Digoxin Toxicity

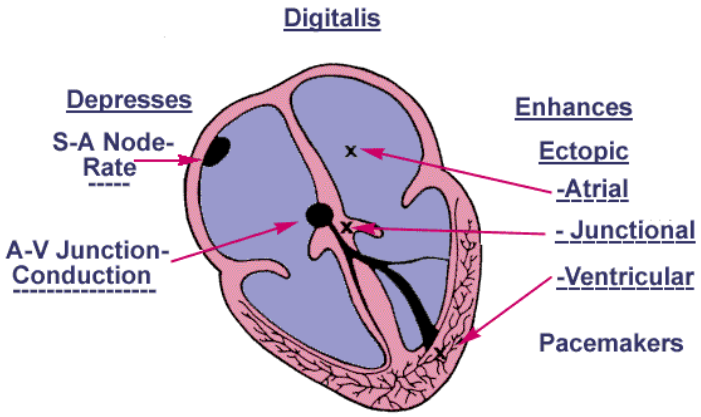
Ahmed S. Mahmood (Ph.D Pharmacology)

Cardiac glycoside

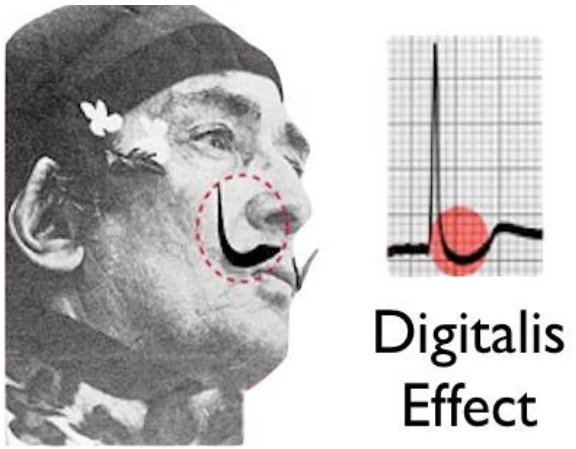
- Digitalis is the oldest compund in cardiovascular medicine.
- The most common pharmaceutical product is digoxin. Other preparations available internationally include digitoxin and ouabain.
- It has +ve intoropic and –ve chronotropic effects.
- Used in Heart failure, Artrial fibrillaiton and Atrial flutter.
- Has low therapeutic index.

Cardioactive Steroids: Effect

- At therapeutic serum concentrations, CAS 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).



