Clinical Toxicology

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Calcium-blockers Toxicity

Calcium channel antagonists (also known as calcium channel blockers or calcium antagonists) are widely used to treat angina pectoris, coronary spasm, hypertension, hypertrophic cardiomyopathy, supraventricular cardiac arrhythmias, Raynaud phenomenon, and migraine headache. Toxicity from calcium antagonists may occur with therapeutic use (often owing to underlying cardiac conduction disease or drug interactions) or as a result of accidental or intentional overdose. Overdoses of calcium antagonists are frequently life-threatening and an important source of drug-induced mortality. As little as one tablet can be potentially life-threatening in a small child.

Classification of Calcium-blockers

- **1-Diphenyl alkylamine:** Verapamil is an e.g. on this type.
- Verapamil is the least selective of any calcium channel blockers and has significant effect on both cardiac and vascular smooth muscle cells.
- **2-Benzothiazopines:** Diltiazem is an e.g. on this type.
- affects both cardiac and vascular smooth muscle cells.
- However, it has a less pronounced negative inotropic effect on the heart than does verapamil.
- **Dihydropyridines:**
- All the dihydropyridine have a much greater affinity for vascular calcium channel than for calcium channel in the heart, although cardiac toxicity may be observed in overdose; agents in this class are amlodipine, felodipine, isradipine, nicardipine, nimodipine, and nisoldipine

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Pathophysiology

- All existing CCBs function by binding to the L-subtype, voltage-sensitive, slow calcium channels in cell membranes.
- The L-type calcium channel blockers decrease the flow of calcium into the cells of the cardiac conduction pathway, which leads to an inhibition of the phase 0 in cardiac pacemaker cells and slows the phase 2 plateau in Purkinje cells, cardiac myocytes, and vascular smooth muscle cells.
- In cardiac muscle and vascular smooth, muscle rapid calcium influx causes myosin and actin binding and contraction.
- The different classes of CCBs, by inhibiting calcium influx, cause decreased myocardial contractility and peripheral arterial vasodilation.

Calcium-blockers Toxicity

- **Pathophysiology**

- Calcium channel blockers have the following four cardiovascular effects:
- Peripheral arterial vasodilatation
- Negative chronotropy(decreased heart rate through sinoatrial node inhibition)
- Negative dromotropy (decreased cardiac conduction through atrioventricular node inhibition)
- Negative inotropy (decreased cardiac contractility)
- Other physiologic responses to CCB overdose include suppression of insulin release from the pancreas and decreased free fatty acid utilization by the myocardium. These factors produce hyperglycemia, lactic acidosis, and depressed cardiac contractility.

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- **Pathophysiology**

- A unique CCB, bepridil, also demonstrates weak cross-reactivity with fast sodium channels and potassium rectifier channels, partially blocking these voltage-gated ion channels, which are responsible for rapid membrane depolarization.
- There is a tendency towards QT prolongation and a risk for torsade de pointes.

Calcium-blockers Toxicity

- **Pharmacokinetics**

- All CCBs are well absorbed orally & undergo hepatic oxidative metabolism predominantly via the CYP3A4 subgroup of the cytochrome P450 (CYP) isoenzyme system.
- After repeated doses, as well as overdose, these hepatic enzymes become saturated.
- Saturation of CCBs metabolism contributes to the prolongation of the apparent half-lives reported following overdose of various CCBs.
- All CCBs are highly protein bound.
- One interesting aspect of the pharmacology of CCBs is their potential for drug–drug interactions. CYP3A4, which metabolizes most CCBs, is also responsible for the initial oxidation of numerous other xenobiotics.
- Unlike diltiazem and verapamil, nifedipine and the other dihydropyridines do not appear to affect the clearance of other xenobiotics via CYP3A4.

