CLINICAL VIGNETTE

Digoxin Toxicity Presenting as "Stomach Upset" and "Fatigue"

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Case Report

An 81-year-old female presented to her primary medical doctor for a routine follow up with symptoms of "the stomach flu" and "fatigue". She reported 2 - 3 days of feeling sick to her stomach with associated nausea, poor PO intake and severe fatigue. She denied vomiting, diarrhea and constipation. She has an extensive cardiac history including atrial fibrillation on anti-coagulation and digoxin, diastolic and systolic heart failure, coronary artery disease, and hypertension. Cardiac medications included digoxin, Apixaban, diltiazem, carvedilol, and atorvastatin. Other medications included levothyroxine and famotidine.

Vital signs were as follows:

BP: 119/72
Pulse: 38 - 66
Resp: 18
Temp: 36.5 °C (97.7 °F)
Weight 99 lb (44.9 kg)
SpO2 98% on RA
BMI 17.54 kg/m2

On physical exam she appeared to be thin but in no acute distress. Heart sounds were bradycardic and irregularly irregular with no significant murmurs, rubs, or gallops. JVP was flat. Lung sounds were clear to auscultation bilaterally. Extremities were warm and well perfused with no edema. Abnormal findings included bilateral injected conjunctiva, dry mucous membranes, and bradycardic irregularly irregular rhythm.

Labs included Na 136 mmol/L, K 4.2 mmol/L, and creatinine of 1.4 mg/dL (baseline 1.0 mg/dL) Digoxin level was 2.9. Chest x-ray showed no acute pulmonary findings. EKG demonstrated atrial fibrillation with slow ventricular response at 36 bpm and she was admitted to the ICU with symptomatic bradycardia, acute kidney injury due to dehydration, and digoxin toxicity. She was given Digoxin Immune Fab (Digibind) and placed on a dopamine drip to stabilize her heart rate. During her hospitalization, she had episodes of tachycardia as well as bradycardia. Electrophysiology was consulted and placed a permanent pacemaker.

Discussion

Background Information and Mechanism of Toxicity

Digitalis purpurea is a cardiac glycoside derived from the foxglove plant and was discovered in 1785.[1] Digoxin is still widely used over 200 years later for atrial fibrillation, particularly in patients with systolic congestive heart failure, as it is the only oral cardiac inotrope that does not increase mortality in these patients.[1] The mechanisms of action of digoxin are two-fold: 1) inhibit the sodium-potassium-ATPase[2] and 2) increase vagal tone.[3] By increasing intracellular sodium, calcium expulsion is decreased from the myocyte, thereby increasing intracellular calcium which leads to increased inotropy as well as delayed after-depolarizations which can trigger dangerous arrhythmias. Digoxin increases vagal tone which then decreases conduction through the sinoatrial and atrioventricular nodes.[3] Digoxin also decreases the myocardial refractory period and by doing so, increases the risk of arrhythmias by increasing automaticity.[4]

Digoxin has a narrow therapeutic window and unfortunately, digoxin toxicity is common. It has been reported to occur in up to 35% of patients on digoxin.[5] Digoxin is excreted through the kidneys; therefore impairment in renal function can lead to higher plasma concentrations. Renal failure, congestive heart failure, and advanced age can contribute to toxicity by reducing the volume of distribution of the medication. Electrolyte abnormalities such as low potassium, phosphate, or calcium can worsen digoxin toxicity. Certain medications such as amiodarone and calcium channel blockers can increase plasma digoxin levels.

Clinical Features of Digoxin Toxicity

The most common non-cardiac symptoms of digoxin toxicity include anorexia, nausea, vomiting, confusion, headaches, lethargy, and more rarely visual changes. Cardiac manifestations of digoxin toxicity include any type of heart block, brady-arrhythmia, or tachy-arrhythmia.[5] Digoxin toxicity can present as virtually any tupe of arrhythmias except for rapidly conducted atrial arrhythmias.[4] Cardiac toxicity is the most concerning in both acute and chronic toxicity.

Chronic toxicity is often difficult to diagnose as symptoms are insidious. Gastrointestinal symptoms are less dramatic that in acute toxicity. Neurologic symptoms, such as confusion, fatigue, lethargy, weakness, and disorientation may be more

prominent in chronic toxicity. Visual symptoms of digoxin toxicity can include color changes (specifically objects appearing yellow), photophobia, scotomas, or even blindness.[6]

Evaluation of Digoxin Toxicity

The diagnosis of digoxin toxicity is based on clinical and EKG manifestations. It is not based on a serum digoxin concentration because there is a marked overlap of measured plasma levels in patients with and without digoxin toxicity.

A digoxin concentration should be obtained on presentation and approximately 6 hours after ingestion for an acute overdose.[6] The serum digoxin concentration does NOT necessarily correlate with digoxin toxicity; however levels are used to determine the dosing of treatment with antibody (Fab) fragments.

History should include timing of ingestion and information about acute illnesses, such as gastroenteritis, that could lead to dehydration and acute kidney injury, and therefore contribute to toxicity. Medication reconciliation should be performed to evaluate for medications that can increase serum digoxin concentrations, such as verapamil and amiodarone.

Laboratory assessment should also include electrolytes and renal function. Hyperkalemia, due to an inhibition of the sodium-potassium ATPase, is an important marker and the degree of hyperkalemia correlates with mortality.[7] Hypokalemia is a greater concern in chronic toxicity. Low potassium, magnesium and calcium levels increase patient susceptibility to digoxin toxicity.[5]

Continuous telemetry and serial electrocardiograms are recommended since digoxin toxicity can produce a range of arrhythmias and these may evolve rapidly. Premature ventricular contractions are the most common arrhythmias caused by digoxin toxicity.[2] Digoxin toxicity can also present as bradycardia, atrial tachyarrhythmias with AV block, junctional rhythms, ventricular bigeminy, AV nodal blockade, ventricular tachycardia, and ventricular fibrillation. Digoxin is one of the few causes of bidirectional ventricular tachycardia.[6]

Treatment of Digoxin Toxicity

Initial assessment of suspected digoxin toxicity includes assessing and stabilizing airway, breathing, and circulation. Early recognition and treatment with antibody (Fab) fragments is critical for patients with life threatening or hemodynamically unstable arrhythmias,[8] hyperkalemia, or evidence of end-organ damage from hypoperfusion (such as renal failure or altered mental status).[6] Patients presenting with acute ingestion within 1-2 hours may benefit from activated charcoal or cholestyramine for gastrointestinal decontamination.[9] Patients with hypokalemia should have both potassium and magnesium repleted.[10] Hyperkalemia, on the other hand, will reverse on its own once Fab fragment therapy is initiated and the regenerated sodium-potassium ATPase mechanism allows potassium migration back into cells.[6] Fluid resuscitation is recommended in patients with volume depletion.

Patients should be monitored on telemetry and should have serial digoxin and potassium concentrations checked. Intensive care is recommended for patients with unstable cardiac rhythms.

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