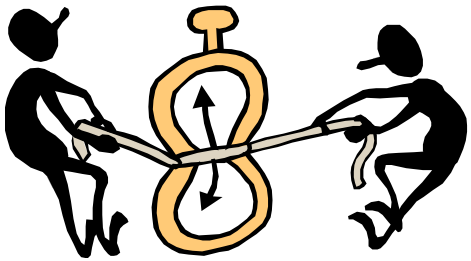
Cardiovascular Drugs:

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

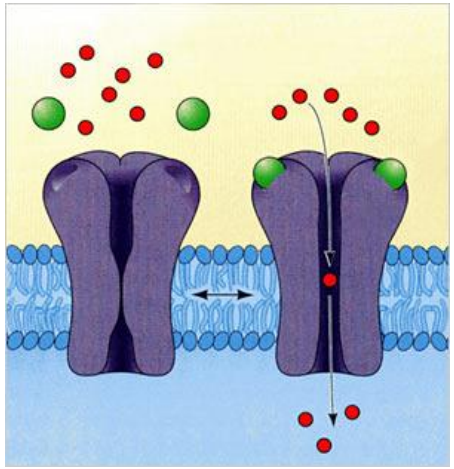
3- Dihydropyridines: Nifedipine, Amlodipine,…

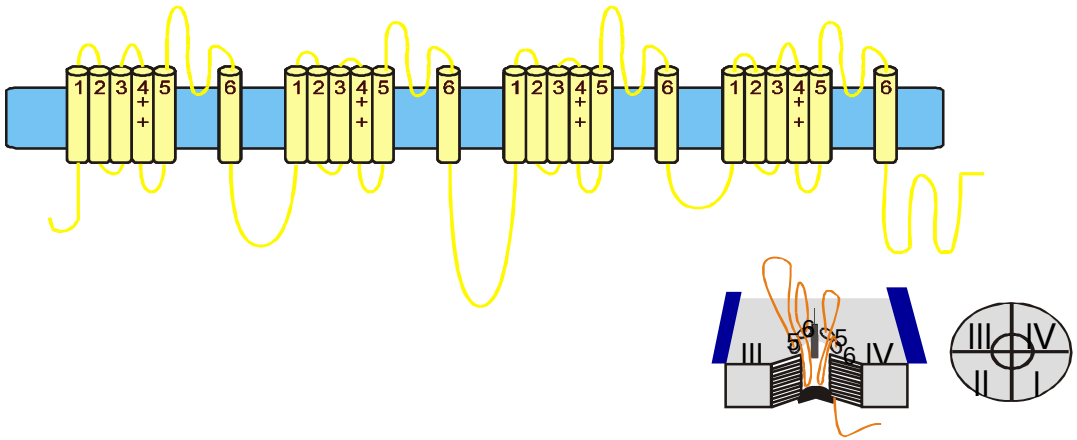
4- Diarylaminopropylethers: Bepridil

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 Preparearions describe a delay in symptoms by as long as 15-24 h.

  (Verapamil, Diltiazem, Nifedipine, Amlodipin)

- Toxic dose??

