

Case Report

Beta-Blocker Overdose Treated with Extended Duration High Dose Insulin Therapy

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Abstract

Poisoning and overdose of beta-blockers may be associated with significant morbidity and mortality. Management is often complicated by failure of initial first-line interventions in severe ingestions. High-dose insulin, or hyperinsulinemia/euglycemia therapy has been well described in calcium channel blocker overdose as well as mixed ingestions of calcium channel- and beta- blocker agents. The data for the use of high-dose insulin in isolated beta blocker overdose is limited, including one human case report and a small number of animal studies. Here we report the successful treatment of a severe metoprolol overdose with a prolonged high-dose insulin infusion, for a total of 116 hours. High dose insulin therapy may be considered as a treatment option for severe beta-blocker overdose unresponsive to standard treatment.

ABBREVIATION

HDI: High Dose Insulin

INTRODUCTION

Beta-adrenergic antagonists (beta blockers) are among the most commonly prescribed medications for cardiovascular disease; in 2010 almost 200 million prescriptions were written for them in the United States. Although generally safe in patients taking beta blockers as prescribed, unintentional and intentional ingestions in both children and adults carry significant morbidity and mortality [1,2]. In 2006, the American Association of Poison Control Centers Exposure Surveillance System reported 9041 beta blocker exposures; 613 cases were considered moderately to severely toxic, and deaths were reported¹. Coingestion with other potentially cardiotoxic medications, such as calcium channel blockers, digoxin, and tricyclic antidepressants, increases morbidity and mortality. The hallmark of beta blocker poisoning is myocardial depression and decreased contractility, leading to bradycardia, hypotension, and in large ingestions, cardiogenic shock [3]. Highly lipophilic beta blockers, such as propranolol, readily cross the blood-brain barrier, and therefore can produce significant central nervous system (CNS) effects, such as seizures and coma. Beta blockers with membrane stabilizing activity, such as propranolol or acebutolol, may prolong the QRS interval and predispose patients to the development of dysrhythmias. General goals of therapy are aimed at improving inotropy and chronotropy. Potential interventions utilized to manage severe

toxicity include intravenous fluids, atropine, glucagon, calcium, and vasopressors. Unfortunately, in severe overdoses, these agents do not consistently improve hemodynamic parameters [4].

High dose insulin (HDI) (hyperinsulinemia/euglycemia) therapy has emerged from recent clinical and experimental evidence as an effective antidote to calcium channel blocker overdose, and may offer more beneficial effects on hemodynamics than standard therapy [5]. HDI has been advocated for use in the management of beta blocker poisoning primarily based on the more extensive study of its use in calcium channel blocker overdose as well as increasing evidence in animal studies[3,6]. Successful treatment for beta-blocker toxicity using HDI was first studied in canines⁷ and has also recently been supported in animal studies with propranolol toxicity [8,9]. To date, no clinical trials of HDI exist in humans, and only one case report has been published describing the use of HDI in the treatment of beta blocker toxicity without calcium channel blocker coingestion [10]. In literature reports of calcium channel blocker and combined calcium channel blocker and beta blocker ingestions, continuous insulin infusion rates have ranged from 0.015 to 22 unit/kg/hour, while the majority of patients have received between 0.5 and 2 unit/kg/hour [11]. Treatment has continued up to 49 hours in one case report [12].

Here we report a case of metoprolol ingestion with severe hemodynamic collapse that was managed with HDI for a longer duration than previously described in human cases.

CASE PRESENTATION

A 27-year old, 87kg woman presented to the emergency department (ED) approximately one hour after ingesting 3000mg of metoprolol and an unknown quantity of citalopram, alprazolam, and doxylamine. Her past medical history included depression and endocarditis requiring homograft replacement of aortic and pulmonic roots, subsequently complicated by pulmonic stenosis at the anastomotic site following a dental procedure. The patient arrived with recently prescribed medication bottles, all of which were empty. On arrival, the patient was notably lethargic, with a Glasgow Coma Scale (GCS) of 12 (eyes 3, verbal 4, motor 5). Her initial heart rate was 76 beats per minute (bpm), blood pressure (BP) was 78/50 mmHg, blood glucose was 101 mg/dL, and temperature was 99.2°F. Intravenous fluids were started immediately, however her blood pressure dropped to 50/31 and her mental status declined, necessitating rapid sequence intubation. She was then given 3mg of glucagon, which initially raised her blood pressure to 69/56; however, her BP failed to improve after a second bolus of 3mg of glucagon, 10 minutes after the first dose. The patient was then started on an epinephrine infusion. Her EKG demonstrated no signs of ischemia or atrioventricular/intraventricular conduction abnormalities. Poison control recommendations at this time included catecholamines and glucagon.

