Cardiac Chaos: Navigating Calcium Channel Blocker and Beta-Blocker Toxicity

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Objectives

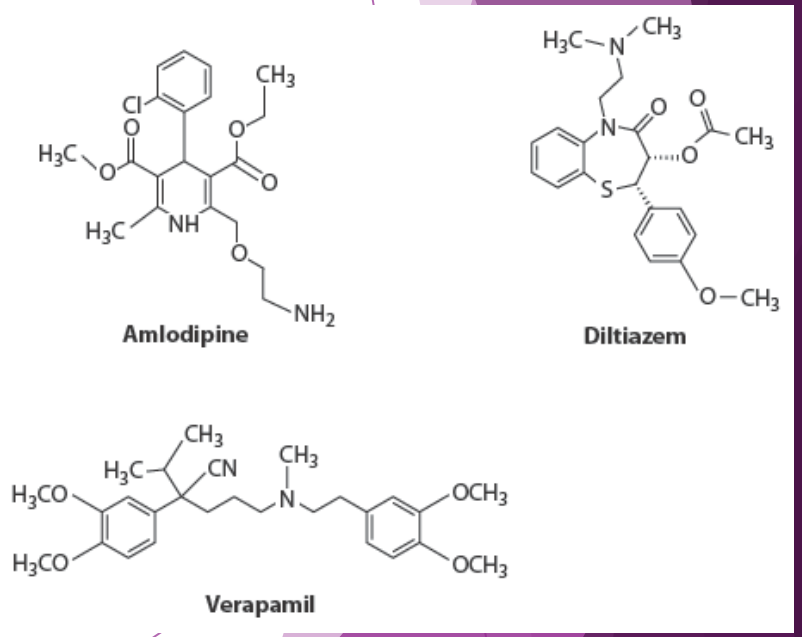
Discuss	Describe	Review	Identify
Discuss the clinical presentation of calcium channel blocker and beta-blocker toxicity	Describe differentiating factors between calcium channel blocker (dihydropyridine vs non-dihydropyridine) and beta-blocker toxicity	Review the pharmacology of first-line antidotes used to manage calcium channel blocker and beta-blocker toxicity	Identify salvage therapies used in the management of calcium channel blocker and beta-blocker toxicity

Calcium channel blockers
Beta-blockers

Overview

Calcium channel blockers (CCBs)

- Mechanism of action: antagonism of L-type voltage-gated calcium channels
- Classified into 2 main groups:
  - Dihydropyridine (DHP)
    - Amlodipine, clevidipine, felodipine, nicardipine, nifedipine, nimodipine
    - Site of action: smooth muscle in peripheral vasculature
  - Non-dihydropyridine (non-DHP)
    - Verapamil, diltiazem
    - Site of action: sinoatrial (SA) and atrioventricular (AV) nodal tissue



Jang DH. Goldfrank's Toxicologic Emergencies. 2019: 945-952.

CCBs: Pharmacokinetics

- Absorption: well-absorbed orally
- Distribution: highly protein bound, large volume of distribution
- Metabolism
  - Extensive hepatic first-pass metabolism
  - Hepatic oxidative metabolism (CYP3A$)
    - Overdose → enzymes saturated → decreased first-pass effect → increase active drug absorbed

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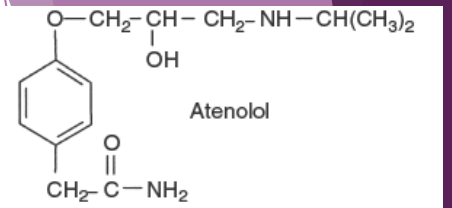
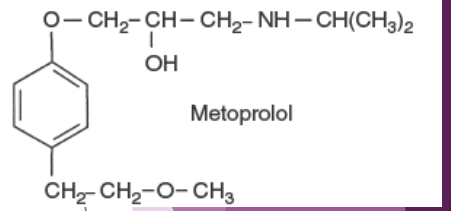
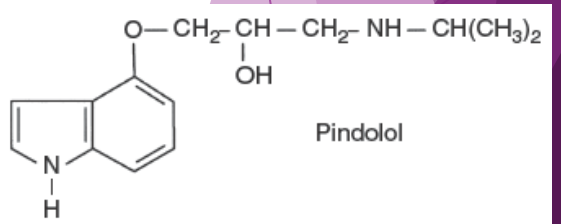
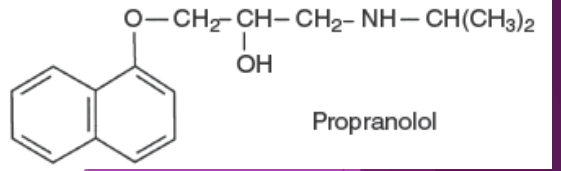
Beta-adrenergic antagonists (BAAs)
Beta-blockers (BBs)

- Mechanism(s) of action
  - $Beta_1$-receptor blockade: decreased heart rate & contractility
  - $Beta_2$-receptor blockade: bronchoconstriction, hypoglycemia, hyperkalemia
- Classification
  - Selective vs non-selective
    - Selective: antagonize $beta_1$ receptors
      - Atenolol, bisoprolol, esmolol, metoprolol
    - Non-selective: antagonize $beta_1$ and $beta_2$ receptors
      - Nadolol, pindolol, propranolol









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BBs: Additional Receptor Activity

- Labetalol & carvedilol
  - Non-selective
  - Alpha$_1$ blockade
- Propranolol
  - Sodium channel blockade
- Sotalol
  - Potassium channel blockade

Brubacher JR. Goldfrank's Toxicologic Emergencies. 2019: 926-940.

