Evidence for High Dose Insulin Therapy

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High dose insulin (HDI) or high insulin euglycemic therapy (HIET) is currently a controversial treatment for Calcium Channel Blocker (CCB) and Beta Blocker (BB) toxicity. CCB and BB overdoses are some of the most common toxic ingestions seen in the ED. The AAPCC TESS reported that deaths by CCB and BB are second to abused sympathomimetics. In 2012, there were 24,465 BB exposures reported to poison centers in the US. Signs and symptoms of CCB and BB toxicity typically present 2-6 hours after ingestion and include **bradycardia, hypotension, dysrhythmias, AMS, seizures, hypoglycemia, and most concerning cardiogenic shock**.

The treatment for both CCB and BB toxicity is similar. **ABCs** should always be assessed first and addressed appropriately. If patients are evaluated within one hour, **activated charcoal** can be administered. **IV fluids and atropine** are given to treat hypotension and bradycardia. Patients should then be given **IV glucagon and calcium** salts. If patients remain hypotensive **vasopressors** can be started. If the patient is refractory to these interventions, **high dose insulin therapy** should be considered and utilized. Typical treatment may not be effective because glucagon has a transient increase in inotropy but is not maintained, vasopressors increase systemic vascular resistance which can decrease cardiac output, and perfusion and atropine is short lived. Considering failure of these treatments, increasing evidence demonstrates that patients may have better outcomes with administration of HDI.

HDI therapy was first utilized in postoperative CABG patients. It was first used to treat verapamil toxicity in humans in 1993. Insulin has positive inotropic properties while being inexpensive with a minimal adverse effect profile. The mechanism of action is not well defined but it is theorized that during shock myocardium utilizes glucose as a substrate for energy instead of free fatty acids and insulin increases intracellular glucose transport in the myocardium. HDI also produces vasodilation, which improves systemic perfusion.

The following are multiple articles with increasing evidence for use of HDI:

- **"Insulin is a superior antidote for cardiovascular toxicity induced by verapamil in the anesthetized canine." (1993)**
    - Kline et al. compared insulin vs. epinephrine vs glucagon vs calcium chloride and a control of normal saline as treatment for dogs with verapamil toxicity. 24 canines received 0.1mg/kg/min of verapamil until a toxic dose defined by a 50% decrease in MAP or AV dissociation for 30min was reached.
    - Rates of survival of the canines per arms:
        - 0/6 for normal saline
        - 4/6 epinephrine
        - 3/6 for glucagon and calcium chloride
        - 6/6 for insulin/dextrose.
- **"Insulin improves survival in a canine model of acute B-blocker toxicity." (1997)**

    - Kerns et al performed a similar study to Kline but used propranolol instead of verapamil. Canines received 0.25mg/kg/minute of propranolol until a 25% decrease in HR x mean BP and then were treated with HDI, glucagon, epinephrine, and normal saline.
    - Rates of survival for the canines followed by treatment regiments:
        - 0/6 for normal saline
        - 4/6 glucagon (50mcg/kg then 150mcg/kg/hr infusion)
        - 1/6 epinephrine (1mcg/kg/min)
        - 6/6 HDI (4 units/min)
    - This canine study showed a statistically significant rate of survival in insulin treated dogs compared to glucagon ($p<0.05$) and epinephrine ($P<0.02$)
- **"Insulin-Glucose as adjunctive therapy for severe calcium channel antagonist poisoning." (1999)**
    - Yuan, Kerns et al, described a case series of 5 patients treated with HDI for calcium channel toxicity.
    - Four patients had verapamil toxicity and one patient had an amlodipine and atenolol overdose.
    - All of the patients were in cardiogenic shock with four of them having a 3rd degree AV block. Three of the patients were hyperglycemic
    - Hemodynamics did not improve with conventional treatment and all patients received HDI and survived without sequelae.
    - Patients were not treated with a standard protocol however so each patient received variable rates of insulin/glucose and other inotropic agents.
- **"Insulin versus vasopressin and epinephrine to treat B-Blocker toxicity." (2007)**
    - Holger et al compared HDI versus vasopressin/epinephrine in 10 pigs that received 0.5mg/kg bolus of propranolol followed by an infusion until toxicity
    - Primary outcome was survival over 4 hours.
    - All HDI pigs survived 4 hours with an increase in CO and all vasopressin/epinephrine pigs died within 90 minutes with a marked increase in SVR.
- **"High-dose insulin: A consecutive case series in toxin-induced cardiogenic shock" (2011).**
    - Holger et al. published a case series of 12 patients in cardiogenic shock treated with a standard protocol of HDI therapy from 2007-2010.
    - Five patients had a BB overdose, 2 CCB, 2 combined CCB/BB, 1 TCA overdose, and 2 polydrug overdoses.
    - 11/12 patients survived
        - The patient that did not survive was 9 hours into HDI which was stopped and vasopressors were re-initiated and then went into PEA arrest one hour later
        - 7 patients received vasopressors that were tapered off while on HDI
        - 2 patients in PEA arrest prior to HDI

- 6 patients experienced hypoglycemic events
- 8 patients developed hypokalemia (K <3.0)

- Standard protocol insulin therapy

Step 1: Fluid bolus with 20-40 ml/kg Normal Saline over the first hour. Goal for maintenance fluids is minimum urine output of 0.5 ml/kg/hr.

Step 2: Infuse calcium IV with an ionized goal of 2 mmol/L (12 mg/dL, total) (especially in calcium channel blocker ingestions).

Step 3: Administer 50ml of dextrose 50% IV if blood glucose is <200gm/dL.

Step 4: Regular insulin bolus at 1 U/kg IV push.

Step 5: Insulin infusion at 1 U/kg/hour (10 U/ml in Normal Saline) with a 10% dextrose infusion at 100 ml/hour, to maintain glucose > 100 mg/dL (dextrose 50% infusion via central line preferred to avoid fluid overload).

Step 6: Increase insulin infusion 1–2 U/kg/hour (maximum 10 U/kg/hr) every 10–15 minutes to clinical response.

Step 7: Maintain K+ >3.0 mmol/L and <4.5 mmol/L.

There is no official guideline or protocol for instituting this therapy but the most common recommendation is similar to the one used in the case series by Holger. If the patient is **hypokalemic or hypoglycemic**, this must be corrected first. The patient should be given a **1 unit/kg bolus of regular insulin followed by an infusion of 0.5-1.0 units/kg/hr**, which can be titrated every 30 minutes until a response in blood pressure or a **max of 10 units/kg/hr**. While the insulin infusion is running, an infusion of 5-10% dextrose at 0.5-1.0 g/kg/hr should be running simultaneously to maintain euglycemia. POC glucose should be checked every 15-30 minutes until stable and then every hour during treatment while potassium should be checked every 30 minutes until stable then every 1-2 hours. Goal endpoints of treatment should be improvement of EF >50%, increased systolic blood pressure >90, HR >60, adequate urine output, and no cardiac conduction abnormalities.

Based on these articles, I believe there is support for treating CCB/BB toxicity with HDI and utilizing it earlier in the treatment protocol. There may be hesitancy and resistance by support staff but with education this intervention should be used. HDI has a low adverse effect profile of hypoglycemia and hypokalemia that can be easily corrected.

References / Further Reading:

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