Two Cases of Refractory Cardiogenic Shock Secondary to Bupropion Successfully Treated with Veno-Arterial Extracorporeal Membrane Oxygenation

C. William Heise^{1,2} · Aaron B. Skolnik² · Robert A. Raschke³ · Huw Owen-Reece³ · Kimberlie A. Graeme²

Received: 9 November 2015 / Revised: 22 December 2015 / Accepted: 28 January 2016 / Published online: 8 February 2016
© American College of Medical Toxicology 2016

Abstract Bupropion inhibits the uptake of dopamine and norepinephrine. Clinical effects in overdose include seizure, status epilepticus, tachycardia, arrhythmias, and cardiogenic shock. We report two cases of severe bupropion toxicity resulting in refractory cardiogenic shock, cardiac arrest, and repeated seizures treated successfully. Patients with cardiovascular failure related to poisoning may particularly benefit from extracorporeal membrane oxygenation (ECMO). These are the first cases of bupropion toxicity treated with veno-arterial EMCO (VA-ECMO) in which bupropion toxicity is supported by confirmatory testing. Both cases demonstrate the effectiveness of VA-ECMO in poisoned patients with severe cardiogenic shock or cardiopulmonary failure.

Keywords ECMO · Cardiogenic shock · Overdose · Bupropion · Extracorporeal membrane oxygenation · Status epilepticus

This work was performed at Banner – University Medical Center Phoenix and the University of Arizona College of Medicine Phoenix.

All authors have reviewed and contributed to this paper.

✉ C. William Heise
craig.heise@bannerhealth.com

¹ Center for Toxicology and Pharmacology Education and Research, University of Arizona College of Medicine Phoenix, Phoenix, AZ, USA

² Department of Medical Toxicology, Banner University Medical Center Phoenix, 925 E. McDowell Road, 2nd Floor Medical Toxicology, Phoenix, AZ 85006, USA

³ Department of Medicine, Section of Critical Care, Banner University Medical Center Phoenix, Phoenix, AZ, USA

Introduction

Bupropion is a substituted cathinone structurally similar to amphetamine that inhibits the uptake of dopamine and norepinephrine [1, 2]. It carries FDA indications for the treatment of major depressive disorder, seasonal affective disorder, and smoking cessation. Bupropion is a common adjunct to the SSRI class of antidepressants, due to the weight loss and lack of sexual side effects associated with its use [3]. Over 11,000 cases were reported to poison control centers according to the most recent National Poison Data System Annual report, with 338 major outcomes and 4 deaths [4]. Metabolism by CYP2B6 produces hydroxybupropion, an active metabolite.

Seizures are the most common problem after bupropion overdose and may occur without warning. Seizures may be delayed in onset, prolonged, and progress to status epilepticus. Agitation, tremor, and altered mental status may precede respiratory failure. Cardiac conduction delay also occurs in toxicity. This effect may be due to changes in gap junctions between myocytes and is generally not responsive to sodium bicarbonate [5, 6]. Tachycardia and hypertension may develop into ventricular arrhythmias and cardiogenic shock. Vomiting and metabolic acidosis can also ensue in overdose.

We report two cases of severe bupropion toxicity resulting in status epilepticus and cardiogenic shock treated successfully with veno-arterial extracorporeal membrane oxygenation (VA-ECMO). One previous case in the medical literature reports the use of ECMO to treat presumed bupropion toxicity in an infant [7].

Case 1

A 15-year-old girl with a history of depression ingested greater than 50, and perhaps as many as 90, bupropion 150-mg

tablets. While being transported to the emergency department (ED), she had a generalized seizure. She arrived to the ED in pulseless electrical activity (PEA) and received about 20 min of cardiopulmonary resuscitation (CPR) before return of spontaneous circulation (ROSC). During CPR, she was intubated. Initial vital signs were heart rate 126 beats per minute, blood pressure not detectable, and oxygen saturation 62 %. She was noted to be in status epilepticus which resolved with diazepam. She received a loading dose of phenytoin. The patient was air-transported to our Medical Toxicology service. In the helicopter, she had hypoxia and recurrent PEA requiring an additional minute of CPR before ROSC.

On arrival to our tertiary care center, she was seizing and was given a loading dose of 20 mg/kg phenobarbital with resolution of convulsive activity. On exam, her vital signs were HR 133 beats per minute, BP 96/61 mmHg, RR 26, and O₂ saturation 88 % on the ventilator. Physical examination of the head, ears, nose, throat, abdomen, extremities, skin, and chest were unremarkable. She had marked mydriasis with fixed pupils. She was noted to make some spontaneous nonconvulsive movements prior to receiving additional sedation.

