

Cardiovascular Drugs: Toxicity and Treatment

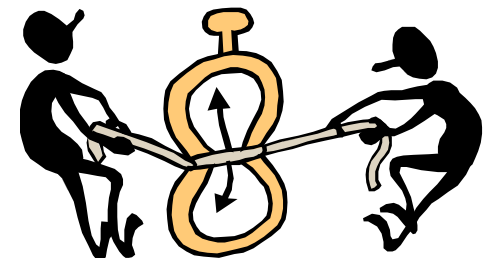




Calcium Channel- Blocking Agents

Digilatis

β Adrenergic Antagonists



Calcium Channel-Blocking Agents



- ✓ Calcium channel blockers (CCBs) were initially introduced for use in the United States in 1981, and extended-release formulations were available 10 years later.
- ✓ Indications for use of these drugs are angina, hypertension, arrhythmias, subarachnoid hemorrhage and migraine prophylaxis.

Calcium Channel-Blocking Agents



✓ Structure

1- Phenylalkylamines: Verapamil

2- Benzothiazepines: Diltiazem

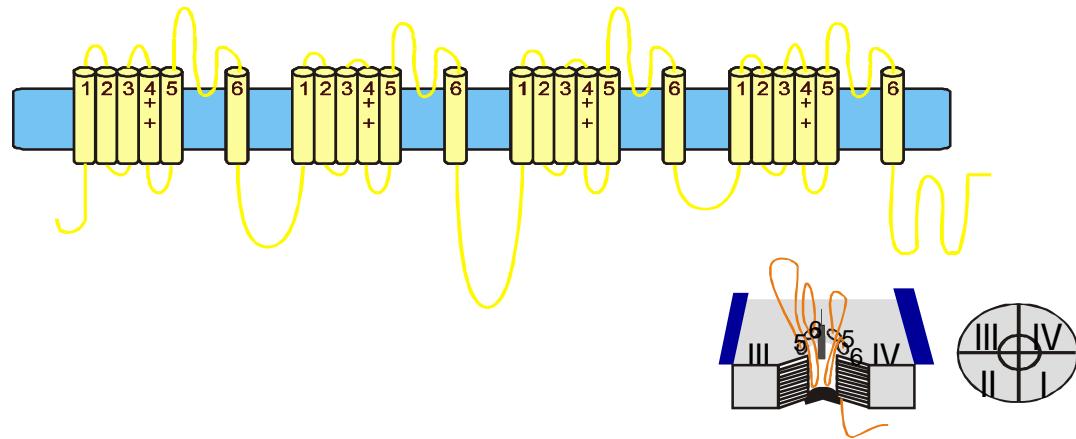
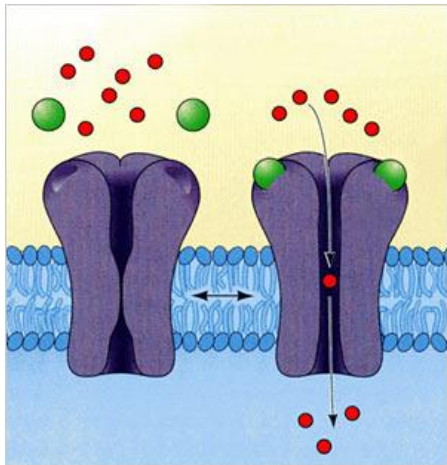
3- Dihydropyridines: Nifedipine, Amlodipine,...

4- Diarylaminopropylethers: Bepridil

5- Tertraline Derivatives: Mibefradil

Pharmacology

- ✓ The CCB currently available act on **L-Type** channel of cardiac and vascular smooth muscle cells.