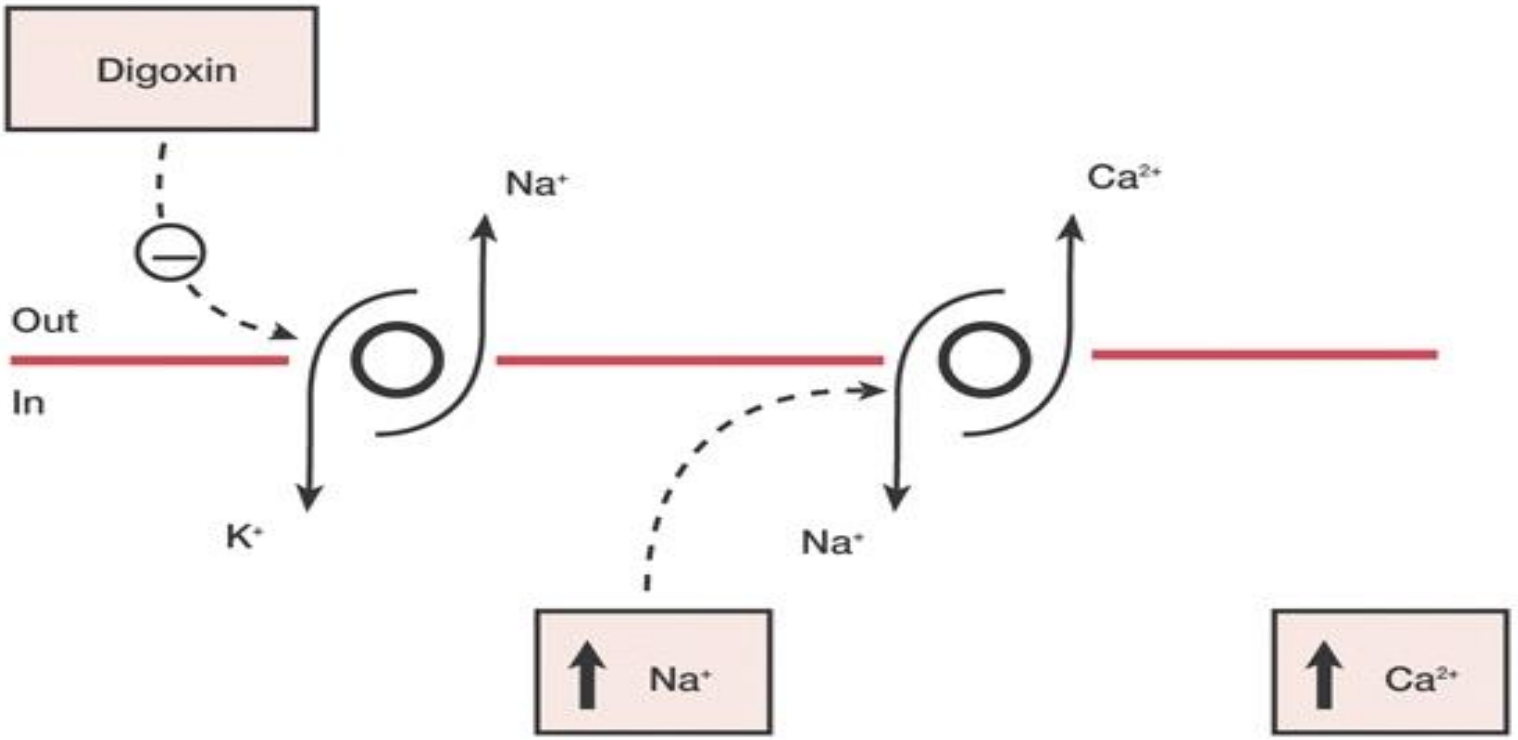
Formulations

Injection
(IV; rarely used IM)

Oral Solution

Tablets

Digoxin: Mechanism



Arispe N, Diaz JC, Simakova O, Pollard HB. Heart failure drug digoxin induces calcium uptake into cells by forming transmembrane calcium channels. Proc Natl Acad Sci. 2008;105:2610-2615.
Middlekauff HR. Int Med 1998; 37: 112-122.

Clinical effects

- Digoxin increase vagal efferent activity to the heart, reduces sinoatrial firing rate (decreases hart rate; negative chronotropy and reducs conduction velocity of electrical impulses through the atrioventricular node

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 onset of Effect: 5-30 Minutes
Time to Peak Effect: 2-6 Hours	Time to Peak Effect: 1-4 Hours

Digoxin Toxicity

Overall use of digoxin has declined approximately 10% in hospitalized acute decompensated heart failure patients.
(from 31.4% in 2001 to 23.5% in 2004)

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 increased digoxin binding 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 (includes any arrhythmia except supraventricular tachydysrhythmias).

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

Digoxin: Causes of Toxicity

Drug interactions:
many commonly used drugs interact with digoxin

Loop and Thiazide Diuretics decrease serum potassium levels:

- furosemide
- hydrochlorthiazide

Digoxin: Causes of Toxicity

Drug interactions:
many commonly used drugs interact with digoxin

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

- verapamil
- diltiazem
- quinidine
- amiodarone

Digoxin: Causes of Toxicity

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
- St. John’s wort
- Sulfasalazine

Digoxin: Causes of Toxicity, Con't

Enhanced Pharmacodynamic Effects

- Beta-blockers
- Calcium
- Verapamil
- Diltiazem
- Succinylcholine
- Sympathomimetics
- Diuretics

Antagonize Pharmacodynamic Effects

- Thyroid hormones

Digoxin: Toxicity

Signs/symptoms of acute toxicity

Gastrointestinal

nausea, vomiting, abdominal pain

Neurological

weakness, confusion

Electrolyte

Hyperkalemia
(> 5.5 mEq/L is a poor prognostic sign)

Cardiac

bradycardia, heart block, several types of arrhythmias

Digoxin: Toxicity

Signs/symptoms of chronic toxicity

Gastrointestinal

Patients may have more subtle 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

Interpreting 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. 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)

Diagnosis of Digoxin Toxicity

What is needed?

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

Diagnosis of Digoxin Toxicity

What is needed?

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

Diagnosis of Digoxin Toxicity

What is needed?

Signs and Symptoms

Acute overdose:

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

Diagnosis of Digoxin Toxicity

What is needed?

