Massive Atenolol, Lisinopril, and Chlorthalidone Overdose Treated with Endoscopic Decontamination, Hemodialysis, Impella Percutaneous Left Ventricular Assist Device, and ECMO

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Abstract

Background Overdose of cardiovascular medications is increasingly associated with morbidity and mortality. We present a case of substantial atenolol, chlorthalidone, and lisinopril overdose treated by multiple modalities with an excellent outcome.

Conclusion Aggressive medical intervention did not provide sufficient hemodynamic stability in this patient with refractory cardiogenic and distributive shock. Impella® percutaneous left ventricular assist device and extracorporeal membrane oxygenation provided support while the effects of the overdose subsided. We present concentrations demonstrating removal of atenolol with continuous venovenous hemodiafiltration. This is the first report of esophagogastroduodenoscopy decontamination of this overdose with a large pill fragment burden.

Keywords Atenolol · Impella percutaneous left ventricular assist device · Esophagogastroduodenoscopy decontamination · Beta blocker · Continuous venovenous hemodiafiltration atenolol clearance

Introduction

β-blocker (BB) toxicity can manifest as bradycardia, heart block, hypotension, cardiogenic shock, coma, and seizures [1]. Cardiovascular toxicity in BB intoxication is thought to be mediated partly through membrane stabilizing activity (MSA). MSA in the context of clinical BB intoxication involves myocyte sodium channel blockade and/or altered calcium ion flux [2]. There are few reported examples of MSA with atenolol [2, 3]. Hemodynamic compromise can result from BBs without MSA but are less common [3]. Medical treatment during BB cardiotoxicity typically consists of fluids, glucagon, vasopressors, inotropes, and supportive care. Failure of medical management in severe BB cardiotoxicity has involved invasive modalities such as hemodialysis (HD), transvenous pacing, and intra-aortic balloon pump (IABP) implantation [4–6]. We present a case of severe cardiovascular toxicity following ingestion of atenolol, lisinopril, and chlorthalidone requiring treatment with multiple modalities.

Case Report

A previously healthy 44-year-old woman ingested atenolol (4.5 g), chlorthalidone (2.25 g), and an unknown quantity of 40 mg lisinopril tablets the night before admission. The medications were prescribed to her boyfriend and filled earlier that day. Vital signs in the emergency department 6 h after ingestion included a blood pressure (BP) 50/33 mmHg, heart rate (HR) 46 bpm, respiratory rate 20 breaths/min, and oxygen saturation 97 % on 2 L. Pertinent physical exam findings included altered mental status with Glasgow Coma Scale of 13 and diminished peripheral pulses. Remaining physical exam findings were unremarkable. The patient remained hypotensive despite fluid boluses, glucagon bolus and infusion, and norepinephrine infusion. She eventually required

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intubation for declining mental status. Phenylephrine and epinephrine were added upon transfer to the intensive care unit.

Upon arrival in the intensive care unit 10 h after ingestion, the patient remained profoundly hypotensive (67/32 mmHg). Electrocardiogram showed sinus bradycardia with HR 45 bpm, PR 180 ms, QRS 88 ms (widest 98 ms), and QTc 440 ms. The patient remained unresponsive to noxious stimuli despite no use of sedatives. Vasopressors were dramatically increased due to clinical deterioration. Maximal infusions rates included simultaneous epinephrine 125 mcg/min, norepinephrine 125 mcg/min, phenylephrine 200 mcg/min, vasopressin 0.04 units/min, and glucagon 10 mg/h. She received multiple ampules of calcium chloride and sodium bicarbonate prior to initiating infusions of both (20 g/h and 50 mEq/h, respectively). Initial labs included a white blood cell count of 15.3 k/MM3 (4–11 k/MM3), hemoglobin 13.4 g/dL (12–16 g/dL), platelets 136 k/MM3 (130–450 k/MM3), protime 14.6 s (11.8–14.7 s), glucose 345 mg/dL (65–99 mg/dL), sodium 123 mmol/L (135–145 mmol/L), potassium 4.0 mmol/L (3.5–5.2 mmol/L), chloride 96 mmol/L (96–110 mmol/L), calcium 5.6 mmol/L (8.7–10.4 mmol/L), CO₂ 18 mmol/L (21–31 mmol/L), blood urea nitrogen 11 mg/dL (8–25 mmol/L), and creatinine of 1.38 mg/dL (0.6–1.4 mmol/dL). Lactic acid was 1.8 mmol/L (0.5–2.2 mmol/L) on presentation and rose to 5.5 mmol/L within 12 h. Arterial blood gas on FiO₂ of 60 revealed a pH 7.32 (7.35–7.45), pCO₂ 33.3 mmHg (35–45 mmHg), pO₂ 84.7 mmHg (76–100 mm Hg), HCO₃ 16.7 mmol/L (22–28 mmol/L), and base deficit of 8 mmol/L. Drug screening was done with GC/MS and did not demonstrate any other cardiovascular drugs. A transthoracic echocardiogram was performed revealing a left ventricular ejection fraction (LVEF) of 55 % with moderate diastolic dysfunction with above vasopressor treatment. Hyperinsulinemia euglycemia and intralipid emulsion were not considered secondary to the preserved LVEF and atenolol being water-soluble. A 9-h serum atenolol concentration was 14,000 µg/L (therapeutic range 200–500 µg/L). Lisinopril and chlorthalidone concentrations were not measured, because they are not available.

