

Therapeutics Bulletin

Management of calcium channel and beta-blocker overdose

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Overdoses with beta-adrenergic blockers (ß-blockers) and calcium-channel blockers (CCBs) are associated with significant morbidity and mortality. Adult intentional self-harming ingestions and accidental ingestions by exploring toddlers constitute the majority of cases. Severely poisoned patients may have profound bradycardia and hypotension refractory to standard vasopressors and in this Therapeutic Bulletin will review the additional treatment options that could be considered.

Mechanism of toxicity

Calcium (Ca) is crucial for cardiovascular function as its flow across cell membranes is necessary for cardiac automaticity, conduction, contraction and maintenance of vascular tone. ß-blockers and CCBs interfere with Ca flux across cell membranes via different mechanisms. CCBs directly block L-type calcium channels found in the heart, vasculature and pancreas, whereas ß-blockers decrease Ca flow by modifying the L-type calcium channels via second messenger systems.

The resultant decreased intracellular Ca produces cardiovascular dysfunction which results in cardiovascular collapse in severe overdose situations. The physiological and toxic effects of ß-blockers and CCBs are similar despite their different mechanisms of action, and are therefore reviewed together.

- CCBs exhibit different selectivity for cardiac Ca versus vascular Ca channels. Dihydropyridines (e.g. amlodipine and nifedipine) are predominantly peripheral vasodilators and are less cardiotoxic compared with non-dihydropyridines (diltiazem and verapamil) which may cause pronounced negative chronotropic, inotropic and dromotropic effects. In addition, Ca mediated insulin secretion by pancreatic tissue and decreased free fatty acid utilization by the myocardium may be impaired in all types of CCB toxicity and cause hyperglycaemia, acidosis and further depress cardiac contractility.
- Classification of ß-blockers to predict toxicity is less clear, as the toxicity of ß-blockers vary according to various molecular properties (lipophilicity, membrane stabilising activity, α-blockade etc).

Management

ß-blockers and /or CCBs toxicity may produce hypotension and bradycardia that is difficult to treat, and often requires simultaneous therapies of intravenous fluids, vasopressors, calcium, glucagon, high-dose insulin with dextrose, and intravenous lipid emulsion therapy. The algorithm below should be followed in a stepwise fashion, optimising each step before moving over to the next. In severe cases, several treatment options may be started at once, depending on the clinical picture and availability of drugs.

Management of Acute Beta Blocker or Calcium Channel Blocker Overdose in Adults

NB: The following treatment options should be used SIMULTANEOUSLY in severe poisonings with persistent hypotension. Be sure to OPTIMISE each one!

Persistent Hypotension

Optimise treatment before adding additive treatments

Ensure basic life support has been provided
IV Line access, continuous cardiac monitoring, check glucose, activated charcoal (if safe and within first hour)

Hypotension **(SBP < 100mmHg OR MAP < 65)** and/or Bradycardia **(Heart rate < 60bpm)**

- Intravenous fluid resuscitation
- Atropine for bradycardia 0.5-1mg IV every 2 - 3 minutes; **TOTAL MAX DOSE 3mg**

Glucagon *Time to effect 15 min*

NOTE: Only if overdose is known **to include a Beta Blocker**, give Glucagon as follows:

- Glucagon Bolus: 5-10mg IV slowly over 1-2 min; If **NO** response within 10 minutes, repeat bolus
- Only if response is noted after 10min, start continuous infusion: 5-10mg/hr

Calcium *Time to effect 15 min*

- 10% Calcium Gluconate (via peripheral venous line) 30-60ml IV over 10mins **OR** 10% Calcium Chloride (via central venous line) 10-20ml IV over 10 min
- If **NO** response in 15min, start continuous infusion: 10% Calcium Gluconate 1 ml/kg/hr **OR** 10% Calcium Chloride 0.3 ml/kg/hr

NOTE: Monitor levels every 2hr while on infusion; may consider increasing the dose of calcium only if known calcium channel blocker overdose

Vasopressors *Time to effect 15 min*

- Epinephrine (Adrenalin) 5-35mcg/min, titrate as required
- If **NO** response, add Dopamine **OR** Dobutamine (And start high dose insulin euglycemia therapy)

High Dose Insulin Euglycemic Therapy *Time to effect 30-60 min*

NOTE: If glucose levels are less than 11mmol/l give 50ml of 50% Dextrose bolus
If potassium less than 3mmol/l give 20mEq/l IV. Monitor levels every 30min until stable thereafter every 2 hrs