Effect of drug interaction

Important **drug interactions** may result in toxicity:

1. Hypotension is more likely to occur in patients taking beta blockers, nitrates, or both, especially if they are hypovolemic after diuretic therapy.
2. Patients taking disopyramide or other depressant cardioactive drugs and those with severe underlyingmyocardial disease are also at risk for hypotension.
3. Macrolide antibiotics, grapefruit juice, and other inhibitors

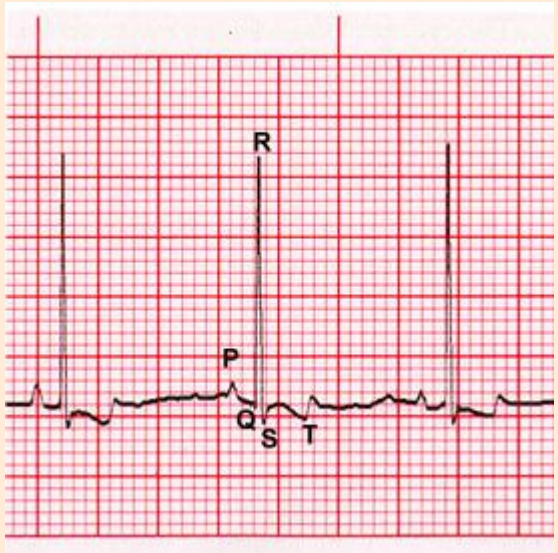
of the cytochrome P-450 enzyme CYP3A4 can increase the blood levels of many calcium antagonists.

4. Life-threatening bradyarrhythmias may occur when beta blockers and verapamil are given together, and asystole has occurred after parenteral administration. Propranolol also inhibits the metabolism of verapamil.

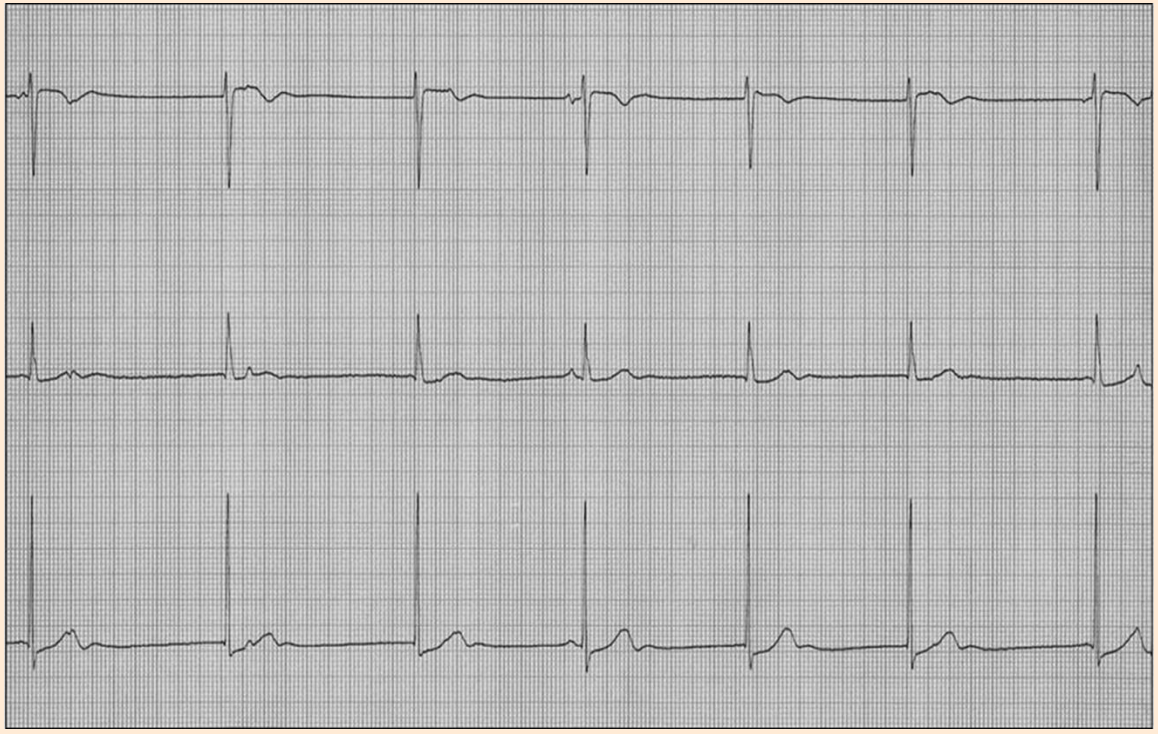
5. Fatal rhabdomyolysis has occurred with concurrent administration of diltiazem and statins.

