Cardiac glycoside poisoning (including digoxin)

May 13, 2021 by Josh Farkas

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mechanism of action of digoxin

1. Digoxin inhibits the cardiac Na/K antiporter (orange oval, above). This causes an increase in intracellular sodium and a decrease in intracellular potassium.
   - The decrease in intracellular potassium is what causes hyperkalemia in patients with digoxin overdose.
2. The increase in intracellular sodium causes an increase in excretion of sodium through the Na/Ca exchanger, which in turn increases intracellular calcium levels.
3. Increased intracellular calcium increases inotropy.
4. Increased inotropy often causes a reflexive increase in vagal tone. For patients in atrial fibrillation, increased vagal tone will decrease the conduction rate through the atrioventricular node, thereby slowing the ventricular rate.

pharmacokinetics of digoxin

- The oral bioavailability is 40-90%. Onset of action occurs 2-6 hours after ingestion.
- The digoxin molecule is too large to be removed via hemodialysis.
- The volume of distribution is ~6 liters/kg.
- Excretion occurs mainly via the kidneys. The half-life is ~40 hours (with variation depending on renal function).
- Digoxin is secreted into the urine by P-glycoprotein:
  - P-glycoprotein inhibitors will increase digoxin levels, for example:
    - Amiodarone, carvedilol, ranolazine, ticagrelor.
    - Verapamil, tacrolimus, cyclosporine.
    - Azithromycin, erythromycin, clarithromycin.
    - Azole antifungals.
  - P-glycoprotein inducers will decrease digoxin levels, for example:
    - Carbamazepine, fosphenytoin, phenobarbital.
    - Rifampin.

epidemiology

digoxin intoxication
Most cases of digoxin intoxication are chronic and unintentional, due to gradual accumulation of digoxin over time. Precipitating factors for chronic intoxication may include the following:

- (a) Digoxin is renally cleared, so any cause of kidney injury may cause accumulation.
- (b) Drug interactions can reduce digoxin metabolism (see above).
- (c) Tissue sensitivity to digoxin may be increased by hypokalemia, hypomagnesemia, hypercalcemia, myocardial ischemia, and hypoxemia.

**other cardiac glycosides**

- Various cardiac glycosides are found in plants (e.g., oleander, henbane, foxglove, milkweed, lily of the valley). Ingestion of these plants is not uncommon in some locales.
- Bufadienolide is a cardioactive steroid found in the skin of Bufo toads, which is utilized as an aphrodisiac.

### clinical manifestations

#### acute vs. chronic toxicity

- **Acute toxicity:** Generally starts with gastrointestinal symptoms, with neurologic symptoms developing later (as the drug subsequently distributes to the brain).
- **Chronic toxicity:** Insidious onset of neurologic symptoms, with fewer gastrointestinal symptoms.

#### a variety of arrhythmias may be seen:

- Sinus bradycardia or high-degree AV block.
- Supraventricular tachycardias with atrioventricular block are classic for digoxin toxicity:
  - Atrial fibrillation with slow ventricular rate.
  - Atrial fibrillation with junctional escape rhythm.
  - Focal atrial tachycardia with AV block.
- Junctional tachycardia.
- Ventricular arrhythmias are more often seen in chronic toxicity:
  - Ventricular bigeminy.
  - Ventricular tachycardia, ventricular fibrillation.
  - *Bidirectional ventricular tachycardia* strongly suggests the presence of digoxin.

#### GI

- Anorexia, nausea/vomiting.
- Abdominal pain.
- Diarrhea.

#### neurologic

- Delirium.
- Fatigue.
- Visual disturbances (altered color perception, blurred vision, photophobia, diplopia, blindness).
- Seizures rarely may occur.

### EKG features

1) **some uncommon arrhythmias may particularly suggest the possibility of digoxin toxicity**

- Bidirectional ventricular tachycardia.
- Paroxysmal atrial tachyarrhythmias with AV block.
- Junctional tachycardia. ([28572865](https://pubmed.ncbi.nlm.nih.gov/28572865/))
2) EKG revealing *digitalis effect*

- *Digitalis effect* refers to the following morphological pattern:
  - Scooped ST segment with ST depression ("Salvador Dali mustache").
  - Flattened/inverted T-wave, which may be followed by a prominent U-wave.
  - Shortened QT interval.
- *Digitalis effect* reveals the presence of digoxin, but doesn’t correlate with clinical digoxin toxicity. So this may be helpful to identify patients with exposure to cardiac glycosides – but it is otherwise non-specific (especially in a patient who is known to be on digoxin).

3) Paced EKGs

- A pacemaker may impair the ability to diagnose digoxin toxicity:
  - It may prevent the occurrence of some arrhythmias (e.g., bradydysrhythmias).
  - It may obscure the presence of digitalis effect.