The patient was taken emergently to the cardiac catheterization lab 13 h postingestion. A Swan-Ganz catheter was placed. Initial measurements included a mean right atrial pressure of 25 mmHg (2–6 mmHg), mean right ventricular pressure of 27 mmHg (7–16 mmHg), pulmonary capillary wedge pressure of 32 mmHg (4–12 mmHg), systemic vascular resistance of 1,257 dyn·s/cm⁵ (800–1,200 dyn·s/cm⁵), cardiac output of 7.1 L/min (4–8 L/min), cardiac index of 3.8 L/min/m² [2] (2.6–4.2 L/min/m² [2]), left ventricle end-diastolic pressure (LVEDP) of 31 mmHg (4–12 mmHg), and LVEF of 55 %. The LVEF of 55 % in the setting of four high dose vasopressors represented a much lower than expected LVEF along with the elevated LVEDP demonstrated marked cardiac dysfunction.

In addition, a preemptive temporary right ventricular pacemaker was placed. After Impella percutaneous left ventricular assist device (pLVAD; Abiomed, Danvers, MA) placement, gastroenterology was consulted for decontamination via esophagogastroduodenoscopy (EGD), because the patient may not have survived further medication absorption. An EGD was performed 15 h postingestion revealing a substantial load of pill fragments adherent primarily to the gastric cardia (Figs. 1 and 2). This large confluence of tablets was successfully removed over 30 min with a total of 1.5 L of fluid cleared with suction. Activated charcoal was then injected into her duodenum.

The patient was started on continuous venovenous hemodiafiltration (CVVHDF) 16 h after ingestion for anuric renal failure and inability to eliminate atenolol. A Prismaflex M100 cartridge (Gambro, Lakewood, CO) was used with a blood flow rate 12 L/h, a pre-pump dilution rate 0.75 L/h, and a dialysate flow rate 2 L/h. A pre-cartridge atenolol concentration of 12,750 µg/L (corrected for dilution) was collected with a dialysate concentration of 10,000 µg/L (Fig. 3). It took 83 min to collect a 5 L bag of dialysate. This is equal to the removal of 50 mg of atenolol each 83 min during the first day.

The patient deteriorated 22 h after ingestion with a drop in mean arterial pressure (MAP) to 45 mmHg with a marked decline in cardiac output, becoming nearly completely dependent on the output from the pLVAD. Blood pressure significantly responded to two ampules of sodium bicarbonate despite being on a sodium bicarbonate infusion to a MAP of 70 mmHg. An EKG was not obtained prior to administration of bicarbonate. The HR remained in the 60s during this time. An echocardiogram 28 h after presentation confirmed proper position of the pLVAD and unchanged LVEF. Over the next 48 h, she maintained her MAP >65 mmHg with high-dose vasopressors and pLVAD set at a cardiac output of 3 L/min.