Calcium-blockers Toxicity

Normal ECG



ECG changes in CCBs toxicity



Calcium-blockers Toxicity

- **Typical Symptoms of CCB toxicity**

- Myocardial depression & peripheral vasodilation occur, producing hypotension and bradycardia. Myocardial conduction may be impaired, producing AV conduction abnormalities, idioventricular rhythms, and complete heart block.
- Pulmonary crackles, signs of failure
- Hyperglycemia
- Initially stable may deteriorate quickly
- Early or mild symptoms include dizziness & fatigue whereas more severely poisoned patients may manifest lethargy, altered mental status, coma, & death.
- Seizure, cerebral ischemic events, ischemic bowel & renal failure, occurring in the presence of CCBs-induced cardiogenic shock also reported.

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- Symptoms usually occur in the first six hours but with some forms of the medication may not start until 24 hours
- In contrast, nifedipine, & other dihydropyridines may produce tachycardia or normal heart rate initially, with bradycardia developing only in patients with more substantial ingestions because of their limited myocardial binding, while deaths are more commonly associated with verapamil & diltiazem.

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- **Diagnosis**

- Including patient history, physical examination findings, and results of basic diagnostic testing.
- Exposures to other drugs and toxins can present with bradycardia and hypotension so that assessment of electrolytes, particularly potassium & magnesium, renal function, & digoxin conc. may be helpful.
- ECG & continuous cardiac monitoring performed to assess heart rate & rhythem, as well as any conduction abnormalities.
- Serum chemistry analysis for metabolic acidosis.
- Because calcium channel blockers poisoning can impair insulin secretion from the pancreas, hyperglycemia may be detected. A recent retrospective study suggests that serum glucose concentrations correlate with the severity of the poisoning.

Calcium-blockers Toxicity

Treatment

1-Stabilization

- Correct immediate life threatening complications
- For CCB overdose most commonly hypotension and bradycardia

  Intubation

  IV access, fluids

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Treatment

2-GI Decontamination

- Oro-gastric lavage
  - Within 1-2 hours of ingestion
- Activated Charcoal
  - Within 1 hour of ingestion
- Whole Bowel Lavage

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Treatment

3-Antidote(s)

Correction of acidosis

- Correct acidosis to a pH within the normal range, L calcium channel function is impaired when the pH falls outside the physiological range
- Acidosis enhances the effect of verapamil and decreases the effect of calcium
- Sodium bicarbonate significantly improved myocardial contractility and cardiac output in a swine model of verapamil poisoning

Calcium-blockers Toxicity

- Calcium loading is the most logical and appears to be the most effective agent to use in calcium channel blocker poisoning
- It is primarily indicated in patients with heart block (who have usually taken verapamil or diltiazem)

Administration of calcium salts:

- Used to overcome CV effects of CCBs
- Calcium chloride: 3x bioavailable calcium than Ca-gluconate; nonacidotic patients
- Calcium gluconate: preferred in acidotic patients; less bioavailable calcium
- Often ineffective because CCB produce a non-competitive block

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Treatment

4-Supportive therapy

A-Vasopressors

- Following fluid resuscitation:
- Dopamine, phenylephrine, norepinephrine, epinephrine
- Positive inotropy, chronotropy and vasoconstrictive effects of agents

B-Glucagon

- Increases intracellular cyclic AMP which activates calcium channels
- Increases heart rate, 5mg IV push (repeat at10 minute intervals)
- infusion

Calcium-blockers Toxicity

4-Supportive therapy

C-Insulin and Glucose

- Hyperinsulinemia euglycemia (HIE) therapy has become the treatment of choice for patients who are severely poisoned by CCBs.
- CCBs inhibit calcium mediated insulin secretion from the β-islet cells in the pancreas, resulting in glucose uptake in myocardial cells becoming dependent upon concentration gradients rather than insulin-mediated active transport.
- There are now several reported cases of CCB-poisoned patients in whom adjuvant HIE therapy successfully improved hemodynamic function mainly by improving contractility, with little effect on heart rate

