



# Pharmacy Friday

Brief pearls related to acute care pharmacology and evidence-based medicine

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## Calcium Channel Blocker (CCB) and Beta Blocker (BB) Toxicity

### Introduction

1. Myocardial depression, bradycardia, and hypotension result from both CCB and BB toxicity
2. Management of hemodynamic instability resulting from toxicity of CCBs and/or BBs follows similar principles
3. GI decontamination may be warranted for patients who have ingested significant amounts of BB or CCB
4. Initial management options include glucagon, high-dose insulin, calcium, and catecholamines with beta-adrenergic activity
5. Symptoms should occur within 6 hours post-ingestion, with the exception of sotalol and extended release formulations

### Pharmacology

Properties	Glucagon	High Dose Insulin Euglycemia	Calcium Salts	Catecholamins (epinephrine, isoproterenol, dopamine)
<b>Dose</b>	<u>Peds</u> : Initial: 50 mcg/kg IV <u>Adult</u> : Initial: 3 to 5 mg IV over 1-2 min  May start a glucagon infusion based on response dose/hr	LD: 1 u/kg regular insulin IV MD: 1-10 u/kg/hr IV, max 10 units/kg/hr  <b>PLUS</b> Dextrose 10-50% @ 0.5 gm/kg/hr IV to maintain euglycemia (BG goal 150-250)	Adult: 1-3 gm IV Peds: 60 mg/kg IV up to 3 gm  May repeat every 10-20 minutes up to 9 gm in adults and 180 mg/kg in peds	Usual doses; Titrated to clinical effect with hemodynamic monitoring
<b>Onset of Action</b>	5-20 min Tachyphylaxis after 12-24h	Delayed, 15-60 min	Mins, titrate to effect	Mins, titrate to effect
<b>Adverse Effects</b>	Emesis, hyperglycemia, hypercalcemia,	Hypokalemia, hypoglycemia	Vasoconstriction, renal failure	Tachyarrhythmia, hypertension, ischemia
<b>Mechanism of action</b>	Bypasses inhibited beta receptors, ↑ cAMP leading to ↑ chronotropy and inotropy	Inhibits Na <sup>+</sup> /Ca <sup>2+</sup> antiporter, ↑ myocardial Ca <sup>2+</sup> , ↑ carbohydrate delivery to myocardium, mild vasodilation ↑ perfusion	↑ Ca <sup>2+</sup> concentration gradient, ↓ the negative inotropy, impaired conduction, and hypotension. No effect on heart rate.	Providing ↑ adrenergic activity at <b>α + β</b> receptors
<b>Comments</b>	If full 10mg dose fails, start drip at 10mg/hr because glucagon will have synergistic effects with subsequent antidotes. Patients may develop tachyphylaxis.	Must administer with dextrose source. <b>Monitor glucose every 15 min initially.</b> Consider addition of potassium 20-40 mEq/L of dextrose infusion to prevent hypokalemia	Calcium Chloride:Gluconate concentration ratio 1:3  Calcium chloride has a higher risk of extravasation	To be used after or in addition to other agents. Attempt to wean off vasopressors first.

### Additional Therapies

Pharmacologic:	Non Pharmacologic:
Methylene Blue Vasopressin Milrinone Intralipid Emulsion	Pacing ECMO MARS

## Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Doepker, 2014	<b>Case series:</b> <u>Patient 1:</u> PEA post-amlodipine, verapamil, and metoprolol ingestion <u>Patient 2:</u> cardiogenic shock post- amlodipine, simvastatin, lisinopril, and metformin ingestion	<u>Both treated with:</u> Calcium, glucagon, vasopressors, high-dose insulin, and IV lipid emulsion	Both initially treated with glucagon, calcium, and vasopressors  Both had subsequent hemodynamic improvement, resolution of shock, and full neurologic recovery
Holger, 2011	<b>Case Series:</b> <ul style="list-style-type: none"> <li>• BB overdose, n=5</li> <li>• CCB overdose, n=2</li> <li>• BB + CCB overdose, n=2</li> <li>• Poly-drug, n=2</li> </ul>	High-dose insulin + dextrose	AEs: Hypoglycemia in half of patients, hypokalemia  High-dose insulin therapy based on a 1-10 U/kg/h dosing guideline appears to be effective in these cardiotoxic overdoses
Page, 2009	<b>Case Report:</b> Massive metoprolol overdose (5 g)	1-2 u/kg regular insulin IV x4, then insulin drip @ 10 u/kg  Additional therapies: Atropine, Isoprenaline, Metaraminol, 0.9% Saline bolus	Improvement in heart rate and blood pressure seen with addition of insulin + glucose.  Patient hemodynamically stable at hour 7.
Stellpflug, 2010	<b>Case Report:</b> Cardiac arrest secondary to intentional BB overdose	IV lipid emulsion and high-dose insulin	Care with intravenous lipid emulsions and insulin therapy up to 21.8 u/kg/hr were utilized for treatment. Patient survived to discharge with baseline neurologic function
Love, 1998	<b>Case Report:</b> Patients with symptomatic bradycardia who failed atropine after beta blocker toxicity N=9	Glucagon post atropine	Glucagon was effective in correcting symptomatic bradycardia and hypotension in 8/9 patients.
Levine, 2013	<b>Retrospective chart review:</b> 48 patients with diltiazem and verapamil overdoses	33 patients treated with vasopressors  8 patients treated with glucagon and/or calcium	<ul style="list-style-type: none"> <li>• 29/33 patients treated with vasopressors survived without complication <ul style="list-style-type: none"> <li>◦ 3 patients had cardiac arrest</li> <li>◦ 1 patient expired</li> </ul> </li> <li>• 8/8 Calcium/glucagon patients survived without complication</li> </ul>
Meany, 2013	<b>Case Report:</b> Amlodipine overdose in combination with unknown amount of ethanol	Intravenous lipid emulsion after failure of activated charcoal, IV fluids and calcium boluses	Hemodynamically unstable on 3 different vasopressors, when intralipid infusion was initiated over 4.5 hours. At end of infusion patient was tapered off 2 vasopressors with stable MAP
Lashari, 2018	<b>Case Report:</b> Unknown ingestion with medication history of Lisinopril, clonidine, chlorthalidone, labetalol and nifedipine	Intravenous lipid emulsion and high dose insulin therapy after failure of atropine, calcium boluses and multiple vasopressors	Patient improvement seen on day 3 when 4/5 vasopressors were tapered off. Patient was off all vasopressors on day 4 and extubated on day 5.

### Conclusions:

- Evidence for CCB and BB toxicity is increasing but still limited to case reports and case series
- In the setting of toxic CCB and/or BB ingestions, there are a variety of therapeutic modalities available
- Treatment may require combined use of the agents described above
- Contact your regional poison center: 1-800-222-1222

### References

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