

Digoxin Toxicity: Regaining a Level of Control

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CardioCase presentation

Rhonda's Regimen



Rhonda, 57, presents to the emergency department (ED) after two days of feeling unwell, including a 12-hour history of non-specific chest pain, nausea, and dizziness.

She has a history of anorexia and complains of occasional

diaphoresis. Her past medical history is significant for atrial fibrillation (AF) and hypertension.

Her medications include ramipril, digoxin, and coumadin.

**What is your interpretation of the echocardiogram (ECG, Figure 1)?
How should the ED manage Rhonda?**

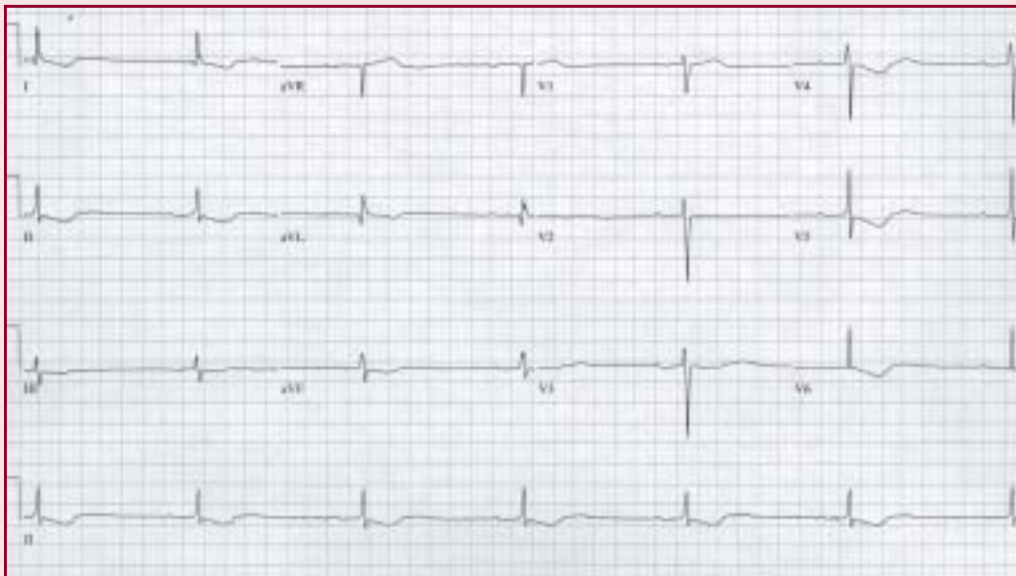


Figure 1. Rhonda's ECG.

What's Your CardioCase Diagnosis?

