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## Severe beta blocker and calcium channel blocker overdose: Role of high dose insulin

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## ABSTRACT

A 54-year-old female presented after taking an overdose of an unknown amount of hydrochlorothiazide, doxazosin, atenolol and amlodipine. She was initially refractory to treatment with conventional therapy (intravenous fluids, activated charcoal, glucagon 5 mg followed with glucagon drip, calcium gluconate 10%, and atropine). Furthermore, insulin at 4 U/kg was not effective in improving her hemodynamics. Shortly after high dose insulin was achieved with 10 U/kg, there was dramatic improvement in hemodynamics resulting in three of five vasopressors being weaned off in 8 h. She was subsequently off all vasopressors after six additional hours. The role of high dose insulin has been documented in prior cases, however it is generally recommended after other conventional therapies have failed. However, there are other reports that suggest it as initial therapy. Our patient failed conventional therapies and responded well only with maximum dose of insulin. Physicians should consider high dose insulin early in severe beta blocker or calcium channel blocker overdose for improvement in hemodynamics. This leads to early discontinuation of vasopressors. It is important that emergency physicians be aware of the beneficial effects of high dose insulin when initiated early as opposed to waiting for conventional therapy to fail; as these patients often present first to the emergency department. Early initiation in the emergency department can be beneficial in these patients.

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## 1. Background

Beta-blocker ( $\beta$ -blocker) or calcium channel blocker (CCB) overdose is a frequent and potentially lethal occurrence [1]. The most common cause of poison induced cardiogenic shock (PICS) is  $\beta$ -blocker toxicity, with 24,465 exposures to  $\beta$ -blockers reported by the American Association of Poison Control Centers' National Poison Data System in 2012 [1]. While conventional therapies such as atropine, glucagon and calcium have been effective in treating overdose, the role of high dose insulin is important. It has been shown to improve hemodynamics in severe cases [1]. Our case highlights the rapid change in hemodynamics with high dose insulin.

## 2. Case

A 54-year-old female with a past medical history of hypertension presented with abdominal pain after taking an overdose of an unknown amount of hydrochlorothiazide 12.5 mg, doxazosin 8 mg, atenolol 50 mg and amlodipine 10 mg with suicidal intent. On examination she was drowsy, blood pressure (BP) 72/53 mmHg, pulse 50 bpm, respiratory rate 18 bpm, sPO<sub>2</sub> 100% on room air. She was intubated in the emergency department for airway protection and admitted to medical intensive care unit (ICU). Her pupils were 4 mm bilaterally and non-

reactive to light. Heart sounds were normal, and air entry in both lungs was equal without crackles or wheeze. Abdomen was soft, with mild tenderness and without guarding or rebound. Electrocardiogram showed sinus bradycardia with a rate 48 bpm. CT brain was without infarct or bleed. Other results showed sodium 135 (135–145) mmol/L, potassium 3.0 (3.5–5.1 mmol/L), chloride 100 (101–110 mmol/L), creatine 0.77 (0.5–0.9 mg/dL), glucose 139 (71–99 mg/dL), calcium 8.3 (8.6–10 mg/dL), AST 17 (14–33 IU/L), ALT 13 (10–42 IU/L) and bilirubin all within normal limits. WCC 5 (4.5–11  $\times$  10<sup>3</sup>/uL), Hb 10 (12–16 g/dL), platelet 188 (140–440 thou/cu mm) and serum cortisol 27 (0.4–62.9 mcg/dL). Echocardiogram showed ejection fraction 60%, without any abnormalities. Her blood cultures were normal, and urine drug screen negative.

She was given intravenous fluids, activated charcoal, glucagon 5 mg followed with glucagon drip 5 mg/h, calcium gluconate 10% and atropine without response in blood pressure and pulse.

Insulin was started at 1 U/kg/h and titrated up to 4 U/kg/h. Dextrose 10% was used to maintain euglycemia. Renal function was monitored closely and potassium replacements were given. She also required five vasopressors for blood pressure support which included norepinephrine, vasopressin, phenylephrine, epinephrine and dopamine which were all titrated up to maximum doses. Toxicology and nephrology teams were also consulted.

She was started on dialysis in the ICU with hope that this would assist in removal of the atenolol which was a named dialyzable beta blocker. Lipid emulsion therapy was also given. Despite all these there

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were no improvement in blood pressure and pulse and she still required maximum doses of glucagon and five vasopressors.

Her insulin was titrated up to max 10 U/Kg/h on day 2 admission and dextrose 20% used to maintain euglycemia. Serum electrolytes were monitored every hour and glucose checked every 30 min. Two hours after max dose of insulin achieved, there was improvement in her blood pressure and pulse with a MAP maintaining >65 mmHg. Over the next 8 h her epinephrine, dopamine, and phenylephrine was weaned off, and norepinephrine down to 2 mcg/min. Over the next 6 h she was then weaned off the norepinephrine and vasopressin.

