Hydroxocobalamin and extracorporeal membrane oxygenation (ECMO) for severe refractory shock in bupropion and citalopram overdose: a case report

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Abstract

Introduction: Management of refractory shock in the setting of overdose can be challenging. We describe a case of vasodilatory and cardiogenic shock after bupropion and citalopram overdose. Vasopressors and conventional therapies failed to stabilize the patient resulting in placement of venoarterial extracorporeal membrane oxygenation (VA ECMO) for patient rescue and recovery.

Case summary: A 23-year-old male presented after intentional bupropion and citalopram overdose. He developed seizures, acute respiratory failure, metabolic acidosis, severe refractory vasodilatory, and cardiogenic shock. The patient received mechanical ventilation, Advanced Cardiac Life Support (ACLS), Intralipid® therapy, vasopressor support, and VA ECMO. Total duration of ECMO was 72 h. Serum laboratory studies drawn on the day of admission showed serum concentrations of citalopram (3400 ng/mL, reference range 9-200 ng/mL) and bupropion (597 ng/mL, reference range 50-100 ng/mL). The patient was extubated on hospital day 18 and discharged home with referral to outpatient psychiatry, 28 days after intentional overdose.

Conclusions: This case illustrates successful recovery after hydroxocobalamin and VA ECMO in severe vasodilatory and cardiogenic shock following overdose of bupropion and citalopram.

Introduction

Management of bupropion and citalopram poisonings remain largely supportive, though more invasive treatments have begun to emerge, such as ECMO [1]. Once conventional therapies with vasopressors and lipid emulsion (Intralipid®, Baxter Healthcare Corp., Deerfield IL) failed to mitigate worsening multifaceted shock, our patient was given hydroxocobalamin, to temporarily alleviate vasoplegia, and placed on VA ECMO. We present in accordance with the CARE guidelines, a case illustrating the successful use of hydroxocobalamin and VA ECMO in an overdose after the failure of early management strategies.

Case report

A 23-year-old male arrived to the Emergency Department (ED) thirty minutes after confirmed intentional overdose of his prescription medications, bupropion and citalopram. Prescription bottles labeled with bupropion 150 mg sustained release, bupropion 300 mg extended release, and citalopram 40 mg were found (maximum possible ingestion approximately 3.3 grams of bupropion and 1.9 grams of citalopram). Samples were drawn to confirm and quantify drug serum concentrations. Paramedics reported multiple seizures en-route to the hospital with cessation of seizure activity following a 2 mg intravenous bolus of lorazepam.

Upon arrival, vital signs included a heart rate of 123 beats per minute, respiratory rate 52 breaths per minute, blood pressure 107/60 mm Hg, oxygen saturation of 95% on three L of oxygen per minute, and temperature of 36.3 degrees Celsius (°C). Physical exam revealed rapid labored respiratory effort, hypotensive bowel sounds, and Glasgow Coma Score of 13.
Serum laboratory chemistries appear in Table 1. Electrocardiogram showed sinus tachycardia (HR 166 bpm) with a QRS duration of 108 ms, QT interval of 337 ms, and a calculated QTc 551 ms. This indicated high risk for ventricular dysrhythmias based on the QT nomogram [2]. Echocardiogram revealed acute biventricular systolic heart failure with an ejection fraction of approximately 15%.

The patient suffered another seizure shortly after arrival with additional lorazepam (2 mg) given. Due to concerns for airway protection and obtundation, potential sequelae from drugs ingested, and the magnitude of ingestion, rapid sequence endotracheal intubation was performed using rocuronium (80 mg) and midazolam (2 mg). After intubation, the patient continued to experience wide complex arrhythmias resulting in cardiac arrest requiring cardiopulmonary resuscitation (CPR). Cardiac arrest was multifactorial with tachydysrhythmias, severe acidosis, and further loss of vascular tone with intubation. Return of spontaneous circulation (ROSC) was obtained with ACLS therapies. However, refractory shock persisted, and the patient continued to have poor cardiac output while requiring high doses of norepinephrine and epinephrine (max dose of both medications: 0.6 mcg/kg/min). The patient developed worsening acidosis despite ventilator support and sodium bicarbonate administration. Arterial blood gas demonstrated a pH 7.1, PaCO2 38 mm Hg, and PO2 186 mm Hg. Based on an estimated weight upon arrival, the patient received a 75 mL bolus (1.5 mL/kg) of 20% lipid emulsion (Intralipid ®), followed by continuous infusion (2.4 mL/kg/hr), with minimal improvement in patient hemodynamics or stability. Regardless of efforts made, the patient’s condition continued to deteriorate.

Approximately two hours after presentation to the ED (three hours after ingestion), the patient was taken for emergent implantation of peripheral VA ECMO. Initial attempts to cannulate were unsuccessful due to significant vascular collapse. The patient received hydroxocobalamin (5 grams over 15 min) with rapid improvement in mean arterial pressure by an increase of 30 mm Hg. The patient was then successfully cannulated, placed on ECMO flows of 4.5 L/min, and transferred to the intensive care unit (ICU). Eighteen hours after ECMO initiation, lactate had cleared from 20 mmol/L to 2.0 mmol/L, vasopressors were titrated off, and dobutamine at 2.5 mcg/kg/min was started to help with contractility. Dobutamine was weaned and discontinued the next day with an improved ejection fraction. ECMO flow rates were decreased two days after cannulation, and the patient was decannulated after a total of 72 h. The patient experienced high fevers (temperature maximum 38.9 degrees Celsius) throughout hospitalization, caused by serotonin syndrome. As a complication of ECMO cannulation, the patient experienced critical stenosis of his left common femoral artery requiring angioplasty. Prolonged ventilation took place due to aspiration pneumonitis causing severe acute respiratory distress syndrome (ARDS). The patient was extubated on hospital day 18, moved to inpatient rehabilitation on day 25, and discharged home on day 28 with a referral to outpatient psychiatry.