The patient's hypotension was refractory to epinephrine requiring the addition of norepinephrine and dobutamine, as well as a glucagon infusion, initiated at 0.5mg/hr. Normal saline boluses were repeated, for a total of 4L in the ED. Despite these interventions, her systolic blood pressure (SBP) continued to remain in the 50s. Phenylephrine and vasopressin infusions were added. The patient was also empirically treated for sepsis with broad spectrum antibiotics and stress dose steroids. Her systolic blood pressure remained below 60 but she did not become bradycardic. Just prior to her transfer to the intensive care unit (ICU), an intravenous lipid emulsion infusion was administered, dosed at 120mL once (~1.5mL/kg).

Upon admission to the ICU, the patient was receiving significant cardiac pressor support with norepinephrine (25mcg/minute), phenylephrine (300mcg/minute), epinephrine (10mcg/minute), dopamine (20mcg/kg/minute), dobutamine (10mcg/kg/minute), and vasopressin (0.04units/minute). Despite these efforts, she remained hypotensive with SBP only maintained in the mid 60s. At this time, approximately 4 hours after initial presentation, HDI therapy was initiated. One insulin bolus (0.25 units/kg) was administered, followed by a regular insulin infusion, initiated at 0.3 units/kg/hour and increased to 0.5 units/kg/hour approximately 30 minutes later. Dextrose 10% solution was administered at the start of insulin infusion, at a rate of 50mL/hour. During initiation and titration of insulin, glucose concentrations were checked every 10 minutes and dextrose infusion was titrated to maintain glucose concentrations above 100mg/dL.

The patient's hemodynamics began to stabilize (93/59 mmHg), and her condition improved within two hours of HDI initiation. Vasopressors were each titrated down slowly, and by 13 hours after the start of the insulin drip, dopamine, phenylephrine, dobutamine, and epinephrine were all discontinued. The patient

continued to require low dose norepinephrine (4mcg/minute), which in combination with insulin therapy (continued at 0.5units/kg/hour), was able to maintain mean arterial pressure (MAP) goals of 65mmHg or greater. Her glucose during this time never dropped below 75mg/dL (range 75-209mg/dL), and her serum potassium remained between 4.0-4.6 mEq/L. Fifteen hours after the original initiation of insulin infusion, the decision was made to begin weaning off the insulin infusion by 5units/hour, with the norepinephrine drip maintained at 6mcg/minute. During the insulin wean, which took place over six hours, her hemodynamics remained consistent, with her SBP remaining in the upper 80s. However, approximately thirty minutes after the insulin infusion was discontinued, our patient rapidly decompensated with a drop in blood pressure to 56/37 mmHg. The norepinephrine infusion was titrated to 30mcg/minute, and over the next hour, dopamine, vasopressin, phenylephrine, epinephrine, and dobutamine were sequentially restarted. The insulin infusion was also restarted at a rate of 0.3units/kg/hour and her MAPs remained between 57 and 89 mmHg.

Over the next 48 hours, she continued to require vasopressors with gradual blood pressure stabilization. She remained on high dose insulin therapy at 0.3units/kg/hour along with norepinephrine at 10-20mcg/minute, dopamine at 5-10mcg/kg/minute, and vasopressin at 0.04units/minute. Within 72 hours of restarting the insulin infusion, our patient was awake and following commands. Both the dopamine and the vasopressin infusion were weaned off. Her norepinephrine infusion remained at 10mcg/minute, and, with the insulin infusion, her SBP remained stable in the upper 80s to low 90s. An attempt was again made to wean off the high dose insulin infusion, decreasing at a rate of 5 units/hour every 4 hours. The insulin was titrated down over 16 hours, with a total duration of insulin therapy for 116 hours. The patient remained stable throughout this process, and subsequently her norepinephrine drip was slowly weaned off. The patient developed ischemic hepatitis and acute kidney injury (AKI) on day one of admission secondary to prolonged hypotension. Anuric AKI required the initiation of continuous veno-venous hemofiltration. Although the patient developed end-organ damage during her hospital course, there were no major adverse effects from the insulin infusion such as hypoglycemia or hypokalemia, and the patient was discharged from the hospital several days later with no obvious physical or mental abnormalities.

