Digoxin

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Reading

• Required:
  – Bauer chapter 6
• Suggested:
  – Applied Therapeutics, 8th edition. Chapter 19 (Kradjan)
Digoxin

- A cardiac glycoside (digitalis lanata – Foxglove)
  - The only one used clinically

Heart Failure

- Inability of heart to provide adequate blood flow to sustain normal tissue perfusion.
- Systolic dysfunction.
  - Myocardial muscle function loss; “Pump failure”
- Activation of sympathetic nervous system and the renin-angiotensin-aldosterone system
  - Vasoconstriction and increased heart rate
  - Resistance to cardiac output (afterload on heart)
  - Stress on heart due to continued heart stimulation
  - Reduced blood flow to kidney
Treatment of Heart Failure

• Goals:
  – Relieve symptoms
  – Prevent/slow progression of disease
  – Improve survival

• Drug treatment:
  – Loop diuretics – reduce congestion, fluid accumulation
  – ACE-I (or ARB if ACE is poorly tolerated) – reduce effects of angiotensin and aldosterone
  – Beta-blockers – reduce sympathetic tone
  – Digoxin – positive inotrope vs reduced sympathetic tone; declining use

Digoxin use in Heart Failure

• Place in therapy
  – Improves clinical status and improves heart failure symptoms.
    • Withdrawal can cause re-emergence of symptoms
  – Digoxin provides no mortality benefit
  – May be added on to patients who continue to have symptoms despite optimal therapy

• Optimal serum level: 0.5-0.8 ng/mL
Atrial Fibrillation

Digoxin Mechanism in Atrial Fibrillation

• Rate control, not rhythm control
  – Increased vagal tone; parasympathetic activity
  – Block conduction through the AV node
    • Decreases conduction velocity and prolongs the refractory period of the AV node
    • Prolongs PR interval on EKG and slow ventricular response rate
• Less effective than beta blocker or calcium channel blocker
  – Especially during exercise
• Optimal serum level: not known
  – Efficacy and serum concentrations do not correlate
**Digoxin dosage forms**

- **Tablet**  
  (Lanoxin and generic)  
  - 0.125 mg (125 mcg)  
  - 0.25 mg (250 mcg)  
  - 0.5 mg (500 mcg)
- **Elixir**  
  - 0.05 mg/mL
- **Liquid filled capsule**  
  (Lanoxicaps)  
  - 0.05 mg  
  - 0.1 mg  
  - 0.2 mg
- **Injection**  
  - 0.25 mg/mL

**Absorption/ Bioavailability**

- **Absorption**  
  - Amount absorbed (F) is dependent on the dosage form used  
  - Significant interpatient variability
- **Note**: much of this data is over 30 years old  
  - Problems with dissolution and rate of absorption, not extent of absorption.
Bioavailability
(fraction of dose absorbed: \( F \))

- Tablet = 0.75 (0.7 – 0.8)
  - Lanoxin vs AB rated generics (Digitek) vs older products
- Liquid filled capsule (Lanoxicaps) = 0.95 (0.8-1.0)
- Elixir (pediatric) = 0.80 (0.65 – 0.90)
  - Most studies done using injectable product in juice

Factors affecting Bioavailability

- P glycoprotein substrate
  - Multi drug transporter that acts as a drug efflux pump across cell membranes in epithelial and endothelial cells of intestine, liver, and kidney.
  - Transport drugs from the blood back into the gut lumen.
  - Promote clearance by enhancing renal tubular secretion and inhibiting renal tubular reabsorption.
- “Gut edema” from heart failure
- Gut metabolism?
  - \(~10\%\) of patients. GI flora metabolize digoxin to inactive metabolites. Relevant mostly for slowly absorbed tablets, not liquicaps or elixir.
  - Erythromycin or clarithromycin may reduce gut flora and allow increased bioavailability. Clinical relevance = ??
- Enterohepatic recycling – minimal (6.8%) (higher with digitoxin)
Volume of Distribution (V)

