Tachycardia (VT), which progressed into asystole. Epinephrine (0.5 ug/kg/min), Norepinephrine (0.5 ug/kg/min), Neo-Synephrine (0.5 ug/kg/min), Vasopressors (0.04 units/min), and Dopamine (10 ug/min) were administered on route as the patient had worsening hypotension. Bedside Transthoracic Echocardiogram (TTE) showed 10% EF but no cardiac standstill. The patient was again administered Epinephrine (0.5 ug/kg/min), Levophed (1 ug/kg/min), Neo-Synephrine (0.2 ug/kg/min), and Vasopressors (0.1 units/min). The patient's systolic blood pressure continued to drop to the 20's and TTE showed 5% EF resulting in a Pulseless Electrical Activity (PEA) arrest. The patient showed evidence of frank pulmonary hemorrhage recognized by blood seen in the endotracheal tube originating from the airway, indicating catastrophic deterioration. The patient was pronounced dead after no Return of Spontaneous Circulation (ROSC) despite prolonged CPR.

DISCUSSION

We present a case with massive bupropion overdose associated with cardiotoxicity, seizures, and death following cardiogenic shock. It is estimated that our patient ingested approximately 28.2 g of bupropion based on limited information regarding the date her prescription refill and the number of pills dispensed. Previously reported postmortem blood concentrations of bupropion overdose range from 3.12 mg/L to >20 mg/L [3]. Although extended release products can exhibit toxicity up to 24 hours after ingestion, this patient exhibited toxicity symptoms within 60 minutes. A negative urine toxicology screen confirmed that this presentation was solely due to the reported overdose on bupropion and oxcarbazepine and no other substances. This case is unique in that it highlights the development of cardiogenic shock with no recovery despite aggressive treatment. Bupropion is associated with numerous cardiovascular side effects including QT prolongation, QRS prolongation, tachycardia, and hypotension.

One report noted that 3 out of 116 patients with bupropion overdose developed seizures, supraventricular tachycardia, and conduction delays but recovered within 2-4 days following ingestion. It is important to note that despite the rare occurrence of conduction delays, severe life-threatening arrhythmias were not observed in any patient. The most commonly reported symptom of cardiovascular toxicity was sinus tachycardia, seen in 40% of cases [4]. Bupropion exhibits inhibition of delayed rectifier potassium current (IKr) in isolated guinea pig hearts, which can explain the QT prolongation seen in some overdose cases. Meanwhile, observed QRS widening could be due to the disruption of cardiac intracellular coupling *via* gap junctions or to blockade of voltage-gated sodium channels [5,6].

Oxcarbazepine is known to suppress action potential firing by blocking voltage-gated sodium channels and potassium currents [7]. Bupropion has also been found to suppress Phase 0 of myocardial action potential by binding to voltage-gated sodium channels in the heart, thereby causing QRS prolongation and interfering with conduction by depressing myocardial activity [8]. The blockade of these channels can be partially reversed by hypertonic sodium bicarbonate, although it may not be effective for QRS changes secondary to bupropion ingestion [6]. The patient's acute presentation of seizures and cardiotoxicity can be explained by the massive bupropion overdose, as there is less supporting evidence for oxcarbazepine-induced cardiotoxicity.

Bupropion also induces the release of catecholamines, which have a positive inotropic effect on the myocardium. Bupropion increases peripheral resistance and stress-induced plasma norepinephrine levels, potentially leading to the depletion of catecholamines stores due to autonomic hyperactivity. As a result, patients could experience loss of vascular tone leading to bradycardia and hypotension [9]. One study found that 83% of patients who overdosed on bupropion alone experienced tachycardia while 53% experienced hypertension [10]. Our

patient presented with hypotension with tachycardia, illustrating classic symptoms of cardiogenic shock.

Bupropion's exact role in causing myocardial dysfunction is currently unknown. In one case report, a 26-year-old male ingested 23 g of bupropion and developed seizures, hypoxia, and cardiac arrest. He died due to brain death on his fourth day of hospitalization despite aggressive therapy [11]. This patient ingested an extremely high dose of bupropion and exhibited QT interval prolongation and death similar to our patient. A female adolescent experienced intraventricular conduction delay on ECG and seizures after ingesting 1.5 g, suggesting cardiotoxicity at even lower doses [12]. In patients overcoming a massive overdose, death following asystolic cardiorespiratory arrest has been observed due to delay between ingestion and the start of aggressive treatment [4,11]. Importantly, the data suggests that less than 0.5% of reported bupropion overdose result in death [3].

