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Case Report

Atypical Antidepressant Toxidrome: A Case Report and a Proposed New Toxicity Syndrome

Hanna S. Sahhar*, Lauren Bailey, Erica Rubin

Department of Pediatric, Edward Via College of Osteopathic Medicine (VCOM)-Carolinas, Spartanburg, South Carolina 29303, United States

ABSTRACT

We report a case of intentional bupropion overdose in an adolescent female who presented with seizure, altered mental status, tachycardia, elevated anion gap, and hyperglycemia. Bupropion is an Atypical Anti-Depressant (AAD) that is typically used to treat major depressive disorder, seasonal affective disorder, and selective serotonin reuptake inhibitor-induced sexual dysfunction. Though there are documented cases of bupropion and other AAD overdose cases in pediatric literature with established presentations, AAD toxicity can still be challenging to recognize. Patients presenting with bupropion toxicity often require high level life sustaining care including airway stabilization and mechanical ventilation, vasopressor and inotropic support, and even extracorporeal membrane oxygenation, making early clinical identification of this toxicity especially important. AAD toxicity should be included in the toxicologic differential of patients with suspected overdose and symptoms including mydriasis, hypertension, tachycardia, or seizures. We propose a new AAD toxidrome to help healthcare providers more quickly identify the toxicity and better care for these patients.

Keywords: Bupropion; Overdose; Toxicity; Antidepressants; Adolescent

INTRODUCTION

Antidepressant medications are used to treat a variety of conditions including Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and Post-Traumatic Stress Disorder (PTSD). Antidepressants can be divided into typical and atypical antidepressants based on their differing neurotransmitter effects. Typical Anti-Depressants (TADs) are divided into four classes: Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), and Monoamine Oxidase Inhibitors (MAOIs) [1]. Atypical Antidepressants (AADs) are those that do not fit into the typical antidepressant classes. Food and Drug Administration (FDA) approved AADs used to treat depression include bupropion, mirtazapine, trazadone, vilazodone, nefazodone, and vortioxetine. Each AAD medication affects serotonin, dopamine, and norepinephrine levels in the brain in distinctive ways to render therapeutic effects [1].

Bupropion is an AAD that is typically used to treat MDD, seasonal affective disorder, and SSRI-induced sexual dysfunction. Additionally, bupropion can be used to assist patients with smoking cessation [2]. Bupropion is available in extended release (XR) and Sustained Release (SR) formulations. When taken as prescribed, SR formulation is generally taken twice per day. By comparison, XR formulation is taken once per day. Both formulations act as an antagonist for dopamine and norepinephrine receptors in the brain to inhibit neurotransmitter reuptake [3].

The use of bupropion monotherapy and add-on therapy has grown in popularity in the last two decades [4]. Like many pharmaceuticals, people may abuse bupropion without having a personal prescription for supposed therapeutic use. Intentional and unintentional toxicities may occur when bupropion is taken in larger doses than prescribed. Bupropion toxicity presentation can differ depending on toxicity levels. In mild overdose cases, patients may present with central nervous system stimulation including increased anxiety, tachycardia, hypertension, tremors,

Correspondence to: Hanna S. Sahhar, Department of Pediatric, Edward Via College of Osteopathic Medicine (VCOM)-Carolinas, Spartanburg, South Carolina 29303, United States, E-mail: hsahhar@vcom.edu

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and hallucinations. In severe overdose, patients may present with QTc prolongation, altered mental status, seizures, cardiac arrythmias, and even death. Even at therapeutic levels, bupropion can induce seizures and status epilepticus by lowering the seizure threshold [2]. AAD overdose requires immediate attention and treatment. Due to adverse effects in overdose, some have even suggested limiting bupropion treatment in patients diagnosed with major depression who have an increased risk of self-harm [5].

Though there are documented cases of bupropion and other AAD overdosage cases in pediatric literature with established presentations [6-8], AAD toxicity can still be challenging to recognize. Patients presenting with bupropion toxicity often require high level life sustaining care including airway stabilization and mechanical ventilation, vasopressor and inotropic support, and even extracorporeal membrane oxygenation (ECMO) [5], making early clinical identification of this toxicity especially important. We propose a new AAD toxidrome to help healthcare providers more quickly identify the toxicity and better care for these patients.