Clinical Presentation

Clinical Presentation

Calcium channel blockers

- Dihydropyridine
  - Hypotension with reflex tachycardia
  - Hyperglycemia
  - Vasoplegic shock
- Non-dihydropyridine
  - Bradycardia
  - Hypotension
  - Hyperglycemia
  - Cardiogenic shock

Beta blockers

- Bradycardia
- Hypotension
- Cardiogenic shock
- Hypoglycemia
- Hyperkalemia (rare)

- **Propranolol:** QRS widening, AMS, seizures
- **Sotalol:** QTc prolongation, Torsade de Pointes

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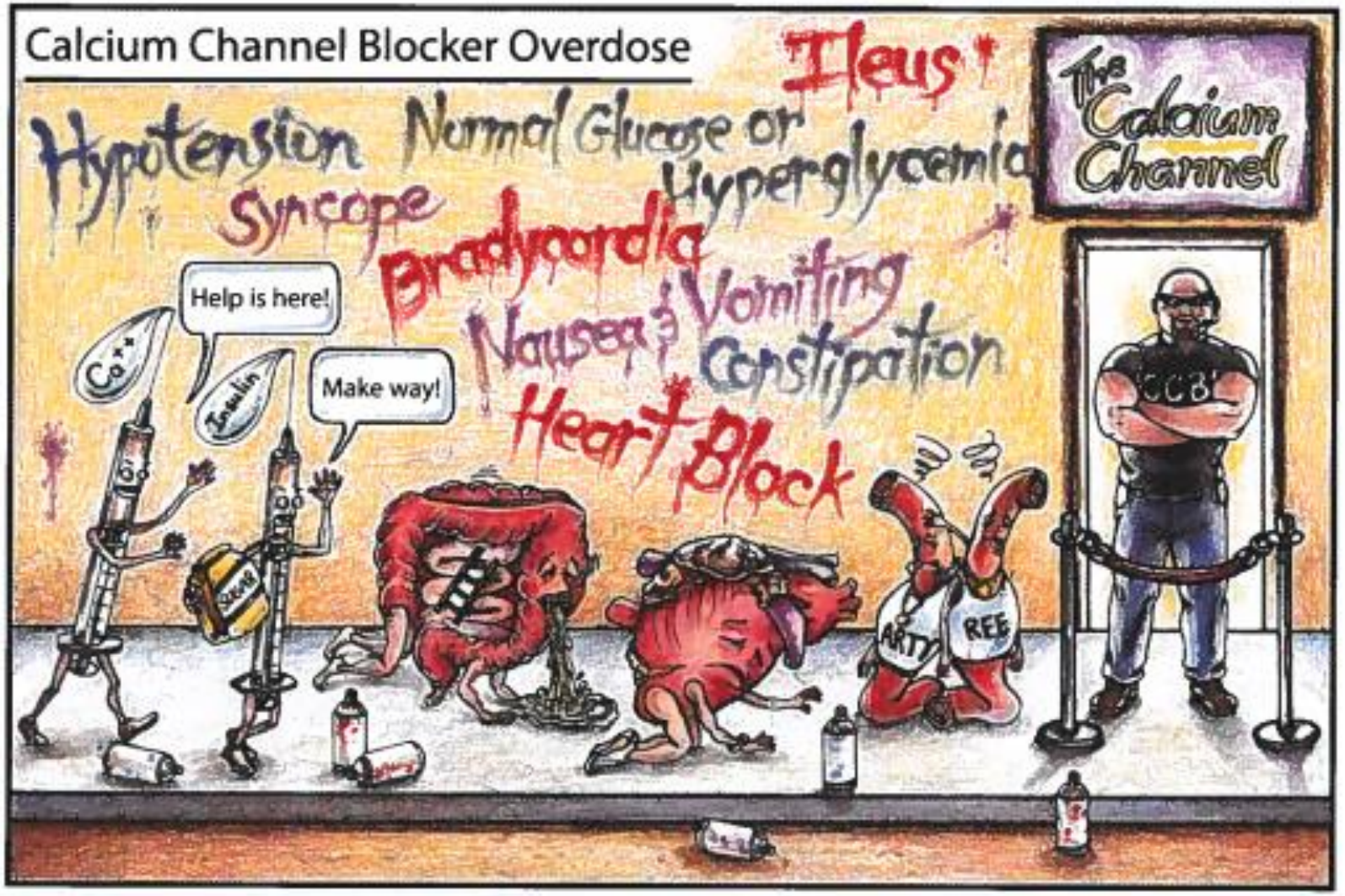
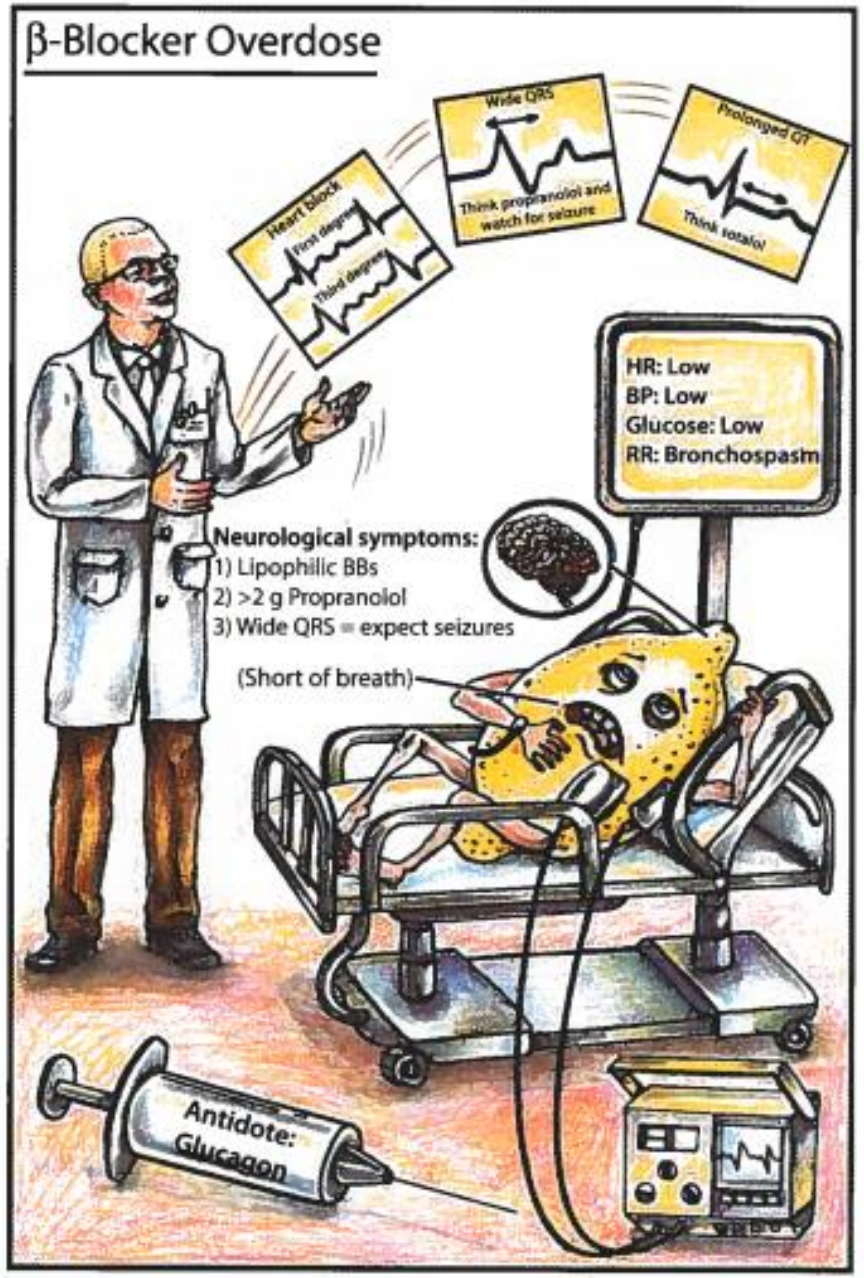


Kloss BT, Bruce T. Toxicology in a Box. 2013.