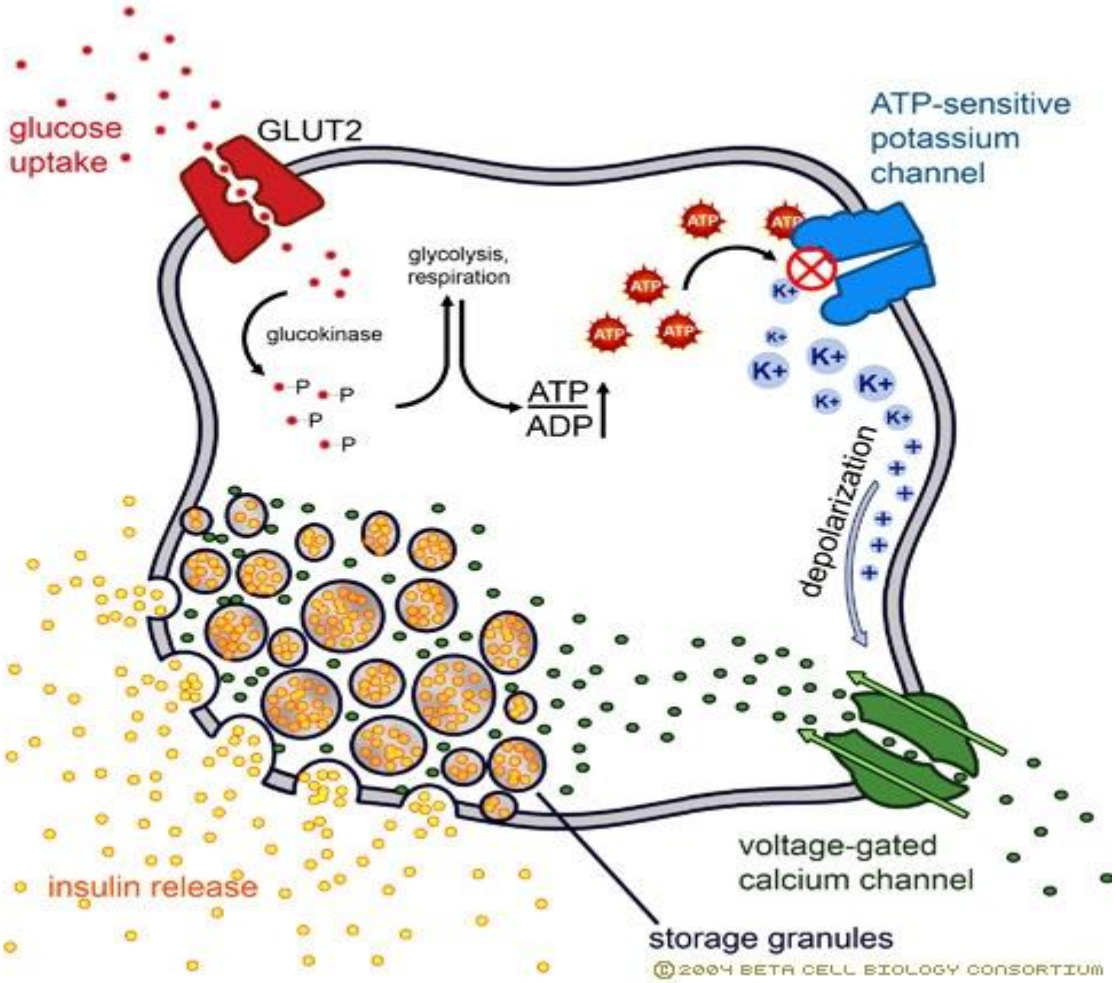
- Chronic toxicity

  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 