Signs and Symptoms

Chronic overdose (symptoms usually insidious in onset):

Gastrointestinal:
anorexia, nausea, vomiting, weight loss

Central Nervous System:
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)

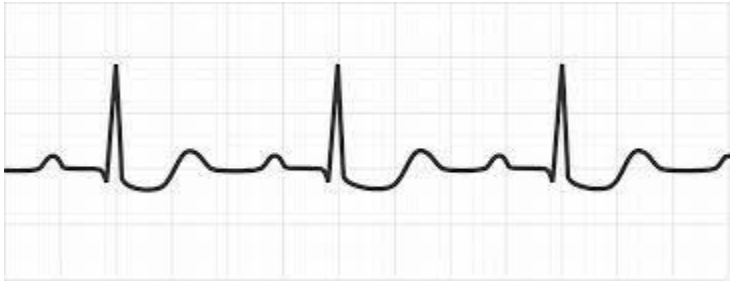
Cardiac Signs:
bradydysrhythmias (often unresponsive to atropine) ventricular tachydysrhythmias

Diagnosis of Digoxin Toxicity

What is needed?

ECG

Almost any arrhythmia or conduction abnormality may be seen with digitalis toxicity. We seen curved ST segment depression.



Diagnosis of Digoxin Toxicity

What is needed?

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

Diagnosis of Digoxin Toxicity

What is needed?

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.

Digoxin Toxicity: Available Treatments

Decontamination/enhanced elimination

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

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

Digoxin Toxicity: Available Treatments

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:

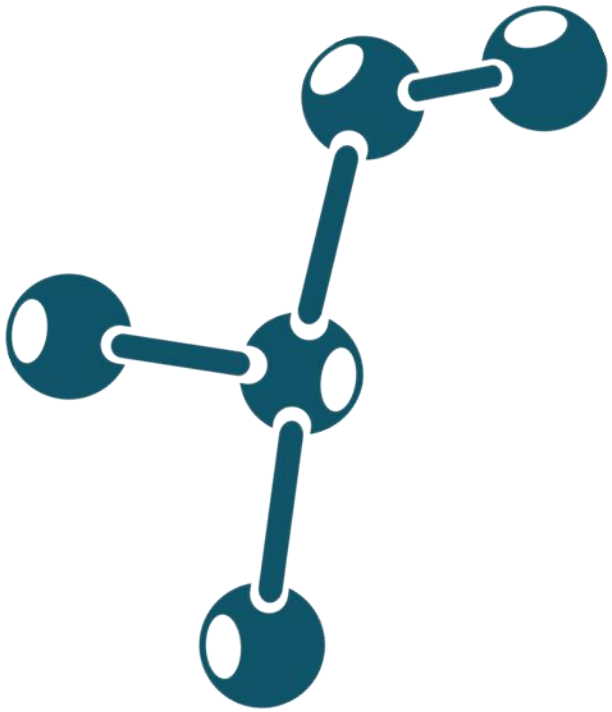
- Severe ventricular arrhythmias
- Progressive bradycardia
- Second or third degree heart block unresponsive to atropine
- Serum potassium levels > 5.5 mEq/L (adults) or 6 mEq/L (children) with rapidly progressive signs and symptoms of digoxin toxicity

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

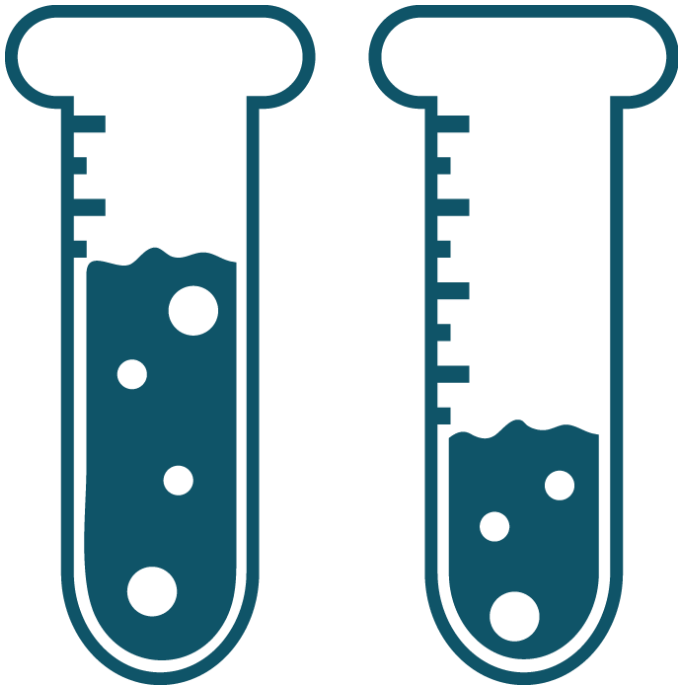


Digoxin immune fab (ovine): Dosing

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

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

* 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 ≥ 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): Preparation