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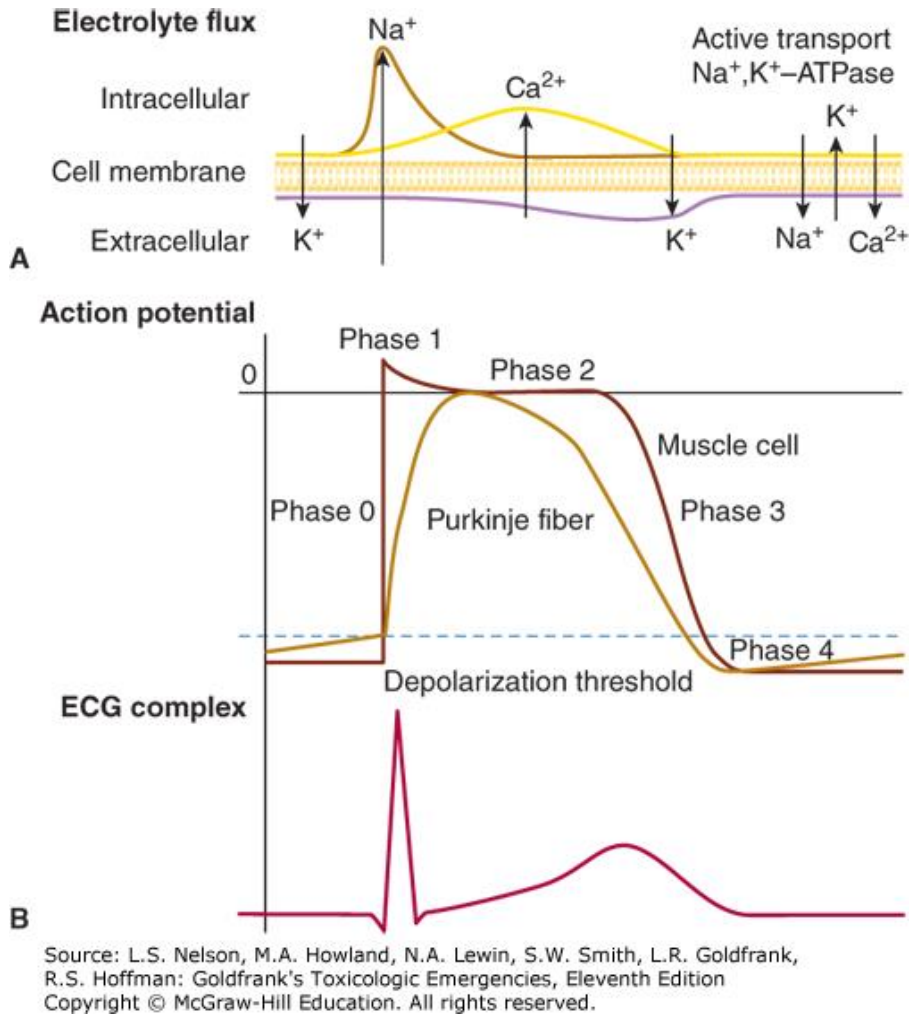
Diagnosis

- History of ingestion
- CCB levels and BB levels are not routinely available

- Recommended laboratory / diagnostic studies
  - Electrolytes
  - Glucose
  - BUN, serum creatinine
  - EKG
  - Consider cardiac echo (CCBs)



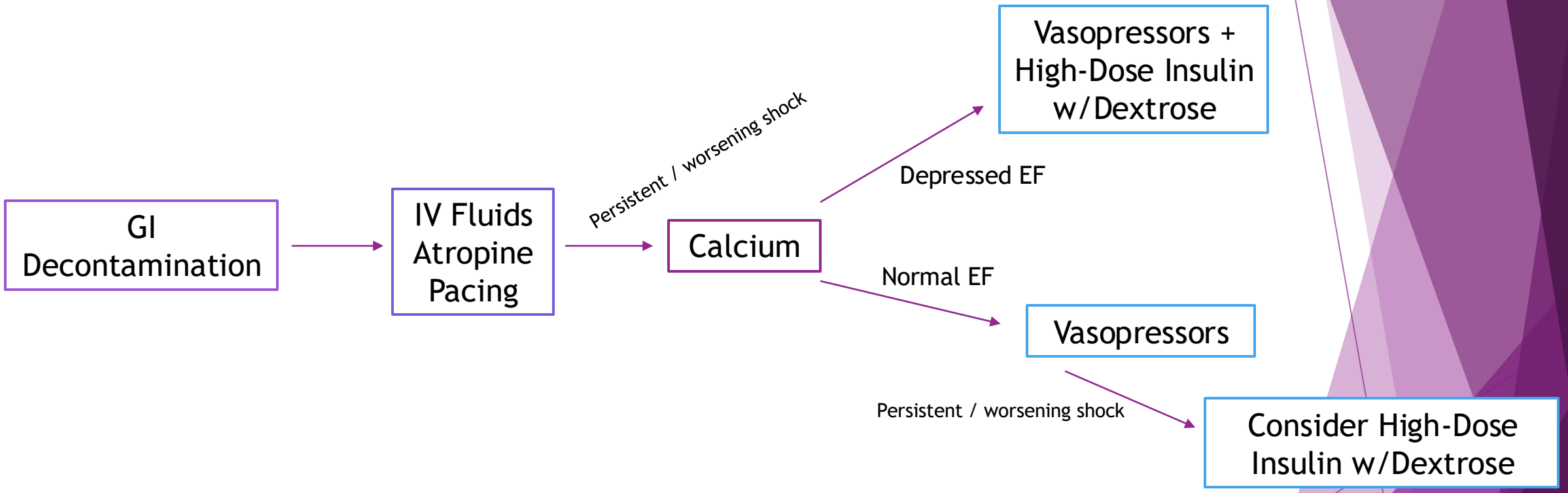
Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank, R.S. Hoffman: Goldfrank's Toxicologic Emergencies, Eleventh Edition

Relationship of electrolyte movement across the cell membrane (A) to the action potential and the surface ECG recording (B) over a single cardiac cycle.