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**differential diagnosis**

common differential diagnostic considerations:

- Calcium channel blocker intoxication or beta-blocker intoxication ([link](https://emcrit.org/ibcc/cob/)).
- Alpha-agonist intoxication (e.g., clonidine) – may cause greater somnolence and miosis than digoxin.
- Hypothyroidism ([link](https://emcrit.org/ibcc/myxedema/)).
- Hypothermia ([link](https://emcrit.org/ibcc/hypothermia/)).
- Myocardial infarction.
- Hyperkalemia ([link](https://emcrit.org/ibcc/hyperkalemia/)) of any etiology.
  - BRASH syndrome ([link](https://emcrit.org/ibcc/brash/)).
Chronic cardiac conduction system disease.

related differential diagnoses

- Differential diagnosis of bradycardia.
- Differential diagnosis of delirium.

digoxin levels

when to check a digoxin level:

- (1) A patient who is chronically on digoxin, with any of the following:
  - Renal failure.
  - Acutely ill enough to require hospital admission.
  - Any signs or symptoms suggestive of digoxin poisoning.
- (2) Clinical constellation suggestive of cardiac glycoside intoxication.

timing of the digoxin level

- Digoxin requires >6 hours to distribute into the tissues, after oral intake. Only post-distribution levels reflect the severity of intoxication and help calculate the dose of antiserum.
- For acute intoxication, check a baseline digoxin level and then repeat another level six hours after the ingestion.
- For chronic intoxication, a single digoxin level is adequate, provided that it is obtained >6 hours after the last dose.

interpretation of the digoxin level in digoxin intoxication

- Therapeutic level: 0.5-2 ng/ml (0.6-2.6 nM/L).
  - For chronic outpatient therapy, 0.5-1 ng/mL (0.6-1.2 nM/L) is probably ideal.
- Potentially scary:
  - Chronic intoxication: >4 ng/ml (>5.1 nM/L).
  - Acute intoxication: >10 ng/ml (>12.8 nM/L).
- However, serum digoxin levels don't correlate well with tissue levels and clinical toxicity.
  - Toxicity can occur with mildly elevated levels, or even levels at the top of the "therapeutic" range.
  - Patients can have elevated digoxin levels, without clinical toxicity.
  - After receiving antibody fragments, levels are meaningless (the lab will measure free and also bound digoxin).

interpretation of the "digoxin level" in intoxication with other cardiac glycosides

- For patients with non-digoxin glycosides, digoxin level may be used as a qualitative assay.
- A positive "digoxin level" may suggest the presence of a cardiac glycoside, but the exact level lacks clinical significance.
- The performance characteristics with different glycosides is largely unknown, but in the appropriate context this could help support the diagnosis of a non-digoxin cardiac glycoside intoxication.

decomntation

- Activated charcoal may be given if a patient presents within roughly an hour of an acute digoxin ingestion.
- By the time patients develop symptoms of digoxin toxicity, they will be outside the window of time when decontamination is beneficial.

digoxin-specific antibody fragments (DSFab)

.Optional note: Assess need for DSFab early and order promptly, because the time delay from ordering to clinical benefit is generally at least ~2 hours.
**Indications**

- Stronger indications:
  - Significant dysrhythmia or hemodynamic instability.
  - Potassium over 5-5.5 mEq/L (if hyperkalemia appears to be caused by an acute digoxin intoxication).
- Weaker indications:
  - Acute ingestion of >10 mg.
  - Moderate to severe GI symptoms.
  - Serum digoxin level >10-12 ng/ml drawn >6 hours after ingestion.
  - Renal failure.
  - Altered mental status.

- Most indications for DSFab are not well defined. When in doubt, consult a toxicologist or poison control (in the United States 1-800-222-1222).

**Potential complications from DSFab**

- Hypokalemia (due to potassium shifting into cells).
- Exacerbation of heart failure or atrial fibrillation, due to sudden withdrawal of digoxin therapy.
- Serum sickness.
- Anaphylaxis.

**Dose**

- Two brands are available, Digibind and DigiFab, which seem interchangeable.
- DSFab is dosed in vials. Each vial contain 40mg of antibody fragments, which neutralize 0.5 mg of digoxin.
- Formulae for calculating the number of vials required:
  - **Chronic poisoning**: Number of vials is estimated as (digoxin level in ng/ml)x(wt in kg)/100. However, lower doses may be considered initially, for patients with chronic digoxin toxicity who are clinically stable (e.g., initiate therapy with three vials and follow clinically to determine whether additional treatment is warranted).  
  - **Acute ingestion of known dose**: Number of vials is estimated as (mg of digoxin ingested)x(1.6)
  - **Empiric administration if levels are unknown**:
    - Acute toxicity: give 5 vials (if hemodynamically stable) or 10 vials (if unstable), reevaluate clinically in 30 minutes.
    - Chronic toxicity: start with 3-6 vials, reevaluate clinically.
  - **MDCalc online calculator** can also help to determine the number of vials of DSFab.
- Some clinical response should be seen within ~20 minutes, with a full response occurring within very roughly ~1.5-3 hours.
- DSFab may be effective in non-digoxin cardiac glycoside intoxication (e.g., plant or animal toxins). Digoxin levels in these situations are not quantitatively meaningful, so DSFab must be dosed empirically based on clinical severity. For patients with critical cardiac dysfunction, 10-20 vials may be utilized. Larger doses may be needed than for digoxin intoxication, since DSFab may have lower affinity for non-digoxin cardiac glycosides.