On hospital day 5, the pLVAD was removed. The patient was on minimal vasopressor support. Later the same day, acute respiratory distress syndrome worsened. We placed her on venovenous extracorporeal membrane oxygenation (ECMO)

Fig. 1 Substantial load of pill fragments adherent primarily to the gastric cardia

Fig. 2 Same view after EGD lavage/decontamination

after all other interventions failed including bronchoscopy and administration of inhaled nitric oxide to improve hypoxemia. The patient was off EMCO 2 days later. Vasopressors were stopped on day 7. She was transitioned to high flux HD on day 8 and extubated on day 11. At time of transfer to the inpatient psychiatric unit on day 12, she continued to require intermittent HD and was able to ambulate on her own without neurological deficits. A month after presentation, HD was discontinued with return of normal renal function.

Discussion

Beta-blocker cardiotoxicity from atenolol typically results in myocardial depression with bradycardia and hypotension. Kerns et al. hypothesized that BB toxicity results from cardiac

hyperpolarization via the K_{Ca} channel which is activated by increased cytosolic calcium. The increase in cytosolic calcium results in an outward flow of potassium through K_{Ca} channels resulting in plasma membrane hyperpolarization [1]. Another mechanism is sodium channel blockade also known as MSA. Atenolol is reported to be without MSA [2, 3], yet QRS prolongation has been reported in overdose [3, 5–7]. Our patient developed coma, refractory hypotension, bradycardia, and circulatory collapse all typical of BB cardiotoxicity. The widest QRS measured was 98 ms. Our patient's blood pressure responded significantly to two ampules of sodium bicarbonate with a substantial increase in MAP from 45 to 75 mmHg. Although the degree of QRS prolongation was not large, we hypothesize by the positive effect of sodium bicarbonate that atenolol may have MSA in significant overdose. Other explanations include the increased fluid load, the reversal of acidemia, or reduction of tissue load by redistribution. As we have witnessed continued clinical decline in past BB toxicity from worsening bradycardia and asystole, a temporary right ventricular pacemaker was placed.

The pLVAD was first utilized as circulatory support in postcardiotomy heart failure and cardiogenic shock cases refractory to high-dose inotropes and IABP [7, 8]. Currently, the pLVAD carries indications for use in partial or full circulatory support for 6 h; continued use is left to the discretion of the treating physician. Since its development, uses for the pLVAD have evolved. There are several published studies and cases reports describing successful use during high-risk percutaneous coronary interventions and cardiogenic shock of different etiologies including use during an amlodipine overdose [9–12].

The major complications of using the device are vascular injury, hemolysis, thrombocytopenia, and impairment of valve

Fig. 3 Time serum and dialysate atenolol concentrations

function [13, 14]. Mild hemolysis was suspected in this case, but it was not severe enough to require early discontinuation of the device, nor blood transfusion.

Current guidelines recognize IABP as the mechanical circulatory support system of choice for patients with cardiogenic shock [15]. The IABP provides approximately 1 L a minute of cardiac output and augments diastolic flow to the coronary arteries. The pLVAD provides 2.5–5 L/min depending on the model. In this case, the 3.5 L/min device was used. O'Neill et al. demonstrated that when compared to IABP, the pLVAD provided superior hemodynamic support with maximal decrease in cardiac power output from baseline among patients undergoing high-risk coronary intervention, but no randomized control study has shown a proven mortality benefit of using the pLVAD over IABP [16]. Similarly, a prospective randomized study performed by Seyfarth et al. suggested that among patients with cardiogenic shock, the implantation of the pLVAD significantly increased their cardiac index 30 min postimplantation compared to those with IABP implantation [17].

The decision to utilize the Impella 3.5 over IABP was based on the severe cardiac toxicity manifested by the markedly elevated LVEDP and an EF of 55 % despite the use of four vasopressors. Maintaining her MAP above 65 mmHg would not have been achieved with an IABP. We were concerned that her cardiac function might continue to decline as the toxicity from the atenolol and lisinopril reached maximum effect, which did in fact happen within 24 h of presentation. There was a period of an hour where the patient's cardiac output was nearly entirely dependent on the pLVAD.