Citation: Chapter 15 Cardiologic Principles I: Electrophysiologic and Electrocardiographic Principles, Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. *Goldfrank's Toxicologic Emergencies, 11e;* 2019. Available at: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2569&sectionid=210259136 Accessed: February 13, 2025

Management of CCB & BB Toxicity

Treatment Pathway



Persistent / Worsening Shock

- Adjuncts: methylene blue, glucagon, lipid emulsion
- Consider ECMO, ventricular assist devices

**Practice will vary between poison centers and toxicologists

Initial Measures

Remember your ABCs → Airway / Breathing / Circulation

- Obtain IV access, place on cardiac monitor
- Consider GI decontamination: activated charcoal
  - Present within 1-2 hours (possibly longer if SR formulation)
  - No nausea / vomiting
- **Hypotension**: IVFs (max 30 mL / kg)
  - Do not over-resuscitate!
- **Bradycardia**: can consider atropine, pacing (unlikely to capture)
  - Atropine: 0.5-3mg IV (up to 3mg)

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Calcium

- Greater improvement in blood pressure over heart rate
- Benefit usually short-lived
- Severely poisoned patients unlikely to improve with calcium alone

- Calcium gluconate: 60mg/kg IV bolus over 5-10 min (max 3-6g/dose)
  - Consider IV infusion: 60-120mg/kg/hr
- Calcium chloride: 20mg/kg IV bolus over 5-10 min
  - Consider IV infusion: 20-40mg/kg/hr

- Titrate to 1.5-2x upper limit of normal for institution's lab value
- Monitor for signs of hypercalcemia

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Vasopressors

- No one vasopressor considered superior above another
- **Use concentrated infusions**: high risk of pulmonary edema in CCB overdose

- CCBs
  - Norepinephrine, epinephrine, phenylephrine
- BBs
  - Epinephrine, vasopressin, dopamine
  - Caution: isoproterenol
    - High doses required → may cause dysrhythmias & vasodilation
- Which vasopressor should be used?
  - Readily available
  - Provider comfortable using vasopressor

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High-Dose Insulin w/Dextrose

- High-dose insulin euglycemia (HDI, HIE, HIET)
- Mechanisms of action:
  - Increased inotropy
  - Vascular dilatation
  - Increased intracellular glucose transport
- Recommend bedside echo to assess for depressed EF
  - Most benefit for patients with depressed EF

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High-Dose Insulin w/Dextrose: Dosing

Regular insulin

- Bolus: 1 unit/kg
- Infusion: 1 unit/kg/hr – 10 units/kg/hr
  - May increase by 1 unit/kg/hr every 15-30 min until desired effect
  - **Recommend concentrating insulin infusion to 10 units/mL
- Improved mentation and increased urine output may be only signs of effect

