DIGOXIN TOXIICITY 5TH STAGE

LECTURER SALIM DAWOD 2021-2022

Introduction

Derived from the foxglove plant (Digitalis spp.), digoxin is a cardiac glycoside that historically was used for "dropsy" (edema) and is currently used as an inotrope to improve systolic dysfunction in patients with congestive heart failure (CHF) and as an atrioventricular nodal blocking agent for managing atrial tachydysrhythmias. Digoxin may improve the quality of life in CHF patients, but it does not confer a mortality benefit, and its narrow therapeutic index limits its utility. Digoxin toxicity can present acutely, by an intentional or accidental overdose (i.e., therapeutic misadventure), or chronically, such as when patients on digoxin develop an acute kidney injury. Similar toxicity can occur after exposure to cardioactive steroids in plants such as oleander, red squill, or dogbane or from animals such as Bufo toads

Etiology

Digoxin exhibits its therapeutic and toxic effects by poisoning the sodium-potassium ATPase. The subsequent increase in intracellular sodium leads to increased intracellular calcium by decreasing calcium expulsion through the sodium-calcium, cation exchanger. Higher intracellular calcium increases inotropy which can be of symptomatic benefit in CHF. At toxic levels, automaticity can be increased as well. Digoxin also increases vagal tone by decreasing dromotropy at the AV node. This can be used to control atrial tachydysrhythmias

Epidemiology

Approximately 1% of CHF patients treated with digoxin develop toxicity. Additionally, 1% of adverse drug effects in patients greater than age 40 are due to digoxin toxicity; the incidence rises to greater than 3% in patients over age 85. Plant ingestions account for 80% of pediatric exposure; the remaining 20% of pediatric ingestions arise from medications. In general, ventricular dysrhythmias are more common in the elderly whereas supraventricular dysrhythmias are more common in children

Pathophysiology

Increased intracellular calcium from the poisoning of the Na-K transporter and AV nodal blockade from increased vagal tone are the primary causes of digoxin toxicity. The former leads to increased automaticity and inotropy; the latter leads to decreased dromotropy. Hyperkalemia can be a marker of severe toxicity in acute poisoning. The role of potassium is less clear in chronic toxicity, although it has been linked to higher mortality despite traditional teaching that hypokalemia worsens the dysfunction at the Na-K transporte

Toxicokinetics

Digoxin's therapeutic half-life is between 30 to 40 hours, but this may change in overdose. Digoxin excretion is primarily renal, and for this reason, patients with poor or worsening renal function, such as patients who are elderly or have CKD, are more likely to develop toxicity. Digoxin levels start to plateau at 6 hours, which is after tissue redistribution has occurred; earlier levels may thus be misleadingly high. Cardiovascular toxicity may have delayed manifestation of up to 8 to 12 hours post ingestion

History and Physical

Gastrointestinal upset is the most common symptom of digoxin toxicity. Patients also may report visual symptoms, which classically present as a yellow-green discoloration, and cardiovascular symptoms, such as palpitations, dyspnea, and syncope. Elderly patients frequently will present with vague symptoms, such as dizziness and fatigue. The most important historical detail in evaluating a random digoxin level is the time of the last dose

Evaluation

For patients with acute digoxin toxicity, it is critical to obtain an ECG, a basic metabolic panel, and digoxin levels on arrival. These tests should be repeated at 6 hours post ingestion.
Digoxin effect on the ECG is characterized by diffuse scooping of the ST segments which can be seen with therapeutic levels and is not associated with toxicity. The most common ECG abnormality is frequent PVCs, although the "pathognomonic" ECG finding is bidirectional ventricular tachycardia. However, this has been reported in aconitine poisoning. [8][9][10]
In the setting of acute overdose, acetaminophen and aspirin levels can help screen for occult overdose.
In chronic toxicity, the cause of toxicity should be sought. Common causes include infection, renal failure, and accidental overdose. Serum digoxin levels do not always correlate with toxicity given variable tissue levels and other factors affecting digoxin's toxicodynamic effects

Treatment / Management

Digoxin-specific antibody antigen-binding fragments (DSFab), brand name Digibind or Digifab, are an effective antidote that directly binds digoxin.

DSFab is indicated for life-threatening toxicity including:

- Ventricular arrhythmias
- High-grade heart blocks
- Hypotension
- Symptomatic bradycardia
- Potassium greater than five meq/L in acute overdose
- Acute ingestions greater than 10 mg in an adult or greater than 4 mg in a child
- Digoxin Concentration greater than 15 ng/mL measured at any time
- Digoxin Concentration greater than 10 ng/mL measured 6 hours post ingestion

Care should be taken to completely reverse digoxin in patients who are chronically taking digoxin, as reversal may exacerbate their underlying disease. These patients should be closely monitored afterward for the same reasons.

If DSFab is not available, then treatments such multidose-activated charcoal, atropine, and antidysrhythmics such as phenytoin or lidocaine may be employed. Cardioversion and pacing may induce dysrhythmias and are typically not used, but they may be needed in patients without other therapeutic options.

Dialysis also may be indicated in the patient with acute renal failure or refractory hyperkalemia; however, it is not useful as a treatment for digoxin toxicity itself.

Disposition depends on the patient's symptoms and stability as well as their potassium and digoxin levels

Pearls and Other Issues

Many analyzers cannot measure free digoxin concentrations, and in this setting, digoxin levels should not be followed after administration of DSFab.

In patients with the end-stage renal disease, dissociation of the DSFab-digoxin complex may occur and cause recurrent toxicity.

Calcium is traditionally considered contraindicated in hyperkalemic patients with digoxin toxicity for fear of 'stone heart syndrome,' an irreversible state of global myocardial contraction. This is based on animal evidence and case report, but more recent literature found no evidence of increased mortality with calcium administration. In general, hyperkalemia in the setting of digoxin toxicity should be treated primarily with DSFab fragments if available

Enhancing Healthcare Team Outcomes

Digoxin toxicity can present in many ways and is best managed by an interprofessional team that includes a cardiologist, emergency department physician, poison control, internist and a nephrologist. Because digoxin toxicity can result in life threatening arrhythmias, prompt monitoring and treatment are vital. The key is patient education about drug safety. Parents should store the drug in a locked cabinet away from the reach of children. in addition, any old pills should be returned back to the pharmacist. When treated promptly, the outcomes are good but any delay in treatment can lead to death.[12][13] (Level V)