Cardiovascular Drugs: Cardiac glycosides

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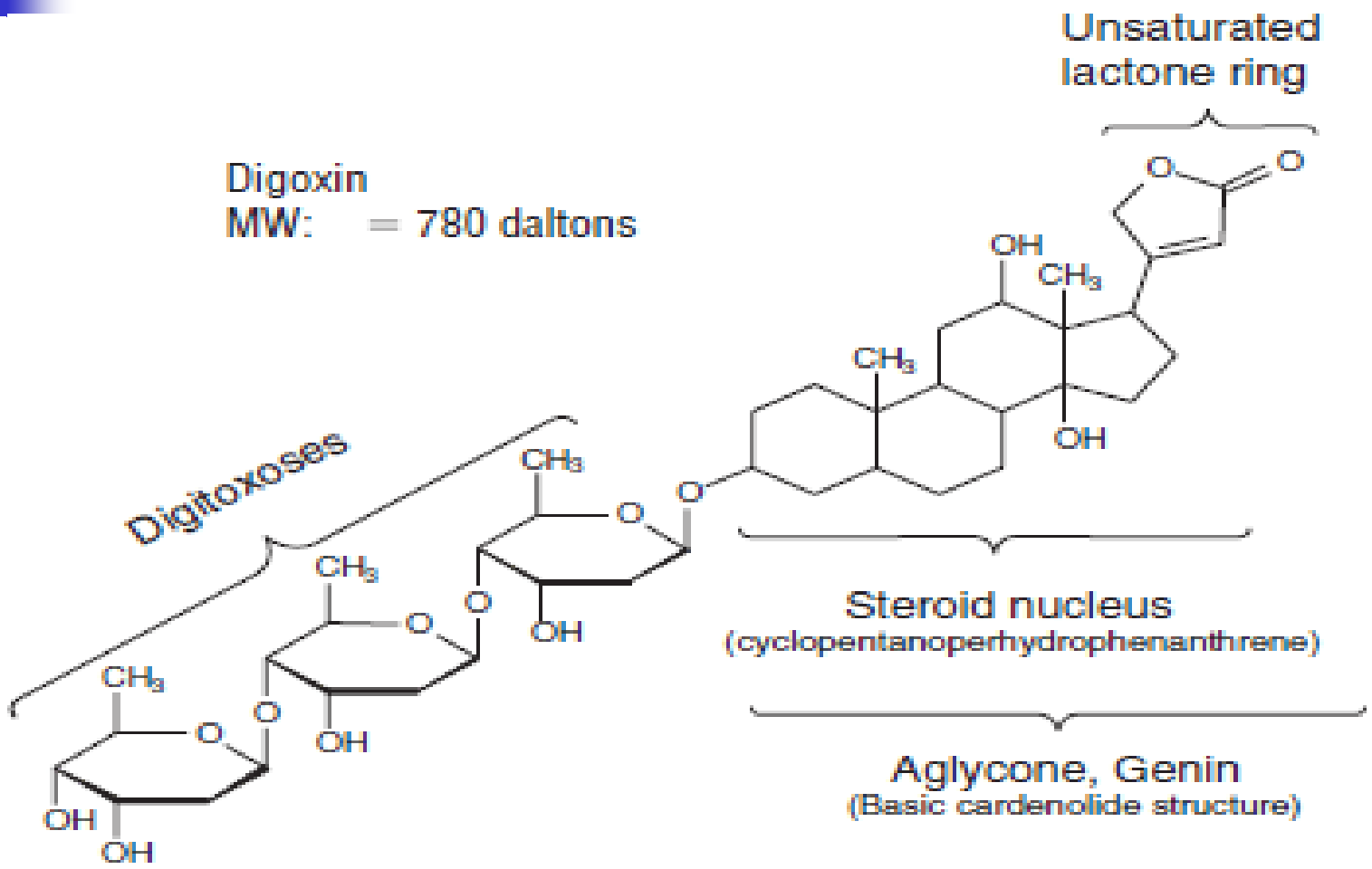
Cardiac glycosides



Cardiac glycosides

- Cardioactive Steroids (CAS), or *cardiac glycosides,* developed their name from the strong cardiac 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 that the Egyptians used plants containing CAS at least 3000 years ago.

Cardiac glycosides

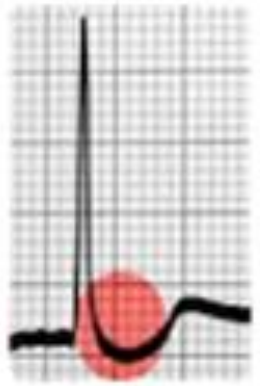
Many plants contain cardioactive steroids:

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.