- Normal renal function: 6.7 (4 - 9) L/kg
  - 70 kg individual = 470 L
  - Protein binding 20-30% (low)
- Renal failure: 4.7 (1.5 – 8.5) L/kg
  - Decreased due to changes in protein binding
- Largely distributed to lean muscle
- Very small distribution into fat
  - Use ideal body weight when actual weight is 30% greater than ideal body weight
- **Net effect: Very small amount in serum/plasma**

Distribution

- Distribution
  - Concentration-time curve follows a 2-compartment model
  - Distribution phase: 8-12 hours
  - Any measurement of serum concentration should take place at least 6 hours after dose
FIGURE 6-1 Digoxin serum concentrations after 250-μg doses given intravenously (circles with solid line) and orally as a tablet (squares with dashed line). After an intravenous dose, digoxin serum concentrations are very high, because all of the drug is initially contained in the blood. During the distribution phase, digoxin begins to move out of the vascular system into the tissues. It is also cleared from the body during this phase. Digoxin serum concentrations decline relatively rapidly over an 8- to 12-hour time period until the blood and tissues are in pseudoequilibrium with each other. During the elimination phase, digoxin serum concentrations in patients with good renal function (creatinine clearance >80 mL/min) decline with a half-life of about 36 hours. After oral tablet administration, about 70% of a digoxin dose is absorbed from the gastrointestinal tract. Maximum, or peak, concentrations occur about 1.5 to 2 hours after oral dosing with tablets, and the distribution phase still lasts 8 to 12 hours. During the elimination phase, intravenous and oral digoxin have the same terminal half-life.
Volume of distribution

Adjustment for renal impairment

\[ V = \left[ \frac{226 + 298 \times \text{Clcr}}{291.1 + \text{Clcr}} \right] \left[ \frac{\text{Wgt (IDW if >30% overweight)}}{70 \text{ kg}} \right] \]
Clearance

• Renal clearance (unchanged drug)
  – ~70-75% after IV dose (normal renal fxn)
  – ~50-60% after oral dose (normal renal fxn)
    • Glomerular filtration and active secretion
    • P-glycoprotein promotes renal clearance by
      enhancing renal tubular secretion and inhibiting
      tubular reabsorption
• Non-renal clearance ~20-55%
  – ~20-55% hepatic metabolism/ biliary excretion
  – P-glycoprotein is the primary transport protein
    in biliary excretion

Effect of disease states

• Renal dysfunction
  – Most important disease state that will affect
    pharmacokinetic parameters
  – Digoxin clearance is proportional to creatinine
    clearance
  – Volume of distribution is also decreased in renal
    dysfunction
  – Because both clearance and Vd are decreased in
    renal dysfunction, the half-life is shorter than would be
    expected if clearance alone were decreased
Clearance

• Clearance is affected by renal and non-renal clearance
  – Digoxin $Cl = 1.02 \ Clcr + 57 \ ml/min$
  – Digoxin $Cl = 1.303 \ Clcr + 40 \ ml/min$
    • Renal clearance exceeding $Clcr$ indicates a small portion of tubular secretion
• For $Clcr$ of 100 ml/ min = 159 – 173 mL/min
  – What percentage is renally cleared?
• For $Clcr$ of 0 ml/min = 40-57 mL/min
  – What percentage is renally cleared?
• Heart failure affects both renal and non-renal clearance.
  – (Non-renal clearance ~20 mL/min)

Effect of Disease States

• Heart failure
  – Decreased cardiac output results in decreased blood flow to the liver
  – Moderate to severe heart failure (NYHA Class III-IV) causes decreased hepatic metabolism
  – Need to decrease estimate of non-renal clearance when estimating total plasma clearance in this situation
  – Also decreased renal blood flow
Digoxin Clearance

Digoxin clearance = 1.303.Cl_{Cr} + Cl_{NR} (mL/min)

Severe HF:
Cl = 0.88.Cl_{Cr} + Cl_{NR} (mL/min)

Cl_{NR} = 40-53 mL/min. Reduced to 20 mL/min in NYHA class III or IV

Dose (mg) = target serum concentration (ng/mL) x digoxin clearance (mL/min)