**Rebound**

- DSFab is generally excreted in the kidneys with a half-life of ~15-20 hours. Digoxin has a longer half-life (~40 hours). Therefore, it is possible that DSFab could be renally excreted and subsequently free digoxin levels could begin to rise again leading to rebound toxicity.
- Rebound can occur ~20 hours after DSFab is given, but it may occur up to ten days later in patients with renal dysfunction.
- The treatment of rebound is readministration of DSFab. The decision to treat must be based on symptoms and EKG findings, rather than digoxin levels (since digoxin levels will be unreliable after administration of DSFab).
hemodynamic stabilization

volume resuscitation

- Fluid should often be used carefully, because many patients on digoxin have severe underlying heart disease.
- Bedside echocardiography may help assess the potential benefit from fluid resuscitation.

bradycardia

- ⚠️ The best treatment is generally DSFab.
- **Atropine** is a good temporizing measure (since patients with digoxin toxicity have excess vagal tone). A reasonable dosing scheme might be to start with 1 mg and repeat as needed, to a maximum total cumulative dose of 3 mg. (26505271)
- Avoid pacing or beta-agonists if possible, as these may provoke ventricular tachycardia.

hypomagnesemia

- Hypomagnesemia may exacerbate digoxin toxicity (since magnesium is a cofactor in the Na/K exchange channel).
- Treat hypomagnesemia aggressively, particularly in patients who are having arrhythmias (more on this here).

hypokalemia

- Hypokalemia is a favorable prognostic sign, but it doesn't guarantee a good outcome (for example, the patient may have an independent disease process causing hypokalemia).
- **Hypokalemia may exacerbate digoxin toxicity**, so it must be treated aggressively (more on this here).
- If DsFab is administered, this may cause potassium to enter the cells – thereby exacerbating the hypokalemia. In severe hypokalemia, DsFab may be withheld initially, to prevent the development of severe hypokalemia (similar to the way an insulin infusion is initially withheld in a patient with diabetic ketoacidosis who is hypokalemic).

hyperkalemia

- Hyperkalemia is a poor prognostic sign. Among one series of patients with digoxin intoxication prior to the availability of DsFab, all patients with potassium levels above 5.5 mM died. (4715199)
- DsFab is the preferred treatment for hyperkalemia.
- Treatment of hyperkalemia may be initiated while awaiting DsFab, if hyperkalemia is believed to be causing clinical harm (e.g., contributing to AV block and bradycardia). (33476509)
- Treatment of hyperkalemia while awaiting DsFab may include the following:
  - IV insulin and glucose.
  - Isotonic bicarbonate fluid resuscitation.
  - Potassium-wasting diuretics plus crystalloid (to facilitate renal potassium excretion).
  - Oral potassium binder (sodium zirconium cyclosilicate).
  - More on the management of hyperkalemia here.
- Avoid treating hyperkalemia too aggressively.

https://emcrit.org/ibcc/dig/
In the context of digoxin intoxication, hypokalemia is more dangerous than mild hyperkalemia. Mild hyperkalemia could theoretically help drive potassium into cardiomyocytes via Na/K-ATPase, which could theoretically be beneficial (figure below).

- DSFab will cause a potassium shift into cells, so aggressive treatment of hyperkalemia plus DSFab could cause an overshoot hypokalemia.

- Calcium is contraindicated for the management of hyperkalemia due to severe digoxin intoxication.

- It's debated whether calcium is *safe* in this context, but there is no compelling evidence of *benefit* here, so calcium is probably best avoided.

![Diagram of calcium and potassium balance](https://emcrit.org/?attachment_id=480931)


To keep this page small and fast, questions & discussion about this post can be found on another page [here](https://emcrit.org/pulmcrit/hyperthermia/).

Going further:

- Tox & Hound: [To bind or not to bind?](https://emcrit.org/toxhound/bindornot/), By Jeanna Marraffa
- The Poison Review: [Treating digoxin toxicity: is less more?](http://www.thepoisonreview.com/2014/08/29/treating-digoxin-toxicity-is-less-more/)
- EMCrit RACC: [Can we place neck lines in digoxin toxicity?](https://emcrit.org/emcrit/can-we-place-neck-lines-in-digoxin-toxicity/)
references


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.