Serum laboratory studies showed Na 147 mmol/L, K 2.7 mmol/L, Cl 112 mmol/L, CO₂ 26 mmol/L, creatinine 0.63 mg/dL, BUN 11 mg/dL, creatine kinase 120 U/L, glucose 204 mg/dL, albumin 2.2 g/dL, calcium 6.0 mg/dL, AST 24 U/L, and ALT 22 U/L. Serum acetaminophen, salicylate, and ethanol were undetectable. A complete blood count was normal other than leukocytosis. Radial arterial blood gas had a pH of 7.35 with PCO₂ 45.9 mmHg, PO₂ 32 mmHg in spite of 100 % FiO₂ and a PEEP of 18. An electrocardiogram showed sinus tachycardia at a rate of 138 with a QRS duration of 84 ms and QT 224 ms.

She suffered repeated episodes of PEA over the next few hours, each lasting approximately 5 min. Echocardiogram showed acute, biventricular cardiomyopathy with an ejection fraction of less than 25 %. She developed pulmonary edema and had progressive hypoxia despite maximal ventilator support, including inhaled nitric oxide and airway pressure release ventilation (APRV). Due to progressive hypoxia, poor cardiac output while receiving multiple vasopressors (norepinephrine, epinephrine, phenylephrine, vasopressin, and milrinone) and a deteriorating condition, she was cannulated for VA-ECMO. She tolerated VA-ECMO well and appeared to be completely dependent on ECMO to provide her cardiac output shortly after initiating the treatment. Continuous EEG showed no signs of further seizure activity.

Bupropion and hydroxybupropion concentrations were obtained after she was placed on VA-ECMO. Her bupropion concentration in serum was 1883 ng/ml (50–100 ng/ml) and hydroxybupropion concentration 2352 ng/ml (600–2000 ng/ml). Urine comprehensive drug screen showed bupropion, lidocaine, phenobarbital, phenytoin, and

midazolam. All but the bupropion were medications administered. Our institution's comprehensive drug screen is comprised of immunoassays for substances of abuse, urine volatiles, and GC/MS.

She remained on VA-ECMO for 4 days. Her native cardiac output improved, but she suffered pulmonary hemorrhage, so she was transitioned to veno-venous ECMO. She received continuous renal replacement therapy for acute kidney injury, as well as broad spectrum antibiotics for aspiration pneumonia. She was fully decannulated 6 days later (10 days total duration of ECMO). Her creatinine and urine output improved and returned to normal. Follow-up echocardiogram demonstrated a normal heart with an ejection fraction of 60–65 %. She had no evidence of hypoxic brain injury. She was discharged to an acute rehabilitation unit for reconditioning after her 24-day hospital stay.

Case 2

A 16-year-old girl with a history of depression presented to a local ED after ingesting 60 tabs of 150 mg bupropion. She had a seizure en route to the hospital in a private vehicle and another after arrival to the ED. She was given lorazepam, intubated, and a propofol infusion started. She was noted to have a QRS duration of 90 ms. She was transferred to our Medical Toxicology service.

Upon arrival, she was in status epilepticus, with 20 min of generalized tonic-clonic seizures. She received recurrent doses of lorazepam, the propofol drip rate was increased, and she was given a load of phenobarbital totaling 20 mg/kg for control of her seizures. Shortly after the administration of phenobarbital, her seizures ceased.

Her vital signs were HR 131 beats per minute, BP 83/42 mmHg, RR 21, and O₂ saturation 100 %. Physical examination of the head, ears, nose, throat, abdomen, extremities, skin, and chest were unremarkable. She had fixed and dilated pupils. She was deeply sedated and made no spontaneous movements.

Serum laboratory studies showed Na 137 mmol/L, K 3.3 mmol/L, Cl 113 mmol/L, CO₂ 24 mmol/L, creatinine 0.68 mg/dL, BUN 11 mg/dL, creatine kinase 1694 U/L, glucose 137 mg/dL, albumin 3.2 g/dL, calcium 6.1 mg/dL, AST 66 U/L, and ALT 33 U/L. Acetaminophen and salicylate were undetectable. Complete blood count was only remarkable for mild leukocytosis. Arterial blood gas had a pH of 7.20, PCO₂ 43.6 mmHg and PO₂ 168 mmHg on synchronized intermittent mandatory ventilation mode with a rate of 12 breaths per minute with 50 % FiO₂ and PEEP of 5.

