Digoxin Toxicity
This presentation is intended for health care practitioners in the United Kingdom only.
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
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

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

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.
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.
Hyponatremia: Causes of Toxicity

<table>
<thead>
<tr>
<th>Hypokalemia</th>
<th>Hypercalcemia</th>
<th>Hypomagnesemia</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>
<td>Can sensitize the heart to digitalis-induced arrhythmias (includes any arrhythmia except supraventricular tachy dysrhythmias).</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

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# Digoxin: Causes of Toxicity

<table>
<thead>
<tr>
<th>Increased Serum Levels</th>
<th>Decreased Serum Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Oral aminglycosides</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Al+/Mg+ containing antacids</td>
</tr>
<tr>
<td>Bepridil</td>
<td>Antineoplastics</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Activated charcoal</td>
</tr>
<tr>
<td>Diphenoxylate</td>
<td>Cholestyramine</td>
</tr>
<tr>
<td></td>
<td>Colestipol</td>
</tr>
<tr>
<td></td>
<td>Kaoline / pectin</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Neomycin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Penicillamine</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Propanthelene</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
</tr>
</tbody>
</table>

*Note: This table lists interactions that can increase or decrease the serum levels of digoxin. It is important to manage these interactions carefully to prevent toxicity.*
# Digoxin: Causes of Toxicity

## 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

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients may have more subtle signs of acute digoxin toxicity (nausea, anorexia)</td>
<td>confusion, drowsiness, headache, hallucinations</td>
</tr>
</tbody>
</table>

### Visual

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

Schaeffer TH, Mlynarchek SL, Stanford CF. JAOA 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. 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

Digoxin: Laboratory Analyses

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.

Free digoxin

Useful following administration of digoxin-specific Fab fragments

Total digoxin

- 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
- 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

**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

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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)

- 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

[Hack JM, Lewin NA. Cardioactive Steroids. Goldfrank’s Toxicologic Emergencies, 8th edition. 971-982.]
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)
  - Protherics UK 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.
DigiFab®: Contraindications

DigiFab is contraindicated in patients with hypersensitivity to the active substance or any of the excipients.
DigiFab®: Special warnings and precautions for use

- It is advised to discuss management of patients with digoxin toxicity with the UK National Poisons Information Service at the following contact phone number: 0844 892 0111.

- Infusion-related or Hypersensitivity reactions are possible. Monitor patients for signs and symptoms of anaphylaxis and acute allergic reaction. Medical support must be readily available when administering DigiFab.

- The likelihood of an allergic reaction may be higher in subjects who:
  - are allergic to sheep-derived proteins (as may be found in cheeses and meats). Digoxin immune Fab is produced from sheep protein.
  - are allergic to papain, an extract of the papaya fruit. Papain is used to cleave the whole antibody into Fab and Fc fragments: traces of papain or inactivated papain residues may be present in DigiFab. Papain shares allergenic structures with (i) chymopapain and other papaya extracts, (ii) bromelain found in pineapple, (iii) dust mite allergens and (iv) latex allergens.
DigiFab®: Special warnings and precautions for use

- Digoxin assay kits may not be able to measure accurately digoxin concentrations greater than 5 ng/mL (6.4 mmol/L). Exercise caution when using digoxin concentrations above these figures to calculate the dose of DigiFab is required.

- DigiFab may interfere with digoxin immunoassay measurements. Therefore, standard serum digoxin measurements may be clinically misleading until the Fab fragments are eliminated from the body. This may take several days or more than a week in patients with impaired renal function.

- The total serum digoxin concentration as measured by immunoassay may rise rapidly following administration of DIGIFAB. Serum digoxin will be almost entirely bound by DigiFab and therefore not able to react with receptors in the body.
DigiFab®: Undesirable effects

- Adverse reactions may occur up to 14 days after the infusion has been administered.
- Exacerbation of low cardiac output states and congestive heart failure or a rapid ventricular response in patients with atrial fibrillation may occur owing to withdrawal of effect of digoxin.
DigiFab®: Undesirable effects

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) very rare (<1/10,000), including isolated reports.

Adverse reactions reported from 23 subjects in clinical studies are listed below according to system organ class.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Hypokalaemia, hyperkalaemia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache, confusional state</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea, vomiting, diarrhoea, constipation, abdominal distension</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Worsening of cardiac failure, Chest pain, Hypotension, Orthostatic hypotension</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
<td>Influenza-like illness</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Renal failure</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Fatigue, Infusion site phlebitis</td>
</tr>
</tbody>
</table>
Digoxin immune fab (ovine): Mechanism of action

Digoxin immune fab (ovine) has a high affinity for digoxin

Digoxin immune Fab (ovine) binds digoxin, reducing the concentration of free digoxin
Digoxin immune fab (ovine): Posology

Acute digoxin poisoning

Half the estimated dose required for full neutralisation can be given initially followed by monitoring for 6-12 hours if there is a full response. The remainder may be given if there is no clinical response within 2 hours.

