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 also available in the U.K

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

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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

- This transport system moves Na+ ions out of the cell and potassium ions into the cell
- Many cells including cardiac cells have this transport system

- As the Na+ concentration inside the cell increases, so does the Ca+2 concentration inside the cell
- An increase in Ca+2 inside the cell increases contractility of the cell (inotropy)
- Increased inotropy causes smooth muscle contraction and vasoconstriction

- May be a benefit in heart failure secondary to neurohumoral effects (decrease in sympathetic activity) rather than its inotropic effects
- Decreases heart rate via other mechanism not well understood

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Digoxin: Therapeutic Role

Disease states used in:

- Atrial fibrillation
- Heart failure
- Supraventricular tachycardia

*Used in adults and paediatrics*

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# 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>Steady state: 7-10 Days</td>
<td></td>
</tr>
</tbody>
</table>

Giardina EG, Sylvia L. Up to Date, Rose BD (ED), Waltham, MA, 2012.
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**: 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 (includes any arrhythmia except supraventricular tachydysrhythmias).

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

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# 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 aminatingosides
- Al+/Mg+ containing antacids
- Antineoplastics
- Activated charcoal
- Cholestyramine
- Colestipol
- Kaoline / pectin
- Metoclopramide
- Neomycin
- Penicillamine
- Rifampin
- St. John’s wort
- Sulfasalazine
## Digoxin: Causes of Toxicity

<table>
<thead>
<tr>
<th>Enhanced Pharmacodynamic Effects</th>
<th>Antagonize Pharmacodynamic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Beta-blockers</td>
<td>- Succinylcholine</td>
</tr>
<tr>
<td>- Calcium</td>
<td>- Sympathomimetics</td>
</tr>
<tr>
<td>- Verapamil</td>
<td>- Diuretics</td>
</tr>
<tr>
<td>- Diltiazem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Thyroid hormones</td>
</tr>
</tbody>
</table>
# Digoxin: Toxicity

## 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>
Patients may have more subtle signs of acute digoxin toxicity (nausea, anorexia).

Confusion, drowsiness, headache, hallucinations.

Sensitivity to light, yellow halos around lights, blurred vision.

Schaeffer TH, Mlynarchek SL, Stanford CF. JAOA 2010; 110: 587-592
Hyperkalemia: > 5.5 mEq/L in the acutely poisoned digoxin patient

Poor prognostic sign in acute toxicity. Antidote warranted when > 5 mEq/L. May be seen in chronic toxicity but not as serious.

Hypokalemia: can predispose the patient to further dysrhythmias and should be corrected with close monitoring to avoid hyperkalemia.
Interpreting laboratory values in the digoxin poisoned patient

Hypomagnesemia may cause refractory hypokalemia

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>
<tbody>
<tr>
<td>Total digoxin</td>
<td>□ Serum concentrations predict cardiac concentrations&lt;br&gt;□ 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?

### 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 |

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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

<table>
<thead>
<tr>
<th>Gastrointestinal: anorexia, nausea, vomiting, weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System: delirium, hallucinations, confusion, lethargy (seizures are possible but rare)</td>
</tr>
<tr>
<td>Visual: photophobia, changes in color vision (such as yellow halos around lights)</td>
</tr>
<tr>
<td>Electrolyte changes: hyperkalemia (sometimes hypokalemia especially if diuretics are used)</td>
</tr>
<tr>
<td>Cardiac Signs: bradydysrhythmias (often unresponsive to atropine) ventricular tachydysrhythmias</td>
</tr>
</tbody>
</table>

Chronic overdose (symptoms usually insidious in onset):
Diagnosis of Digoxin Toxicity

What is needed?

EKG

Almost any arrhythmia or conduction abnormality may be seen with digitalis toxicity.
Diagnosis of Digoxin Toxicity

What is needed?

Digoxin levels

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\(^1\))

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.K. products:

DigiFab® digoxin immune fab (ovine)
BTG International Limited
DigiFab®: Indications

For the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine where measures beyond withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.
<table>
<thead>
<tr>
<th>Resources</th>
<th>Customer Service including availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK National Poisons Information Service</strong></td>
<td><strong><a href="mailto:productsupplies@btgplc.com">productsupplies@btgplc.com</a></strong></td>
</tr>
<tr>
<td>0844 892 0111</td>
<td></td>
</tr>
<tr>
<td><strong>BTG Medical Info and patient registry forms</strong></td>
<td><strong>DigiFab® Adverse Event Reporting</strong></td>
</tr>
<tr>
<td><a href="mailto:medical.services@btgplc.com">medical.services@btgplc.com</a></td>
<td><a href="mailto:EUSafety@ubc.com">EUSafety@ubc.com</a></td>
</tr>
</tbody>
</table>

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