CardioCase *discussion*

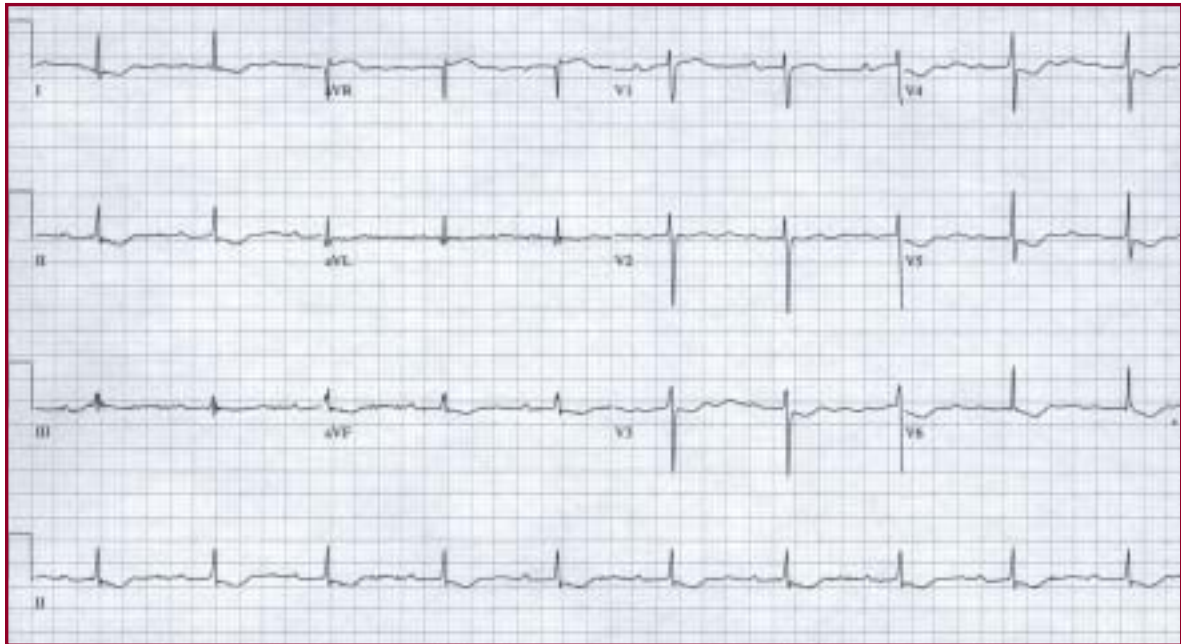


Figure 2. ECG 24 hours after administering digibind.

What’s Rhonda’s diagnosis?

Rhonda’s ECG shows coarse atrial fibrillation (AF) with a wide, complex, regular escape rhythm and a left bundle branch block pattern. The presence of a supraventricular dysrhythmia, with aortic valve (AV) nodal blockade and ST depression in the lateral leads, is highly suggestive of digoxin toxicity.

On further history, it was discovered Rhonda started verapamil a week ago to treat the hypertension. She also described classic symptoms of impaired colour perception over the last 48 hours. Her digoxin level was 5.7 ng/mL, potassium was 7.8 meq/L, and creatinine was 150 µmol/L.

About the authors

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Table 1

Predisposing factors to digoxin toxicity

Conditions that increase total body digoxin

- Medications
 - Cardiac (verapamil, amiodarone, quinidine)
 - Antibiotics (erythromycin, clarithromycin)
- Renal failure
- Inappropriate dosing (large weight, but low muscle mass)

Conditions that increase cardiac sensitivity to digoxin

- Cardiac diseases:
 - Active cardiac ischemia
 - Myocarditis
 - Cardiac amyloid
 - Cor pulmonale
- Old age
- Metabolic disturbances (hypokalemia, hypomagnesemia, hypercalcemia)

Table 2

Generalized approach to digoxin toxicity

General principles in digoxin intoxication	Agents to be administered	Special considerations in digoxin toxicity
Gastrointestinal decontamination	Gastric lavage	Be cautious of vagal stimulation worsening bradycardia
Decreased absorption	Charcoal Cholestyramine may be considered	Repeated doses may be given; Charcoal shown to be safe
Bradycardia	Atropine may be effective but may need transvenous pacing	Avoid Isoproterenol, may be pro-arrhythmogenic
Hypokalemia	Correct with potassium	Cautious potassium supplementation necessary as hyperkalemia may worsen aortic valve blockade
Hyperkalemia	Treat aggressively as increases risk of mortality	Calcium as cardioprotective agent contra-indicated
Antidote	Digoxin-specific antibodies, fab fragments (<i>i.e.</i> , digibind)	Digoxin levels post digibind therapy cannot be used to monitor progress

Rhonda was given digibind and her potassium was treated with conventional anti-potassium therapy without the use of calcium chloride. Twenty-four hours after treatment of hyperkalemia, sinus rhythm returns and the ventricular escape rhythm is no longer present (Figure 2). Rhonda was discharged after 48 hours of observation and was advised not to take verapamil again.

Delving deeper into digoxin

Thanks to a better understanding of the pharmacokinetics of digoxin, as well as an appreciation of drug interactions that lead to higher serum digoxin levels, the overall incidence of definite digoxin toxicity has significantly decreased from 40% to < 1%.

Originally reported in 1785 by Sir William Withering, digoxin inhibits the membrane-bound Na-K-ATPase transport, causing the intracellular

loss of potassium and gain of sodium and calcium. Its cardiovascular effects include increased contractility and AV nodal blockade. Because its action depends on tissue concentration, plasma levels can be used to monitor compliance and toxicity. Since skeletal muscle is the major depot for digoxin, the likelihood of toxicity is related to muscle mass rather than total body weight. Renal failure, cardiac diseases, and age can also be precipitants of digoxin toxicity (Table 1).

Overall incidence of digoxin toxicity has dropped from 40% to < 1%.

It is important to note that although hypokalemia predisposes to digoxin toxicity, a massive overdose can lead to hyperkalemia.

