CORPUS PUBLISHERS

Corpus Journal of Case Reports (CJCR)

Volume 2 Issue 1, 2021

Article Information

Received date : November 08, 2021

Published date: November 26, 2021

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Keywords

Beta-Blockers; Propranolol; Bupropion Overdose; Intentional Overdose; Shock; Cardiogenic Shock; ECMO; Intraaortic Baloon Pump; Extracorporeal Life Support (ECLS); Lipid - Emulsion Therapy; High Dose Insulin; Critical Care; Toxicology

Case Report

The Utility of Ecmo and Intraaortic Balloon Pumps in Lipophilic Beta Blocker and Bupropion Overdose

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Abstract

Patient: Female, 21 year old

Final Diagnosis: Cardiogenic shock due to ingestion

Symptoms: Encephalopathy, seizures

Medication: Propranolol, Bupropion

Clinical Procedure: ECMO, Intraaortic Balloon Pump

Specialty: Critical Care, Toxicology

Background

Combined massive ingestion of Beta Adrenergic Blocking Medications (BBs), Calcium Channel Blockers (CCBs), and behavioral modulators can be dangerous due to their cardiotoxicity leading to hypotension and severe refractory cardiogenic shock. Beta blockers can cause serious myocardial depression by decreasing calcium influx into cells. Some beta blockers exhibit sodium channel blockade, while others cross the blood brain barrier due to their lipophilicity causing CNS toxicity. Behavioral modulators, specifically Bupropion, cause significant cardiac depression as well by acting as a potential cardiac gap junctions blocker and therefore decreasing intercellular communication.

Case Report

We present a case of combined massive drug ingestion leading to severe refractory cardiogenic shock where invasive mechanical support was implemented. Patient was a 21-year-old female who presented after polyingestion in a suicide attempt. Patient took a large amount of propranolol and bupropion. She initially presented in cardiogenic shock, and seizing. She was intubated for airway protection, started multiple vasopressors, and high - dose insulin. Despite multiple therapies, she continued to deteriorate and her ejection fraction continued to worsen, at which point she was cannulated for Extracorporeal Membrane Oxygenation (ECMO) and an Intraaortic Balloon Pump (IABP) for refractory cardiogenic shock. She was in the intensive care unit for multiple weeks. Her cardiac function improved and she was able to be weaned off the mechanical support devices and vasopressors. She was discharged to a rehab facility with a good neurological outcome.

Conclusion

The use of ECMO contributed to the overall outcome of our patient. ECMO has a direct impact on drug pharmacokinetics. ECMO can be used to alter drug levels based on altering clearance as well as direct extraction from the circuit. Based on these results, implementation of early ECMO should be considered in patients with massive overdoses in refractory cardiogenic shock.

Background

In 2019, over 70,000 deaths occurred in the United States due to drug overdoses [1]. Most Americans take at least one medication daily [2]. Ingestion of various medications can lead to severe adverse effects [2]. Beta Adrenergic Blocking Medications (BBs), Calcium Channel Blocking Agents (CCBs), behavioral modulators, and anticholinergic agents are some common medications used in intentional and unintentional overdoses [2]. BBs, CCBs, and behavioral modulators are especially dangerous due to their cardiotoxicity, which can lead to severe refractory cardiogenic shock and cause significant morbidity and mortality [3]. BBs are widely used for the treatment of a multitude of medical conditions including hypertension, angina, congestive heart failure, arrhythmias, migraines, and thyroid storm [4]. BB toxicity is associated with high mortality and morbidity [2-4].Toxicity results from direct myocardial depression and impaired myocardial conduction leading to bradycardia, hypotension, and in fatal doses, cardiogenic shock [4]. A 10-year review of BB and CCB overdoses was found to cause moderate to severe effects in 37% of the cases whereas stimulant toxicity were the second most common to cause moderate to severe effects at 17% [2]. BBs can cause significant hypotension and cardiogenic shock by decreasing the influx of Cyclic Adenosine Monophosphate (CAMP) and calcium into cardiac myocytes [3-5]. BBs can be differentiated based on receptor selectivity, which influences their pharmacodynamics and pharmacokinetic properties [5]. These properties can play a key role at toxic doses [3]. For example, lipophilic BBs, such as propranolol, can cross the blood brain barrier causing CNS toxicity resulting in altered mental status, seizures, and coma [4,5]. Bupropion is a common behavioral modulator used to treat depression, mood disorders, and tobacco dependence [6]. Bupropion is a synthetic norepinephrine/dopamine/serotonin reuptake inhibitor and is available in three formulations including immediate release, sustained release, and extended release [7]. Bupropion has three major bioactive metabolites, of which hydroxybupropion is the most clinically relevant [7, 8]. Both Bupropion and hydroxybupropion are highly lipophilic and plasma protein bound [7,8]. Bupropion is generally well tolerated, the most common side effects being dry mouth and insomnia [6]. A serious complication of Bupropion is that it can lower the seizure threshold in certain patients even at low doses, especially patients with Bulimia Nervosa [9]. In a study of 55 non-depressed patients with bulimia nervosa, bupropion administration caused generalized seizures in four patients [9]. At higher doses, it can cause agitation, hallucinations, tachycardia, tremors, and seizures [6,7]. Fatal doses can result in status epilepticus, coma, and cardiotoxicity resulting in QRS widening and QTc prolongation [6]. Significant QT prolongation is observed in a dose dependent manner due to its potassium channel blockade,