One vial contains 40 mg of digoxin immune fab protein
- Contains no preservatives and is for one-time use only

Reconstitution: add 4 mL Sterile Water for Injection (10 mg/mL solution of digoxin immune fab protein) and gently mix

Use immediately or store in refrigerator for up to 4 hours (do not freeze)

Digoxin immune fab (ovine): Preparation

Add reconstituted product to appropriate 0.9% sodium chloride for injection

For infants and very small children

- use undiluted reconstituted solution using tuberculin syringe
- reconstituted vial can also be diluted with an additional 36 mL of isotonic saline for 1mg/mL concentration

Visual inspection

Do not use if solution is cloudy, turbid or contains particulates

Digoxin immune fab (ovine): Administration

30 minute slow IV infusion

Can be given by IV bolus injection if cardiac arrest is imminent

Digoxin immune fab (ovine): Dosing/administration

If toxicity is not adequately reversed or recurs, measure free (not total) serum digoxin concentrations

Repeat doses may be guided by clinical judgment

If digoxin toxicity is not at all reversed, consider another diagnosis

Digoxin immune fab (ovine): Use in Special Populations

Pregnancy category C	Nursing mothers
Unknown if may cause fetal harm. Should be given to pregnant patient only if clinically indicated	Unknown if excreted in breast milk

Pediatric use	Geriatric patients
Pediatric safety data are limited. Pediatric dosing estimations are based on adult dosing	Renal function needs to be monitored closely for recurrent toxicity

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 reactions

Digoxin immune fab (ovine): Adverse effects (most common)

Worsening of congestive heart failure	13%
Hypokalemia	13%

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

Worsening atrial fibrillation	7%

Digoxin immune fab (ovine):

Minimum stocking recommendation: 15 vials (for approximately 8 hours of initial therapy)

Emergency department stocking: for availability within one hour

Digoxin Toxicity: Case 1

76 year old woman (body weight 108 Kg) with history of atrial fibrillation, hypertension, renal
impairment, breast cancer, osteoarthritis. Stroke 1 month prior to admission.

Medications: digoxin 250 mcg once daily, amlodipine, lisinopril, indapamide SR, simvastatin, clopidogrel, bisoprolol, omeprazole, erythromycin

Presents with nausea, vomiting, change in vision, lethargy

VS: BP “normal”; HR 35-38 bpm

Labs

Digoxin levels: prior to admission: 3.4 ng/mL (0.8-2 ng/mL normal range for this lab)

On admission: 2.9 ng/mL

Increased digoxin dose from 125 mcg/day to 250 mcg/day 28 days ago

Digoxin Toxicity: Case 1

Summary: elderly patient with renal impairment, signs/symptoms of (chronic) digoxin poisoning with elevated digoxin level

Potential drug interactions:

Amlodipine	Bisoprolol	Erythromycin
(Ca^{+2} channel blocker) can increase digoxin level and enhance digoxin AV blocking effect	(ß blocker) can enhance digoxin's bradycardic effect	(macrolide antibiotic) can increase digoxin level

Digoxin Toxicity: Case 1

Received digoxin-specific antibody fragments (Fab)

Weight 108 kg

Digoxin level: 2.9 ng/mL

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

3 vials administered

Digoxin Toxicity: Case 1

6 hours post digoxin Fab infusion: digoxin 1.9 ng/mL

At discharge (91 hours post digoxin Fab infusion): digoxin 1 ng/mL, HR 65 bpm, digoxin toxicity signs/symptoms resolved

Monitoring

HR: improved (35-38 bpm to 65 bpm at discharge)	BP: remained stable	EKG: unchanged from baseline (atrial fibrillation)	K^+ not provided in this report (although this was a chronic toxicity not acute)

Digoxin Toxicity: Case 1

Approaches to digoxin poisoning in the chronically poisoned patient will depend on the status of the patient (signs/symptoms, age, renal function, cardiac status)

This was an elderly patient with impaired renal function who clearly had digoxin toxicity and an elevated level.

The clinical decision was made to treat promptly with digoxin Fab rather than prolong her clinical course.

Supplemental slides

(includes off-label information)

Treating non-pharmaceutical sources of cardioactive steroids

Natural cardioactive steroid sources:

- Yellow oleander
- Oleander
- Squill
- Lily of the valley
- Bufos marinus toad

DigiFab® is not FDA-approved for treating poisoning from these naturally occurring steroids; however, there is evidence in the literature for its use.


Thank you
for listening