Digoxin Toxicity
Cardioactive Steroids
also known as cardiac glycosides

Digitalis: Plant derived cardioactive steroid

Digoxin is the most commonly prescribed form of digitalis

Digitoxin is not currently available in the U.S.

Digitoxin is being studied as an anti-cancer agent for various tumor types

Giardina EG, Sylvia L. Up to Date, Rose BD (ED), Waltham, MA, 2012.
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

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Digoxin: Therapeutic Role

Formulations

- Injection
  (IV; rarely used IM)
- Oral Solution
- Tablets

Mechanism of Action

Inhibits the ion transfer system known as sodium-potassium ATPase

[Diagram showing the mechanism of action of digoxin, with arrows indicating the movement of ions like Na+, K+, and Ca++.]
Digoxin: Therapeutic Role

Disease states used in:

- Atrial fibrillation
- Heart failure
- Supraventricular tachycardia

Used in adults and pediatrics

Giardina EG, Sylvia L. Up to Date, Rose BD (ED), Waltham, MA, 2012.
# Digoxin: Kinetics

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

Giardina EG, Sylvia L. Up to Date, Rose BD (ED), Waltham, MA, 2012.
Digoxin Toxicity

Overall use of digoxin has declined approximately 10% (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

<table>
<thead>
<tr>
<th>Hypokalemia</th>
<th>Hypercalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results in increased digoxin binding increasing its therapeutic and toxic effects.</td>
<td>Enhances digitalis-induced inotropy leading to possible Ca+2 overload and increased susceptibility to digitalis-induced arrhythmias.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypomagnesemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can sensitize the heart to digitalis-induced arrhythmias (includes any arrhythmia except supraventricular tachydysrhythmias).</td>
</tr>
</tbody>
</table>
Digoxin: Causes of Toxicity

Drug interactions: many commonly used drugs interact with digoxin

Via decreased renal clearance of digoxin (class of drugs/examples)

- calcium channel blockers: (Nondihydropyridine): verapamil, diltiazem
- NSAIDs: ibuprofen, naproxen sodium

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Digoxin: Causes of Toxicity

Drug interactions: many commonly used drugs interact with digoxin

Via decreased serum potassium levels (loop and thiazide diuretics):

- furosemide
- hydrochlorothiazide

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Digoxin: Causes of Toxicity

Drug interactions:
many commonly used drugs interact with digoxin

Via altering the mechanism of digoxin excretion (and hence elimination) via renal or intestinal p-glycoprotein activity

- verapamil
- diltiazem
- quinidine
- amiodarone

Giardina EG, Sylvia L. Up to Date, Rose BD (Ed), Waltham, MA, 2012.
# Digoxin: Causes of Toxicity

## Increased Serum Levels
- Amiodarone
- Benzodiazepines
- Bepridil
- Cyclosporine
- Diphenoxylate
- Indomethacin
- Itraconazole
- Macrolides
- 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

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Digoxin: Causes of Toxicity Con’t

Enhanced Pharmacodynamic Effects

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

Antagonize Pharmacodynamic Effects

- Thyroid hormones

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# Digoxin: Toxicity - Acute

## Signs/symptoms of acute toxicity

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>nausea, vomiting, abdominal pain</td>
<td>weakness, confusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia (&gt; 5.5 mEq/L is a poor prognostic sign)</td>
<td>bradycardia, heart block, several types of arrhythmias</td>
</tr>
</tbody>
</table>

Schaeffer TH, Mlynarchek SL, Stanford CF. JADA 2010; 110: 587-592
Digoxin: Toxicity - Chronic

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

Schaeffer TH, Mlynarchek SL, Stanford CF. JADA 2010; 110: 587-592
Digoxin: Laboratory Analyses

Interpreting laboratory values in the digoxin poisoned patient

**Hyperkalemia:** > 5.5 mEq/L in the *acutely* poisoned digoxin patient

Poor prognostic sign in acute toxicity. Antidote warranted when > 5 mEq/L.

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

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.

<table>
<thead>
<tr>
<th>Free digoxin</th>
<th>Useful following administration of digoxin-specific Fab fragments</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Total digoxin</th>
<th>□ Serum concentrations predict cardiac concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ Fab fragments of digoxin-specific antibodies will cause a rise in total digoxin levels (as Fab bound digoxin is also being measured)</td>
</tr>
</tbody>
</table>
Diagnosis of Digoxin Toxicity

What is needed?