irritation 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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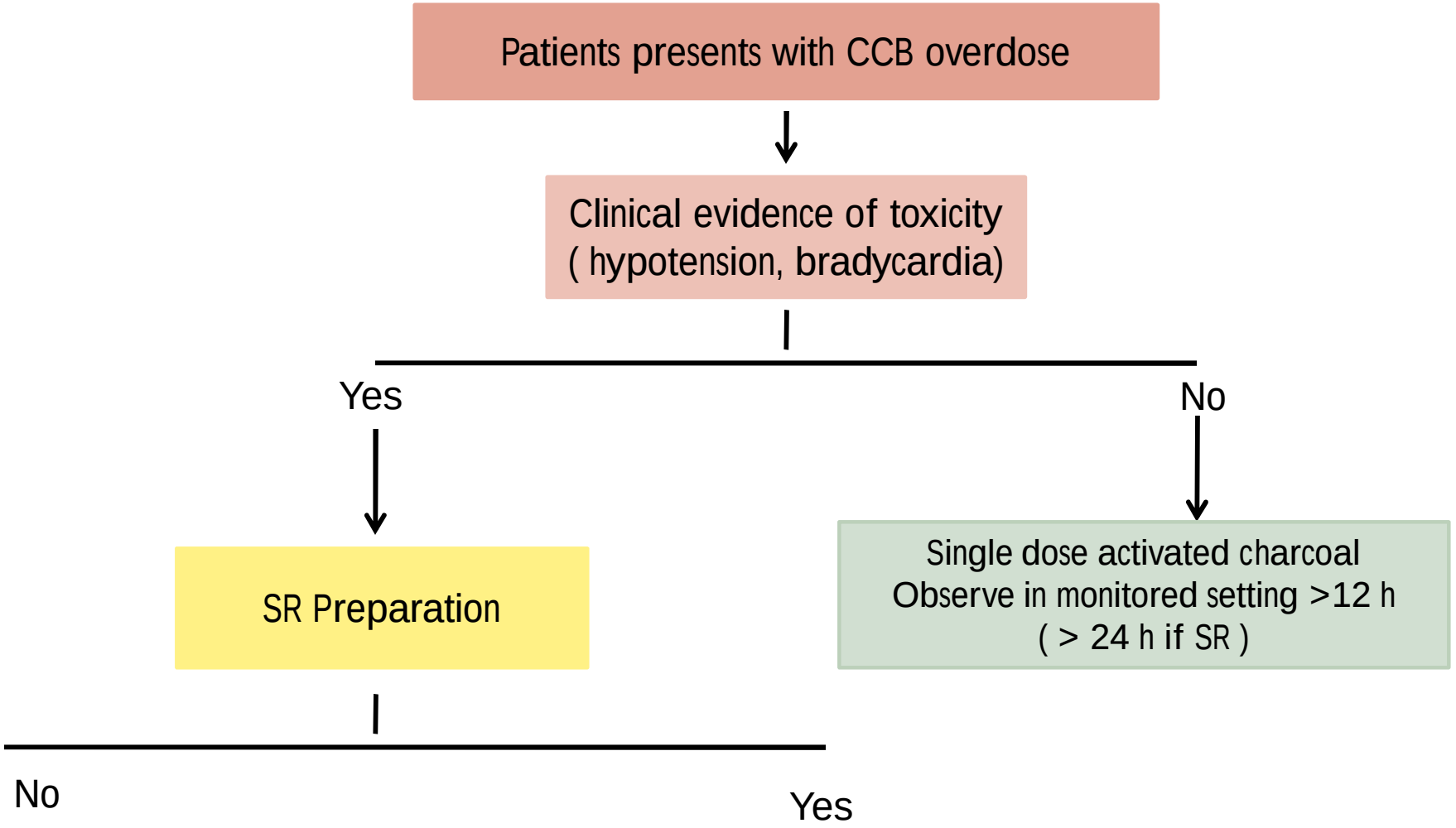
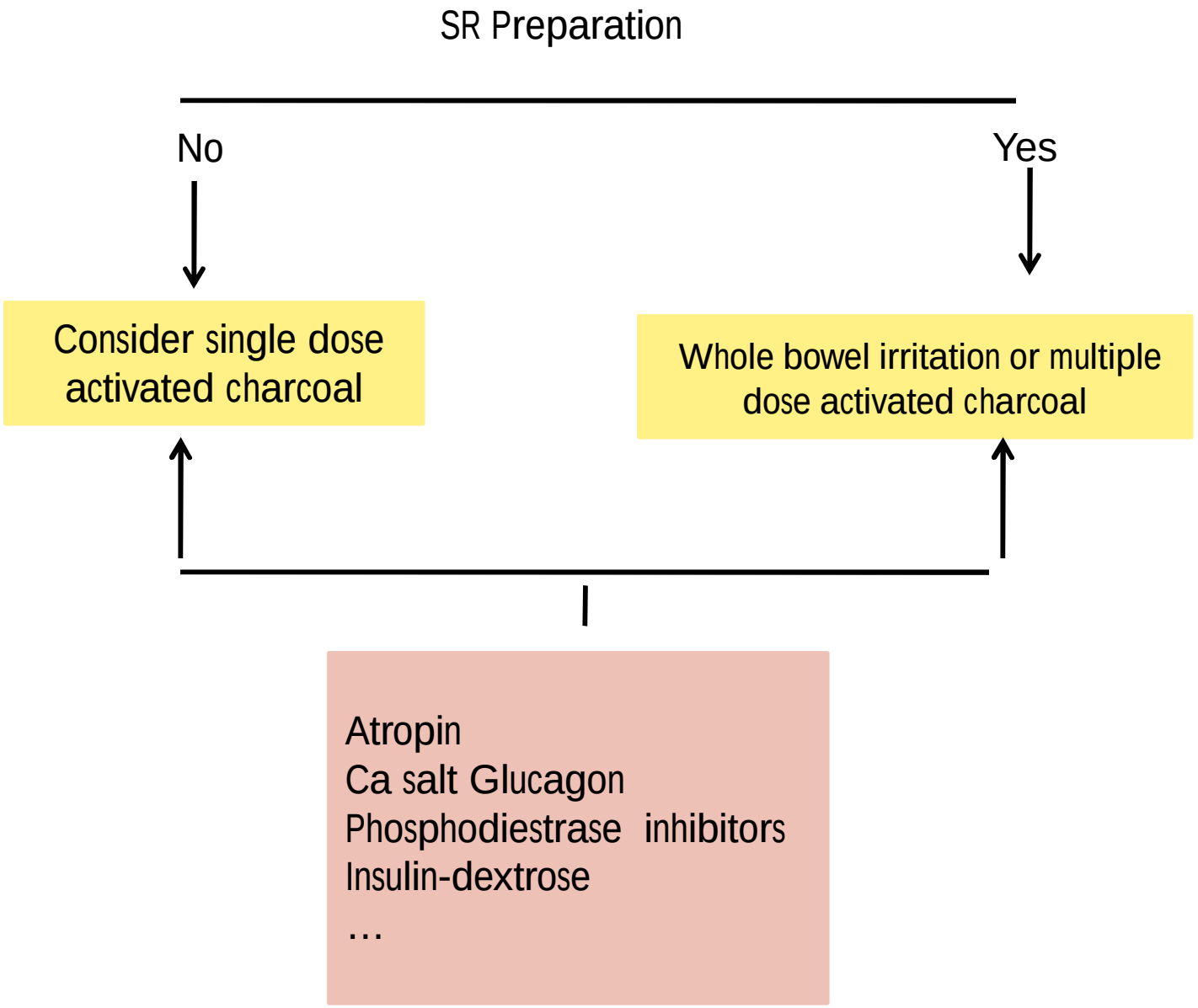