Although a toxic dose is not well established, an acute ingestion of < 5 mg by a healthy digoxin-naïve adult is unlikely to result in life-threatening toxicity. In contrast, patients on chronic digoxin therapy for heart disease may become toxic after ingesting > 2 mg.

How does digoxin toxicity present?

Clinical manifestation of digoxin toxicity are often nonspecific, including:

- neurologic symptoms (*i.e.*, blurred vision, impaired color perception, confusion, and delirium);
- gastrointestinal (GI) symptoms (*i.e.*, anorexia, nausea, vomiting, and diarrhea); and
- conduction abnormalities.

In a retrospective look at patients diagnosed with definite digoxin toxicity, Williamson *et al* found the most common ECG findings to be:

- heart block (33%),
- bradycardia (24%),
- junctional tachycardia (15%), and
- AF (12%).²

Ingesting > 2 mg may be toxic for patients on chronic digoxin therapy.

One of the most suggestive ECG features is the presence of underlying AF with a regular junctional or ventricular escape rhythm.

Steady state therapeutic serum digoxin levels range from 0.5 ng/mL to 2.0 ng/mL; however, cardiotoxicity has been reported within the therapeutic range, particularly in patients with

Table 3

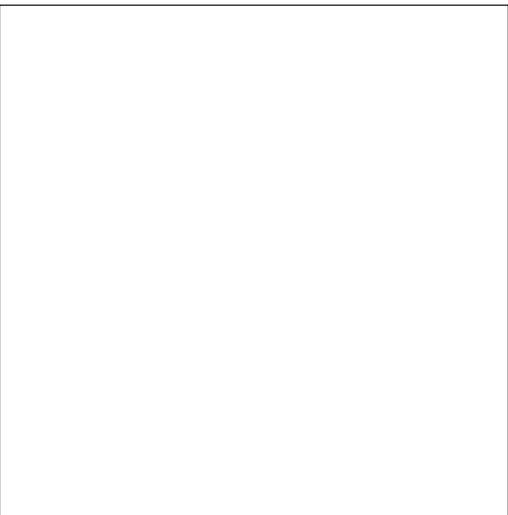
Indications for digibind

- Serum digoxin level > 12.8 nmol/L (10 ng/mL) in acute ingestion
- An acute ingestion of > 10 mg in adult
- Serum potassium > 5.0 mmol/L (4.0 mEq/dL) in acute ingestion
- Life threatening cardiotoxicity:
 - Ventricular dysrhythmia
 - Progressive bradycardia
 - Second or third degree block not responsive to atropine

chronic therapy. Unless there is concomitant hypokalemia, toxicity is defined as serum digoxin levels > 2 ng/mL, along with accompanying symptoms, and a suggestive ECG. False positive elevations have been reported in neonates, children, during pregnancy, renal failure, and in patients taking large doses of steroids. Only serum digoxin levels taken at least six hours after the last oral digoxin dose are interpretable.

How is it treated?

Although a general approach to intoxication is necessary when managing digoxin toxicity, particular attention should be paid to some of digoxin's cardiovascular effects (Table 2). When con-



sidering GI decontamination, take caution to avoid vagal stimulation which may worsen existing conduction block. Charcoal is effective and safe if ingestion has occurred within six to eight hours. Metabolic derangements, particularly hypokalemia, should be corrected.

Acutely intoxicated patients may present with severe hyperkalemia requiring therapy with insulin and bicarbonate. Administering calcium as a cardio-protective agent is generally not recommended in this setting. Severe bradyarrhythmias can be treated with atropine, 0.5 mg to 2 mg, but intravenous pacing may be necessary.

Antidote therapy is available for digoxin toxicity. Digibind, a digoxin-specific antibody,

rapidly binds to the pharmacologically active extracellular circulating digoxin resulting in a favorable concentration gradient for the efflux of digoxin out of cells. Indications for this antidote are illustrated in Table 3.

The plasma potassium concentration, which begins to decline within one hour, is complete within four hours. Potential side-effects of this therapy include:

- congestive heart failure,
- increased ventricular response in AF patients, and
- hypokalemia.

It takes four hours for complete plasma potassium concentration.

It is important to remember that plasma digoxin measurements are unreliable for one to two weeks after fragment therapy because of interference with conventional assay. Although of limited use in digoxin removal, hemodialysis or hemoperfusion can help control hyperkalemia or volume overload in patients with concurrent renal failure. 