Pharmacokinetics for the nephrologist: Influence of renal disease and dialysis on drug dosing

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Disclosure:
Consultant to: Sigma Tau Pharmaceuticals, GlaxoSmithKline, Consumer Healthcare Products Association, Kowa Research Institute, Maple Leaf Ventures/Worldwide Clinical Trials, Novo Nordisk, 3D Communications, Catabasis Pharmaceuticals, Allergan, Medtronic, NovaDigm Therapeutics, Arena Pharmaceuticals, Bayer, Amgen, World Self-Medication Industry, Optimer Pharmaceuticals, Gen-Probe Incorporated, AtriCure, Inc., Talon Therapeutics, Merck, NeurogesX, Ironwood Pharmaceuticals, NPS Pharmaceuticals, HeartWare International, Inc., Johnson & Johnson/McNeil

Equity in: Calistoga Pharmaceuticals, Catabasis
Objectives

• Review principles of pharmacokinetics

• Discuss impact of extracorporeal therapies on pharmacokinetics

• Illustrate the influence of extracorporeal therapies on antimicrobial pharmacokinetics
Pharmacokinetics

• Defines in quantitative terms the processes of drug absorption, distribution and elimination that determine the time course of drug action

• Mathematically, expressing

\[ [\ ] = f(t) \]

• Utility lies in defining drug efficacy or toxicity, or

\[ \text{Action} = f([\ ]) \]
Pharmacokinetics – Getting the drug into the system

Bioavailability – Fraction of the administered dose that reaches the systemic circulation

-- Degree of absorption
-- Pre-systemic clearance

Propranolol
Oral dose: 40 mg
IV dose: 1-2 mg

Mathematically, systemic bioavailability expressed as F, the fraction of dose reaching systemic circulation
Rate vs. extent of absorption

Which curve represents the highest bioavailability?

- Toxic concentration
- Minimally effective concentration
DISTRIBUTION PHASE

Equilibration of drug between plasma and tissue compartment(s)

• Determined by physical-chemical properties of drug
  – lipid solubility
  – protein binding
• Volume of distribution ($V_d$)
  – Idealized volume relating total drug in body vs. plasma drug concentration

\[ V_d = \frac{\text{Amount of drug in body}}{\text{Plasma drug concentration}} \]
LOADING DOSE AND THE VOLUME OF DISTRIBUTION

Plasma concentration = Amount of drug/(Vd)

- Indicates the distribution of drug between plasma and extra-plasma compartments
- Amount of drug in the body usually NOT known except for acute additions – loading doses

Consider patient with no drug in system, given a bolus dose...

Amount of drug in the body = Dose given

Thus,

Resulting drug concentration = \( \frac{\text{Dose} \times F}{Vd} \)
Importance of plasma protein binding

• Only unbound, or “free” drug can:
  – Interact with target receptors, exert pharmacologic effects
  – Diffuse from plasma compartment (usually)
  – Provide substrate for metabolic enzymes
  – Be filtered by glomerulus

• Most drug assays measure “total” drug (bound + free)
Pharmacokinetics - drug elimination

FIRST ORDER ELIMINATION

- Constant *fraction* of drug in the body eliminated per unit time
- Exponential decay vs. time – linear log [ ] vs. time
- Most common elimination pattern clinically
Clearance – Quantitative description of drug elimination

Clearance relates the *amount* of drug eliminated to the plasma drug concentration.

How much plasma would need to be *completely* cleared of drug to account for the amount of drug eliminated?

**Clearance** = \[
\frac{\text{Amount of drug eliminated per time}}{\text{Plasma drug concentration}}
\]

For drugs with first order kinetics, clearance is independent of concentration.
What determines the steady state concentration of a drug?

