Digoxin Toxicity

Dr. Muhammed Malik

Cardioactive Steroids

- Cardioactive Steroids (CAS), or *cardiac glycosides,* developed their name from the strong effect on the heart.
- The most common pharmaceutical product is digoxin.
- Other preparations available internationally include digitoxin, ouabain, lanatoside C, deslanoside, and gitaline.
- There is evidence in the Ebers Papyrus that the Egyptians used plants containing CAS at least 3000 years ago.

Cardioactive Steroids: Sources

Many plants contain cardioactive steroids

- *Digitalis purpurea* (foxglove), *Nerium oleander* (oleander), *Convallaria majalis* (lily of the valley), *Drimia maritima* (red squill)
- Toxicity may result from use of herbal products or teas derived from such plants or direct ingestion of the plant itself

Bufo marinus toad – dried secretions are a supposed aphrodisiac and contain a cardioactive steroid

Mechanism of action:

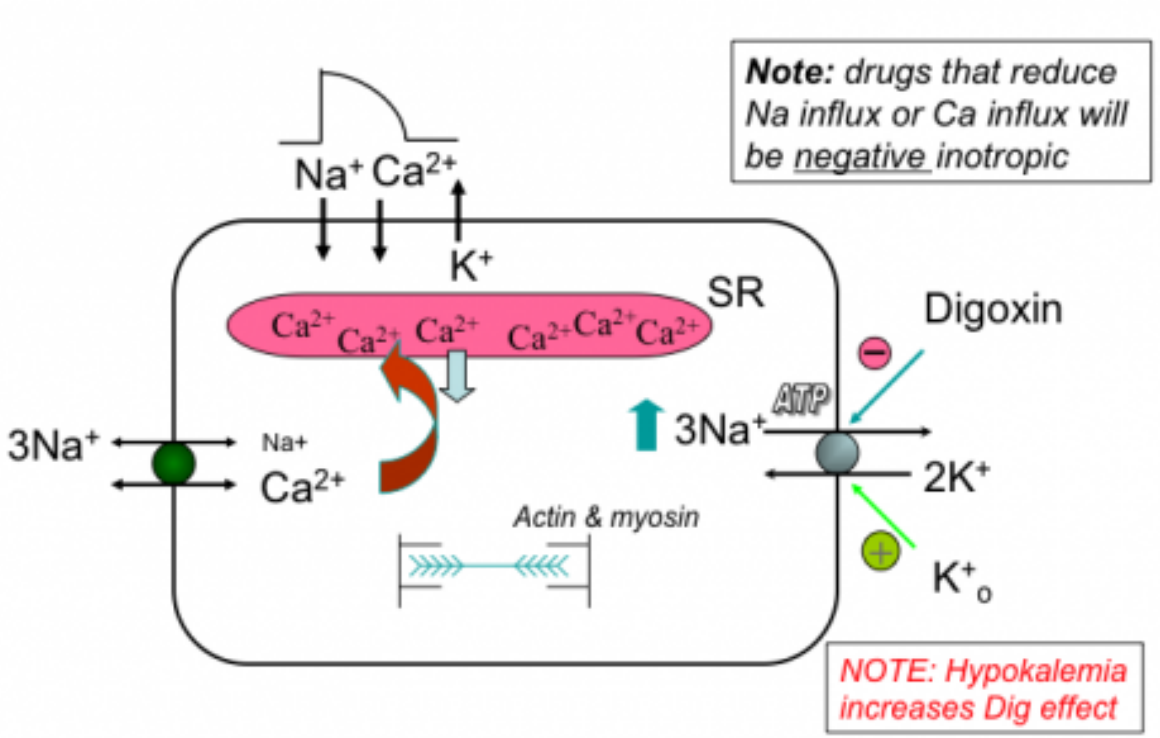
Formulations

Injection
(IV; rarely used IM)

Oral Solution

Tablets

Mechanism of Action



Digoxin: Therapeutic Role

Disease states used in:

Atrial fibrillation:
Control of ventricular response rate in patients with chronic atrial fibrillation

Heart failure:
Increases left ventricular ejection fraction by increasing exercise capacity, and decreasing heart failure-related hospitalizations and emergency room visits.

Used in adults and pediatrics

Digoxin: Kinetics

Volume of Distribution	Protein Binding	Half Life	Time to peak (serum)
5-7 L/kg	25%	Age, Renal, and cardiac function dependent Approximately 38 Hours (parent drug)	Oral: 1-3 hours Distribution phase: 6-8 hours Steady state: 7-10 Days

Digoxin Toxicity

Overall use of digoxin has declined approximately 10% in hospitalized acute heart failure patients.

Number of patients with admitted digoxin poisoning has remained stable (approximately 1,500/year)

Use of digoxin-specific antibody fragments has increased (approximately 20%)

In 2011, there were 2,513 cases involving cardiac glycosides reported to U.S. poison control centers. Of these, 90 experienced major effects (i.e, life threatening resulting in prolonged hospitalization) and 26 died.

Risk Factors for Digoxin Toxicity

Kidney Injury: digoxin is primarily eliminated by the kidneys

Age: elderly are more likely to have decreased renal function and taking potentially interacting concomitant medications

Electrolyte Imbalance: increases sensitivity to digoxin effects

Fluid Status: fluid loss or poor fluid intake can lead to electrolyte imbalances

Digoxin: Causes of Toxicity

Hypokalemia

Results in increasing its therapeutic and toxic effects.

