digoxin

general

- In the critical care setting, digoxin is used mostly to treat atrial arrhythmias, predominantly atrial fibrillation.
- In chronic atrial fibrillation, digoxin is useful for controlling the ventricular rate in patients with left ventricular systolic dysfunction.
- Digoxin has inotropic, neurohormonal, and vagomimetic effects with a delayed onset of action and a narrow therapeutic window.

dynamics

- Digoxin is a cardiac glycoside with specific effects on the myocardium.
- Inhibition of the sodium-potassium adenosine triphosphatase (Na+, K+-ATPase) pump increases the intracellular sodium concentration and subsequently increases the intracellular calcium concentration by stimulation of sodium-calcium exchange.
- The vagal effects of digoxin result in slowed conduction and prolongation of AV-node refractoriness, which slows the ventricular response in patients with atrial fibrillation.
- The overall response to digoxin is an increase in cardiac output and reduction in pulmonary artery pressure, systemic vascular resistance, plasma norepinephrine level, and pulmonary capillary wedge pressure. Minimal changes in blood pressure occur with initiation of therapy

kinetics

- most oral formulations provide only 60% to 85% bioavailability.
- The distribution phase of digoxin metabolism is prolonged after oral or intravenous administration. After intravenous administration, onset occurs in 5 to 30 minutes, and peak effect is observed within 1 to 5 hours.
- Digoxin is extensively bound to multiple tissues, particularly to Na+, K+-ATPase in cardiac and skeletal muscle, and demonstrates a large volume of distribution.
- With normal renal function, the elimination half-life is 36 to 48 hours. Elimination is prolonged in patients with renal dysfunction, being about 3.5 to 5 days in anuric patients.
- Metabolism occurs primarily in the liver, but the drug also is metabolized by bacteria within the large intestine after oral administration.
- Excretion of digoxin is predominantly in the urine as unchanged drug.
- Given the CrCl, estimates of daily digoxin elimination can be made by the following equation:

$$\text{Daily percentage of digoxin eliminated} = 14 + [\text{CrCl} \div 5]$$

drug interactions

- An increase in digoxin concentration may occur with concomitant administration of: amiodarone, verapamil, quinidine, spironolactone, clarithromycin, itraconazole, or captopril.
- A decrease in digoxin concentration may occur with concomitant administration of cholestyramine, colestipol, kaolinpectin, oral antacids, metoclopramide, neomycin, sulfasalazine, levothyroxine, or rifampin.

therapeutic levels

SVT

- For treatment of supraventricular tachyarrhythmias, the usual therapeutic range for serum digoxin concentration is 1 to 2 ng/mL. However, patients can require serum concentrations as great as 3 ng/mL.

CCF

- Evidence to support the use of serum concentrations to ensure efficacy in the treatment of heart failure is lacking.
- Lower digoxin concentrations (0.5 to 0.8 ng/mL) appear to provide equal or superior efficacy and avoid toxicity.

timing

- Proper timing of digoxin measurements is critical. Although digoxin is found in the plasma compartment within a brief period after administration, the medication distributes slowly into the heart and other tissues.
- Because the heart is the site of action, digoxin concentrations measured less than 4 hours after intravenous administration, or 6 hours after oral administration, are misleading.
- The optimal time to measure digoxin levels is 12 to 24 hours after administration.

presentation

- Acute manifestations of digoxin toxicity are often more severe than are chronic adverse effects.

Cardiac effects:
- Numerous cardiac arrhythmias may result from digoxin toxicity.
- Cardiac effects can manifest as an increase in vagal tone causing sinus bradycardia.
- Other arrhythmias that may become evident are paroxysmal atrial tachycardia, atrial flutter or atrial fibrillation with AV block, dysfunction of the conduction system, and ventricular ectopic beats.

Non-cardiac effects:
- Noncardiac digoxin toxicities include gastrointestinal effects (anorexia, nausea, vomiting, diarrhea, abdominal pain), central nervous system abnormalities, and hyperkalemia.
- Possible central nervous system effects include lethargy, confusion, weakness, headache, delirium, psychosis, transient amblyopia, photophobia, blurred vision, scotomata, photopsia, decreased visual activity, and color irregularities such as yellow-green or red-green halos around lights.
- Hyperkalemia results from excessive blockade of the Na+, K+-ATPase pump and is an index for outcome.

treatment

resuscitation

- In acute overdoses, prevention of further absorption using activated charcoal should be instituted.
- The administration of syrup of ipecac, insertion of a gastric tube, and gastric lavage should be avoided, because vomiting induced by these methods intensifies vagal tone.

electrolyte & acid-base abnormalities

- Supportive care is required to manage electrolyte disturbances and dysrhythmias.
- Hyperkalemia should be treated by the standard approaches and, if hyperkalemia is severe, digoxin immune Fab should be administered.

specific therapies

- In the case of life-threatening arrhythmias, digoxin immune Fab should be administered. If administration of digoxin immune Fab is delayed or treatment is needed until the onset of the effect of this agent, advanced cardiac life support (ACLS) protocols should be followed.
- Calculation of the number of vials of Fab product required for an adult patient who is experiencing digoxin toxicity is based on the serum digoxin level (in nanograms per milliliter) and the patient's weight in kilograms):

$$\text{Number of vials} = \frac{(\text{Serum digoxin concentration}) \times (\text{Weight})}{100}$$

underlying causes

- potential causes include deliberate overdose, iatrogenic overdose, acute renal failure, changes in medication, genetic predisposition.