CASE PRESENTATION

A 13-year-old Caucasian female with no significant past medical history presented to the Emergency Department (ED) after intentionally ingesting approximately 15 tablets of bupropion XR (150 mg strength tablet). The patient's mother was present for the initial patient encounter. The mother said that the patient had been depressed recently. Before arrival to the ED, the patient told her mother that she had taken the pills 2.5 hours prior and brought her mother an empty bottle. The patient thought she was taking acetaminophen but instead, she took bupropion that was previously prescribed to her mother for postpartum depression. The mother stated that she did not have acetaminophen in the house.

Upon arrival to the ED, the patient had one generalized tonic-clonic seizure that was treated successfully with two doses of lorazepam. The patient also received a 20 ml/kg normal saline fluid bolus. Physical examination was notable for a conscious but altered and delirious patient with injected conjunctiva and normal muscle tone. The patient was able to answer questions with repeated questioning. Pupils were equal, round, and reactive at 3 mm diameter bilaterally. Vital signs were notable for increased heart rate at 125 bpm and low normal oxygen saturation at 94% on room air. Initial laboratory investigations included a Complete Blood Count (CBC) that was unremarkable. Comprehensive Metabolic Panel (CMP) revealed low serum potassium of 2.9 mmol/L (NR 3.5-5.2 mmol/L), normal corrected total serum calcium of 8.7 mg/dL (NR 8.5-11.5 mg/dL), normal serum sodium of 144 mmol/L (NR 133-146 mmol/L), low serum carbon dioxide of 16.4 mmol/L (NR 23.0-32.6 mmol/L), anion gap was elevated at 22 mmol/L (NR 6-13 mmol/L), and blood glucose was mildly elevated at 125 mg/dL (NR 60-100 mg/dL). Lactic acid level was elevated at 6.2 mmol/L (NR 0.3-2.1 mmol/L). Salicylate, acetaminophen, and ethanol levels were negative. Urine pregnancy test was negative.

Nasogastric tube was placed, and a single dose of activated charcoal was given. Potassium repletion was started with potassium chloride infusion of 20 mEq given over 3 hours. The patient vomited multiple times and was given ondansetron intravenously and repeated as needed. Initial Electrocardiogram (ECG) showed sinus tachycardia with normal QRS duration of 82 msec (normal mean of 70 msec and 98th percentile of 100 msec for age) and normal QTc of 426 msec (normal ≤ 460 msec for age). The patient was admitted to the Pediatric Intensive Care Unit (PICU) for further evaluation and management.

In the PICU, vital signs revealed sinus tachycardia with heart rate of 131 bpm. Blood pressure, respiratory rate, and oxygen saturation were within normal limits for age. Physical examination was largely unremarkable, though the patient was alert and no longer in a post-ictal state. Repeat CBC in 24 hours was within normal limits. Electrolytes abnormalities were corrected, and metabolic acidosis was resolved. Blood glucose remained mildly elevated at 150 mg/dL (NR 60-100 mg/dL).

Psychiatric consultation revealed MDD and overdose with suicidal intent. Questioning and examination showed an anxious, dysphoric patient with constricted affect and poor insight. The psychiatrist recommended initiating involuntary commitment to an inpatient psychiatry unit for further treatment because the patient remained a risk to herself. It was recommended that the patient take Fluoxetine at a dose of 10 mg orally every day. On hospital day three, the patient was medically cleared and back to baseline, although she remained tachycardic at discharge with heart rate of 120 bpm. The patient was discharged to an inpatient psychiatry unit for further care (Table 1).

Table 1: The proposed new atypical antidepressant toxidrome, selected drugs, presentation of toxicity, and treatment options.

Toxidrome	Agents/Drugs	Presentation				Treatment/ Antidote
		Vital signs	Skin	Pupils	Neuro/Mental status	
Atypical Antidepressant	Bupropion Venlafaxine Desvenlafaxine Duloxetine	Hypertension Tachycardia Hyperthermia or Normothermia	Normal or Diaphoretic	Normal or Mydriasis	Agitation Sedation Seizures	Supportive Care Benzodiazepines (for Seizures)

Mirtazapine	Sodium bicarbonate (for prolonged QRS)
Vilazodone	Magnesium sulfate (for prolonged QTc)
Milnacipran	
Nefazodone	

RESULTS AND DISCUSSION

AAD overdose has been characterized in literature by symptoms of seizures, agitation, sedation, tachycardia, hallucinations, and serotonergic symptoms [9]. We describe a case of bupropion overdose in an adolescent female presenting with altered mental status, tachycardia, seizure, hyperglycemia and elevated anion gap. Patients presenting with known AAD overdose should be treated with supportive care. Supportive care may include benzodiazepines for seizures, sodium bicarbonate for prolonged QRS complexes and magnesium sulfate for prolonged QTc on ECG, and correction of electrolyte abnormalities. There is no specific antidote for bupropion toxicity [9].