Steady state:

\[ \text{IN} = \text{OUT} \]

\[ \text{IN} = \text{DOSE} \times \text{F} \]

\[ \text{DRUG OUT} = \text{Volume of plasma cleared of drug per unit time} \times [\text{drug}] \text{ in plasma} \]

\[ \text{DRUG OUT} = \text{Clearance} \times [\text{Drug}] \]

OR

\[ \text{DOSE} \times \text{F} = \text{Cl} \times [\text{Drug}] \]
Clearances are mechanism independent

\[ \text{Dose} \times F = \text{Cl} \times [\text{Drug}] \]

If more than one route of elimination, then:

\[ \text{Cl}_{\text{Total}} = \text{Cl}_{\text{Hepatic}} + \text{Cl}_{\text{Renal}} + \text{Cl}_{\text{Other}} \]
Relationship between renal clearance and creatinine clearance

- Renal Cl often tracks CrCl making predictions easy
- What might it mean if slope of line greater than 1?
- What might it mean if slope of line less than 1?
- What if the y-axis was Cl_{Total} and y-intercept of line was 50 ml/min?
Extracorporeal drug removal: Hemodialysis and simple diffusion

- Extraction = \((C_{in} - C_{out})/C_{in}\); if 100% removed, then \(E = 1\)
- If \(E = 1\) than \(C_{dialysis} = \text{blood flow rate}\)
Extracorporeal drug removal: Hemodialysis and simple diffusion

Plasma  Semi-permeable Membrane  Dialysate

Only “free” drug can equilibrate effectively decreasing E and thus $C_l_{dialysis}$
But don’t forget about Volume of Distribution!

Even if $E = 1$, if drug is sequestered in tissue, clinical impact of extracorporeal clearance may be minimal. True for treatment of poisonings with large Vd drugs (Digoxin, TCA’s)

- Doxepin OD
- $E$ for charcoal hemoperfusion approx = 1
- But Vd = 25 L/kg

- So, hemoperfusion acutely lowered plasma concentration,
- But drug in tissues then entered plasma causing rebound in [ ] and symptoms
Extracorporeal drug removal: Hemofiltration and convection

- Pressure drives fluid movement, drug follows fluid
- Sieving Coefficient \( (S_c) = \frac{C_{UF}}{C_P} \)
Determinants of sieving coefficient

- Protein binding
  \[ Sc = 1 - \text{fraction protein bnd} \]
- Molecular weight
- Charge
- Water solubility

<table>
<thead>
<tr>
<th>Drug</th>
<th>Expected Sc</th>
<th>Observed Sc</th>
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</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.80</td>
<td>0.69</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.83</td>
<td>0.90</td>
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<tr>
<td>Ceftriaxone</td>
<td>0.15</td>
<td>0.20</td>
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<tr>
<td>Cyclosporine</td>
<td>0.10</td>
<td>0.58</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.80</td>
<td>0.70</td>
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<tr>
<td>Phenytoin</td>
<td>0.10</td>
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<tr>
<td>Metronidazole</td>
<td>0.80</td>
<td>0.84</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>0.10</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Plumbing circuitry matters

**A** Hemofiltration: 
*Postdilution mode*
Solute removal by convection

**B** Hemofiltration: 
*Predilution mode*
Solute, diluted by substitution fluid, removed by convection

**C** Hemodialysis:
Solute removal by diffusion depending on molecular weight

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**Drugs clearance**
- **A**: ultrafiltration rate
- **B**: (UF rate × blood flow)/ (blood flow + SF flow rate)
- **C**: depends on molecular weight (see Fig. 2)

*Bohler, Donauer & Keller, KI 72:S24-28, 1999*
Determinants of clearance by using hemofiltration

• Hemofiltration with post-dilution fluid replacement
  \[ Cl_{HF} = Q_{UF} \times S_c \]

• Hemofiltration in predilution mode, drug diluted prior to filtration
  \[ Cl_{HF} = (Q_{UF} \times S_c \times Q_{BF})/(Q_{BF} + Q_{RF}) \]
An example: vancomycin

Molecular weight 1486
Hydrophyllic

• 10 – 20% Plasma protein bound

• $\text{Cl}_{\text{sys}}$ approx 7.8 L/hr (130 ml/min) in healthy adult

• $\text{Cl}_{\text{Renal}}$ approx 5.4 L/hr (90 ml/min) in healthy adult

• $\text{Cl}_{\text{Non-renal}}$ therefore approx 2.4 L/hr (40 ml/min) in healthy adult
Predicting hemofiltration clearance for vancomycin

\[ \text{Cl}_{HF} = \frac{(Q_{UF} \times S_c \times Q_{BF})}{(Q_{BF} + Q_{RF})} \]