however QRS widening is due to blockade of gap junctions in the cardiac muscle and not due to sodium channel blockade [10]. Bupropion mimics two gap junctional inhibitors and causes cardiac conduction disturbances by altering intercellular cardiac communication [10].

BBs and Bupropion are medications that can cause severe cardiotoxicity and cardiac depression. There are specific treatments for each of these medications. However, in fatal overdoses, the patients can be in severe cardiogenic shock and refractory to these therapies. During these cases, patients need mechanical support with Intra-Aortic Balloon Pumps (IABPs) and Extracorporeal Membrane Oxygenation (ECMO) to keep cardiac output appropriate and sufficiently perfuse vital organs in the body. The purpose of this case report is to highlight a case where a patient presented after a massive multiple overdose where mechanical support was successfully used to treat severe refractory shock.

Case Report

A 21-year-old female was transferred to the Emergency Department from a referring hospital for an overdose in a suicide attempt. EMS was called to the patient's home and found multiple empty bottles including 100mg Trazadone, 300mg bupropion XL, 800mg Ibuprofen, 75mg Venlafaxine, 10mg Propranolol, 50mg Hydroxyzine, and 5mg Aripiprazole. At the referring hospital she was administered 3L of Lactated Ringers, 50mEq of sodium bicarbonate, 5mg Glucagon IV, and initiated on a norepinephrine drip. An insulin bolus was allotted followed by infusion at 10 units/hr. On arrival to the emergency department, history was limited due to encephalopathy. Initial vitals were Blood Pressure (BP) 84/60, Heart Rate (HR) 66, Respiratory Rate (RR) 25, and Temperature (T) 36.7C. Finger Stick Blood Glucose (FSBG) level on arrival was 36. She was subsequently given 50mL of 50% dextrose and started on an Epinephrine drip due to worsening shock. She began seizing which was treated with 4 mg of Lorazepam. Seizures were initially thought to be due to hypoglycemia, however, the patient continued to seize despite being normoglycemic (Figure 1). Central access was obtained, and she was started on an insulin drip at 1 U/kg/hr, as well as a D50 glucose drip. Echocardiogram was obtained in ER, which showed an ejection fraction (EF) of ~20%. Cardiothoracic surgery was consulted for Veno-Arterial ECMO evaluation and the patient was placed on ECMO.

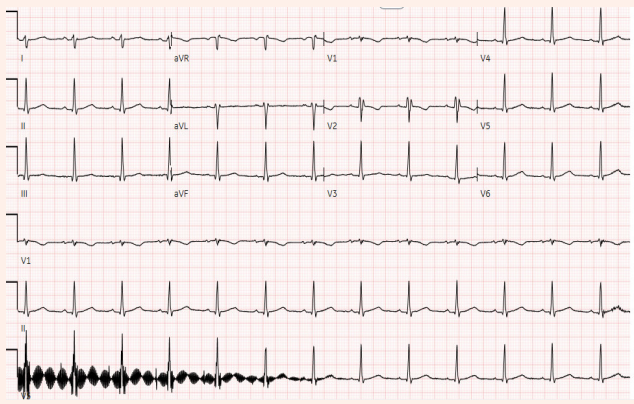

Figure 1: Patient EKG upon arrival to the emergency department.