In a recent study of 385 intentional bupropion overdoses, seizures occurred on average within 6 hours of ingestion, although seizures did occur up to 24 hours after overdose, which could be explained by medication formulation differences [13]. In one 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. The median ingested dose in this study was 36 tablets, or 5.1 g of the drug [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 [14-16]. The patient's presentation was consistent with acute metabolic encephalopathy characterized by generalized depression of cerebral function, and seizures due to the toxic buildup of the drug and its metabolites in the Central Nervous System (CNS). Acute respiratory failure is a common complication of drug abuse, especially in the setting of polysubstance overdose as seen in our patient. Suppression of the respiratory center in the medulla oblongata may cause CNS depression in a dose-dependent fashion. This can impair the function of the respiratory pump. This is often manifested by carbon dioxide retention with hypoventilation and atelectasis leading to hypoxemia [17].

From 2013-2017, 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 eight deaths recorded in the study [18]. 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 side effects. Given this patient's limited medical history, it is possible that she may have also suffered from bulimia. Of note, frequent vomiting and laxative use in bulimic patients can cause intermittent hypokalemia, which increases the risk of QT prolongation. Additionally, bulimia can cause dehydration and electrolyte imbalances. Therefore, drugs that prolong the QT interval should be avoided, and renally excreted drugs like bupropion should be used with caution as their impaired elimination may increase the risk of seizures [19].

The patient's labs showed signs of metabolic acidosis with low pH, low bicarbonate, and a high anion gap. Metabolic acidosis and hyperphosphatemia are known to share a pathogenic relationship, especially in the case of kidney disease. Of note, this patient presented with hyperphosphatemia, which is inconsistent with the electrolyte findings of hypophosphatemia seen in other bupropion overdose reports [20]. In the literature, bupropion overdose has been shown 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 [21]. Severe metabolic acidosis following epileptic attacks, 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 [22]. 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 [23].

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 bradyasystole resulting in seizures and hypoxia [11]. Monitoring of blood and CSF concentrations of bupropion and its metabolite hydroxybupropion can be useful to predict toxicity symptoms and determine appropriate therapy. Intralipids can be administered to reduce myocardial depression following drug toxicity by providing 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 [24]. Intralipids have been used in critical care settings for life-threatening bupropion toxicity after other agents have failed or after ROSC, but there is some evidence of this treatment causing cardiac toxicity as a complication [25]. Furthermore, the use of lipid infusion in conjugation with plasmapheresis for treatment of acute bupropion toxicity has shown to promote stabilization by elimination of bupropion complexed to lipids and proteins. However, few cases of plasmapheresis have been reported due to the difficulty in timely delivery of this therapy upon ED admission [26]. Interestingly, Intralipids did not have a beneficial clinical effect on this patient despite administration before severe cardiac deterioration [27]. While this patient died before receiving VA-ECMO therapy, she may have benefitted from plasmapheresis and early ECMO. These therapies are shown to increase survival in young adult patients with severe cardiovascular collapse due to beta blockers, calcium channel blockers, antiarrhythmics, and antidepressants [28-30].

Other strategies for removing bupropion after an overdose include administering activated charcoal and performing whole bowel irrigation. Activated charcoal, when administered within 60 minutes of a relatively small drug ingestion, can bind

lipophilic bupropion and prevent gastrointestinal contamination if aspiration risk is low [31]. Whole bowel irrigation can be used to remove toxic substances from the gut before they are absorbed and should be considered for a large ingestion of sustained release tablets. The efficacy of this treatment for bupropion specifically has not been proven, and there are several known complications including abdominal distention, hypotension, and vomiting [32].

Global hypokinesis, or reduced ventricular contraction, was observed on echocardiogram and may result in mitral regurgitation due to volume overload. These findings can be explained by bupropion's inhibitory effects on the myocardial action potential, thereby reducing the mechanical activity of the ventricles. A similar case highlighted a 12 g bupropion overdose that resulted in combined right and left ventricular hypokinesia without ventricular dilatation. Similar to our patient, the shortening 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 restoration of normal cardiac output [33]. However, our patient failed to respond appropriately to intralipids and vasopressors which were administered to increase her contractility, indicating the severity and rapid progression of her cardiovascular collapse.

CONCLUSION

We present a case of massive bupropion overdose and highlight the acute development of seizures, cardiotoxic symptoms, and cardiogenic shock with unsuccessful recovery. Physicians should familiarize themselves with symptoms of toxicity following a bupropion overdose and provide aggressive supportive therapy. This includes stabilization of hemodynamics and the administration of anti-seizure medication, lipid emulsion therapy, plasmapheresis, and VA-ECMO to prevent cardiac arrest and respiratory failure.

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