Affects of renal dysfunction and CHF

FIGURE 6-2 Digoxin clearance is proportional to creatinine clearance for patients with (circles with solid line: Cl = 1.303[CrCl] + 20) and without (squares with dashed line: Cl = 1.303[CrCl] + 40) moderate to severe (New York Heart Association class III or IV) heart failure. Nonrenal clearance (y-intercept) is lower for patients with moderate to severe heart failure, because reduced cardiac output results in decreased liver blood flow and digoxin hepatic clearance.
Effect of Disease States

• Hyperthyroidism
  – Thyroid hormone- regulates body’s basal metabolic rate
    • Influences every major organ system
    • Affects heart rate and cardiac output
    • Affects liver blood flow and function of drug metabolizing enzymes
    • Affects renal blood flow and GFR
  – Results in increased clearance

Estimating Half-Life

• \[ t_{1/2} = \frac{0.693 \times V}{\text{Cl}} \]
  • \( V = 6.7 \text{ L/Kg} = \sim 470 \text{ L} \)
  • \( \text{Cl} = \sim 160 \text{ mL/min} = 0.16 \text{ L/min} = 9.6 \text{ L/hr} = 230 \text{ L/24 hr} \)
  • Allow \sim 5 \text{ half-lives} \text{ to pass before obtaining digoxin level (steady state)}
Half life (t \( \frac{1}{2} \))

- Adult, normal kidney function, not in heart failure: 36-40 hours (1.6 - 2 days)
- Adult, renal failure: \( \geq 4.4 \) days
- Adult, renal impaired: see clearance
- Adult, hyperthyroidism: 24 hours (1 day)
- Children, healthy: 0.7 – 1.5 days
  - E.g., more rapid clearance

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Time to steady state</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mL/min</td>
<td>22 days</td>
</tr>
<tr>
<td>10 mL/min</td>
<td>19 days</td>
</tr>
<tr>
<td>20 mL/min</td>
<td>16 days</td>
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<tr>
<td>30 mL/min</td>
<td>14 days</td>
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<tr>
<td>40 mL/min</td>
<td>13 days</td>
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<tr>
<td>50 mL/min</td>
<td>12 days</td>
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<tr>
<td>60 mL/min</td>
<td>11 days</td>
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<tr>
<td>70 mL/min</td>
<td>10 days</td>
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<tr>
<td>80 mL/min</td>
<td>9 days</td>
</tr>
<tr>
<td>90 mL/min</td>
<td>8 days</td>
</tr>
<tr>
<td>100 mL/min</td>
<td>7 days</td>
</tr>
</tbody>
</table>
Choosing an initial Css target and dose

• Things to consider:
  – Disease state you are treating
    • Heart failure vs A. fib.
  – Age, weight, (gender for Clcr)
  – Frailty of patient
  – Lab values – renal, hepatic, thyroid fxn
  – History of digoxin toxicity
    • At what Css?
  – Concurrent medications and medical problems

Therapeutic Serum Concentration

• “normal” = 0 !!
• Heart failure: target 0.5 – 1.0 ng/mL.
  ideal <0.8 ng/mL
• Atrial fibrillation: 0.8-1.5 ng/mL
• CAUTION: older guidelines and modeling based on target of 1 – 2 ng/ml
• Caution: note units when using dosing equations. Dose in mg. Volume in L.
  Serum concentration in ng/mL or mcg/L.
Loading dose

- Loading doses are not necessary in treatment of heart failure
  - Digoxin is not indicated for management of acute decomposition of heart failure

- May be used in atrial fibrillation
  - Depends on what other rate controlling medications patient is on
  - Not done for outpatients

Dosing of digoxin

Loading Dose

- Only if need rapid response
- 0.5-1 mg IV/PO over 24 hr
  - (0.01-0.02 mg/kg)
- 50% of total loading dose to start followed by 25% x 2 at 4-6 hr intervals.
- Remember: do not measure serum levels for at least 24 hours after last dose.
Calculation of loading dose

• Primary variable is volume of distribution
• \( LD = \text{Css} \times \frac{V}{F} \)
• Be careful with units
  – Dose in mg or mcg
  – \( \text{Css} \) in ng/ml or mcg/L
  – \( V = 6.7 \text{ L/Kg} = \sim 470 \text{ L} \)

