Chapter 193: Digitalis Glycosides

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INTRODUCTION

The medicinal benefits of cardiac glycosides have been recognized for centuries, and even with other alternative medications, digitalis preparations, such as digoxin, are still used for the treatment of atrial fibrillation and symptomatic congestive heart failure. In addition to availability as pharmaceuticals, cardiac glycosides are also found in plants such as foxglove, oleander, red squill, and lily of the valley. Similar cardioactive steroids are also found in the skin of toads in the Bufonidae family and in some herbal medications. Despite declining use of digoxin, the prevalence of patients diagnosed with digoxin toxicity has remained constant, and the use of digoxin-specific antibody fragments has increased. Digitoxin, a cardiac glycoside similar in structure to digoxin but with a longer half-life, is no longer commercially available in the United States, but is available in Canada and elsewhere in the world.

PATHOPHYSIOLOGY

Digoxin is a cardiac glycoside available for oral or intravenous use. Following oral absorption, digoxin reaches a maximal serum concentration 1 to 3 hours after ingestion. It is approximately 25% protein bound and has a large volume of distribution (6 to 7 L/kg). The drug is primarily eliminated through the kidneys.

Digoxin, like other cardiac glycosides, inhibits sodium-potassium ATPase. This inhibition results in increased intracellular sodium and increased extracellular potassium. As a result of the increased intracellular sodium, the sodium-calcium antiporter is not able to effectively remove calcium from the myocyte. Consequently, there is an increase in intracellular calcium, which augments inotropy. The increased intracellular calcium can contribute to delayed after-depolarizations, which may lead to premature ventricular contractions and dysrhythmias. In addition, there is a decreased refractory period of the myocardium, which increases automaticity and hence is associated with an increased risk of dysrhythmias. Furthermore, cardiac glycosides shorten atrial and ventricular repolarization, thereby decreasing the refractory period and thus increasing automaticity.

Cardiac glycosides also increase vagal tone via action at the carotid body, thereby reducing conduction through the sinoatrial and atrioventricular nodes. In toxic concentrations, cardiac glycosides can increase sympathetic tone. Digoxin can reduce plasma renin concentrations in patients with advanced heart failure,
thereby resulting in peripheral vasodilation. In contrast, in those without heart failure, digoxin can cause vasoconstriction. This difference is likely due to increased sensitivity of the carotid baroreceptors in patients with advanced, chronic heart failure.

**CLINICAL FEATURES**

Digoxin has a narrow therapeutic index, and toxicity results from an exaggeration of its pharmacologic activity. The timing and clinical presentation of acute versus chronic digoxin toxicity differ significantly (Table 193–1). In addition to cardiac manifestations such as syncope and dysrhythmia, digoxin toxicity may present with GI distress, dizziness, headache, weakness, malaise, delirium, or confusion. Thus, an elderly patient taking digoxin who presents with mental status changes should be evaluated for toxicity.

Table 193–1  
**Clinical Presentation of Digitalis Glycoside Toxicity**

<table>
<thead>
<tr>
<th></th>
<th>Acute Toxicity</th>
<th>Chronic Toxicity</th>
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<tbody>
<tr>
<td>Clinical history</td>
<td>Intentional or accidental ingestion</td>
<td>Typically elderly cardiac patients taking diuretics; may have renal insufficiency</td>
</tr>
<tr>
<td>GI effects</td>
<td>Nausea and vomiting, abdominal pain, anorexia</td>
<td>Nausea, vomiting, diarrhea, abdominal pain</td>
</tr>
<tr>
<td>CNS effects</td>
<td>Headache, dizziness, confusion, coma</td>
<td>Fatigue, weakness, confusion, delirium, and coma are often prominent features</td>
</tr>
<tr>
<td>Cardiac effects</td>
<td>Bradydysrhythmias or supraventricular tachydysrhythmias with atrioventricular block</td>
<td>Almost any ventricular or supraventricular dysrhythmia can occur; ventricular dysrhythmias are common</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>Hyperkalemia</td>
<td>Normal, decreased, or increased serum potassium, hypomagnesemia</td>
</tr>
<tr>
<td>Digoxin level</td>
<td>Marked elevation (if obtained within 6 h)</td>
<td>Minimally elevated or within &quot;therapeutic&quot; range</td>
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</table>