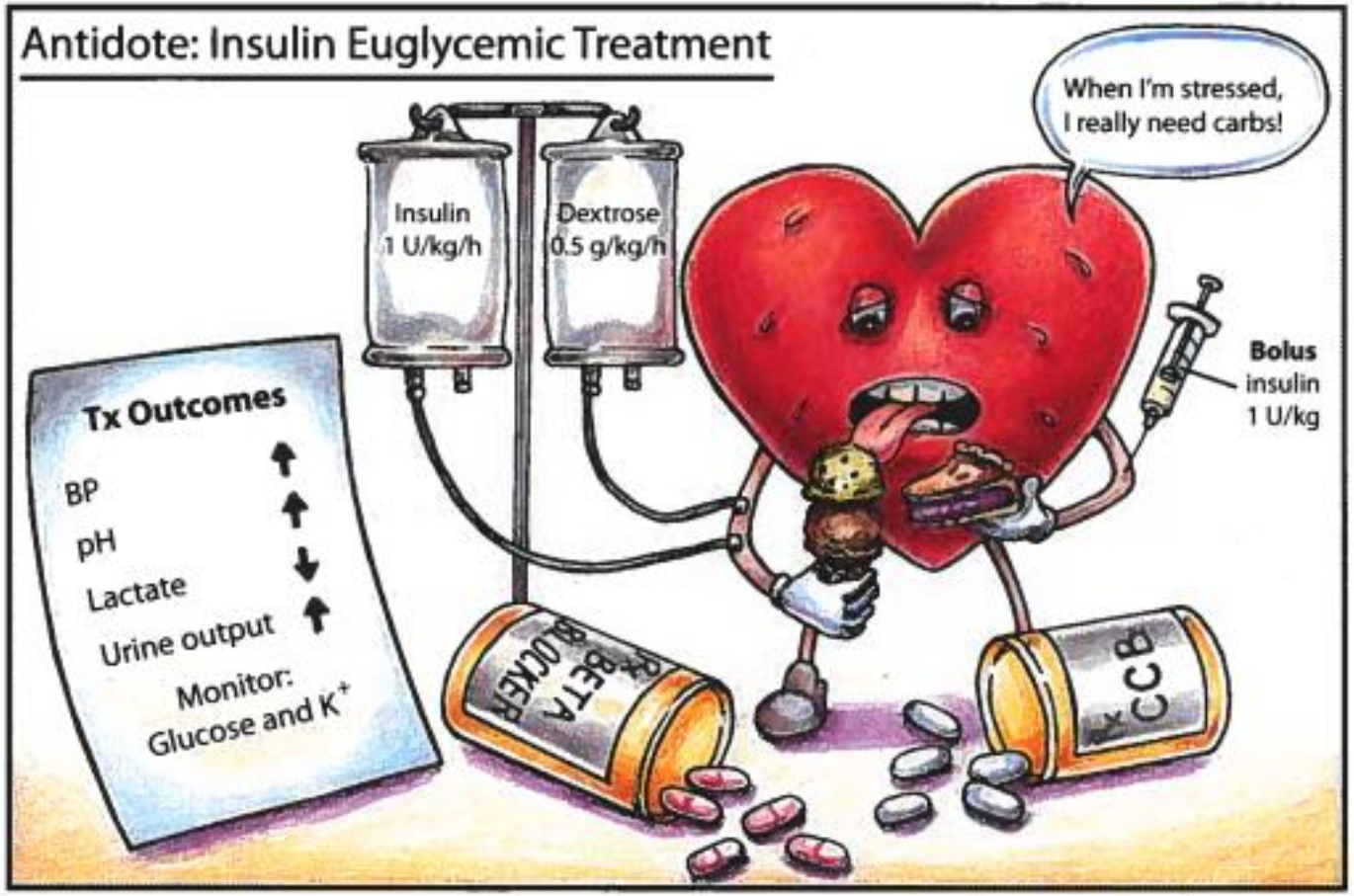
Dextrose

- Consider bolus of D50 if initial BG < 200 mg/dL (D25 for peds)
- Infuse D20W (or D20 ½ NS) at 50 mL/hr **or** D10W (or D10 ½ NS) @ 100mL/hr

High-Dose Insulin w/Dextrose: Monitoring

- Electrolyte monitoring
  - Potassium: every 4h x 24h, then at least q8h if therapy continues
- Glucose
  - Maintain BG between 100-200 mg/dL
  - Recommend fingerstick q15min x4 → space to q30min x4 if stable → space to q1-2h if stable (and insulin infusion rate stable)
- Pulmonary edema
  - Very high-risk patient population
  - **Use concentrated infusions** when possible (vasopressors, insulin, dextrose)

High-Dose Insulin w/Dextrose



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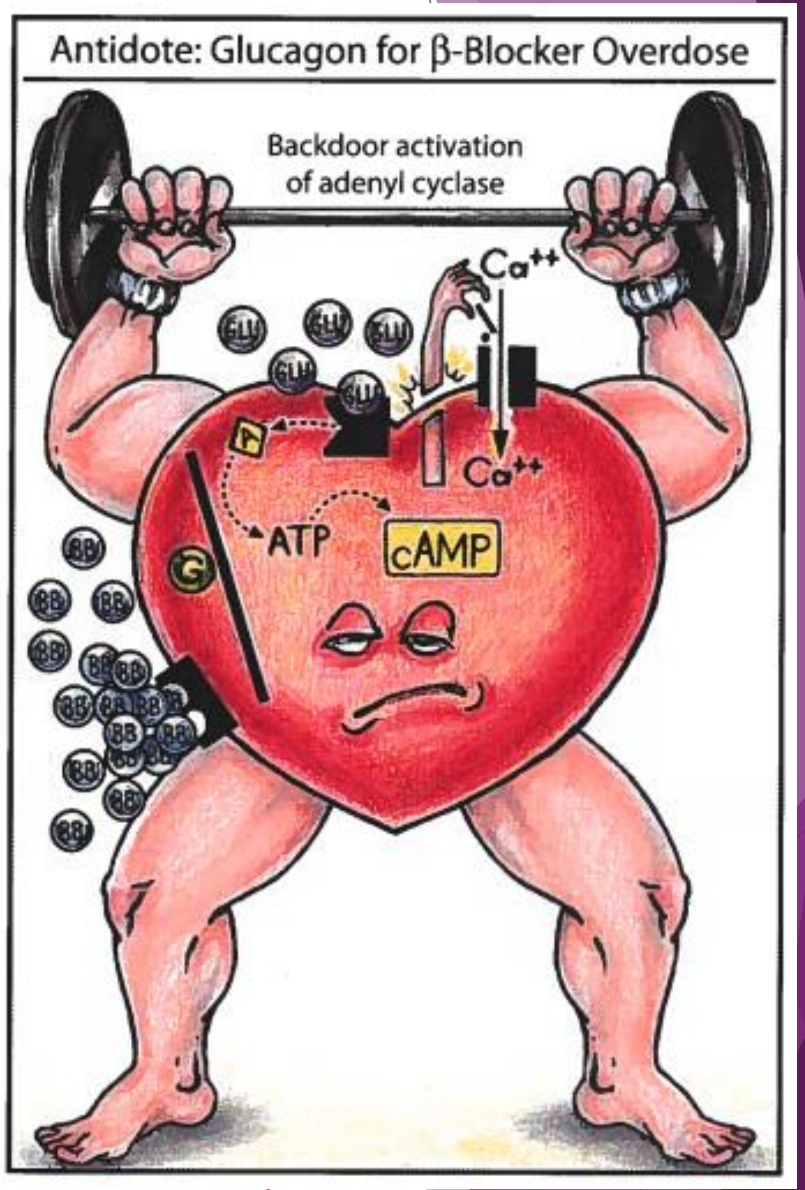
Glucagon