- \( S_c \) estimate at 0.8 based on protein binding
- \( Q_{BF} = 200 \text{ ml/min} \)
- \( Q_{UF} = 2 \text{ L/hr} \)
- \( Q_{RF} = 2 \text{ L/hr} \)

\[ \text{CL}_{HF} = 1.4 \text{ L/hr} \]

(remember \( \text{CL}_{Nonrenal} = 2.4 \text{ L/hr} \) in healthy, \( C_{SYS} \) would be predicted as 3.8 L/hr on HF)
### Vancomycin clearance during CVVHDF

DelDot ME, Lipman J and Tett SE, Br J Cin Pharmacol 58: 259, 2004

<table>
<thead>
<tr>
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<th>Predict</th>
<th>Actual</th>
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<tbody>
<tr>
<td>$\text{Cl}_{\text{CVVHDF}}$</td>
<td>1.4 L/hr</td>
<td>1.8 L/hr</td>
</tr>
<tr>
<td>$\text{Cl}_{\text{SYS}}$</td>
<td>3.8 L/hr</td>
<td>2.5 L/hr</td>
</tr>
<tr>
<td>$\text{Cl}_{\text{Nonrenal}}$</td>
<td>2.4 L/hr</td>
<td>0.7 L/hr</td>
</tr>
</tbody>
</table>

Nonrenal clearance decreased in renal failure!
Linezolid

MW = 337

- Protein binding 30%
- Renal and non-renal elimination

\[ \text{Cl}_{\text{Total}} = 120 \text{ ml/min} \]

\[ \frac{\text{Cl}_{\text{Renal}}}{1/3} \]

\[ \frac{\text{Cl}_{\text{Nonrenal}}}{2/3} \]
Linezolid and hemofiltration

• Estimate using $S_c$ of 0.7 $Cl_{HF} = 20 \text{ ml/min}$
  – vs. Healthy subjects est. $Cl_{Renal} 40 \text{ ml/min}$ and $Cl_{Nonrenal} 80 \text{ ml/min}$

• Data (Mauri LKS et al Am J Kid Dis 47:83, 2006)
  – $Cl_{HF} = 16 \text{ ml/min}$
  – $Cl_{Total} = 189 \text{ ml/min}$

• Thus, theory and data suggest linezolid dosing while on hemofiltration similar to that of healthy subjects
Doripenem

- Estimate $Sc = 0.9$
- Thus, if ultrafiltrate flow 2L/hr, estimate CL hemofiltration as 1.8 L/hr
- Observed = 1.22 L/hr (actual $Sc = 0.67$)

$MW = 438$
Protein binding = 8%
Healthy subjects
  - CL renal = 9.2 L/hr
  - CL nonrenal = 6.7 L/hr

Effect of flow rates on fluconazole hemofiltration clearance

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{Total}}$ (ml/min)</th>
<th>$C_{\text{HF}}$ (ml/min)</th>
<th>$C_{\text{Non-HF}}$ (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF 1L/hr</td>
<td>30</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>UF 2 L/hr</td>
<td>37</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

Bergner et al NDT 21:1019, 2006
Some last thoughts…

• Renal failure or severe illness may affect PK parameters other than Cl (protein binding, third spacing of fluid, etc)

• Half-life as hybrid parameter

\[ t_{1/2} = (0.69) \times \text{Vd/Cl} \]

• Vary amount per dose or dosing interval?
  – Does peak concentration matter, time above MIC or AUC/MIC (for efficacy or toxicity)
Some last thoughts…

References with specific information:
– Trotman et al, Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy, Clin Infect Dis, 41: 1159, 2005
SUMMARY

- Pharmacokinetics can:
  - Quantify the time course of drug concentrations/action
  - Allow prediction of factors that affect drug handling, both on population and individual patient levels

- Hemodialysis (by diffusion) and hemofiltration (by convection) can result in drug elimination
  - Factors affecting drug elimination by these modalities well understand and can be predicted
  - Understanding of the principles underlying drug elimination by these techniques and of pharmacokinetic principles allows for rational drug dosing