On the following day, an IABP was placed as the patient continued to have poor hemodynamics and remained in shock. She also remained on a high dose insulin drip during this time. On day, three of the hospital stay patient's EF had improved on bedside echo to ~30%. On day four of the hospital stay, the patient had a severely worsening oliguric acute kidney injury leading to acidosis and renal replacement therapy was initiated. On the sixth day of hospitalization repeat echocardiogram revealed an EF>55%. She was decannulated from ECMO on day seven of the hospital stay and had the IABP removed. The patient remained intubated for multiple days, as she was severely encephalopathic. She was extubated on day 19 of hospital stay (Figure 2). Her renal function subsequently improved and hemodialysis was discontinued on day 24. The patient was transferred to the floor on day 26 where she was also seen by the psychiatric department and started on multiple medications. At time of discharge, the patient was noted to be alert, answering all questions appropriately, without any residual focal neurological deficits. She was discharged on day 35 to a rehab facility.

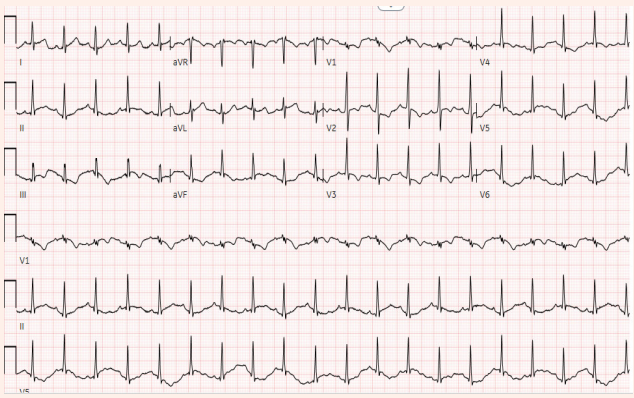

Figure 2: EKG performed on 1/31/2021 4d after initial visit discharge. Patient found to have left empyema and LLL PE.

Discussion

Multiple drug overdoses in high doses can be very fatal, especially when drugs involved can cause severe cardiotoxicity. Our case highlights a multiple drug overdose with bupropion and propranolol where severe cardiogenic shock required mechanical support. Treatment of Bupropion. In the early stages of bupropion toxicity, one needs to obtain an initial ECG emergently to evaluate for possible cardiac dysrhythmias [11]. Intravenous fat emulsion therapy has been reported to benefit some patients with bupropion toxicity in patients with cardiogenic shock [12]. However, there are also many case reports where this has not benefitted the patient [13].Treatment of beta-blocker overdose includes crystalloid bolus, atropine, glucagon, high dose insulin, intralipid, and cardiac pacing [4]. However, these treatment options can fail when serious overdoses occur. Atropine is only a temporizing medication and often does not work secondary to significant beta blockade within the myocardium [3,14]. Glucagon is presumed to work due to its direct interaction with cardiac glucagon receptors, which can increase cAMP levels within the cell, creating an inotropic effect [3,14]. The thought behind high dose insulin and glucose is that with doses of around 1 u/kg/hr along with 0.5g/kg of dextrose you will see an increase in cardiac output [3,14]. This can be titrated up to a dose of 10u/kg/h of insulin [3,14]. There is a delayed effect and it generally takes around 15-60 minutes before a noticeable effect is seen [3,14]. Oftentimes cardiac pacing fails to capture. When capture is obtained it can increase the heart rate but not increase blood pressure and true perfusion [14]. Intralipids are thought to be effective with lipid soluble beta blockers such as propranolol, but are largely ineffective in water-soluble beta blockers such as atenolol or metoprolol [3,7,14]. Intralipids were not used for our patient because at the time of presentation our patient was noted to have an ejection fraction of approximately 20% and was peri-arrest on high dose vasopressors. Intralipids exhibit lower efficacy than high dose insulin and glucose in cardiac function and overall hemodynamics [3,7,14]. We recognized that our patient was severely ill and in order to have good favorable neurological outcomes, effort should be put into initiation mechanical support. We initiated a multi-disciplinary conversation regarding mechanically support in the emergency department.