Research continues regarding the use of gastrointestinal decontamination in massive acute overdose. While EGD decontamination has been used successfully for removal of a pharmacologic bezoar, it is rarely used as a direct method of decontamination and there are no controlled studies supporting its use [18]. Esophagogastroduodenoscopy is used to evaluate caustic injury or remaining visible gastric fragments. Clearing of pill fragments from the stomach during the first day of hospitalization in our patient prevented continued drug absorption, represented by the decline in atenolol concentration (Fig. 1). The amount of pill fragments still found at 15 h after ingestion was surprising. The EGD would have been conducted earlier if not for other life-saving interventions taking precedence. This overdose may have been fatal if EGD decontamination was not performed. Studies have shown atenolol, lisinopril, and chlorthalidone bind to charcoal [19], but there are not studies showing improved patient outcomes with its use. Charcoal alone is unlikely to have provided the same amount of benefit based on the quantity adhered to the gastric mucosa.

Atenolol has favorable pharmacokinetic properties making it amenable to extracorporeal elimination. We measured both pre-cartridge and dialysate atenolol concentrations to

demonstrate removal by the CVVHDF. Atenolol is hydrophilic. In therapeutic doses, it has a reported volume of distribution (Vd) of 0.7 L/kg, a molecular weight of 266 kDa, minimal protein binding (<5 %), a half-life of 6–7 h with normal renal function, and elimination by renal excretion (>95 %). Hemodialysis has been used in atenolol toxicity [5, 8, 10]. Our patient underwent CVVHDF instead of HD secondary to refractory hypotension. There was no significant intrinsic renal function during the time serum and dialysate atenolol concentrations were obtained (Fig. 3).

A simulation program (SAAM II v 2.3.1, University of Washington, Epsilon Group) using a one-compartment model was used to calculate Vd and elimination half-life (EHL) in our patient according to an atenolol absorption of 56 % [20]. A Vd of 1.69 L/kg and an EHL of 25.38 h was obtained with first elimination kinetics (Akaike information criterion 6.72). These values are similar to another report of atenolol overdose receiving CVVHDF [10]. When simulating 100 % absorption the Vd increased to 3.03 L/kg without change on EHL. The larger Vd and longer EHL in this patient may be related to altered pharmacokinetics in relation to overdose, changes in intravascular and extravascular fluid compartments, and extravascular space distribution. Massive continued absorption is possible, but unlikely based on removal of substantial pill fragments and declining concentrations. Plasma atenolol concentrations have also been observed to increase post-dialysis reflecting redistribution from the tissue in HD patients [8, 21]. Tissue may therefore be a large reservoir, especially after overdose. Atenolol may slowly be released into the plasma as it is cleared during HD effectively increasing EHL. Atenolol is effectively cleared during HD/CVVHDF. It likely provides similar clearance to normal renal function for treatment of severe atenolol toxicity with concomitant anuric renal failure.

Lisinopril and chlorthalidone surely contributed to her hypotensive state. Chlorthalidone has a half-life of 50 h, large Vd, and 50 % is excreted unmetabolized through the kidney [22]. Studies on chlorthalidone removal via HD were not found searching Medline, Ovid, or PubMed. Lisinopril has a half-life of 38–44 h, small Vd, with elimination essentially by renal clearance [23]. Lisinopril is removed via HD with 50 % removal after 4 h. Lisinopril and chlorthalidone were likely removed via CVVHDF in this case, but it is unclear to what degree and to what effect it had on the overall clinical picture considering concentrations were not obtained [24]. Hemodialysis can be considered if renal impairment exists following an overdose of lisinopril or chlorthalidone as elimination of these medications is primarily renal.

Conclusion

This case demonstrates the multidisciplinary approach and use of several modalities in a patient with refractory shock. We

believe that if any one intervention was not performed the patient would have expired. This case provides evidence that when early aggressive medical therapy fails the clinician has several options to manage cardiotoxicity from an overdose. The use of EGD decontamination, CVVHDF, Impella® percutaneous LVAD, and venovenous ECMO may be considered.