Rationale: in acute digoxin poisoning, the serum digoxin concentration does not reflect total body load and complete neutralisation is not necessary in digoxin-naïve patients.
Digoxin immune fab (ovine): Posology

Acute-on-chronic digoxin poisoning

A full neutralising dose can be given if the amount of digoxin ingested is known. If the amount of digoxin ingested is not known then a half-neutralising dose based on serum digoxin concentration should be used followed by monitoring for 6-12 hours if there is a full response. The remainder may be given if there is no clinical response within 2 hours.

The usual dose for adults and children over 20 kg may vary between one half of a vial to 20 vials. More vials may be needed dependent upon the amount of digoxin consumed.
Digoxin immune fab (ovine): Posology

Chronic digoxin poisoning

Half the estimated dose required for full neutralisation can be given initially followed by monitoring for 6-12 hours. The remainder may be given if there is recurrence of toxicity.

Rationale: in chronic digoxin poisoning, the dose of antibody required for full neutralisation depends on the total body load of cardiac glycoside which has to be counteracted. However, as these patients are receiving digoxin therapeutically, full neutralisation is not necessary.
# Digoxin immune fab (ovine): Dose calculation

## Dose calculation for full neutralization

<table>
<thead>
<tr>
<th>Dose of digoxin ingested known</th>
<th>Number of vials = Amount of digoxin ingested (mg) × 1.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum digoxin concentration known</td>
<td>Number of vials = \left( \text{serum digoxin concentration (ng/mL)} \times \text{weight (kg)} \right) / 100</td>
</tr>
</tbody>
</table>

Round up to the nearest vial. To calculate the number of milligrams to be prescribed, multiply the number of vials by 40.
Digoxin immune fab (ovine): Preparation

One vial contains 40 mg digoxin immune fab protein. To reconstitute, add 4 mL Sterile Water for Injection to each vial and gently mix.

This produces a solution with a protein concentration of 10 mg/mL that may be diluted further to any convenient volume with sterile saline (0.9% NaCl) suitable for infusion.

Vials are single use only and should be used immediately after reconstitution. Do not use if solution is cloudy, turbid or contains particulates.

DigiFab® Summary of Product Characteristics. Protherics UK Limited. December 2017
Digoxin immune fab (ovine): Administration

The final solution of reconstituted and diluted DIGIFAB should be infused intravenously over a 30 minute period.

Record the name of the patient and batch number of the product in order to maintain a link between the patient and the batch of the product.

DigiFab® Summary of Product Characteristics. Protherics UK Limited. December 2017
Digoxin immune fab (ovine): General considerations

Dosage estimates are based on a steady-state volume of distribution of 5 L/kg for digoxin in order to convert serum digitalis concentration to the amount of digitalis in the body. These volumes are population averages and vary widely among individuals.

Ordinarily, improvements in signs and symptoms of digoxin toxicity begin within 30 minutes following completion of administration of DigiFab.

Patients should have continuous electrocardiographic monitoring during and for at least 24 hours after administration of DigiFab. Temperature, blood pressure and potassium concentration should be monitored during and after administration of DigiFab.
Digoxin immune fab (ovine): General considerations

Patients previously dependent on the inotropism of digoxin may develop signs of heart failure when treated with DIGIFAB. After successful management of poisoning, digoxin has had to be reinstituted in some cases.

If, after several hours, toxicity has not adequately reversed or appears to recur, re-administration of DigiFab at a dose guided by clinical judgement may be required. Failure of the patient to respond to DigiFab should alert the physician to the possibility that the clinical problem may not be due to digoxin toxicity.

Suicidal ingestion may involve more than one drug. Toxic effects of other drugs or poisons should not be overlooked, particularly where failure to respond to DigiFab raises the possibility that the clinical problem is not caused by digoxin.
Resources

UK National Poisons Information Service
0844 892 0111

BTG Medical Info
btgpharmamedicalinfo@btgplc.com

Customer Service including availability
productsupplies@btgplc.com

DigiFab® Adverse Event Reporting
Vigilance@btgplc.com
https://yellowcard.mhra.gov.uk/