Example 1: loading dose

• Calculate the loading dose for a 68-year-old man to target a serum concentration of 0.9 ng/mL for rate control in atrial fibrillation. Patient is 70 inches and 72 kg with a serum creatinine of 1.0 mg/dL. Assume IV administration.
Altered Vd affects loading dose

- Estimation of volume of distribution
- Average Vd in patients without disease states: 6-7 L/kg
  - Obesity (>20% over IBW)- use IBW
  - Weight within 20% of IBW- use ABW
  - Weight less than IBW- use ABW
- Renal dysfunction
  - CrCl ≤ 30 mL/min
  - \( Vd = \left[ \frac{226 + \left( \frac{298 \times CrCl}{29.1 + CrCl} \right) \times \frac{Wt}{70} }{29.1 + CrCl} \right] \)

Maintenance doses

- Heart failure, compensated and preserved renal function: 0.125 mg/ day
  - Formerly 0.25 mg/ day
- Heart failure, poorly controlled and/or decreased Clcr: 0.0625 mg/day
  (0.125 mg every other day)
- A. fib, preserved renal function: 0.25 mg/day
**Determination of initial Maintenance dose**

- Clearance is the primary variable
- Estimation of digoxin clearance
- \( Cl = 1.303(CrCl) + Cl_{NR} \)
  - \( Cl_{NR} = 40 \text{ mL/min} \) in patients without HF or with mild symptoms of HF (NYHA Class I-II)
  - \( Cl_{NR} = 20 \text{ mL/min} \) in patients with HF (NYHA Class II-IV)

**Initial dosing**

- \( \frac{\text{Dose/tau}}{\text{F}} = \frac{\text{Css} \times Cl}{\text{F}} \)
- Watch units!!!!
  - **Dose** in mg or mcg
  - **Tau** in days or 24 hrs
  - **Css** in ng/ml or mcg/L
  - **Cl** = \( \sim 160 \text{ mL/min} = 0.16 \text{ L/min} = 9.6 \text{ L/hr} \)
  - \( = 230 \text{ L/24 hr} \)
Practice calculations
Maintenance doses

• Patient 1 - male
  – Age 68, Wt. 80 kg, serum Cr 1.0, A Fib
  – Calculate digoxin clearance
  – What percent of digoxin will be cleared renally?
  – Recommend an oral dose to achieve serum level 0.8 ng/mL

• Patient 2 - female
  – Age 78, Wt. 80 kg, serum Cr 2.5, Stage IV HF
  – Calculate digoxin clearance
  – What percent of digoxin will be cleared renally?
  – Recommend a dose to achieve serum level 0.5 ng/mL

Monitoring

• Serum concentration:
  – Initiation: 5-10 days after start
  – Every 3-6 months for a stable patient
  – Change in clinical status or suspected toxicity

• CHF/AF:
  – Signs and symptoms of disease state
  – Signs and symptoms of toxicity

• Patients with severe heart disease should be monitored more closely for adverse effects
Adjusting dose based on serum concentration

• Digoxin follows linear kinetics
• Can usually do a simple proportion
• \( D_{\text{new}} = \frac{D_{\text{old}} \times C_{ss_{\text{new}}}}{C_{ss_{\text{old}}}} \)

• Dose is in mcg
• \( C_{ss} \) is ng/mL

Example 4

• LB is a 53 year old female
• PMH: type II diabetes, chronic kidney disease (stage IV), CHF (NYHA Class III), hypothyroidism, hyperlipidemia, asthma, and new onset atrial fibrillation
• Medication list:
  – Levothyroxine 0.125 mg daily
  – Lisinopril 40 mg daily
  – Furosemide 80 mg daily
  – Glipizide 10 mg daily
  – Lantus 33 units q HS
  – Aspirin 81 mg daily
  – Atorvastatin 40 mg daily
  – Albuterol inhaler PRN
  – Advair 100/50 1 puff BID
• Objective: 73 kg, 66 inches, SrCr 2.7 mg/dL, TSH 1.9 mIU/L, BP 102/66
• Suggest a target serum digoxin concentration maintenance dose regimen for LB
Dose adjustment example

- Patient from LD Example 2
  - Calculated a dose of 125 mcg q.o.d
- When do we check serum digoxin level?