DISCUSSION

Beta blockers have broad clinical applications, ranging from migraines to thyrotoxicosis, and they are one of the most commonly used medications to treat hypertension and cardiovascular disease. Beta-adrenergic receptors are divided into three sub-types. Beta-1 receptors are primarily found in myocardial tissue, and receptor stimulation results in an increase in the rate of contraction. Beta-2 receptors are most prominent in the bronchial and peripheral vascular smooth muscle, with blockade resulting in vasodilation and bronchiolar relaxation. Beta-3 receptors are found in the heart and fat tissue; although less well understood, they appear to regulate lipolysis and cardiac inotropy. Beta-1-adrenergic stimulation facilitates calcium influx into cardiac myocytes by increasing the levels

of cyclic adenosine monophosphate (cAMP), which in turn upregulates the opening of L-type calcium channels. Formation of cAMP results in phosphorylation of these channels, with resultant opening and calcium entry into myocardial cells [4]. Metoprolol is a beta-1-selective adrenergic blocker; however, in the setting of beta blocker toxicity, receptor selectivity is lost [13]. Metoprolol has moderate lipid solubility, and therefore seizures and other CNS effects seen with highly lipophilic agents such as propranolol are not as commonly seen in metoprolol overdose [14].

The management of beta blocker toxicity is aimed at reversing myocardial depression and thereby improving hemodynamics. The conventional approach to beta blocker toxicity may include isotonic crystalloid boluses, glucagon, atropine, and catecholamines. Glucagon is considered a first-line therapy due to its positive chronotropic and inotropic effects [15,16]. A regulatory hormone produced by the pancreas, glucagon mediates its cardiovascular effects via a beta-adrenoreceptor-independent mechanism that involves cAMP formation with a subsequent increase in calcium influx into cardiac myocytes [15]. However, several human case reports report glucagon failure when used as sole therapy, [17,18] and the increase in inotropy is often transient and unable to be maintained throughout treatment [19]. Vasopressors are also frequently used in the management of beta blocker toxicity as they can increase blood pressure and heart rate. However, they also increase systemic vascular resistance (SVR), which can result in increased myocardial oxygen demand and decreased cardiac output (CO), effects with deleterious consequences in the setting of decreased coronary perfusion [8,11]. The resultant oxygen wasting may elucidate why standard catecholamine treatments often fail to resuscitate severe drug-induced myocardial depression. In addition, catecholamines act on the very receptors that have been blocked, and case reports indicate that they are often unable to overcome the beta-blockade, even at high doses [1,8,16]. Atropine may be utilized for symptomatic bradycardia in moderate toxicity but therapy yields poor response in severe overdose¹³. Treatment failures in severe beta-blocker poisonings have led clinicians to consider alternate therapeutic interventions, including HDI and intravenous lipid emulsion therapy.

HDI is a potential antidote that has not been extensively studied in isolated beta blocker toxicity, and therefore is not routinely recommended. There is greater clinical experience with HDI in the management of calcium channel blocker toxicity, which has a similar pathophysiology to that of beta blocker toxicity. HDI is typically instituted only after conventional therapies have failed; however, it is emerging as a promising intervention that may have a greater effect on hemodynamic stability than historical first-line agents, and it warrants earlier consideration in the management of beta blocker overdose [5,20,21].

Currently, the benefits of insulin in beta blocker and calcium channel blocker toxicity are thought to be related to three primary mechanisms: increased inotropy, increased intracellular glucose transport, and vascular dilatation. Though the inotropic properties of insulin are well established, its mechanism is poorly understood. The cardiac effects were initially thought

to be catecholamine-related because insulin was observed to exhibit adrenaline-like action [3]. This theory was later discounted through research on canine papillary muscle and was also considered unlikely because beta-receptor blockade does not impair the increased inotropy caused by insulin [22]. Additionally, insulin does not exhibit chronotropic effects, which also discredits the idea that insulin's cardiodynamic effects are catecholamine-mediated³. Insulin is now thought to improve myocardial performance through its effects on myocardial metabolism²³. In the unstressed state, the major source of energy for myocardial cells is free fatty-acid oxidation³. However, in conditions of stress, such as beta blocker or calcium channel blocker overdose, myocardial cellular metabolism switches from free fatty-acids to carbohydrates [3,23,24]. Exogenous insulin is thought to improve cardiac function by increasing myocardial carbohydrate metabolism, which in turn facilitates myocardial oxygen delivery and cardiac contractility [23,24]. HDI appears to enhance cardiac contractility without increasing myocardial work, unlike catecholamines [24].