After the hemodynamics was stable she was then weaned of the insulin and glucagon infusions. Her BP and pulse remained stable thereafter. Her hospital course was complicated with pulmonary edema and hypoglycemia during the period which the insulin was weaned off. The hypoglycemia persisted for 48 h after the insulin was stopped. These were managed with dialysis and Dextrose 20% respectively. Her pulmonary edema resolved in 24 h without further need for dialysis. The dextrose was titrated down and stopped over 48 h without further hypoglycemic episodes. She was extubated on day six and did well thereafter.

### 3. Discussion

Overdoses with beta blockers and calcium blockers are associated with significant morbidity and mortality [2]. They have similar presentation and the treatment overlaps. It is often refractory to standard resuscitation measures [2]. This case highlights successful management of severe overdose of antihypertensive medications that required maximum dose of reversal agents. We highlight the improvement in hemodynamics achieved shortly after maximum dose of insulin was achieved. Our patient hemodynamics were initially intractable to treatment on maximum glucagon infusion, five maximum vasopressors, lipid emulsion therapy, dialysis and insulin infusion at a rate of 4 U/kg. After titrating, the insulin at maximum dose at 10 U/kg there was significant improvement in her hemodynamics. Three vasopressors were off within 8 h and the remaining two stopped in the next 6 h.

Multiple therapies are recommended for the management of calcium channel and beta blockers overdose including, glucagon, calcium, adrenergic drugs, and lipid emulsion therapy [2]. High-dose insulin (HDI) with supplemental dextrose and potassium therapy is reserved for refractory cases [2].

The mechanism by which insulin work here is outlined as follows: Insulin at high doses has positive inotropic properties [1]. It can also assist myocardial uptake of carbohydrates, which is the preferred fuel substrate of the heart under stressed conditions [1]. Additionally, exogenous insulin administration can help to overcome the insulin resistance and insulin deficiency that occurs in CCB toxicity [1]. It also produces vasodilation, which improves local microcirculation and aids systemic perfusion [1]. Studies have demonstrated accelerated oxidation of myocardial lactate and reversal of metabolic acidosis with HDI [1]. Response to catecholamines is also improved with addition of HDI [1]. One of the major advantages of high dose insulin over the conventional therapies is that the effects are not transient as seen in the conventional treatment [1].

Physicians should be aware of the therapies available in the management of this disorder and the importance of high dose insulin. Of note, our patient hemodynamics had little response at an insulin infusion of 4 U/kg, and the hemodynamic response was significant at 10 U/kg. We postulate that while our patient was receiving insulin at 4 U/kg it was not sufficient to establish some of the effects mentioned above such as

the positive inotropic properties, as a result the improvement in hemodynamics were delayed until the higher dose was established. High-dose insulin therapy, has been reported an effective treatment, and in some reports superior to conventional therapies for severe beta-blocker and calcium channel-blocker poisoning [3]. There have been reports where these conventional therapies such as atropine, calcium, and glucagon fail to improve hemodynamics in severe overdose, this is also seen in our case [3]. Some reports recommend high dose insulin as initial therapy. Though there is a role for glucagon as reported in other cases, [2] physicians should consider each case individually. We advocate for early initiation of high dose insulin in severe overdose.

One fear starting with high dose insulin early is the adverse effects of hypoglycemia and hypokalemia, as seen in our case. We hypothesize that high dose insulin is not the first chosen method in some cases due to the fear of these adverse effects. However, it is a potentially life-saving therapeutic option. Its popularity is not yet widespread and has been mainly restricted to use as a rescue therapy after conventional methods fail [1]. Furthermore, this limitation is likely due to a lack of randomized, controlled trials and practitioner unfamiliarity [1]. With close monitoring, they can be managed without harm to the patient.

Our patient developed pulmonary edema requiring dialysis. Physicians should anticipate this especially in patients requiring insulin infusion for prolonged duration. Our pulmonary edema responded well to dialysis. Her urine output improved subsequently without further need for dialysis.

These patients will often present first to the emergency department. It is important that emergency physicians be aware of the beneficial effects of high dose insulin when initiated early as opposed to waiting for conventional therapy to fail.

### 4. Conclusion

Consider high dose insulin as initial therapy in severe cases of beta-blocker/calcium channel blocker overdose.

Early administration of high dose insulin can improve patient's hemodynamics.

### Authors declaration

All the authors have nothing to declare and all have no competing interests for the written manuscript.

### Authors contributions

The idea for reporting the case was that of KS and SM. All authors contributed equally in writing and analysis of the submitted manuscript.

### Patient consent

Informed consent was obtained for publication of this manuscript.

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