**ACUTE TOXICITY**
Patients with acute digoxin toxicity tend to have more abrupt onset of symptoms than those with chronic toxicity. In acute cardiac glycoside poisoning, there may be an asymptomatic period of several hours before the onset of symptoms. GI symptoms, such as nausea, vomiting, anorexia, and vague abdominal pain, are often the earliest manifestations of acute toxicity. Increased central vagal tone typically produces cardiac manifestations such as bradydysrhythmias or atrioventricular block. Neurologic manifestations such as weakness or confusion can occur independently of the blood pressure. The classic description of digoxin toxicity includes viewing yellow-green halos around objects, termed xanthopsia. However, patients more frequently describe nonspecific changes in their color vision.\(^7\)

Hyperkalemia is an important finding in acute toxicity and may develop due to inhibition of sodium-potassium ATPase. Digoxin levels obtained with the first 6 hours following an acute ingestion may be falsely elevated as the level represents a predistribution level rather than reflecting the amount ingested. **Overall, the severity of acute toxicity correlates most closely with the degree of hyperkalemia and correlates poorly with the early serum digoxin levels.**\(^8\)

**CHRONIC TOXICITY**

Chronic toxicity occurs most typically in the elderly and is often the result of drug–drug interactions or declining renal function. Some of the more common drug interactions that predispose to chronic digoxin toxicity include calcium channel antagonists, amiodarone, β-receptor antagonists, diuretics, indomethacin, clarithromycin, quinidine, procainamide, and erythromycin. In particular, interaction between digoxin and clarithromycin contributes to increased hospitalizations for digoxin toxicity in elderly patients.\(^9\) A common scenario involves a patient starting to take a diuretic, which results in mild dehydration and hypokalemia; dehydration reduces the clearance of digoxin, and hypokalemia increases susceptibility to digoxin, resulting in chronic toxicity.

Decreases in renal function and lean body mass associated with aging may alter the pharmacokinetics of digoxin, leading to toxicity at normally therapeutic doses.\(^10\) This population may also possess a higher risk due to coexisting diseases and polypharmacy.\(^10,11\)

The patient with chronic digoxin toxicity often has vague and nonspecific signs and symptoms compared to the patient with acute digoxin toxicity. GI symptoms may occur but may be less pronounced. **Neurologic manifestations, such as weakness, fatigue, confusion, or delirium, are more prominent features in chronic toxicity.**\(^6,12\)

**DIAGNOSIS**

The diagnosis of digoxin toxicity is a composite picture, using history, physical examination, and laboratory studies; no single element excludes or confirms the diagnosis. In patients with heart failure and normal renal function, daily digoxin doses are usually between 125 and 250 micrograms. Digoxin toxicity can occur with a...
single ingestion of 1 to 2 milligrams in an adult, and fatalities have been reported following an acute ingestion of 10 milligrams in an adult and 4 milligrams in a child.

Differential diagnosis includes other toxins that may induce bradydysrhythmias such as calcium channel antagonists, β-receptor antagonists, class IA antidysrhythmics (procainamide and quinidine), class IC antidysrhythmics (flecainide and encainide), clonidine and other imidazolines, and organophosphate or carbamate insecticide poisoning. Glycoside-containing and other cardiotoxic plants should also be considered (e.g., foxglove, squill, lily of the valley, oleander, rhododendron, monkshood, tobacco, false hellebore, and yew berry). Sick sinus syndrome, with its combination of supraventricular dysrhythmias and cardiac conduction blocks, can also mimic digoxin toxicity. Hyperkalemia from any cause may produce bradycardia and abnormal cardiac conduction and should be considered in the differential diagnosis.

**ELECTROCARDIOGRAM**

Almost any cardiac dysrhythmia may be observed in digoxin toxicity, with the exception of rapidly conducted atrial dysrhythmias. The most common dysrhythmia in digoxin toxicity is premature ventricular contractions. Ventricular dysrhythmias occur more frequently in chronic than in acute poisonings. Although rare and not pathognomonic for digoxin toxicity, bidirectional ventricular tachycardia should be investigated for possible toxicity because only a few xenobiotics are known to produce this unique dysrhythmia, digoxin included.

Four specific electrocardiographic findings are seen with therapeutic levels of digoxin and are not indicators of toxicity, although they may also be seen in poisoned patients. These findings include T-wave changes such as flattening or inversion, QT-interval shortening, a "scooped" appearance of the ST segment with ST-segment depression, and an increase in U-wave amplitude (Figure 193–1).

