Clinical Pharmacology & Toxicology Pearl of the Week

~ Digoxin Monitoring ~

- ✓ When monitoring digoxin therapy, drug concentrations 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 concentrations should fall between 0.6 – 1.2 nmol/L despite reference ranges of up to 2.6 nmol/L.

Digoxin pharmacokinetics & interpretation of drug concentrations

- ✓ 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:
  - The long half-life means steady state kinetics only occurs after 6-10 days of regular daily dosing
  - 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 concentrations

- ✓ 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, Fireflies
- ✓ Endogenous digoxin-like immunoreactive substances
  - Produced in patients undergoing physiologic stress. It is thought that they increase cardiac inotropy, though exact physiology in 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
- ✓ Intravenous lipid emulsion:
  - Most common digoxin measurement technique involves measurement of light-scatter
  - High serum lipids will interfere with the light-scatter measurement

Can I measure digoxin concentrations 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

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 ensure 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.
- ✓ Since digoxin is mostly renally cleared, adjusted dosing and close monitoring is required in patients with impaired renal function.

I have a serum digoxin concentration 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 concentration 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 concentration 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 elevated serum potassium, life- threatening dysrhythmias, significantly altered mental status, or significant GI side effects.

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.
4. Digoxin therapy for heart failure: an update. Morris SA, Hatcher HF, Reddy DK. Am Fam Physician. 2006;74:613–618.
5. 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.
6. 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.
7. Wells TG, Young RA, Kearns GL. Age-related differences in digoxin toxicity and its treatment. Drug Saf 1992 Mar-Apr; 7 (2): 135-51.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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