What do we do when all of the medications and invasive procedures fail? Modern medicine has now given us several more highly invasive treatment modalities available for certain patients in severe cardiogenic shock. Procedures such as ECMO and IBPAs are used to provide mechanical circulatory support. The decision to cannulate a patient for ECMO requires a multidisciplinary approach and clear communication with patients and family regarding the risks, benefits, life threatening complications and mortality associated with the procedure. ECMO is used to provide circulatory support, pulmonary support, or both. Veno-Venous ECMO (VV ECMO) provides pulmonary support and requires a normally functioning heart to circulate oxygenated blood [15,16]. Veno-Arterial ECMO (VA ECMO) provides both circulatory and pulmonary support and is used in toxin induced hemodynamic compromise [15,16]. VA-ECMO uses cannulae to remove blood from the venous circulation and delivers it to a centrifugal pump [15]. The centrifugal pump is the driving force of blood circulation and returns the blood via an arterial cannula [15]. VA-ECMO in toxin induced refractory cardiogenic shock provides circulatory support and allows time for other treatments to promote recovery [15]. ECMO has a direct impact on drug pharmacokinetics and impacts PK in three primary ways: direct extraction by circuit, increased volume of distribution, and altered clearance [17]. The direct extraction

by the ECMO circuit can be advantageous in cases of drug overdoses [17]. Ex vivo studies have shown increased extraction of highly lipophilic and protein bound drugs directly by the circuit [17]. Direct extraction by the circuit is likely through adsorption, which is primarily a function of the interaction between the drug and circuit material, the binding surface area, and affinity of the drug to the surface [16]. Extraction of a drug can also be influenced by altering the material of tubing and surface coatings of the circuit, which impact the hydrophobic and electrostatic interactions [16,17]. The degree of fentanyl loss in 180 minutes using a silicon membrane oxygenator and a microporous, hollow fiber polypropylene oxygenator was found to be >99% and 66%, respectively [16,17]. Bupropion and Propranolol are both lipophilic and can theoretically be directly extracted using the ECMO circuit. This makes ECMO not only a support mechanism for fatal toxin overdoses, but also a treatment for severe refractory cases. This can potentially be extrapolated to other lipophilic drugs [16].

IABPs can also be used to provide circulatory support in refractory cardiogenic shock until the underlying toxin overdose is treated [18]. IABP is the introduction of synchronized balloon inflation at the end of systole to increase blood pressure in the aorta, ultimately increasing cardiac output and coronary perfusion [18,19]. Placement of the balloon specifically below the carotid arteries ostium also improves central nervous system perfusion [18,20,21]. Several toxin overdose cases resulting in refractory shock have reported improved clinical outcomes with the use of IABPs [19-21]. Both ECMO and IABP can provide mechanical circulatory support in refractory cardiogenic shock [15,18,19]. Additionally, ECMO can also be used as the direct extractor of toxins, especially lipophilic toxins [16,17]. These combined effects of ECMO significantly decrease multi organ failure, including permanent central nervous system injury [15-19]. Extracorporeal therapies have significant complications associated with them. The most common complication is bleeding at the cannulation site or surgical site [22]. Overall bleeding complications occur in approximately 10-36% of patients and intracranial hemorrhage can occur in up to 6% of patients [22]. Therefore, it should be noted that ECMO should be reserved for the most severely ill poisoned patients. Often extracorporeal life support (ECLS) such as ECMO and IABPs are initiated later in the patient's time course in hospital, oftentimes patients suffer multiple cardiac arrest prior to ECLS [23]. Delayed initiation of ECLS has direct implications of neurological outcomes of these patients [23]. We were able to get our patient out of the emergency room and into the ICU where cannulation for ECMO was immediately initiated. Early recognition of severe cardiogenic shock unresponsive to conventional therapies and initiation ECMO early before the patient arrested helped our patient have good neurological outcomes. Patients who have been noted to have good outcomes from extracorporeal therapies like ECMO and IABPs are usually the subset who have drug induced cardiogenic shock not responding to conventional treatment [24]. Daubin et al. noted a survival rate of 76% in patients who received ECLS as rescue treatment, higher than the general survival rate of 58% [24].

Conclusion

BBs and bupropion can cause significant hemodynamic instability and ultimately lead to cardiogenic shock [3,4]. BBs do this by blocking calcium influx into cardiac myocytes, while bupropion does this by inhibiting intercellular cardiac gap junctions [3-8]. There are many suggested treatment options for these overdoses, however most of them have little benefit. ECMO and IABPs are two mechanical devices that can be used in refractory and severe cardiogenic shock [15-19]. ECMO not only provides mechanical support but also can be used as a modality to directly adsorb certain toxins [16]. Toxins, like propranolol and bupropion, that are highly lipophilic can be adsorbed by the tubing on the ECMO circuit which helps remove them from the body. The patient in the case report presented above ultimately had a good recovery and neurological outcome because of these treatment modalities that were utilized early in their care. This case can help serve as a favorable outcome when discussing hospital protocols and indications for activating ECMO teams in hospitals in which they are available.

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