**FIGURE 193–1.**
ECG demonstrating findings seen with digoxin use. A. ECG shows scooping of ST segments and small U waves with a serum digoxin level of 0.9 nanogram/mL (1.15 nmol/L). B. ECG shows scooping of ST segments, flattening of T waves, and first-degree atrioventricular block with a serum digoxin level of 1.2 nanograms/mL (1.54 nmol/L).
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LABORATORY

In acute poisonings, the serum potassium and digoxin levels can provide useful diagnostic information. As noted, acute poisoning of the sodium-potassium ATPase pump may result in markedly elevated serum
potassium levels, and the serum potassium level is a better indicator of end-organ toxicity and a better prognostic indicator than the serum digoxin level in this circumstance.

With chronic toxicity, in contrast to acute poisoning, the serum potassium and digoxin levels are less diagnostic. In these patients, the serum potassium is usually normal or low due to concomitant diuretic therapy, but may be elevated due to renal insufficiency. Thus, in the setting of chronic toxicity, measured serum potassium is more reflective of underlying comorbidities than the degree of inhibition of sodium-potassium ATPase by digoxin. Also, the serum digoxin level does not correlate with the clinical manifestations and may be within therapeutic ranges despite significant cardiac toxicity.

Serum digoxin levels should be interpreted in the overall clinical context and not relied upon as the sole indicator of the presence or absence of toxicity. Generally accepted therapeutic digoxin levels are 0.5 to 2.0 nanograms/mL (1.0 to 2.6 nmol/L), with corresponding toxic levels above 2.5 nanograms/mL (above 3.2 nmol/L). Due to a relatively slow distribution phase, high digoxin levels sampled from the serum following a recent acute ingestion are not always an accurate indicator of concentration at receptor sites. Serum levels are most reliable when obtained 6 hours after ingestion, when distribution is complete. However, given the preceding limitations, it is still common that the higher the serum level, the greater is the likelihood of toxicity.

Importantly, the serum digoxin level should not be the sole factor in establishing the diagnosis of digoxin toxicity, so do not wait for a digoxin level before implementing therapy in an unstable patient.

Digoxin-like immunoreactive substances are substances that can be found in certain individuals that cross-react with the digoxin assay, artificially elevating the serum digoxin level, even in the absence of cardiac glycosides. Digoxin-like immunoreactive substances may be found in neonates, third-trimester pregnant women, patients with subarachnoid hemorrhage, and patients with renal or hepatic dysfunction. In addition, naturally occurring cardiac glycosides and cardioactive steroids from plants and animals may cross-react with digoxin assays. The degree of cross-reactivity is variable, and no reproducible correlation has been established between serum levels of these substances and toxicity.

TREATMENT

Management of a digoxin-poisoned patient includes general supportive care, treatment of specific complications of toxicity, prevention of further drug absorption, enhancement of drug elimination, antidote administration when indicated, and safe disposition (Table 193–2). Although patients with intentional or accidental ingestions may present with no symptoms, life-threatening complications of toxicity should be anticipated. Management of the asymptomatic patient should focus on preventing drug absorption and closely monitoring for the development of toxicity. Continuous cardiac monitoring, IV access, and frequent reevaluations should be provided for any patient with a potentially toxic ingestion of digoxin.
### Asymptomatic patients
- Obtain accurate history
- Secure IV access
- Initiate continuous cardiac monitoring
- GI decontamination: activated charcoal, 1 gram/kg PO, can be considered in an awake, alert, cooperative patient who presents within 1 h of ingestion
- Frequent reevaluation

### Symptomatic patients
- Obtain accurate history
- Secure IV access
- Initiate continuous cardiac monitoring
- GI decontamination: activated charcoal, 1 gram/kg PO, in an awake, alert, cooperative patient who presents within 1 h of ingestion

#### Bradydysrhythmias
- Atropine: 0.5–1.0 milligram IV as a temporizing measure for bradydysrhythmias while awaiting digoxin-specific Fab antibodies
- Transcutaneous pacing while awaiting digoxin-specific Fab antibodies for symptomatic bradycardia that does not respond to atropine
- Digoxin-specific antibody fragments: IV infusion (see discussion below for dose)

#### Cardiac arrest
- CPR with current advanced cardiac life support protocols
- Digoxin-specific antibody fragments: IV bolus (5–10 vials if amount ingested is unknown)

For the patient with life-threatening dysrhythmias, identify and rapidly correct conditions such as hypoxia, hypoglycemia, hypovolemia, and electrolyte abnormalities. IV magnesium may counteract ventricular irritability seen with cardiac-glycoside toxicity. Use atropine and/or transvenous cardiac pacing as a temporizing treatment for bradydysrhythmias while preparing or obtaining digoxin-specific antibody fragments.

