



# Clinical Pharmacology & Toxicology Pearl of the Week

## Digoxin Monitoring

- When monitoring digoxin therapy, drug levels should be drawn when the patient is at steady-state (ie: 4-5 half lives have passed since the last dose change or since drug initiation).
- When monitoring digoxin, blood levels should be drawn **no sooner than 6 hours after the most recent dose.**
- Digoxin levels should be interpreted and acted on **based on clinical signs and symptoms.**
- Therapeutic digoxin levels should fall between **0.6 - 1.2 nmol/L** despite reference ranges of up to 2.6 nmol/L.
- Other cardioactive steroids react unpredictably with the digoxin assay and cannot be reliably ruled out.
- There is no utility in measuring digoxin levels after giving digiFab.

### Digoxin pharmacokinetics & interpretation of drug levels

- ✓ Digoxin has high oral bioavailability (capsule 90-100% vs. elixir 70-85% vs. tablet 60-80%)
- ✓ Peak serum concentrations occur 30-90 mins after an oral dose.
- ✓ Onset of action is 1-2 hours with oral dosing and 5-60 mins with IV; peak effect for heart rate control is 2-8 hours and 1-6 hours for oral vs. intravenous, respectively.
- ✓ Digoxin has a large volume of distribution (5-7.5 L/kg) and redistributes primarily into heart, skeletal muscle, liver and kidneys over 6-8 hours following initial absorption or following intravenous administration.
- ✓ Digoxin's half-life is 30-45 hours in healthy adults
- ✓ Digoxin's pharmacokinetics are clinically relevant in the following ways:
  1. The long half-life means **steady state kinetics only occurs after 6-10 days of regular daily dosing**
  2. The redistribution phase makes **levels drawn sooner than 6-8 hours after the last dose un-interpretable** due to ongoing redistribution to target tissues. (ie: serum concentrations are likely to be higher than expected if measured too soon after a dose).

### False-positive and false-negative digoxin levels

- ✓ Several exogenous cardioactive steroids **unpredictably interact** with the digoxin assay (which may result in a negative serum digoxin level after ingestion, or may give a level that isn't fully representative of total body burden). **Serum digoxin levels cannot be used to rule out ingestion of other non-digoxin cardioactive steroids.**
  - Plant-derived cardioactive steroids: Lily of the Valley, Fox Glove, Oleander, Yellow Oleander, Dogbane, Milk Weed, Red Squill, Sea Mango,
  - Animal-derived cardioactive steroids: Bufo toad, Fire flies
- ✓ Endogenous digoxin-like immunoreactive substances
  - Produced in patients undergoing physiologic stress. It is thought that they increase cardiac inotropy, though exact physiology is unknown (Ex: neonates, end-stage kidney disease or liver disease, subarachnoid hemorrhage, CHF, hypothermia, strenuous exercise, and pregnancy)
- ✓ Other substances known to cause false-positives in some assays:
  - Bilirubin, spironolactone
- ✓ Intra-lipid
  - Most common digoxin measurement technique involves measurement of light-scatter
  - High serum lipids will interfere with the light-scatter measurement

### Can I measure digoxin levels after giving digiFab?

- ✓ DigiFab binds serum digoxin, resulting in a concentration gradient that draws digoxin out of the tissues and into the serum to be bound.
- ✓ Most laboratory testing for digoxin **does not distinguish between free and bound digoxin**
- ✓ Serum concentration of digoxin (ie: both bound + unbound fractions) following digiFab administration **results in an elevated serum digoxin level which is not clinically interpretable**
- ✓ There is therefore no role for routine measurement of digoxin levels after giving digiFab
- ✓ If you suspect **ongoing** digoxin toxicity, call the clinical biochemist on call for your lab and toxicologist to discuss feasibility and utility of obtaining a free digoxin level

## When should I measure digoxin for therapeutic drug monitoring?

- ✓ Only measure digoxin level 6-10 days after initiation of therapy or following a dose change to insure serum concentration reflects steady state.
- ✓ Be sure to draw the sample at least 6-8 hours after the last dose to avoid falsely elevated serum levels.
- ✓ The Canadian Cardiovascular Society and the American Academy of Family Physicians recommend therapeutic digoxin levels of 0.6 – 1.2 nmol/L despite an upper limit of normal within the Calgary region of 2.6 nmol/L
- ✓ Since digoxin is mostly renally cleared, adjusted dosing and close monitoring is required in patients with impaired renal function.

## I have a serum digoxin level that is above or below therapeutic target, now what?

- ✓ If the digoxin level is below therapeutic target, consider:
  - Is my patient taking the digoxin as prescribed?
  - Has there been a substantial change in renal function?
  - Has my patient been prescribed a p-glycoprotein inducer?
    - P-glycoprotein is an efflux transporter that pumps digoxin into the lumen of the intestine and into the collecting ducts of the kidneys. Induction of this transporter decreases serum digoxin levels.
  - Have we achieved the clinical effect desired despite the low level?
- ✓ If the digoxin level is above therapeutic target, consider:
  - Is my patient taking the digoxin as prescribed?
  - Has there been a substantial change in renal function?
  - Has my patient been prescribed a p-glycoprotein inhibitor?
    - P-glycoprotein is an efflux transporter that pumps digoxin into the lumen of the intestine and into the collecting ducts of the kidneys. Inhibition of this transporter increases serum digoxin levels.
  - Was the digoxin level drawn at an appropriate time (>6 hours after last dose)?
  - Is my patient experiencing any adverse effects from the digoxin?
- ✓ Dose adjustments to achieve the appropriate serum concentration can be made according to Formula 1
- ✓ An elevated digoxin level alone is rarely an indication to give digiFab. More important indications include life-threatening dysrhythmias, significantly altered mental status, or significant GI side effects.
  - Any level > 19 nmol/L or a >6-hour level >12.8 nmol/L are often considered an indication for digiFab alone
  - Consult your local toxicologist to discuss indications for digiFab

$$\frac{\text{Concentration Measured}}{\text{Target Concentration}} = \frac{\text{Current Dose}}{\text{New dose}}$$

Formula 1: Adjusting Digoxin Dose

 The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click [HERE](#) for clinical issues the CP service can assist with.

 The Poison and Drug Information Service ([PADIS](#)) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

## References:

1. Lewis S. Nelson et al, Goldfrank's Toxicologic Emergencies. 11th ed. New York: McGraw Hill Medical; c2019
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3. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA*. 2003;289:871-8.
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6. Calgary Lab Services: CH-2.24 Half-Life and Time to Steady State. <http://www.calgarylabservices.com/files/LabTests/HalfLifeTime.pdf>. Accessed Jan 8<sup>th</sup>, 2020
7. Jogestrand T, Sundqvist K. Skeletal muscle digoxin concentration and its relation to serum digoxin concentration and cardiac effect in healthy man. *Eur J Clin Pharmacol* 1981 Jan; 19 (2): 89-95.

8. Jogestrand T. Digoxin concentration in right atrial myocardium, skeletal muscle and serum in man: influence of atrial rhythm. *Eur J Clin Pharmacol* 1980 Apr; 17 (4): 243-50.
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