An electrocardiogram was done which showed QRS of 160 ms. Over the next 4 h, she deteriorated, with cardiogenic shock secondary to biventricular cardiomyopathy. Serial echocardiography revealed progressive decline with an

ejection fraction (EF) of 10 % during infusion of norepinephrine, epinephrine, phenylephrine, and vasopressin. Rapid progression from tachycardia to bradycardia with a HR of 44 beats per minute and widening of the QRS complex were noted. She developed PEA, and she received CPR for a total of 28 min, facilitated by Lucas® device. She received 1.5 ml/kg of 20 % intravenous fat emulsion without any appreciable change. A transvenous pacer achieved capture with a weakly palpable pulse at a rate of 100 beats per minute. Given her poor cardiac output with pacing and multiple high dose vasopressors, she was emergently placed on VA-ECMO.

Bupropion and hydroxybupropion serum concentration blood tubes were drawn shortly after CPR, but unfortunately were not promptly frozen, so testing was not done. Comprehensive urine drug screen done the day of admission showed the presence of bupropion, propofol, and polyethylene glycol (excipient).

She was decannulated 3 days later. The ECMO was weaned. Her echocardiogram revealed an EF of 60 %. She was extubated 2 days later. She had a full recovery to normal neurological status, and an MRI was negative for any hypoxic injury.

Her course was complicated by compartment syndrome of her right lower leg, below femoral ECMO cannulation. This was probably due to a period of ischemia during cannulation, in spite of placement of a distal arterial cannula. She developed rapidly progressive rhabdomyolysis with a peak CK (define) of 21,373 IU/L (28–142) and required fasciotomy of all four compartments of her lower leg. This necessitated closure with a split thickness skin graft 5 days after fasciotomy.

Due to weakness in the right lower extremity, she was discharged to an acute rehabilitation unit 16 days after initial hospital admission.

Discussion

The use of ECMO in poisoned patients is not yet well-studied. Patients with cardiovascular failure related to poisoning may particularly benefit from ECMO. Toxicity is likely to resolve over several days if the patient can be adequately supported. Toxicology patients are often young and relatively free of comorbidity compared to patients with non-toxicological causes of cardiogenic shock. ECMO has been reported to have been used as supportive therapy in pediatric and young adult patients with cardiovascular collapse due to beta-blockers, calcium channel blockers, anti-arrhythmics, and antidepressants [8–10]. Mortality for critically ill, non-poisoned patients receiving ECMO in recent literature is often 25–30 % [11]. One small study showed that survival is enhanced with the use of ECMO in patients with severe shock due to a poison (86 % survival vs. 48 %) [12]. There is also some evidence that the

use of ECMO is cost effective in the patient poisoned with a cardiac toxin [13]. The current literature in the poisoned patient is observational and probably suffers from selection bias due to the greater likelihood of reporting cases with good outcome.

Both of our patients had refractory cardiogenic shock, cardiac arrest, and repeated seizures. We believe that neither patient would have survived without ECMO treatment, although this cannot be proven from two cases. Early preparation for possible ECMO treatment is important once the patient begins to suffer refractory cardiotoxicity since considerable time is often required to assemble the necessary ECMO resources [14]. We notify family and other surrogate decision-makers that if ECMO is initiated, decisions regarding the duration of ECMO will be made by the physicians. Complications of ECMO are common and include hemorrhage, clotting, hemolysis, limb ischemia, and machine failure [15].

In both of our patients, seizure control was obtained after a loading dose of phenobarbital was given. Receiving multiple doses of benzodiazepines was effective for a short time. Phenytoin blockades voltage-gated sodium channels to prevent propagation of seizure activity. It generally will not oppose the neural excitability in toxin-induced seizures [16]. ECMO may complicate treatment of seizures by altering the pharmacokinetic properties of anti-epileptics [17]. ECMO may increase the volume of distribution, including increasing plasma volume (by 25 % in adults and as much as 125 % in neonates, due to the added volume of the ECMO circuit) [17]. These effects have been proposed as the mechanism for increased dosing requirements observed for phenobarbital, phosphenytoin, and midazolam given during ECMO in small studies mostly involving neonates [18].

Intravenous fat emulsion (ILE) has been reported to benefit patients poisoned with bupropion, but did not seem to have a clinical effect in our patient [19]. ECMO oxygenation thrombosis and failure has been reported in association with ILE, thought due to ILE adsorption into the oxygenator membrane [20].

Unfortunately, we were not able to obtain serum concentrations from our second patient. Bupropion is unstable in serum unless promptly frozen [21]. In the first case, there were exceptionally high serum concentrations. These are certainly among the highest ever reported in a patient who survived. In both cases, confirmatory testing showed the presence of bupropion and the absence of other xenobiotics which would cause similar toxicity.

This report is limited by the observational character of two case reports. As such, it is not generalizable, is retrospective, and can be over-interpreted based on the small number of patients. Confirmatory testing was obtained as well as retrospective history, but it is possible that another ingestion was missed.