Hypercalcemia

Digoxin enhances Ca^{+2} absorption into cardiac myocytes, which is one of the ways it increases inotrophy. This can also lead to Ca^{+2} overload and increased susceptibility to digitalis-induced arrhythmias.

Hypomagnesemia

Can sensitize the heart to digitalis-induced arrhythmias. k/Na+ ATPas dependent on Mg so it will enhance digoxen inactivation for the receptor enzyme

Digoxin: Causes of Toxicity

Drug interactions:
many commonly used drugs interact with digoxin

No P450 Interactions

Drugs that alter renal clearance can affect digoxin concentration.

Loop and Thiazide Diuretics decrease serum potassium levels:

furosemide

hydrochlorthiazide

Various drugs alter the mechanism of digoxin renal excretion or intestinal p-glycoprotein activity

- verapamil
- diltiazem
- quinidine
- amiodarone

Increased Serum Levels

- Amiodarone
- Benzodiazepines
- Bepridil
- Cyclosporine
- Diphenoxylate
- Indomethacin
- Itraconazole
- Macrolide Antibiotics
- Propafenone
- Propantheline
- Quinidine
- Quinine
- Spironolactone
- Tetracyclines
- Verapamil

Decreased Serum Levels

- Oral aminglycosides
- Al^{+}/Mg^{+} containing antacids
- Antineoplastics
- **Activated charcoal**
- Cholestyramine
- Colestipol
- Kaoline / pectin
- Metoclopramide
- Neomycin
- Penicillamine
- Rifampin
- Sulfasalazine

Signs/symptoms of acute toxicity

Gastrointestinal	Neurological
nausea, vomiting, abdominal pain	weakness, confusion

Electrolyte	Cardiac
Hyperkalemia	bradycardia, heart block, several types of arrhythmias

Signs/symptoms of chronic toxicity

Gastrointestinal

Patients may have more signs of acute digoxin toxicity (nausea, anorexia)

Neurological

confusion, drowsiness, headache, hallucinations

Visual

sensitivity to light, yellow halos around lights, blurred vision

Digoxin: Laboratory Analyses

laboratory values in the digoxin poisoned patient

Hyperkalemia: > 5.5 mEq/L in the *acutely* poisoned digoxin patient (100% Mortality)

Poor prognostic sign in acute toxicity. Antidote warranted when > 5 mEq/L due to 50% mortality for potassium 5 mEq/L – 5.5 mEq/L

Hypokalemia: Can predispose the patient to further dysrhythmias and should be corrected with close monitoring to avoid hyperkalemia.

Digoxin: Laboratory Analyses

Digoxin levels in the poisoned patient

Obtaining an immediate digoxin level in an acutely poisoned patient will not reflect the peak serum level as the distribution phase of digoxin is long. An initial 4-6 hour post-ingestion level is appropriate.

Unbound digoxin	Useful following administration of digoxin-specific Fab fragments
Total digoxin (bound & unbound)	❖ Serum concentrations predict cardiac concentrations ❖ Fab fragments of digoxin-specific antibodies will cause a rise in total digoxin levels (as Fab bound digoxin is also being measured)

Diagnosis of Digoxin Toxicity

- History
- Signs and symptoms
- ECG
- Digoxin levels 
- Electrolytes

History

Risk factors for digoxin toxicity including age of patient
(for patients chronically using digoxin therapeutically)

Initiation or discontinuation of drugs that potentially interact with digoxin	Any disease changes (such as thyroid disease)	Altered renal function

Signs and Symptoms

Acute overdose:

Gastrointestinal:	Central Nervous System:	Electrolyte changes:	Cardiac Signs:
nausea, vomiting	confusion, weakness, lethargy	hyperkalemia	sinus bradycardia, second or third degree AV block. Any type of dysrhythmia is possible

Signs and Symptoms

Chronic overdose

GIT:
anorexia, nausea, vomiting, weight loss

CNS: delirium, hallucinations, confusion,, lethargy (seizures are possible but rare)

Visual:
photophobia, changes in color vision (such as yellow halos around lights)

Electrolyte changes:
hyperkalemia (sometimes hypokalemia especially if diuretics are used)

Cardiac Signs:
bradydysrhythmias (often unresponsive to atropine) ventricular tachydysrhythmias

ECG

Almost any arrhythmia or conduction abnormality may be seen with digitalis toxicity.

Digoxin levels

Therapeutic range of digoxin has historically been 0.5 - 2.0 ng/mL.

Current FDA Package Insert recommends 0.5 - 1.0 ng/mL.

Toxicity begins >2.0 ng/mL

However, this can be misleading in the acutely poisoned patient Stat levels may not correlate with the severity of the poisoning especially in acute ingestions Digoxin's long distribution phase results in high serum levels for 6-12 hours prior to completed tissue distribution

Electrolytes

Hypokalemia results in increased digoxin binding increasing its therapeutic and toxic effects.

Hypercalcemia enhances digitalis-induced inotropy leading to possible Ca^{+2} overload and increased susceptibility to digitalis-induced arrhythmias.

Hypomagnesemia can sensitize the heart to digitalis-induced arrhythmias.

Available treatments:

Decontamination/enhanced elimination

For acute overdose:
Activated charcoal can adsorb digoxin in the gut

Enhanced elimination (dialysis, hemoperfusion) may be effective in remove digoxin due to large volume of distribution and relatively high protein binding

Thank you