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- Not all patients need glucose because CCB may cause
- hyperglycemia
- At high doses insulin will actually act as an inotrope
- 120-150 units/hr…monitor glucose

- **4-Supportive therapy**

D- Atropine

- Atropine is considered by many to be the drug of choice for patients with symptomatic bradycardia.
- Initial treatment with calcium might improve the efficacy of atropine.
- Dosing should begin with 0.5 to 1.0 mg (0.02 mg/kg in children) minimum 0.1mg), IV every 2 or 3 minutes up to a maximum dose of 3 mg in all patients with symptomatic bradycardia

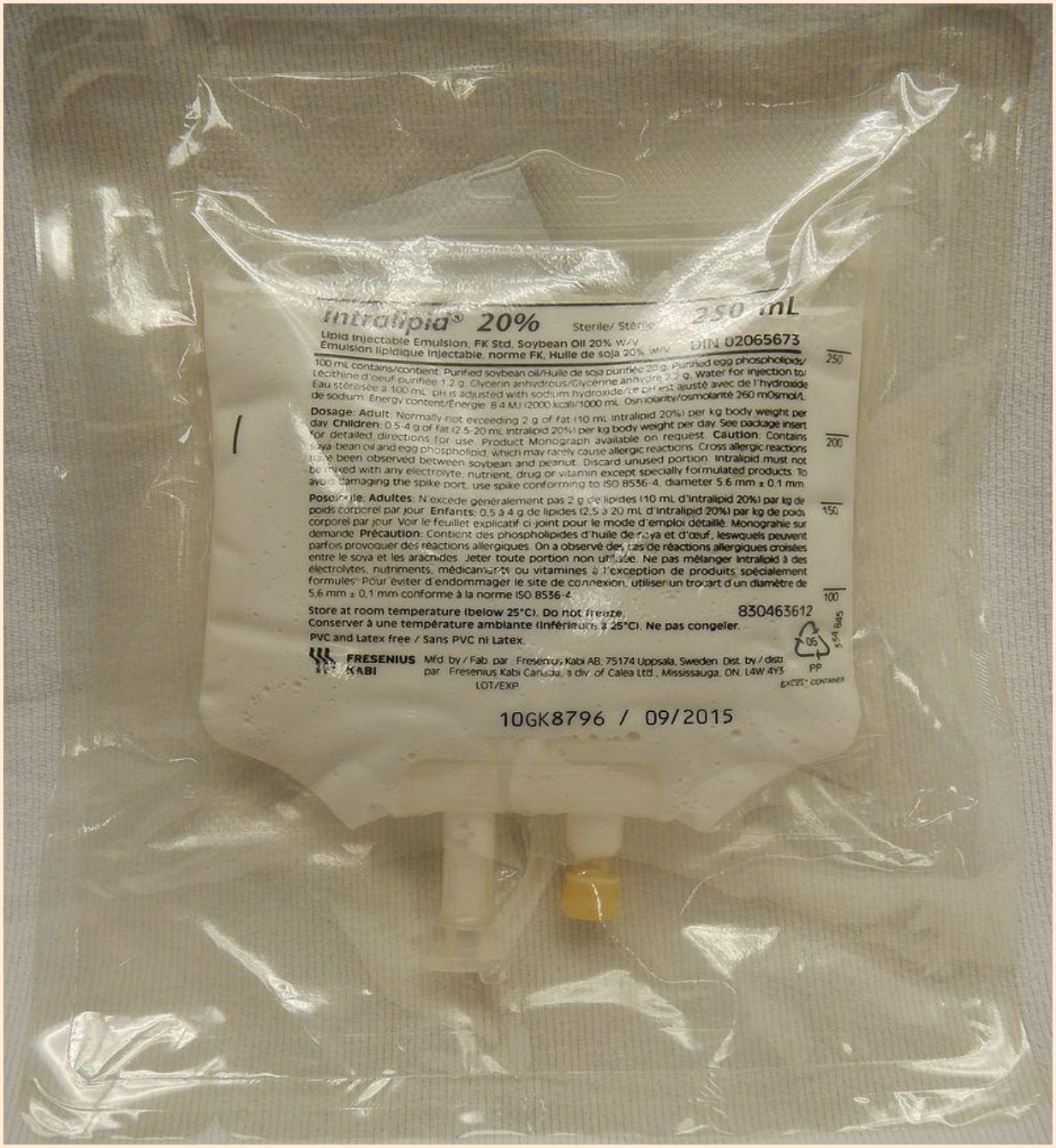
Calcium-blockers Toxicity

Treatment

4-Supportive therapy

E-Lipid Emulsion Therapy

- Lipid surrounds CCB drug molecule, prevents it from binding to calcium channel
- Also proposed that lipid provide readily available energy source for myocardial cells
- Dosage 1.5 mg/kg IVP, infusion 25ml/kg/min


Intralipid® 20% Sterile/ Stérile 250 mL
Lipid injectable Emulsion, FK Std, Soybean Oil 20% W/V
Émulsion lipidique injectable, norme FK, Huile de soja 20% W/V
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100 mL contains/contient: Purified soybean oil/Huile de soja purifiée 20 g, Purified egg phospholipids/Lécithine d'oeuf purifiée 1.2 g, Glycerin anhydrous/Glycérine anhydre 2.2 g, Water for injection to/Eau stérilisée à 100 mL. pH is adjusted with sodium hydroxide/Le pH est ajusté avec de l'hydroxide de sodium. Energy content/Énergie: 8.4 MJ (2000 kcal)/1000 mL. Osmolarity/osmolarité 260 mOsmol/L
Dosage: Adult: Normally not exceeding 2 g of fat (10 mL Intralipid 20%) per kg body weight per day. Children: 0.5-4 g of fat (2.5-20 mL Intralipid 20%) per kg body weight per day. See package insert for detailed directions for use. Product Monograph available on request. Caution: Contains soya bean oil and egg phospholipid, which may rarely cause