Pharmacology

- ✓ Antagonisms of L-Type channels results primarily in effects on the heart and peripheral vascular smooth muscle.
- ✓ Negative chronotropy (decreased heart rate)
- ✓ Negative inotropy (decreased cardiac contractility)
- ✓ Decrease **cardiac out put** and Hypotension

Pharmacokinetics

	Absorption (%)	Volume of Distribution(L/Kg)	Protein Bonding(%)	Terminal half-life (h)
Verapamil	>90	4.7	90	3-7
Diltiazem	>90	5.3	80-90	4
Nifedipine	>90	0.8-1.4	90	5
Amlodipin	100	21.4	>95	35

Toxicity

- ✓ Acute toxicity

Case reports describing Overdose of S-R Preparations describe a delay in symptoms by as long as 15-24 h.

(Verapamil, Diltiazem, Nifedipine, Amlodipin)

- ✓ Toxic dose??

- ✓ Chronic toxicity

CCB are essentially free of Chronic toxicity.

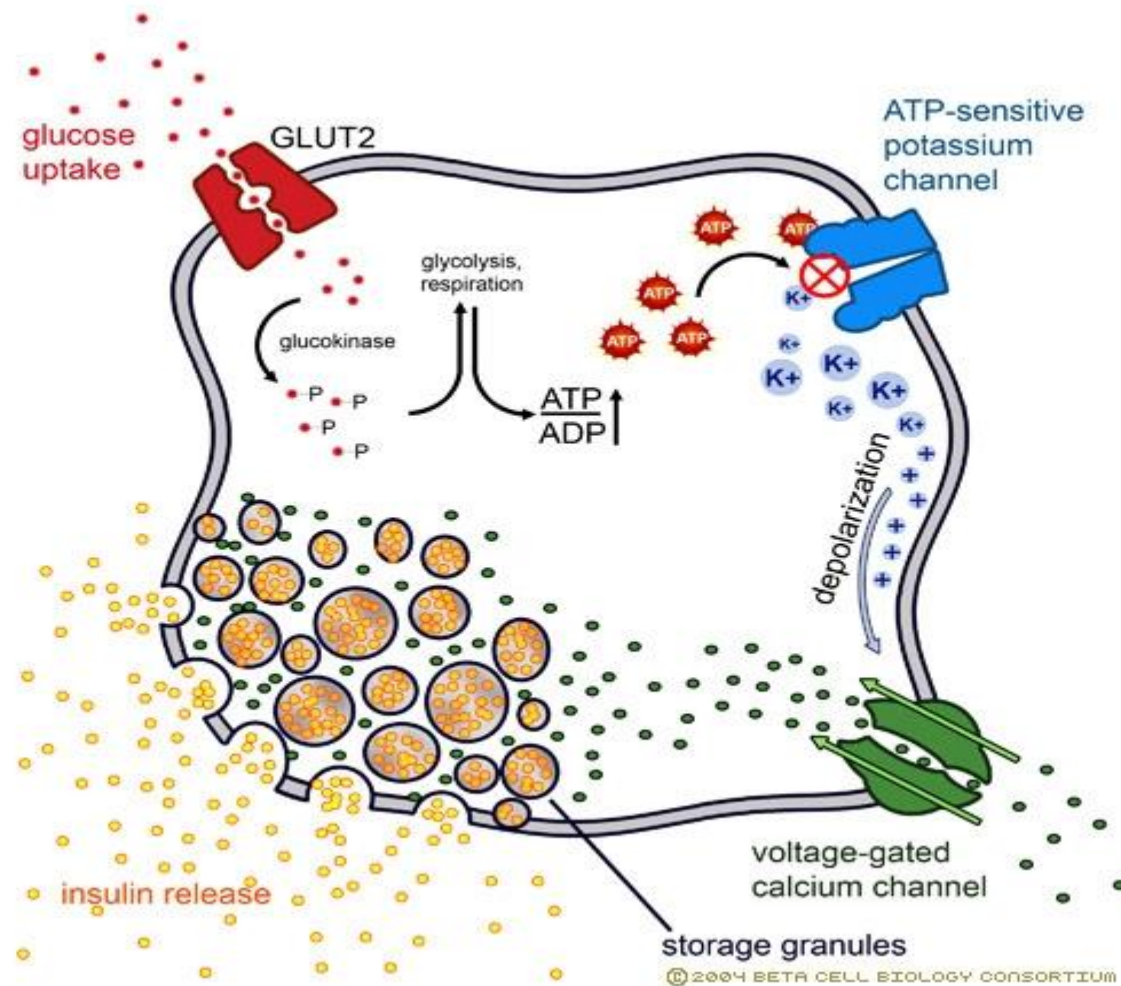


Clinical Presentation

- ✓ Hypotention
- ✓ Cardiac dysrhythmics: **Bradycardia**
- ✓ Gastroanerities
- ✓ Adult Respiratory Distress Syndrome
- ✓ Depressed level of consciousness, ...
- ✓ Hyperglycemia
- ✓ Lactic acidosis



The ionic control of insulin release from human pancreatic β cells



Treatment



- ✓ Establish ABCs, obtain intravenous (IV) access, provide oxygenation
- ✓ Administration of activated charcoal: repeated doses may be used, especially with ingestions of sustained-released agents.
- ✓ Whole bowel irrigation with polyethylene glycol solution (SR)
- ✓ Sodium bicarbonate
- ✓ Atropin