Digoxin-specific antibody fragments (digoxin-Fab) are the treatment of choice in acute poisoning with hyperkalemia (potassium >6.0 mEq/L) and in acute or chronic toxicity with any life-threatening dysrhythmia. Hyperkalemia is not typically the cause of the death; it is a predictor of severe poisoning and increased mortality. Treatment of digoxin-induced hyperkalemia with insulin, dextrose, sodium bicarbonate, or exchange resins does not reduce mortality.
Administration of calcium salts in cardiac glycoside–induced hyperkalemia is controversial. Older literature indicated an increased incidence of ventricular dysrhythmias and a higher mortality when calcium was administered to digoxin-toxic patients. However, data from an animal model and retrospective review of a limited number of human patients with digoxin toxicity who received IV calcium found no increase in ventricular dysrhythmias or mortality.\textsuperscript{23,24,25} In summary, hyperkalemia in acute digoxin poisoning indicates severe toxicity and digoxin-Fab should be given to reduce mortality.

In chronic toxicity, hypokalemia and hypomagnesemia should be corrected, because both predispose to digoxin toxicity.

**GI DECONTAMINATION AND ENHANCED ELIMINATION**

Administering activated charcoal may have utility in early acute ingestion of digoxin.\textsuperscript{22} Activated charcoal may be of benefit following the acute ingestion of yellow oleander, although results of large, randomized trials have been mixed.\textsuperscript{26} Gastric lavage is not recommended; asystole has been reported in a digoxin-toxic patient, presumably from vagal stimulation during lavage, and no clinical benefit has been demonstrated. Cathartics, forced diuresis, hemodialysis, and hemoperfusion have no role in enhancing elimination of digitalis glycosides. In patients with chronic renal failure who develop digoxin toxicity, there are limited data for the use of binding resins such as cholestyramine to help enhance elimination.\textsuperscript{27,28}

**DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS (DIGOXIN-FAB)**

Digoxin-Fab are derived from ovine antibodies to digoxin. Following IV infusion, the antibody fragments bind digoxin in the plasma and distribute widely throughout the body, removing digoxin from tissues. In severely poisoned patients after digoxin-Fab administration, 90\% will show reversal or significant improvement in life-threatening dysrhythmia; in most cases, clinical improvement occurs within 1 hour. Patients in cardiac arrest had a 50\% survival when receiving digoxin-Fab during the resuscitation, which is significantly better than historical survival with treatment with conventional therapies.\textsuperscript{20} Because of cross-reactivity with other cardiac glycosides, digoxin-Fab are also beneficial in treating digitoxin, foxglove, and oleander poisonings, although large doses have sometimes been required.\textsuperscript{17,26} Indications for digoxin-Fab are life-threatening dysrhythmias (including hemodynamically significant bradydysrhythmias unresponsive to standard therapy) and hyperkalemia in excess of 6 mEq/L associated with acute poisoning.

Digoxin-Fab administration is associated with few adverse effects.\textsuperscript{20,21} Cardiogenic shock has been reported in patients dependent on digoxin for inotropic support.\textsuperscript{29} In addition, ventricular response to atrial fibrillation may be increased. Hypokalemia may develop rapidly as digoxin toxicity is reversed. Mild, acute hypersensitivity reactions, including rash, flushing, and facial swelling, have been reported. No incidences of serum sickness or anaphylaxis have been observed, even in patients with repeated administration.\textsuperscript{29} Skin testing has not proven to be useful in predicting allergic responses and may delay urgently needed
Failures to digoxin-Fab therapy have been attributed to inadequate dosing, moribund state before administration, and incorrect diagnosis of digoxin toxicity.