- Likely greater benefit in BBs over CCBs
- Mechanism of action:
  - Binds to cardiac glucagon receptors → stimulates conversion of ATP to cAMP
  - Increased inotropy & chronotropy
- Other actions:
  - Relax smooth muscle of lower esophageal sphincter → vomiting



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Glucagon: Dosing

- 3-5mg IV bolus over 1-2 minutes (max 10mg)
- Consider infusion if effective
  - Start infusion rate at response rate
  - Risk of vomiting, tachyphylaxis

- Limitations:
  - Need significant supply to maintain infusion → coordinate with pharmacy

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Methylene Blue

- Consider in patients with refractory hypotension from DHP-CCB in distributive shock
- Mechanism of action:
  - Inhibition of nitric oxide synthesis
- Dose
  - 1-2 mg/kg bolus (max 100mg) over 20-60min
  - Consider infusion if effective: 0.5-1 mg/kg/hr
- Monitoring
  - Methemoglobinemia, hemolytic anemia, serotonin toxicity (check for clonus)
  - May affect colorimetric labs for up to 6h

de Castro Bras LE, et al. Am J Emerg Med. 2021.

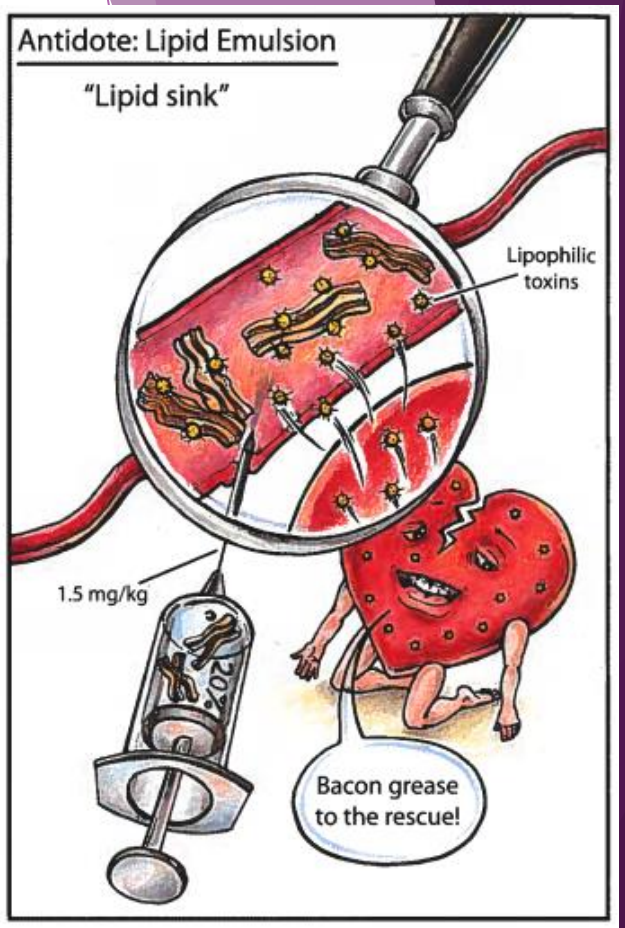
Lipid Emulsion

- Can consider in patients refractory to all other therapies
- Mechanism: ‘lipid sink’ theory
- Consult toxicologist

- Dose:
  - 1.5 mL/kg of 20% IV lipid emulsion (ILE) over 1 min
  - Continuous infusion: 0.25 mL/kg/min for 3 min → 0.025 mL/kg/min up to 6.5hrs

- Limitations
  - Potential interference with ECMO circuits
  - May reduce effectiveness of resuscitation medications (lidocaine)