These are cases of bupropion toxicity treated with VA-ECMO in which bupropion toxicity is supported by

confirmatory testing and demonstrate the effectiveness of VA-ECMO in poisoned patients with severe cardiogenic shock.

Compliance with Ethical Standards

Conflicts of Interest All authors have no conflicts of interest nor financial stake to disclose.

Informed Consent Consent for publication of these cases was obtained and provided to the journal in accordance with JMT policy.

Sources of Funding None

References

- Arias HR, Santamaría A, Ali SF. Pharmacological and neurotoxicological actions mediated by bupropion and diethylpropion. *Int Rev Neurobiol*. 2009;88:223–55.
- Ascher JA, Cole JO, Colin JN, Feighner JP, Ferris RM, Fibiger HC, Golden RN, Martin P, Potter WZ, Richelson E. Bupropion: a review of its mechanism of antidepressant activity. *J Clin Psychiatry*. 1995.
- Fava M, Rush AJ, Thase ME, Clayton A, Stahl SM, Pradko JF, et al. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry*. 2005;7(3):106.
- Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd annual report. *Clin Toxicol*. 2015;53(10):962–1147.
- Curry SC, Kashani JS, LoVecchio F, Holubek W. Intraventricular conduction delay after bupropion overdose. *J Emerg Med*. 2005;29(3):299–305.
- Caillier B, Pilote S, Castonguay A, Patoine D, Ménard-Desrosiers V, Vigneault P, et al. QRS widening and QT prolongation under bupropion: a unique cardiac electrophysiological profile. *Fundam Clin Pharmacol*. 2012;26(5):599–608.
- Shenoi AN, Gertz SJ, Mikkilineni S, Kalyanaraman M. Refractory hypotension from massive bupropion overdose successfully treated with extracorporeal membrane oxygenation. *Pediatr Emerg Care*. 2011;27(1):43–5.
- Johnson NJ, Gaieski DF, Allen SR, Perrone J, DeRoos F. A review of emergency cardiopulmonary bypass for severe poisoning by cardiotoxic drugs. *Jo Med Toxicol*. 2013;9(1):54–60.
- Kolcz J, Pietrzyk J, Januszewska K, Procelewska M, Mroczek T, Malec E. Extracorporeal life support in severe propranolol and verapamil intoxication. *J Intensive Care Med*. 2007;22(6):381–5.
- Durward A, Guerguerian AM, Lefebvre M, Shemie SD. Massive diltiazem overdose treated with extracorporeal membrane oxygenation. *Pediatr Crit Care Med*. 2003;4(3):372–6.
- Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA*. 2009;302(17):1888–95.
- Masson R, Colas V, Parienti JJ, Lehoux P, Massetti M, Charbonneau P, et al. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. *Resuscitation*. 2012;83(11):1413–7.
- St-Onge M, Fan E, Mégarbane B, Hancock-Howard R, Coyte PC. Venoarterial extracorporeal membrane oxygenation for patients in shock or cardiac arrest secondary to cardiotoxicant poisoning: a cost-effectiveness analysis. *J Crit Care*. 2015;30(2):437–e7.
- De Lange DW, Sikma MA, Meulenbelt J. Extracorporeal membrane oxygenation in the treatment of poisoned patients. *Clin Toxicol*. 2013;51(5):385–93.
- Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. 2011;365(20):1905–14.
- Hoffman A, Pinto E, Gilhar D. Effect of pretreatment with anticonvulsants on theophylline-induced seizures in the rat. *J Crit Care*. 1993;8(4):198–202.
- Mousavi S, Levkovich B, Mojtahedzadeh M. A systematic review on pharmacokinetic changes in critically ill patients: role of extracorporeal membrane oxygenation. *Daru: Journal of Faculty of Pharmacy, Tehran University of Medical Sciences*. 2011;19(5):312.
- Elliott ES, Buck ML. Phenobarbital dosing and pharmacokinetics in a neonate receiving extracorporeal membrane oxygenation. *Ann Pharmacother*. 1999;33(4):419–22.
- Sirianni AJ, Osterhoudt KC, Calello DP, Muller AA, Waterhouse MR, Goodkin MB, et al. Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. *Ann Emerg Med*. 2008;51(4):412–5.
- Lee HM, Archer JR, Dargan PI, Wood DM. What are the adverse effects associated with the combined use of intravenous lipid emulsion and extracorporeal membrane oxygenation in the poisoned patient? *Clin Toxicol*. 2015;53(3):145–50.
- Laizure SC, DeVane CL. Stability of bupropion and its major metabolites in human plasma. *Ther Drug Monit*. 1985;7(4):447–50.