Serum obtained 8.5 h after ingestion revealed high concentrations of citalopram (3400 ng/mL, reference range 9-200 ng/mL) and bupropion (597 ng/mL, reference range 50-100 ng/mL).

**Discussion**

According to data published in 2018 by the Association of Poison Control Centers’ National Poison Data System (NPDS), antidepressant exposures over the past 10 years have increased rapidly with the most frequently reported poisonings being bupropion and citalopram, with 14,824 and 8,169 cases respectively [3]. In another review, looking at ECMO cases reported to the NPDS, bupropion was the most common antidepressant in single-ingestion cases, further illustrating the seriousness of bupropion overdoses [1].

Bupropion is a weak inhibitor of norepinephrine and dopamine reuptake. At therapeutic doses (150-450 mg daily), bupropion is well tolerated with mild side effects including dry mouth and insomnia. In mild to moderate overdoses, it can produce agitation, hallucination, tachycardia, and tremor. Bupropion is structurally related to numerous drugs of abuse including amphetamine, methamphetamine, and methylenedioxymethamphetamine (MDMA or “ecstasy”) [4]. Its sympathomimetic amine structure suggests that it may act via catecholamine release in the central nervous system and possibly lead to hypothalamus stimulation, explaining seizures seen in cases of bupropion overdose [5]. Seizure due to intentional or unintentional overdose is among the most reported toxic effect in addition to coma, hypotension, QRS widening, QTc prolongation, and ventricular

| Table 1. Serum laboratory chemistries upon admission. |
|---------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Na (mmol/L) | K (mmol/L) | Cl (mmol/L) | CO2 (mmol/L) | SCr (mg/dL) | BUN (mg/dL) | Glucose (mg/dL) | Lactate (mmol/L) | WBC (K/mcl) |
| 141 | 2.4 | 102 | 17 | 1.5 | 12 | 352 | 20 | 16.5 |
dysrhythmias [6–8]. Unlike bupropion, citalopram is a selective serotonin reuptake inhibitor (SSRI) with mild side effects reported at therapeutic doses. However, among the SSRIs, citalopram may have the most potential for cardiac and neurologic toxicity, especially at doses greater than 600 mg [9–11]. Citalopram overdose may produce bradycardia, QRS prolongation, or QT prolongation, which may lead to torsades des pointes (TdP) [12,13].

Though they have different mechanisms of action, both medications have similar pharmacokinetic properties. They are rapidly absorbed, reach a peak serum concentration within six hours, demonstrate a high degree of serum protein binding, and can have long elimination half-lives with sustained activity due to active metabolites [14–16]. In overdose, elimination times can be prolonged by the saturation of metabolic enzymes and delayed absorption leading to serotonin syndrome, rhabdomyolysis, central nervous system (CNS) depression, failure of vital organs, and death.

Goals of initial overdose management include stopping further drug absorption and enhancing drug elimination. Enteral activated charcoal, used to impede drug absorption, was not possible as the patient was obtunded and had no enteral access. Intravenous lipid emulsion was administered as its properties may sequester highly lipophilic drugs – including bupropion (predicted log $p = 3.47$) – to reduce toxicity [17,18]. While there are no evidence-based dosing guidelines for intravenous lipid emulsion, case reports and available data recommend a 1.5 mL/kg bolus followed by a 0.25 mL/kg/min infusion, continued for 30-60 min [19,20]. Due to our patient’s critical status upon arrival, his weight used for dosing was underestimated which could explain why our use of lipid emulsion proved futile. Due to rapid decompensation, respiratory failure, and refractory shock, VA ECMO was ultimately required. Initial attempts to cannulate the arterial system for ECMO proved challenging due to arterial spasm with high dose vasopressors. To reverse the refractory vasoplegia, hydroxocobalamin, an analog of vitamin $B_{12}$, or methylene blue could have been used. Case reports and pharmacotherapeutic reviews suggest that both agents alleviate vasoplegia via inhibition of nitric oxide synthase [20–23]. However, due to the serotoninergic properties of the agents ingested, serotonin syndrome being a contraindication for the use of methylene blue and literature supporting the use of hydroxocobalamin as an alternative, hydroxocobalamin was administered.

In patients like ours, with refractory cardiogenic and vasodilatory shock, VA ECMO can be used to support the cardiopulmonary system by mechanically replacing 60-80% of normal cardiac output. Recent literature indicates that ECMO for intentional and/or unintentional overdose, has exponentially increased in the past decade, though no guideline recommendations have been made [2,24]. The use of ECMO in overdose can be lifesaving, but its use comes with possible complications such as major bleeding, thrombosis, limb ischemia and other vascular complications [25,26]. Vascular complications occur in 10-70% of VA ECMO patients and early identification and correction of these complications is key in the prevention of worse outcomes [27–29].

VA ECMO is not a treatment for patients with acute overdoses but instead provides a stabilizing bridge in refractory shock with depressed left ventricular function. This enables additional therapies to safely take place, give the body time to metabolize and excrete medications, while supporting the heart and lungs’ ability to recover [30]. The development of institutional protocols that help in recognizing refractory shock, to enable early access for stabilization, are vital in preventing irrecoverable organ damage and successful patient survival in many cases like ours.

**Conclusions**

Bupropion and citalopram toxicity can result in cardiovascular collapse and rapid organ failure. The described case demonstrates the successful use of hydroxocobalamin for refractory vasoplegia and successful institution of ECMO as a bridge to recovery in refractory shock secondary to acute bupropion and citalopram toxicity.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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