- **Note: ILE not recommended in 2023 AHA Resuscitation update for CCB overdose



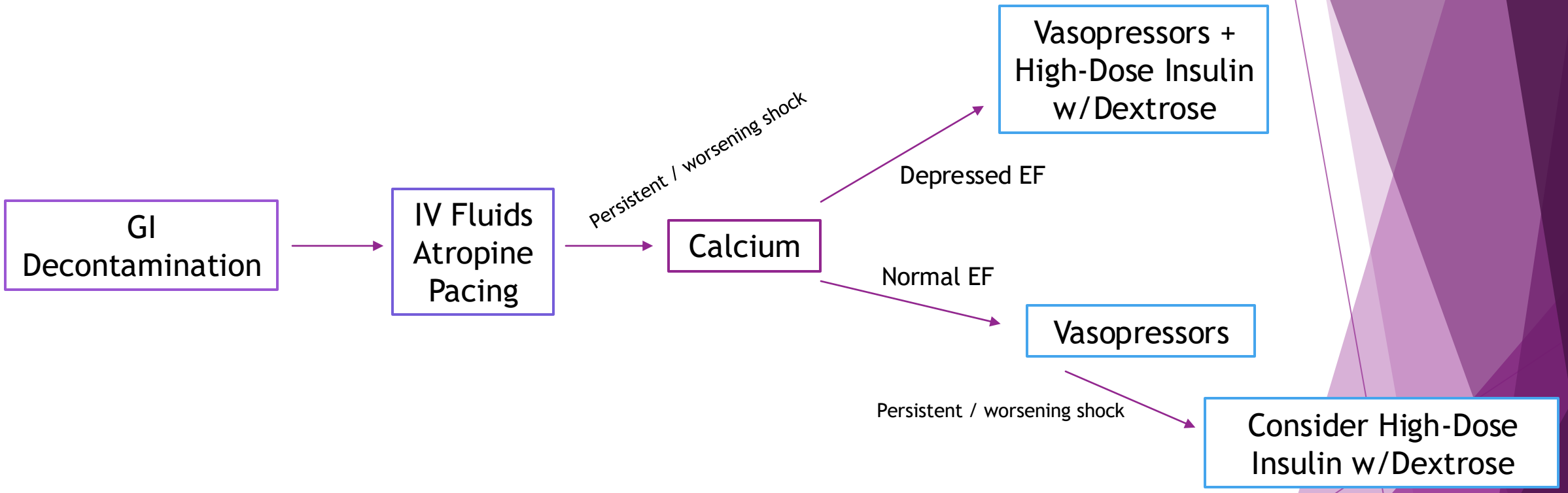
Lavonas EJ, et al. Circulation. 2023; 148:e149-e184.
Kloss BT, Bruce T. Toxicology in a Box. 2013.

ECMO & Mechanical Life Support

- Consider in patients with refractory cardiogenic shock unresponsive to other therapies
- Mechanical life support
  - Intra-aortic balloon pump
- ECMO
  - Recommend VA-ECMO

St-Onge M, et al. Clinical Toxicology, 52:9, 926-944.
Rotella JA, et al. Clinical Toxicology, 58:10, 943-983.

Treatment Pathway



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Recommended Reading

CLINICAL TOXICOLOGY
2020, VOL. 58, NO. 10, 943–983
https://doi.org/10.1080/15563650.2020.1752918

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REVIEW

Treatment for beta-blocker poisoning: a systematic review

Joe-Anthony Rotella[a,b], Shaun L. Greene[a,c], Zeff Koutsogiannis[a,b], Andis Graudins[a,d,e], Yit Hung Leang[a], Kelvin Kuan[f], Helen Baxter[g], Elyssia Bourke[a] and Anselm Wong[a,e,h]

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Clinical Toxicology (2014), **52**, 926–944

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healthcare

REVIEW ARTICLE

Treatment for calcium channel blocker poisoning: A systematic review

M. ST-ONGE,[1,2,3] P.-A. DUBÉ,[4,5,6] S. GOSSELIN,[7,8,9] C. GUIMONT,[10] J. GODWIN,[1,3] P. M. ARCHAMBAULT,[11,12,13,14] J.-M. CHAUNY,[15,16] A. J. FRENETTE,[15,17] M. DARVEAU,[18] N. LE SAGE,[10,14] J. POITRAS,[11,12] J. PROVENCHER,[19] D. N. JUURLINK,[1,20,21] and R. BLAIS[7]

Summary

- CCBs: bradycardia, hypotension, hyperglycemia
  - DHP CCBs (may have reflex tachycardia)
- BBs: bradycardia, hypotension, hypoglycemia
  - Lipophilic agents are most toxic: propranolol
- Selectivity of beta-blockade varies widely with the drug class
  - Special cases w/additional activity: propranolol, sotalol, carvedilol & labetalol
- CCB toxic patients are highly susceptible to pulmonary edema & fluid overload
  - **Concentrate infusions whenever possible!**
- High-dose insulin therapy likely more effective in patients with depressed EF
- Use of lipid emulsion is considered a salvage therapy
- Consult a poison center or toxicologist to assist with case management

Poison Control

CENTRAL OHIO POISON CENTER

POISON HELP 1-800-222-1222 POISONHELP.ORG

- Specially trained nurses & pharmacists
- Staffed 24/7/365
- Professional callers: consultation with board-certified medical toxicologist
- National phone number – routed by caller's location

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