- Serum level came back 0.4 ng/mL
- Calculate a new dose/regimen to target a serum concentration of 0.8 ng/mL

Conversion between dosage forms

- \( D_{IV} = D_{PO} \times F \)
- Because oral doses must be rounded to the nearest strength available, \( C_{ss} \) will change
- Change in steady state concentration:
  - \( C_{ss_{new}} = \frac{C_{ss_{old}} \times D_{rounded}}{D_{computed}} \)
Dosage form conversion example

- AF is a 68 year old woman who was started on IV digoxin for rate control in atrial fibrillation. She had been receiving 200 mcg daily, with a steady state serum concentration of 1.0 ng/mL.
- Calculate an oral tablet dose that will maintain digoxin concentrations at approximately the same level.
- Estimate the change in steady-state concentration that will occur with the oral dose.

Drug Interactions

- May lower serum concentration
  - Decreased bioavailability by adsorption in gut
    - Antacids, cholestyramine (Questran), Colestipol (Colestid), kaolin-pectin, bran, fiber (Metamucil)
  - Decreased bioavailability by gut hypermotility
    - Laxatives, metoclopramide
    - Relevant only if slow absorber in first place
  - Decrease bioavailability, unknown mechanism
    - Cyclophosphamide + vincristine, neomycin, sulfasalazine
  - Decreased bioavailability by induction of gut P-glycoprotein: Rifampin, St. John’s Wart
Drug Interactions

• May raise serum concentration
  – Inhibition of P-glycoprotein. Decreased digoxin renal clearance or increased absorption
    • Atorvastatin, calcium channel blockers (especially verapamil), clarithromycin, cyclosporine, propafenone,
  – Erythromycin – altered gut metabolism (10% of patients) or inhibition of gut P-glycoprotein
  – Slow gastric emptying
    • Propantheline (slow absorbers of digoxin only)
  – Unknown mechanism
    • Alprazolam, amiodarone, captopril, itraconazole, telmisartan

Drug Interactions

• Quinidine
  – Decreases both renal and non-renal clearance as well as the volume of distribution
  – Inhibition of p-glycoprotein may play a role
    • Inhibition of intestinal PGP increases bioavailability (less efflux back into gut)
    • Inhibition of renal PGP reduces renal clearance by inhibiting tubular reabsorption and enhancing tubular secretion.
  – Result: serum digoxin levels increase by 30-70%
Figure 4.4. Displacement of Digoxin by Quinidine. The digoxin plasma concentration with no quinidine (---) and following the administration of two quinidine doses (--). Note that as the quinidine plasma concentrations rise and then fall, the digoxin levels also rise and then fall. The elevation of digoxin levels appears to be minimal at quinidine levels below 1 mg/L.39

Figure 4.3. Digoxin. Figure 4.3 represents the anticipated changes in digoxin concentration following the initiation of an interacting agent. The solid line A represents the effect of a drug which changes the volume of distribution in proportion to the decrease in the digoxin clearance. Broken line B represents the effect of a drug which produces a decrease in volume of distribution that is less than proportional to the decrease in digoxin clearance (e.g., quinidine). Line C represents the effect of a drug which decreases the digoxin clearance to approximately the same extent as quinidine, but produces no apparent change in the volume of distribution (e.g., amiodarone). Line D represents the effect of a drug which decreases digoxin clearance to a lesser extent than that observed with quinidine (e.g., verapamil).
Toxicity

- Related to serum concentration
- GI: anorexia, nausea, vomiting, diarrhea, abdominal pain, constipation
- CNS: headache, fatigue, insomnia, confusion, vertigo
- Visual disturbances: blurred vision, changes in color vision
- Cardiac: AV dissociation, bradycardia, PVCs, v-tach, other arrhythmias
- Electrolytes: wasting of K

Treatment of severe overdose

- Digibind (digoxin immune Fab)
  - Antibody segments that recognize digoxin
  - Used in severe overdose situation
  - Improvements in toxicity may be seen within 30 min
  - Digoxin serum concentrations are not useful after Digibind has been used
  - Allergic reactions may occur