Cardiac glycosides

- At therapeutic serum concentrations, cardiac glycosides increase automaticity and shorten the repolarization intervals of the atria and ventricles.
- Changes in nodal conduction cause a decrease in ventricular response rate to suprajunctional rhythms and by PR interval prolongation (digitalis effect).



Digitalis Effect

Digoxin: Mechanism of Action

Formulations

Injection (IV; rarely used IM)	Oral Solution	Tablets

Mechanism of Action:

Inhibit active transport of Na+ and K+ across the cell membrane during repolarization by binding to a specific site on the extracellular face of the alpha-subunit of the membrane Na-K-ATPase

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: Pharmacokinetics

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: Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations

Tablets	IV/Injection
Time to onset of Effect: 0.5-2 Hours Time to Peak Effect: 2-6 Hours	Time to onset of Effect: 5-30 Minutes Time to Peak Effect: 1-4 Hours

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	Hypercalcemia	Hypomagnesemia
Results in increased digoxin binding increasing its therapeutic and toxic effects.	Digoxin enhances Ca^{+2} absorption into cardiac myocytes, which is one of the ways it increases inotropy. This can also lead to Ca^{+2} overload and increased susceptibility to digitalis-induced arrhythmias.	Can sensitize the heart to digitalis-induced arrhythmias (includes any arrhythmia except supraventricular tachydysrhythmias).

Digoxin: 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

Digoxin: Drug interactions

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

  verapamil

  diltiazem

  quinidine

  amiodarone

Digoxin : Signs and symptoms of acute Toxicity

Gastrointestinal	Neurological
nausea, vomiting, abdominal pain	weakness, confusion

Electrolyte	Cardiac
Hyperkalemia (> 5.5 mEq/L is a poor prognostic sign)	bradycardia, heart block, several types of arrhythmias

Digoxin : Signs and symptoms of Chronic Toxicity

Gastrointestinal	Neurological
Patients may have more subtle signs of acute digoxin toxicity (nausea, anorexia)	confusion, drowsiness, headache, hallucinations

Visual
sensitivity to light, yellow halos around lights, blurred vision

Digoxin: Laboratory Analyses

Interpreting laboratory values in the digoxin poisoned p

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. Goal Potassium level 4.0 mEq/L - 5.0 mEq/L

Digoxin: Laboratory Analyses

Interpreting laboratory values in the digoxin poisoned patient

Hypomagnesemia may cause refractory hypokalemia

Administration of magnesium is contraindicated in:

- Bradycardia
- Heart block
- Pre-existing hypermagnesemia
- Decreased renal function or failure

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)**

Digoxin: available treatment

Decontamination/enhanced elimination

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

Enhanced elimination (dialysis, hemoperfusion) does not effectively remove digoxin due to large volume of distribution and relatively high protein binding

Digoxin: available treatment

Fab fragments of digoxin-specific antibodies

Available U.S. products:

DigiFab®
digoxin immune fab (ovine) BTG International, Inc.

Digoxin immune fab (ovine): Indications

Life-threatening or potentially life-threatening digoxin toxicity or overdose, which includes:

Known suicidal or accidental Ingestion of fatal digoxin doses:

- 10 mg or more in healthy adults
- 4 mg (0.1 mg/kg) or more in healthy children
- An amount that results in steady state digoxin concentrations of > 10 ng/mL

Chronic ingestions:

- Serum digoxin > 6 ng/mL in adults or 4 ng/mL in children

Digoxin immune fab (ovine): Indications

Life-threatening or potentially life-threatening digoxin toxicity or overdose, which includes:

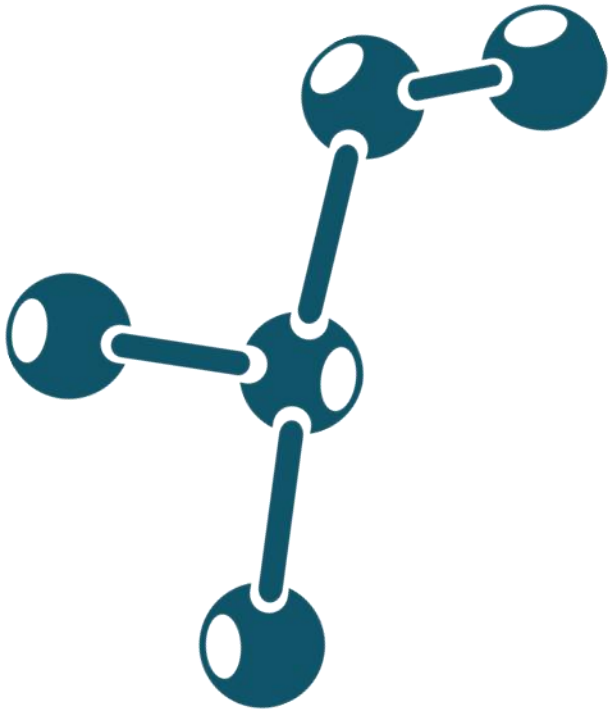
- Severe ventricular arrhythmias
- Progressive bradycardia
- Second or third degree heart block unresponsive to atropine
- Serum potassium levels > 5.5 mEq/L (adults) or 6 mEq/L (children) with rapidly progressive signs and symptoms of digoxin toxicity