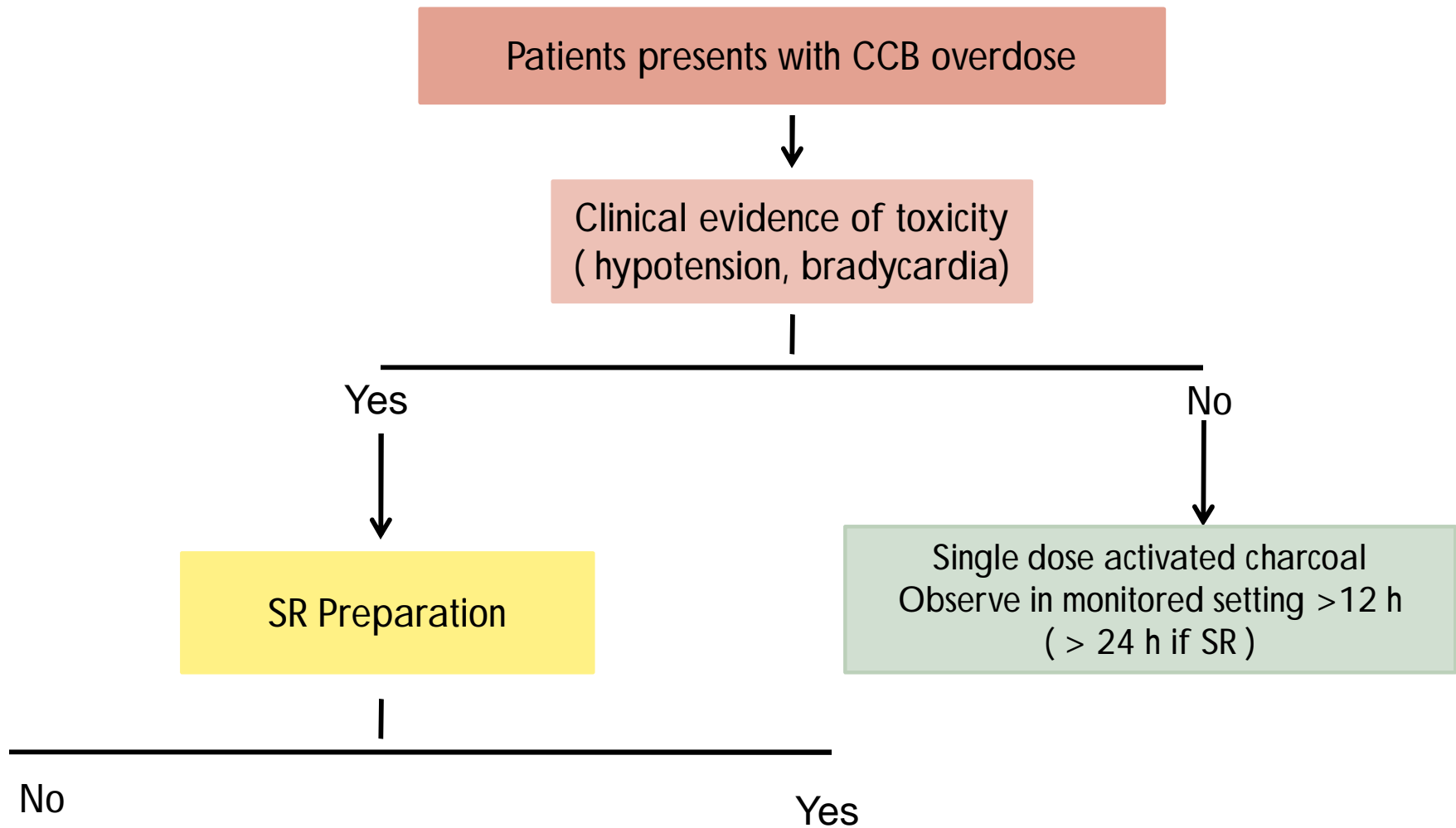
Treatment

- ✓ Ca salt: CaCl_2 10 % (Verapamil and Diltiazem)
- ✓ Glucagon (5-10 mg, 2-10 mg/h): Acts via cAMP to increase cardiac contractility and also may decrease heart block
- ✓ Inamrinone (inhibitor of phosphodiesterase III)
- ✓ Insulin-Dextrose: 0.1-1 Units/kg/h IV, with mean doses of 0.5 Units/kg/h
- ✓ Hemodialysis and hemoperfusion are not effective