Beta-blockers

- 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

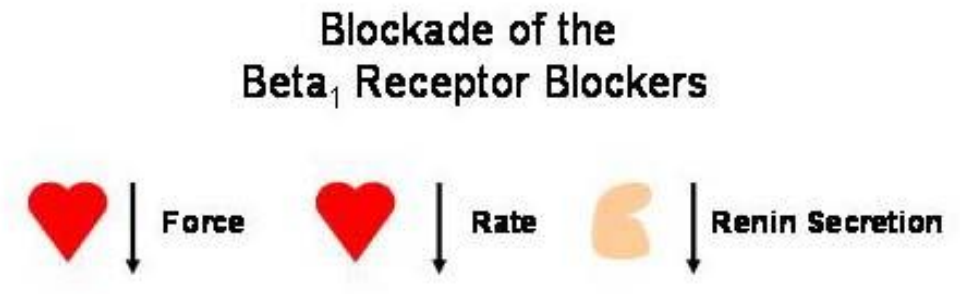
Nonselective beta-blockers : Propranolol, carvedilol, Sotalol, timolol, ..

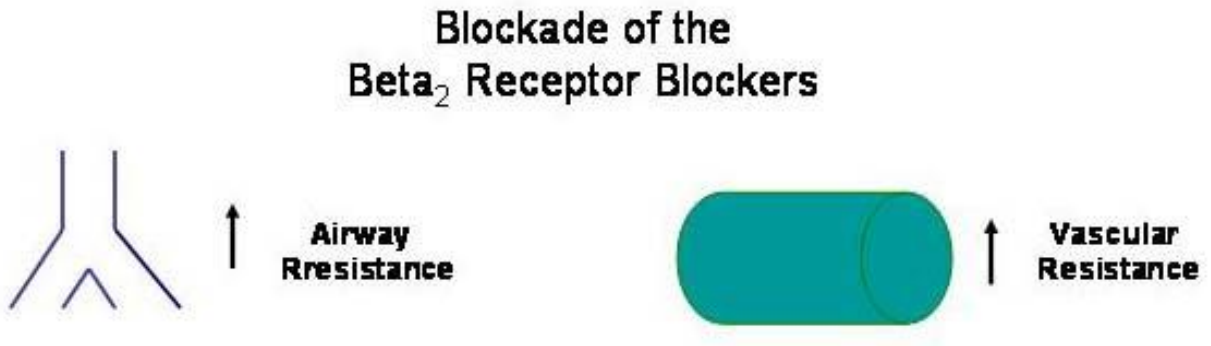
Selective beta-blockers: Atenolol, Metoprolol,…

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





Pharmacokinetics

	Oral Bioavailibility (%)	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 deffects
- 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.

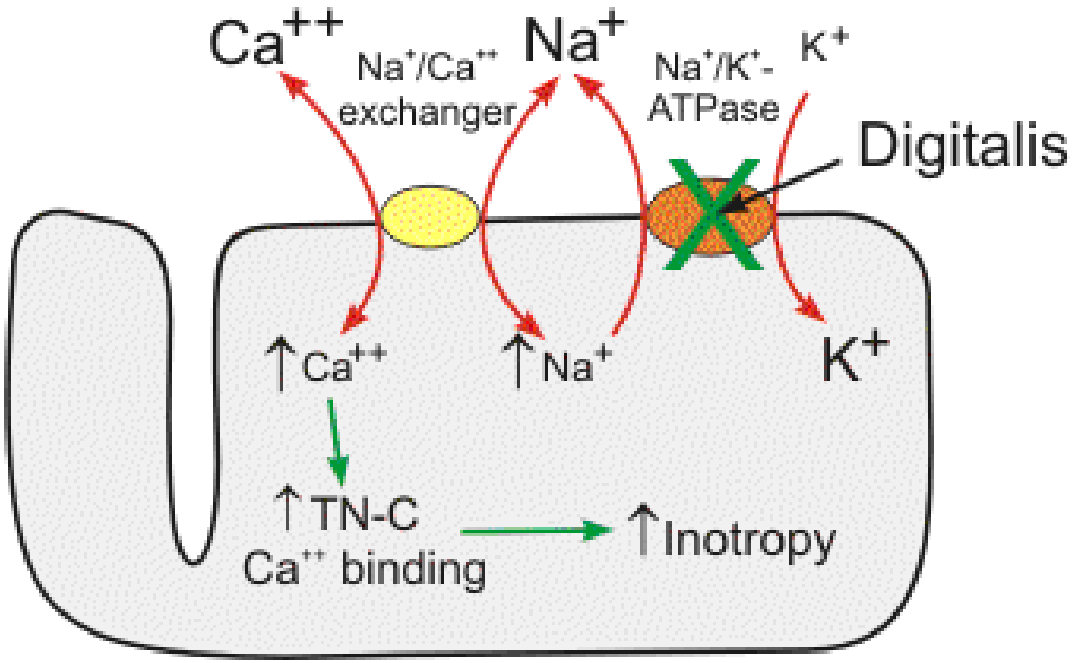
Digoxin

- 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 inflamation, 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 occure 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 ×serum level (ng/ml) ×5.6 × Weight (Kg)/ 1000

Acute Toxicity: 10 – 20 vial

Chronic Toxicity: 3 – 6 vial

Thank you