Digoxin immune fab (ovine): Mechanism of action

Binds to digoxin molecules, reducing free digoxin levels

Results in a shift in the equilibrium away from receptor binding

Fab-digoxin complexes are cleared by the kidney and mononuclear phagocyte system

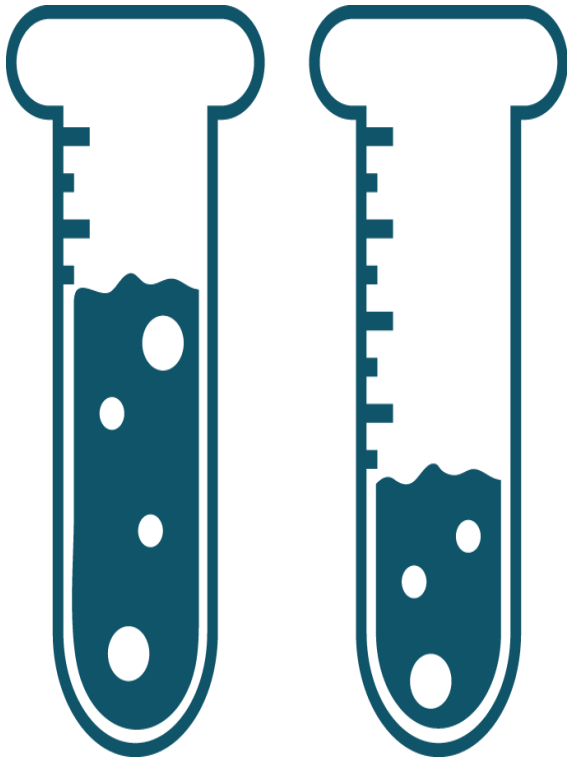


Digoxin immune fab (ovine): Dosing

Acute ingestion: unknown amounts of digoxin and unknown serum concentration

20 vials of Digoxin immune fab (ovine)

- Monitor for volume overload in children < 20 kg
- Can split dose into 10 vials followed by another 10 vials to avoid a febrile reaction



Digoxin immune fab (ovine): Dosing

Acute ingestion: known amounts of digoxin

$$\text{Dose In Vials} = \frac{\textbf{Amount of digoxin ingested (mg)*}}{\textbf{0.5 mg/Vial}}$$

*** multiply mg by bioavailability of the tablet formulation:**

0.25 mg tabs (80% bioavailability)

0.2 mg tabs (100% bioavailability)

Digoxin immune fab (ovine): Dosing

Chronic ingestion: unknown serum digoxin concentration

6 Vials of Digoxin immune fab (ovine) in Adults and Children $\geq$ 20 Kg

1 Vial of Digoxin immune fab (ovine) in Infants and Children < 20 Kg

Digoxin immune fab (ovine): Dosing

Chronic ingestion: known digoxin serum concentration

$$\text{Dose In Vials} = \frac{\text{(Serum Digoxin ng/mL) x (Weight in kg)}}{100}$$

Digoxin immune fab (ovine): warnings

Monitor potassium level frequently as a rapid drop in serum potassium may occur following digoxin immune fab (ovine): administration

Digoxin immune fab (ovine): warnings

Patients who require digoxin's inotropic action may deteriorate secondary to the withdrawal of digoxin's inotropic action by digoxin immune fab (ovine)

Additional inotropic support may be required for these patients (e.g, dopamine, dobutamine or vasodilators)

Re-digitalization may need to be postponed until digoxin immune fab (ovine) has cleared (several days to more than a week of impaired renal function)

Digoxin immune fab (ovine): warnings

Do not administer digoxin immune fab (ovine) to papaya- or papain-hypersensitive patients unless the benefits clearly outweigh the risks

Patients with allergies to sheep protein or prior treatment with ovine antibodies or Fab are at risk for an anaphylactic reaction

Standard emergency care and termination of digoxin immune fab (ovine) are warranted for patients with anaphylaxis/ hypersensitivity

Digoxin immune fab (ovine): Adverse effects

Worsening of congestive heart failure	13%
Hypokalemia	13%
Worsening atrial fibrillation	7%

A rapid shift of potassium back into the cell can occur when digoxin toxicity is reversed by digoxin immune fab (ovine)

Serum potassium should be followed closely and supplementation should be given cautiously

Homwork

- What are the pharmacokinetic parameters of Digoxin and Digitoxin?