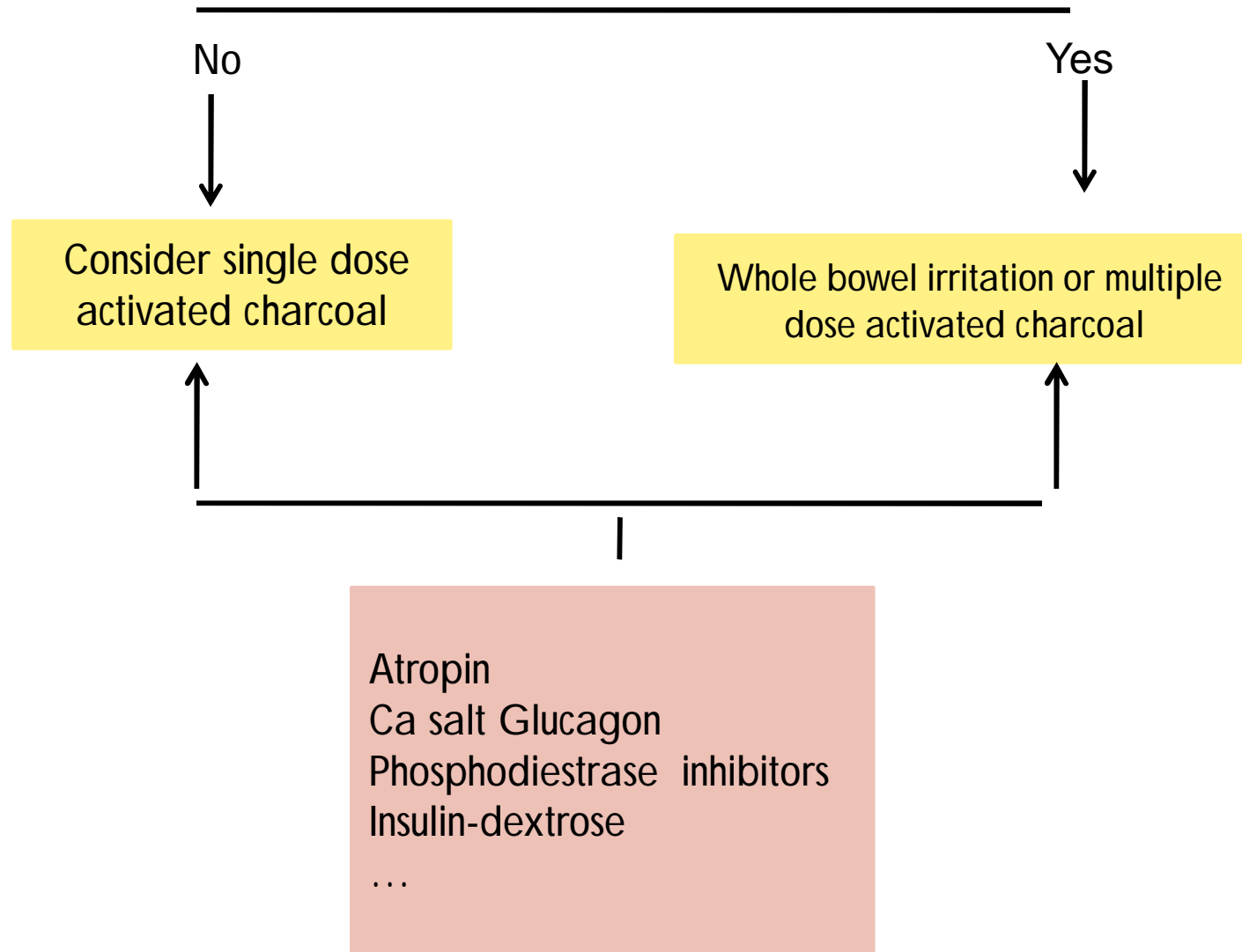


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SR Preparation



Beta-blockers



- ✓ Beta-adrenergic antagonists (ie, beta-blockers) have been in use for nearly 50 years.
- ✓ In addition to their traditional role in treating hypertension and other cardiovascular disorders, beta-blockers are also used for additional purposes such as migraine headaches, hyperthyroidism, glaucoma, anxiety, and various other disorders.

Beta- Receptor

✓ β_1 - β_4

β_1 : Eye, Kidney, Heart

β_2 : Lung, Vascular system, Metabolic system

Nonselective beta-blockers : Propranolol, carvedilol, Sotalol, timolol, ..

Selective beta-blockers: Atenolol, Metoprolol,...

Pharmacology



- ✓ **Beta1-blockers** reduce heart rate, blood pressure, myocardial contractility, and myocardial oxygen consumption.
- ✓ **Beta2-blockers** inhibit relaxation of smooth muscle in blood vessels, lungs and the gastrointestinal system.
- ✓ In addition, beta-adrenergic receptor antagonism inhibits both glycogenolysis and gluconeogenesis, which may result in hypoglycemia.

Pharmacology

Blockade of the Beta₁ Receptor Blockers



Blockade of the Beta₂ Receptor Blockers



Pharmacokinetics

	Oral Bioavailability (%)	Volume of Distribution (L/Kg)	Protein Bonding(%)	Lipid Solubility
Atenolol	50	0.7	15	Low
Carvedilol	25-35	1.6	95	High
Metoprolol	40-50	5.5	12	Moderate- High
Propranolol	30	3.6	90	High

Toxicity

- ✓ After acute oral overdose, signs of toxicity usually begin within **30 min** and peak by **2 h**.
- ✓ The **lipid solubility of beta blockers** can significantly influence the degree of clinical toxicity observed after overdose owing to penetration of blood- brain barrier. (propranolol, metoprolol, carvedilol)

Toxicity



- ✓ The concentration of **propranolol** in **CNS** may exceed that seen in **plasma** by as much as **20 fold**.
- ✓ Toxic dose??
- ✓ In overdose of drugs, the combination of a **Beta blocker** and a **CCB** may lead to **hypotension, bradycardia** and **Death**.