In 1972, investigators demonstrated that insulin significantly improved contractility in depressed canine isolated papillary muscles and intact canine hearts [25]. While insulin is not considered the most potent inotropic agent, exogenous insulin appears to be more effective at improving CO than those inotropic agents that are considered standard therapy for beta blocker or calcium channel blocker toxicity. Animal models of beta blocker and calcium channel blocker toxicity have not only demonstrated insulin's superiority to glucagon and vasopressors in maximizing cardiac energy production and oxygen utilization, but have also shown that HDI leads to superior cardiac performance and survival [24,26-28]. In 1997, Kerns et al investigated acute propranolol toxicity in a canine model, and found that the HDI treatment group had a significantly higher survival rate when compared with the animals who received glucagon or epinephrine [8]. Although insulin showed no effect on HR in the HDI group, all HDI-treated animals exhibited increased myocardial glucose uptake, superior cardiac performance, and improved hemodynamics [8]. In 2007, Holger et al compared HDI versus combined vasopressin and epinephrine therapy in a swine model of propranolol toxicity [20]. In this study, insulin demonstrated superior resuscitative properties compared to vasopressors in terms of survival rate and cardiac performance; the study was terminated early when every pig in the insulin group achieved four-hour survival and all pigs in the comparator vasopressin/epinephrine arm died within the first 90 minutes.

Although no clinical trials have been conducted utilizing HDI treatments in humans, a number of case reports have shown benefit, primarily in calcium channel blocker or mixed calcium channel blocker and beta blocker overdose [5,10,21,23,29-34]. To the authors' knowledge, though there are numerous case reports of HDI used in calcium channel blocker and mixed calcium channel blocker and beta blocker ingestions but only one case report in humans has been published for isolated beta-blocker overdose [10]. In this study, Page et al. documents the successful use of HDI in a massive metoprolol overdose, with doses as high as 10 units/kg/hour and duration of insulin infusion for a total of 17 hours post-ingestion. The patient also co-ingested an unknown quantity of alcohol, and there were multiple

interventions performed, including catecholamines. However, these other therapies were eventually stopped while HDI was continued, and the serum metoprolol concentration was approximately 100-times therapeutic concentration when the patient was managed with insulin alone. There were no major adverse effects from the insulin infusion that were not easily managed (i.e. hypokalemia from intracellular shifts), and the patient was discharged 60 hours later without complications. Our case demonstrates similar hemodynamic benefits to insulin therapy in severe isolated beta blocker overdose refractory to initial measures. The successful use of HDI in these two cases supports the earlier consideration of HDI in severe beta blocker toxicity.

General recommendations for HDI dosing include an initial bolus of 1unit/kg followed by a 0.5-1 unit/kg/hr continuous infusion, although doses of up to 10units/kg/hour have been used in refractory cases [23]. Our patient was treated with 0.5units/kg/hour. Treatment with HDI has continued for up to 49 hours in one previous case report [12]. In our case, the insulin infusion was continued for a total of 116 hours, the longest duration yet reported for either beta blocker or calcium channel blocker overdose. The infusion may have been required for a prolonged period of time in the setting of ischemic hepatitis and likely delayed drug metabolism. No studies have yet demonstrated the optimal way in which to titrate off insulin therapy. Our patient was initially weaned off of insulin rather quickly over 4 hours, with subsequent remarkable hemodynamic decompensation requiring the resumption of HDI. The second time, insulin was titrated off gradually, over 16 hours, with maintenance of hemodynamic parameters. Although the optimal titration of HDI will likely vary on a patient-by-patient basis, our report suggests that a more gradual wean may be required.

Drawing conclusions about an individual intervention in a case that involved the concurrent use of multiple interventions is difficult. In our case, a metoprolol level was unfortunately not obtained. Although beta blocker serum concentrations are not typically clinically useful given the time with which they require to be processed, a metoprolol level would be useful when evaluating the trajectory of the case retrospectively.

Overall, more clinical data is needed to fully define the use of high dose insulin for isolated beta blocker toxicity; though a recent case report and animal studies have noted benefit. Further, insulin is a widely available, inexpensive, and frequently used and familiar therapy to most clinicians [5]. HDI has been utilized in cases of calcium channel blocker, beta blocker, and mixed overdose of both without major adverse effects.

CONCLUSION

HDI therapy is well documented for the treatment of calcium channel blocker overdose. The overwhelming majority of case reports describing HDI for beta blocker overdose involve coingestion with calcium channel blockers. We present a case of using high dose insulin therapy for the treatment of an isolated severe beta blocker overdose. This is the second case report of HDI in isolated beta blocker toxicity and represents the longest reported infusion of insulin, both in beta blocker and calcium channel blocker overdose. Our patient was on high dose insulin

for the treatment of metoprolol overdose for a total of 116 hours and was discharged from the hospital without major sequelae. Our case demonstrates that high dose insulin may be considered in not only calcium channel blocker overdose, but beta blocker overdose as well, and can be used for extended periods of time with positive outcomes and no noted adverse effects.

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