

High-Dose Insulin (HDI) Therapy

Calcium channel blocker (CCB) and beta blocker (BB) overdose can result in life-threatening cardiovascular collapse. There are several pharmaceutical therapeutic interventions that can be initiated to provide cardiovascular support in the setting of bradycardia and hypotension. These include calcium, glucagon, vasopressors (e.g. norepinephrine and epinephrine) and high-dose insulin (HDI) therapy.

Mechanism/Indications: The proposed mechanism of action of HDI includes: 1. increased inotropy, 2. increased glucose metabolism, 3. vascular dilatation. Cardiac tissues preferentially utilize fatty acid as an energy source during normal condition; under stressed conditions (hypotension or drug-induced toxicity), cardiac tissues rely on glucose metabolism as their primary energy source. CCB overdose decreases insulin release from the pancreas by blocking L-type calcium channels, which can further inhibit glucose metabolism in cardiac tissues. Severe CCB or BB overdose may result in cardiogenic shock that is refractory to initial interventions such as calcium, glucagon or vasopressor infusion. High-dose insulin therapy has demonstrated improvement in CCB- or BB-induced hypotension in both animal and human studies. Insulin has a positive inotropic effect on the heart by improving metabolic support of cardiac tissues during hypotensive shock. Some studies have also demonstrated that high doses of insulin can induce endothelial nitric oxide synthase activity and improve microvascular dysfunction by a vasodilatory effect in cardiac and pulmonary vasculature.

High-dose insulin therapy should be initiated in severe CCB and BB overdose with refractory hypotension. Clinical effect may be delayed up to 15 to 60 minutes; therefore, vasopressor support should be initiated in conjunction with HDI and titrated down as tolerated. Further intervention (e.g. intravenous lipid emulsion) should be considered if the patient is refractory to HDI.

Insulin Dosing:

- Starting dose: Insulin (regular) 1 unit/kg IV bolus, then 0.5 – 1 unit/kg/hr continuous infusion.
- Titrate HDI infusion by 1 unit/kg/hr every 30 – 45 minutes to achieve desired hemodynamic status.
- Response to insulin infusion may take 15 – 60 minutes; therefore, vasopressor support should also be initiated and titrated down as needed/tolerated.
- Up to 10 units/kg/hr has been infused in case reports.
- If glucose is < 250 mg/dL, give D50 50mL IV bolus, then initiate dextrose infusion 0.5 gm/kg/hr.
- Consider D20/D25 solutions (vs. D5/D10 solutions) to minimize infusion volume.
- Potassium supplementation may be needed.

Contraindications:

- None

High-dose insulin therapy (continued)

Adverse Effects: Adverse effects associated with administration of high-dose insulin are primarily hypoglycemia and hypokalemia. A dextrose infusion and potassium supplementation may be required.

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For more on HDI:

- *Engebretsen KM et al. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol 2011;49:277-283.*
- *Megarbane B et al. The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and beta-blocker poisoning. Toxicol Rev 2004;23:215-222.*
- *Hariss NS Case 24-2006: A 40-year-old woman with hypotension after an overdose of amlodipine. N Engl J Med 2006;355:602-11.*
- *Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank, LR. (2015). Opioids. In Goldfrank's Toxicologic Emergencies, 10th ed. (pp. 511-514). New York: McGraw Hill Medical.*
- *St-Onge M et al. Treatment for calcium channel blocker poisoning: a systematic review. Clin Toxicol 2014;52:926-944.*
- *Jang DH et al. Toxin-induced cardiovascular failure. Emerge Med Clin North Am 2014;32:79-102.*
- *DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. Toxicol Rev 2004;23:223-38.*

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