allergic reactions. Cross allergic reactions have been observed between soybean and peanut. Discard unused portion. Intralipid must not be mixed with any electrolyte, nutrient, drug or vitamin except specially formulated products. To avoid damaging the spike port, use spike conforming to ISO 8536-4, diameter 5.6 mm ± 0.1 mm.
Posologie: Adultes: N'excède généralement pas 2 g de lipides (10 mL d'Intralipid 20%) par kg de poids corporel par jour. Enfants: 0,5 à 4 g de lipides (2,5 à 20 mL d'Intralipid 20%) par kg de poids corporel par jour. Voir le feuillet explicatif ci-joint pour le mode d'emploi détaillé. Monographie sur demande. Précaution: Contient des phospholipides d'huile de soya et d'œuf, lesquels peuvent parfois provoquer des réactions allergiques. On a observé des cas de réactions allergiques croisées entre le soya et les arachides. Jeter toute portion non utilisée. Ne pas mélanger Intralipid à des électrolytes, nutriments, médicaments ou vitamines à l'exception de produits spécialement formulés. Pour éviter d'endommager le site de connexion, utiliser un trocart d'un diamètre de 5,6 mm ± 0,1 mm conforme à la norme ISO 8536-4.
250
200
150
100
Store at room temperature (below 25°C). Do not freeze.
Conserver à une température ambiante (inférieure à 25°C). Ne pas congeler.
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Calcium-blockers Toxicity

Treatment

4-Supportive therapy

F-Phosphodiesterase inhibitors

- Another class of therapeutics that has some demonstrated usefulness in treating CCB poisoning is the cardiac and vascular phosphodiesterase 3 inhibitors: *inamrinone, milrinone, and enoximone.*
- These agents inhibit the breakdown of cAMP by phosphodiesterase, thereby increasing intracellular cAMP concentrations.
- These noncatecholamine inotropic agents do not increase myocardial oxygen demand and have been traditionally used for congestive heart failure.


THANK
YOU!