Activated charcoal *via* nasogastric tube may be used, as in our patient, for recent ingestion of bupropion [2,10]. Timely administration of activated charcoal may decrease systemic absorption of the ingestants [2,10]. Physicians may opt to proceed with whole bowel irrigation if more than 2 hours have elapsed since ingestion or if the ingestant is a sustained release formulation [11]. In this case, we could have used whole bowel irrigation due to the reported amount of time elapsed since ingestion.

Our patient experienced one known seizure in the ED, about 3 hours after medication ingestion. Bupropion is known to lower the seizure threshold at a dose-dependent rate, even at therapeutic levels [2]. In fact, bupropion administration is contraindicated in patients with eating disorders, including anorexia nervosa and bulimia, due to increased seizure risk [2]. Bupropion is also contraindicated in patients with past seizure history and in those receiving MAOIs [2].

About one third of bupropion overdoses present with seizures [11]. Approximately 32% of bupropion overdose-induced seizures were within 8 hours of ingestion [10]. Although, notably, bupropion XR may have a longer half-life in the body than the SR formulation, resulting in possible prolonged window for seizures up to 24 hours after ingestion [12]. In one retrospective study, the median amount of bupropion ingested by patients 13 years or older that experienced seizures was 4350 mg [5]. Our patient likely only ingested around 2250 mg of bupropion if she did take the 15 tablets she described to her mother. However, it should be noted that our patient's past medical history is significant for febrile seizures as a child who likely increased her risk for seizure with bupropion use [2]. Benzodiazepines are the treatment of choice for seizures. Our patient received lorazepam with resolution of the seizure. Elevated lactic acid level after the patient's seizure was likely the result of lactic acid release from hypoxic muscle cells [13]. Due to risk of recurrent seizures after acute overdose, it is important to use electroencephalogram (EEG) to monitor brain wave activity for at least 48 hours after ingestion [9].

EEG is also a useful tool when evaluating overdose patients presenting with a low Glasgow Coma Scale (GCS) of unknown origin. Our patient had a GCS of 14, making EEG utilization less relevant to our case. It is well documented in literature that severe bupropion toxicity in pediatric and adult patients has been known to present a clinical picture that mimics brain death with diminished or absent brainstem reflexes [6-8]. Additionally, bupropion overdose has been associated with burst suppression EEG pattern [7]. Despite severity of presenting symptoms, even cases of bupropion overdose with absent brainstem reflexes recovered without clinical sequelae [6-8].

Therapeutic use of bupropion may cause hypertension in patients with or without preexisting hypertension [9]. Hypertension may require acute treatment or discontinuation of bupropion. Similarly, bupropion toxicity can cause a severe, acute hypertensive episode requiring antihypertensive treatment. In severe toxicity, cardiac arrythmias, arrest, or failure may occur [9]. Other presentations include QRS widening and QTc prolongation [14]. The cardiac effects of overdose should be monitored with ECG. Occasionally, antiarrhythmics and ECMO may be necessary in addition to electrolyte abnormality correction.

Our patient's laboratory investigations revealed an elevated anion gap on admission. Bupropion overdose has been noted to cause high anion gap metabolic acidosis. One case of a 22-year-old female presenting after bupropion overdose reported a high anion gap metabolic acidosis in the absence of abnormal blood pressure [15]. Our patient also presented with normal blood pressure. As noted previously, our patient did have elevated lactic acid which could be another contributing factor to the metabolic acidosis.

Bupropion has a chemical structure that is similar to amphetamines [14]. Healthcare providers should understand that a positive urine drug screen for amphetamines may not be indicative of coingestants, but rather may represent a false positive result in response to bupropion [16]. Our patient did not have a urine drug screen because of transparency by mother and patient about drug use. We do not suspect that polypharmacy played a role in this case.

CONCLUSION

We propose that AAD should be recognized as a new toxidrome for pediatric and adolescent patients. AAD should be included in the toxicologic differential of patients with suspected

overdose and symptoms including mydriasis, hypertension, tachycardia, or seizures. Other possible physical examination findings include diaphoresis, sedation, and agitation. Patients may be hyperthermic or normothermic. Our patient presented with altered mental status, tachycardia, seizure, hyperglycemia, and elevated anion gap. The patient did not have mydriasis, fever or hypertension.

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