- Start 5% dextrose infusion
- Insulin Bolus: 1U/kg IV
- Start continuous Insulin infusion: 0.5-1U/kg/hr in severe toxicity may need to titrate up to 10U/kg/hr

NOTE: MONITOR GLUCOSE EVERY 15 TO 30 MIN FOR 4 HOURS thereafter hourly (Target: 6 - 11mmol/l)

Intravenous Lipid Emulsion (last ditch rescue attempt after having optimized other therapies) *Time to effect 15 min*

- Intralipid 20% Bolus: 1.5ml/kg IV over 2 min, If **NO** response within 3 min, repeat the bolus
- Start continuous Intralipid infusion 0.25ml/kg/min, decrease to 0.025ml/kg/min once hemodynamically stable (If recurrence of hemodynamic instability, can repeat bolus once and/or increase infusion rate); **TOTAL MAX Duration 6hr and MAX DOSE 10ml/kg**

NOTE: Intravenous lipid emulsion is associated with adverse effects, including cardiac arrest, fat embolism, hypersensitivity and infection

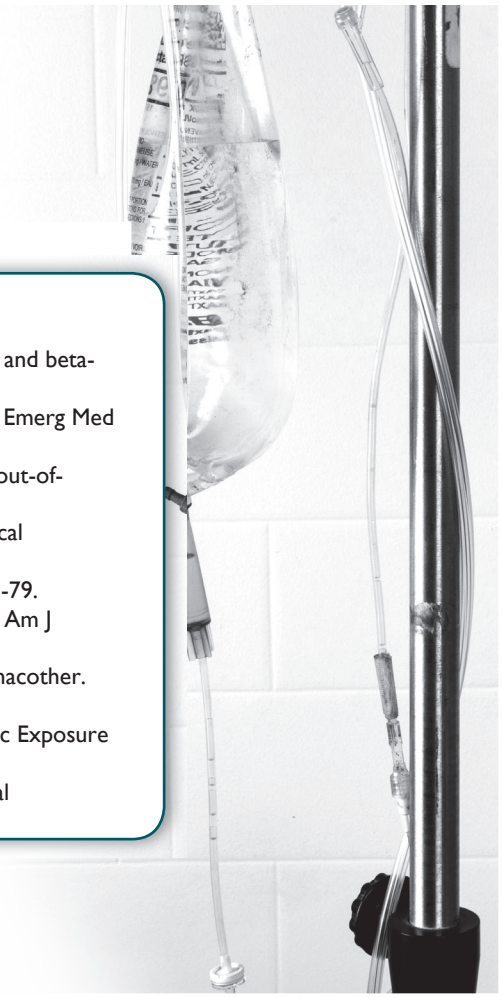
If **NOT** already given, Glucagon Bolus: 3-5mg IV slowly over 1 min; if **NO** response, may repeat dose in 10 min *Time to effect 15 min*

Consider consult with ***Poison Information Helpline or Clinical Pharmacologist*** on call
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Key points:

- Optimise each step before moving on to the next.
- In severe cases simultaneous treatments may be needed.
- Glucagon is associated with severe nausea and vomiting.



References:

1. De Witt et al. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. Toxicol Review. 2004; 23(4):223-38.
2. Kerns W. Management of β-Adrenergic Blocker and Calcium Channel Antagonist Toxicity. Emerg Med Clin N Am. 2007; 25: 309-331.
3. Olson et al. Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol. 2005; 43:797-822.
4. St-onge et al. Treatment for calcium channel blocker poisoning: A systematic review. Clinical Toxicology. 2014; 52: 926-944.
5. Salhanick et al. Management of calcium channel antagonist overdose. Drug Saf. 2003; 26:65-79.
6. Shepherd G. Treatment of poisoning caused by β-adrenergic and calcium-channel blockers. Am J Health-Syst Pharm. 2006; 63: 1828-1835.
7. Shepherd et al. High dose insulin therapy for calcium channel blocker overdose. Ann Pharmacother. 2005; 39:923-30.
8. Watson et al. Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med. 2005; 23:589-666.
9. Wax et al. Beta-blocker ingestion: an evidence based consensus guideline for out-of hospital management. Clin Toxicol. 2005; 43:131-46.