Too Much of a Good Thing: Digitalis Toxicity

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PRESENTATION
Never underestimate a patient’s willingness to alter the prescribed therapeutic plan. A 79-year-old man with a history of permanent atrial fibrillation was brought to the emergency department after 3 days of severe nausea and nonbloody/nonbilious emesis. He also reported a decrease in urine output, extreme fatigue, and worsening blurry vision with “flashing white lights.” Eighteen days prior to his presentation, he had a pharyngeal cyst removed and tracheostomy and gastrostomy tubes were placed. Postoperatively, his digoxin formulation was changed from tablet to an equivalent dosage of liquid preparation. He was discharged on postoperative day 8.

ASSESSMENT
On presentation, the patient’s heart rate was 47 beats per minute, and his blood pressure was 121/87 mmHg. Other vital signs were normal. He appeared cachectic, his mucous membranes were dry, and the jugular venous pulse could not be visualized. Cardiac examination revealed irregularly irregular bradycardia without murmurs, rubs, or gallops. The remainder of the examination was normal. His admission electrocardiogram (ECG) showed an accelerated junctional rhythm (Figure 1). A repeat ECG obtained 4 hours later (Figure 2) disclosed atrial fibrillation with a slow ventricular response (~40 beats per minute). His admission creatinine was elevated to 1.60 mg/dL compared to the postsurgical 1.27 mg/dL measured 10 days earlier. In addition, his blood urea nitrogen was elevated to 51 mg/dL from a postsurgical 36 mg/dL. His serum potassium level on presentation was 4.4 mEq/L.

DIAGNOSIS
The patient’s history of atrial fibrillation, recent changes in his digoxin formulation, and signs and symptoms of nausea and vomiting, vision changes, bradycardia, junctional rhythm, and renal insufficiency, indicated digitalis toxicity. In fact, his serum digoxin level was >6.1 ng/mL (reference range, 0.8–2.4 ng/mL), the maximum obtainable by our laboratory. On further questioning, the patient revealed that he had self-adjusted the amount of digoxin elixir, as he thought the dosage prescribed to him was inadequate. He had been prescribed 2.5 mL of digoxin elixir, 0.05 mg/mL, daily, a dosage equivalent to his prior oral dosage of 125 mcg daily. However, after his discharge from the hospital 10 days earlier, the patient had doubled his dosage to 5 mL of digoxin elixir daily.

Originally described by Sir William Withering in 1785 for the treatment of “dropsy,” digitalis, a cardiac glycoside, is one of the oldest cardiac medications still in wide use.1 Until several decades ago, it was a therapeutic mainstay for the treatment of heart failure and supraventricular arrhythmias. However, it has a narrow therapeutic window and variable pharmacokinetics. Of note, the bioavailability of digoxin, the most commonly used digitalis product, changes with the formulation and route of administration: oral tablets, 70%; elixir, 80%; oral capsules, 90%, and intravenous solution, 100%.2 This inconsistency in bioavailability can affect serum digitalis concentrations and lead to relatively mild adverse effects or as in our patient, life-threatening toxicity.

Digitalis toxicity has a variety of presentations, depending on the duration of drug ingestion and the patient’s serum level. Arrhythmias, which can be spurred by acute or chronic toxicity, are the most common cardiac manifestations. Bradyarrhythmias, such as atrioventricular block, can be caused by vagal stimulation, or like sinus-atrial exit block, from a direct drug effect.3,4 Junctional rhythm is common as an escape mechanism in the
presence of complete heart block. Enhanced atrial automaticity can lead to tachyarrhythmias, such as atrial tachycardia. While the foregoing rhythm disturbances are nonspecific with numerous causes, junctional tachycardia and bidirectional ventricular tachycardia strongly suggest digitalis toxicity.

About 80% of patients with acute toxicity present with anorexia, nausea, emesis, and fatigue. Cardiac toxicity peaks at about 3-6 hours after overdose. Chronic digitalis toxicity usually has an insidious onset over days to weeks. In contrast to acute toxicity, neurologic manifestations such as confusion, disorientation, and fatigue are more frequent. As exemplified by our patient, visual changes, such as halos, flashing lights, and xanthopsia (changes in color vision), can occur. Severe digitalis toxicity can cause extensive Na/K-ATPase inhibition in skeletal muscle, leading to marked hyperkalemia; and the degree of hyperkalemia directly correlates with mortality.

**MANAGEMENT**

Our patient was admitted initially for supportive care. However, atrial fibrillation with slow ventricular response (36 beats per minute) persisted with intermittent junctional bradycardia (25 beats per minute). Digoxin-specific antibody fragments were administered intravenously. The drug binds to free digoxin, forming a digoxin-immune fragment complex that is excreted renally. Approximately 15 hours after administration of 3 vials of digoxin-specific antibody fragments, the patient’s ventricular rate had

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**Figure 1** The patient’s admission electrocardiogram (ECG) showed an accelerated junctional rhythm.

**Figure 2** A repeat ECG obtained 4 hours later revealed atrial fibrillation with a slow ventricular response (40 beats per minute).
increased to about 65 beats per minute in atrial fibrillation, and his visual changes and nausea had resolved.

All patients with digitalis toxicity require supportive care. The manifestations usually dissipate with discontinuation of the drug. Rarely, as in our patient, digoxin-specific antibody fragments are required for management of severe toxicity. Indications for treatment are life-threatening arrhythmias, severe bradycardia unresponsive to atropine, evidence of end-organ damage, and marked hyperkalemia. Administration can also be considered for serum digoxin levels greater than 6.0 ng/mL or an acute overdose of 10 mg in adults. Knowledge of the signs, symptoms, and ECG indications of digitalis toxicity is vital for prompt diagnosis and treatment. In 2007, over 2,500 cases of cardiac glycoside exposure were reported to United States poison control centers. Physicians should be vigilant when prescribing drugs that have a narrow therapeutic index, especially when changing the formulation, and patients should be well-educated regarding any alteration in their drug formulation.

References