References

- Kerns W, Ransom M, Tomaszewski C et al (1996) The effects of extracellular ions on β -blocker cardiotoxicity. *Toxicol Appl Pharmacol* 137:1–7
- Love JN, Elshami J (2002) Cardiovascular depression resulting from atenolol intoxication. *Eur J Emerg Med* 9:111–4
- Love JN, Howell JM, Litovitz TL, Klein-Schwartz W (2000) Acute beta blocker overdose: factors associated with development of cardiovascular morbidity. *Clin Tox* 38:275–81
- Salhanick SD, Wax PM (2000) Treatment of atenolol overdose in a patient with renal failure using serial hemodialysis and hemoperfusion and associated echocardiographic findings. *Vet Hum Toxicol* 42:224–5
- Huang SS, Tirona RG, Ross C, Suri RS (2013) Case report: atenolol overdose successfully treated with hemodialysis. *Hemodial Int* 17:652–5
- Pfaender M, Casetti PG, Azzolini M, Baldi ML, Valli A (2008) Successful treatment of a massive atenolol and nifedipine overdose with CVVHDF. *Minerva Anestesiol* 74:97–100
- Isgro F, Kiessling AH, Rehn E, Lang J, Saggau W (2003) Intracardiac left ventricular support in beating heart, multi-vessel revascularization. *J Card Surg* 18(3):240–4
- Jurmann MJ, Siniawski H, Erb M, Drews T, Hetzer R (2004) Initial experience with miniature axial flow ventricular assist devices for postcardiotomy heart failure. *Ann Thorac Surg* 77(5):1642–7
- Garatti A, Colombo T, Russo C, Lanfranchi M, Milazzo F, Catena E et al (2005) Different applications for left ventricular mechanical support with the Impella Recover 100 microaxial blood pump. *J Heart Lung Transplant* 24(4):481–5
- Farhat F, Sassard T, Attouf Y, Jegaden O (2008) Abdominal aortic aneurysm surgery with mechanical support using the Impella microaxial blood pump. *Interact Cardiovasc Thorac Surg* 7(3):524–5
- Dixon SR, Henriques JP, Mauri L et al (2009) A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (The PROTECT I Trial): initial U.S. experience. *JACC Cardiovasc Interv* 2(2):91–6
- Abuissa H, Roshan J, Lim B, Asirvatham SJ (2010) Use of the Impella microaxial blood pump for ablation of hemodynamically unstable ventricular tachycardia. *J Cardiovasc Electrophysiol* 21(4):458–61
- Boudoulas KD, Pederzoli A, Saini U et al (2012) Comparison of Impella and intra-aortic balloon pump in high-risk percutaneous coronary intervention: vascular complications and incidence of bleeding. *Acute Card Care* 14(4):120–4
- Sibbald M, Dzavik V (2012) Severe hemolysis associated with use of the Impella LP 2.5 mechanical assist device. *Catheter Cardiovasc Interv* 80(5):840–4
- Manzo-Silberman S, Fichet J, Mathonnet A et al (2013) Percutaneous left ventricular assistance in post cardiac arrest shock: comparison of intra-aortic blood pump and IMPELLA Recover LP2.5. *Resuscitation* 84(5):609–15
- O'Neill WW, Kleiman NS, Moses J et al (2012) A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation* 126:1717–27
- Seyfarth M, Sibbing D, Bauer I et al (2008) A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol* 52:1584–8
- Wells CD, Luckritz TC, Rady MY et al (2012) Bezoar formation requiring endoscopic removal after intentional overdose of extended-release nifedipine. *Pharmacotherapy* 26:1802–5
- Neuvonen PJ, Olkkola KT (1986) Effect of purgatives on antidotal efficacy of oral activated charcoal. *Human and Exp Toxicol* 5:255–63
- Mahmood I (1997) Prediction of absolute bioavailability for drugs using oral and renal clearance following a single oral dose: a critical review. *Biopharm Drug Dispos* 18:465–73
- Flouvat B, Decourt S, Aubert P, Potaux L, Domart M, Goupil A et al (1980) Pharmacokinetics of atenolol in patients with terminal renal failure and influence of haemodialysis. *Br J Clin Pharmacol* 9:379–385
- Kountz D, Goldman A, Mikhail J et al (2012) Chlorthalidone: the forgotten diuretic. *Postgrad Med* 124:60–6
- Beermann B (1988) Pharmacokinetics of lisinopril. *Am J Med* 85:25–30
- Kelly JG, Doyle GD, Carmody M et al (1988) Pharmacokinetics of Lisinopril, enalapril and enalaprilat in renal failure: effects of haemodialysis. *Br J Clin Pharmacol* 26:781–6