Clinical Presentation



- ✓ Cardiac

- Bradycardia

- Hypotension

- Cardiac conduction defects

- ✓ Pulmonary

- Respiratory depression

- Bronchospasm

Clinical Presentation

- ✓ Neurologic

 - Drowsiness

 - Coma

 - Seizure

- ✓ The lipid-soluble agents (propranolol) have increased distribution into the brain, and these agents are associated with severe CNS toxicity.
Propranolol: (Direct effect on CNS)

Clinical Presentation

✓ Other

Beta blockers may be expected to cause many potential effects:

Hypoglycemia, Rhabdomyolysis, Acute renal failure on the basis of decreased renal perfusion, and metabolic acidosis secondary to hypoperfusion

Treatment



- ✓ The goal of therapy in beta-blocker toxicity is to restore perfusion to critical organ systems by increasing **cardiac output**. This may be accomplished by **improving myocardial contractility, increasing heart rate, or both**.
- ✓ Cardiac monitoring, oxygen administration, and reliable intravenous access are essential.
- ✓ GI decontaminant: Activated charcoal

Treatment

- ✓ Atropin (0.01-0.03 mg/kg IV)
- ✓ Glucagon (5- 10 mg/ IV bolus, continuous infusion of 1-5 mg/h)
Effect: Increase myocardial heart rate and contractility
Adverse effect: Nausea, Vomiting and hyperglycemia
- ✓ CaCl_2
- ✓ Inamrinone (inhibitor of phosphodiesterase III)

Treatment



- ✓ Benzodiazepines are the drugs of choice if seizures occur.
- ✓ Bronchospasm: salbutamol, Aminophylin
- ✓ Enhanced elimination: Hemodialysis may be useful in severe cases of Atenolol overdoses because of low PB and VD
Propranolol and metoprolol, are not removed by hemodialysis.

Digoxin

- ✓ Digitalis was introduced in to clinical medicine by William Withering in 1785. He reported therapeutic efficacy and toxicity of leaves of *Digitalis purpurea*.

