**Digoxin - Peripheral Brain**

**Important formulas:**

\[
\text{ClCr (ml/min/1.73m}^2\text{)} = 98 - 0.8(\text{age - 20}) \times 0.9 \text{ if female} \\
\text{Scr mg/dl}
\]

Jusko Method: 
\[
\text{Vd (L)} = \left[ 3.2 + \frac{4.26 (\text{ClCr})}{29 + \text{ClCr}} \right] \times \text{IBW (kg)}
\]

NOTE: ClCr here is ml/min/1.73m\(^2\)

Sheiner Method: 
\[
\text{Cl}_1 (\text{ml/min}) = 1.02 \text{ClCr} + [0.88 \text{ ml/kg/min x IBW kg}] - \text{ADULTS w/o severe CHF} \\
\text{Cl}_2 (\text{ml/min}) = 0.88 \text{ClCr} + [0.33 \text{ ml/kg/min x IBW kg}] - \text{ADULTS w/severe CHF}
\]

\[
\text{Css} = \frac{\text{MD(S)}(F)}{\text{Cl} (\tau)}
\]

**Population Parameters:**

**Absorption (Highly Variable):**

- Oral Tablets: 0.75 ± 0.14
- Elixir: 0.80 ± 0.16
- Liquid-filled capsules: 0.95 ± 0.13

**Increase Absorption:**
- Oral antibiotics (in 10% of patients who produce DRPs)
- Erythromycin/Macrolides
- Tetracycline
- Neomycin

**Decrease Absorption:**
- Newborns: Elixir F = 0.72
- Elderly ??
- High Fiber Meal: ↓F tabs 21%, caps 7%
- Malabsorption Syndromes:
  - Radiation: F tabs = 0.54; caps = 0.85
  - Cytotoxic drugs – variable effects
  - AIOH, MgOH, Mg trisilicate: (60ml) ↓F 11-30%
  - Aminosalicylic acid: ↓ abs 20%
  - Cholestyramine: ↓F tabs 21%, caps 22-32%
  - Kaolin-Pectin: ↓F 15-62%
  - Metoclopramide: ↑ motility ↓F 25%
  - Neomycin: USU decr absorpt
  - St. John’s Wort: ↓F 28%
  - Sulfasalazine: ↓F 24%

**Volume of Distribution:**
- (binds to Na-K ATPase in skeletal muscle, crosses placenta)
- Multi compartment with 8 hr equilibrium b/t plasma and tissues including receptor
- Protein Binding: 20-30%
- Skeletal Muscle: 50%
- Obesity: no effect

Weight Used: **Ideal Body Weight**

**Increase Vd**
- Exercise ↑ skeletal muscle binding (temporary)

**Decrease Vd**
- See with Decreased CrCl (chart above) and Decreased Clearance (list below)

**Elimination:**
- 3-compartment model; linear in therapeutic range
- Nonrenal (30%):
  1) GIT to dihydro inactive metabolite by intestinal bacteria (significant in ~ 10% pts) or hydrolyzed in acidic environment to polar (inactive) mets, 2) liver to both active and inactive mets, 3) biliary and possible intestinal secretion → fecal elim (4 - 45% of oral dose; ave 20%, 11% after IV)
- Renal Unchanged (70%): 1º GF with some TS (may be ↑ in children) and TR

**Increase Clearance**
- Rifampin →↑ level 30-50%

**Decrease Clearance**
- Amiodarone ↓renal/nonrenal Cl →↑ level 70-800%
- Cyclosporine ↓Cl & ↓ Vd→↑ CL 50%
- Diltiazem ↓nonrenal Cl by ~ 27% →↑ level 22-70%
- Nifedipine???
- NSAIDs ↓ renal Cl →↑ levels 20-60%
- Propafenone ~ 30%↓ renal/nonrenal Cl, ↓ Vd → may ↑ level >80% (6-254%)
- Quinidine ↓renal/nonrenal Cl, ↓ Vd →↑ level 25-100 % in 90% pts
- Verapamil ↓renal/nonrenal Cl →↑ level 40-70%

**NOTE:** This list of drug interactions is NOT all inclusive. The changes represented in this document are common, but most interactions are extremely variable
<table>
<thead>
<tr>
<th>POPULATION</th>
<th>Vd</th>
<th>half-life</th>
<th>Common IV LD</th>
<th>Common PO LD</th>
<th>Common MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (nml renal fxn)</td>
<td>6.7 ± 1.4 L/kg (range: 4-9)</td>
<td>36 ± 8 hr</td>
<td>0.375mg q6h x 2 doses</td>
<td>10 - 15 µg/kg or 0.5mg q6h x2 doses</td>
<td>0.125 - 0.25 mg/DAY</td>
</tr>
<tr>
<td>Adults (CKD w/o HD)</td>
<td>4 - 5 L/kg (range: 1.5 - 8.5)</td>
<td>79 ± 19 hr</td>
<td>↓ LD for ClCr &lt; 20</td>
<td>0.1875mg q6h x 2 doses</td>
<td>0.25mg q6h x2 doses</td>
</tr>
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<td>Adults w/ ESRD on HD</td>
<td>between normal renal function and CRF??</td>
<td></td>
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</table>

**Information about levels:**

**Evaluation**

- Are the levels at steady state?
- Levels should be drawn at least 6 hours after the dose to ensure that absorption and distribution is complete.
- Are there any interfering substances?
  - FPIA most common
  - Digoxin-Like Immunoreactive Substances – found in neonates, patients w/ renal failure or liver disease, pregnant women (3rd trimester) – All assay methods cross-react.
  - False Elevation: Spironolactone – RIA
  - Others! Ginseng, steroids, etc.
- Are there disease states which alter sensitivity to digoxin?
  - Increase Sensitivity: HYPOthyroidism, ↓ Mg, ↓ K, ↑ pH, ↑ Ca
  - Decrease Sensitivity: HYPERthyroidism

**Goal**

- Peak - NA
- Trough – to prevent toxicity AND be therapeutic
  - CHF: 0.5 – 0.8 µg/L
  - A-fib: 0.8 – 2 µg/L; some patients may require up to 2.6 µg/L