- History
- Signs and symptoms
- EKG
- Digoxin levels
- Electrolytes
Diagnosis of Digoxin Toxicity

What is needed?

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

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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?

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

Diagnosis of Digoxin Toxicity

What is needed?

Therapeutic range of digoxin has historically been 0.5 - 2.0 ng/mL (although current medical practice is evolving and some experts now advocate target levels, < 1.0 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 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.
DigiFab®: 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
DigiFab®: 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
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
DigiFab®: Dosing – Acute Ingestion

Acute ingestion: unknown amounts of digoxin and unknown serum concentration

20 vials of DigiFab®

Monitor for volume overload in children < 20 kg

Can split dose into 10 vials followed by another 10 vials to avoid a febrile reaction
DigiFab®: Dosing – Acute Ingestion

Acute ingestion: known amounts of digoxin

Dose In Vials =

Amount of digoxin ingested (mg)*

0.5 Mg/Vial

* multiply mg by bioavailability of the tablet formulation:
  0.25 mg tabs (80% bioavailability)
  0.2 mg tabs (100% bioavailability)
DigiFab®: Dosing – Chronic Ingestion

Chronic ingestion: unknown serum digoxin concentration

6 Vials of DigiFab® in Adults and Children ≥ 20 Kg

1 Vial of DigiFab® in Infants and Children < 20 Kg
DigiFab®: Dosing – Chronic Ingestion

Chronic ingestion: known digoxin serum concentration

Adult dose estimate of DigiFab® (in number of vials) from steady-state serum digoxin concentration

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Serum Digoxin Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>40</td>
<td>0.5 v</td>
</tr>
<tr>
<td>60</td>
<td>0.5 v</td>
</tr>
<tr>
<td>70</td>
<td>1 v</td>
</tr>
<tr>
<td>80</td>
<td>1 v</td>
</tr>
<tr>
<td>100</td>
<td>1 v</td>
</tr>
</tbody>
</table>

v = vials.
DigiFab®: 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)
DigiFab®: 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
DigiFab®: Administration

30 minute slow IV infusion

Can be given by IV bolus injection if cardiac arrest is imminent
DigiFab®: 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.
DigiFab®: Use in Special Populations

**Pregnancy category C**

Unknown if may cause fetal harm. Should be given to pregnant patient only if clinically indicated

**Nursing mothers**

Unknown if excreted in breast milk

**Pediatric use**

Pediatric safety data are limited. Pediatric dosing estimations are based on adult dosing

**Geriatric patients**

Renal function needs to be monitored closely for recurrent toxicity
DigiFab®: Warnings

Patients who require digoxin’s inotropic action may deteriorate secondary to the withdrawal of digoxin’s inotropic action by DigiFab®

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

Re-digitalization may need to be postponed until DigiFab® has cleared (several days to more than a week in impaired renal function)
DigiFab®: Warnings

Monitor potassium level frequently as a rapid drop in serum potassium may occur following DigiFab® administration
Do not administer DigiFab® 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 DigiFab® are warranted for patients with anaphylaxis/hypersensitivity reactions.
DigiFab®: Adverse effects (most common)

- 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 DigiFab®.

Serum potassium should be followed closely and supplementation should be given cautiously.
Minimum stocking recommendation: 15 vials (for approximately 8 hours of initial therapy)

Emergency department stocking: for availability within one hour
Resources

Website for product information
www.digifab.us

Poison control
800-222-1222

BTG Medical Info/Adverse Event Reporting
877-377-3784

Customer Service including availability
877-852-8542
Digoxin Toxicity: Case 1

76 year old woman 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:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>(Ca channel blocker) can increase digoxin level and enhance digoxin AV blocking effect</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>(β blocker) can enhance digoxin’s bradycardic effect</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>(macrolide antibiotic) can increase digoxin level</td>
</tr>
</tbody>
</table>

Kolev KK. Digoxin – a friend or foe. BMJ Case Reports 2012 Sept 24
Digoxin Toxicity: Case 1

Received digoxin-specific antibody fragments (Fab)

- Weight 108 kg
- Digoxin level: 2.9 ng/mL

(Serum Digoxin ng/mL) (Weight in kg)

Fab Dose In Vials = 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)
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.

Kalev KK. Digoxin – a friend or foe. BMJ Case Reports 2012 Sept 24