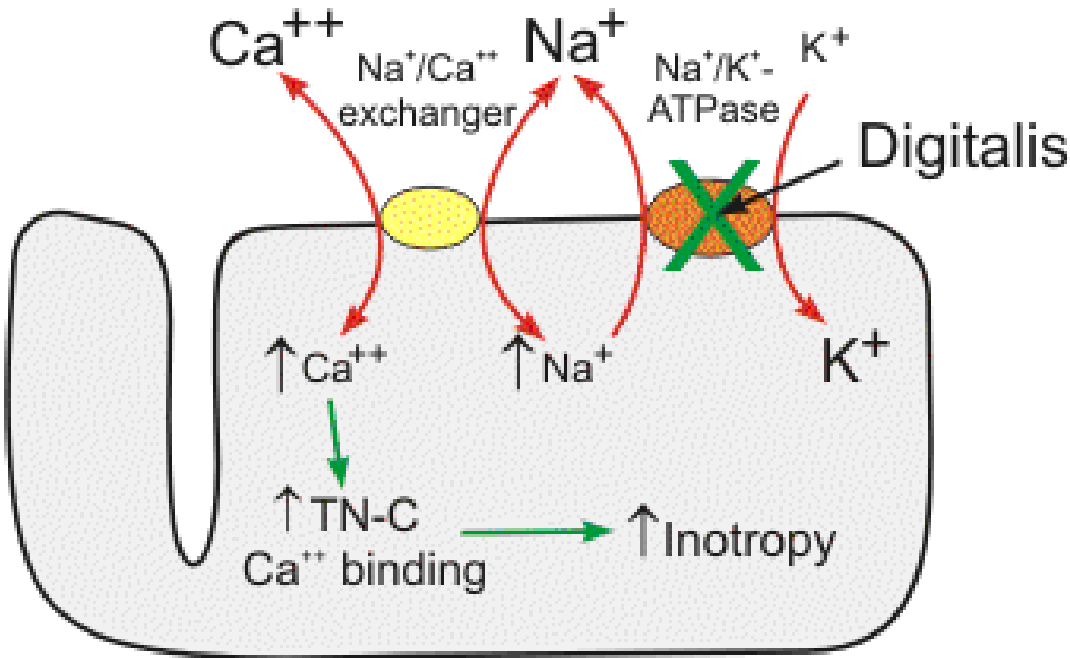


Digoxin

- ✓ Congestive heart failure
- ✓ Atrial fibrillation
- ✓ Atrial flutter



Pharmacology



Pharmacokinetics

	Absorption (%)	Volume of Distribution(L/Kg)	Protein Bonding(%)	Half-life	Clearance
Digoxin	55 -75 90-100	5.6	25	33-34 h	Renal

Toxicity

- ✓ Drug interaction and other factors, such as electrolyte abnormalities, renal or hepatic failure, ischemia, or inflammation, predispose to digoxin toxicity.
- ✓ **Amiodarone** - Reduces renal and nonrenal clearance of digoxin.
- ✓ **Beta-blockers** (propranolol, metoprolol, atenolol) - May have additive effects, carvedilol may increase digoxin blood levels in addition to potentiating its effects on the heart rate.

Toxicity



- ✓ **Calcium channel blockers** - Diltiazem and verapamil increase serum digoxin level.
- ✓ Potentially toxic interaction may also occur with k- sparing diuretics which inhibit tubular secretion of digoxin.

Toxicity

- ✓ Therapeutic range: 0.5-2 ng/ml
- ✓ Lethal range: >15 ng/ml
- ✓ Toxic dose: >2 – 3 mg
- ✓ Lethal dose: >10 mg



Clinical Presentation

Cardiovascular

- ✓ Dysrhythmia
(Brady and Thachyarrhythmia)

CNS

- ✓ Headache
- ✓ Weakness
- ✓ Depression
- ✓ Confusion
- ✓ Disorientation
- ✓ Hallucination

Clinical Presentation

Ocular

- ✓ Disturbances of color vision
- ✓ Blurred vision
- ✓ Photophobia

Gastrointestinal

- ✓ Nausea, vomiting, anorexia, and diarrhea
- ✓ Abdominal pain (uncommon)

Clinical Presentation

Acute Toxicity

- ✓ Hyperkalemia
- ✓ Bradyarrhythmia

Chronic Toxicity

- ✓ Hypokalemia
- ✓ Tachyarrhythmia
- ✓ Digoxin toxicity does not cause hypokalemia, but hypokalemia can worsen digoxin toxicity

Treatment



- ✓ Initiate supportive therapy with oxygen, cardiac monitoring, and IV access.
- ✓ Activated charcoal is indicated for acute overdose or accidental ingestion.
- ✓ Phenytoin and magnesium sulfate
- ✓ Correct electrolyte abnormalities, especially hypokalemia and hypomagnesemia.

Treatment



- ✓ Treat hyperkalemia
Sodium bicarbonate (1mEq/ml).
- ✓ Calcium is not recommended to treat hyperkalemia in this setting because ventricular tachycardia or ventricular fibrillation may be precipitated.
- ✓ Treatment with **digoxin-fab fragments**

Treatment

✓ Digoxin fab fragments:

- 1- Hyperkalemia > 5.5 meq/ml
- 2- Serum digoxin level greater than 10 ng/mL
- 3- Ingestion greater than 5 mg in adults, ...

Number of vials: $2 \times \text{serum level (ng/ml)} \times 5.6 \times \text{Weight (Kg)} / 1000$

Acute Toxicity: 10 – 20 vial

Chronic Toxicity: 3 – 6 vial

Thank you