A full neutralizing dose of digoxin-Fab is based on an estimation of the total-body load of digoxin, which can be calculated from either the dose ingested or a steady-state serum digoxin level (Table 193–3). In an acute poisoning, each vial of digoxin-Fab reverses approximately 0.5 milligram of ingested digoxin. In hemodynamically stable patients, half the calculated full neutralizing dose is infused, and the other half is given if an adequate clinical response is not seen in 1 to 2 hours. Observational studies report that a total of 200 to 480 milligrams of digoxin-Fab (5 to 12 vials) were required to effectively treat severely digoxin-toxic patients. When the ingested dose is unknown and serum level is unavailable, 10 vials are recommended as initial treatment in life-threatening situations. Digoxin-Fab are administered IV through a 0.22-mm filter over 30 minutes, except in cardiac arrest, when the dose is given as an IV bolus.

Table 193–3

<table>
<thead>
<tr>
<th>Calculation of Digoxin-Specific Antibody Fragment Full Neutralizing Dose</th>
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<tbody>
<tr>
<td><strong>Based on suspected amount ingested</strong></td>
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<tr>
<td>Digoxin body load (milligrams) = 0.8 × suspected ingested amount (milligrams)*</td>
</tr>
<tr>
<td>Digoxin body load (milligrams) = serum digoxin concentration (nanograms/mL) × 5.6 L/kg × weight (kg)/1000</td>
</tr>
<tr>
<td>One vial (about 40 milligrams) of digoxin-Fab neutralizes 0.5 milligram of digoxin ingested</td>
</tr>
<tr>
<td><strong>Based on total serum digoxin concentration</strong></td>
</tr>
<tr>
<td>Number of vials = serum concentration (nanograms/mL) × patient weight (kg)/100</td>
</tr>
</tbody>
</table>

*0.95 should be used instead of 0.8 if the preparation is an elixir or gel tablet; 1 should be used if the cardiac glycoside is digitoxin.

Calculations of a full neutralizing dose may overestimate the amount of digoxin-Fab necessary, and smaller doses may adequately eliminate digoxin from the central compartment. An alternative approach in acute poisoning with a hemodynamically stable patient is to give an 80-milligram (two vials) bolus of digoxin-Fab, evaluate the effect, and repeat the dose every 30 to 60 minutes as necessary until dysrhythmias have resolved and potassium has normalized. Such a protocol may reverse toxicity with less than half of a calculated full neutralizing dose.

In chronic toxicity, an acceptable approach in the hemodynamically stable patient is to give a 40-milligram (one vial) bolus of digoxin-Fab and repeat after 1 hour if the patient is still symptomatic. One to three vials (40 to 120 milligrams) of digoxin-Fab are often adequate in reversing chronic toxicity.
Total serum digoxin levels obtained following digoxin-Fab administration have little correlation with clinical toxicity. Because most laboratory assays do not distinguish between antibody-bound and unbound digoxin, total serum levels obtained following digoxin-Fab administration may increase 10- to 20-fold. However, because the Fab-digoxin complex is not pharmacologically active, this increased level does not correlate with clinical toxicity. The Fab-digoxin complex is eliminated by renal excretion.

In the presence of renal failure, the Fab-digoxin complex may persist in the circulation for prolonged periods. Recurrent toxicity can occur up to 10 days after digoxin-Fab administration in patients with renal failure as the complex degrades. Due to the large molecular weight of the Fab-digoxin complex (45,000 to 50,000 Da), hemodialysis does not enhance its elimination, although plasma exchange may be of benefit. New liver support devices incorporating albumin-based dialysis and plasma filtration would be expected to be able to clear the Fab-digoxin complex on the basis of molecular weight alone; some devices have been reported to clear substances up to 100 kDa. However, there is no experience using this technique with digoxin-poisoned patients.

DISPOSITION AND FOLLOW-UP

Extended observation with serial digoxin and potassium levels is recommended for anyone with a confirmed acute ingestion. Asymptomatic patients should be observed until the serum digoxin level is decreasing on serial measurements and the potassium level has remained normal. Patients with signs of toxicity or a history of a large (>6 milligrams in an adult) ingested dose should be admitted to a monitored unit. Consultation with a medical toxicologist or the regional poison control center is recommended. Patients receiving digoxin-Fab require intensive care unit observation for 6 to 12 hours. Patients in renal failure who receive digoxin-Fab may be at risk of delayed toxicity, as the Fab-digoxin complex can dissociate several days later. Finally, patients with suspected suicidality should undergo behavioral health or psychiatric evaluation before discharge.

REFERENCES


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