Effects of Renal Disease on Pharmacokinetics

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GOALS of Effects of Renal Disease on Pharmacokinetics Lecture

A. Dose Adjustment in patients with renal Impairment
B. Effect of Renal Disease on:
   Renal Drug Elimination
   Hepatic Drug Metabolism
   Drug Transporters
   Drug Distribution
   Drug Absorption

GOALS Of Effects of Renal Disease on PK Lecture

• DOSE ADJUSTMENT in Patients with Renal Impairment

Statement of the Problem

How is renal function assessed?

How is drug dose adjusted based on this assessment?
**Central Role of DRUG LABEL**

The DRUG LABEL is the primary source of drug prescribing information and is *reviewed by the FDA* as part of the drug approval process.

As such the drug label is a *distillate of the entire drug development process.*

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**INFORMATION CONTENT OF CURRENT DRUG LABELS***

<table>
<thead>
<tr>
<th>Core Information Category</th>
<th>Inclusion of Desirable Data Elements</th>
<th>MEAN (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MECHANISM OF ACTION</td>
<td>88% (84% - 93%)</td>
<td></td>
</tr>
<tr>
<td>PHARMACODYNAMICS</td>
<td>43% (37% - 49%)</td>
<td></td>
</tr>
<tr>
<td>DRUG METABOLISM</td>
<td>23% (16% - 29%)</td>
<td></td>
</tr>
<tr>
<td>PHARMACOKINETICS</td>
<td>42% (35% - 49%)</td>
<td></td>
</tr>
<tr>
<td>DOSE ADJUSTMENT</td>
<td>37% (32% - 42%)</td>
<td></td>
</tr>
</tbody>
</table>

FDA GUIDANCE FOR INDUSTRY

PHARMACOKINETICS IN PATIENTS WITH IMPAIRED RENAL FUNCTION – Study Design, Data Analysis, and Impact on Dosing and Labeling (1998)

AVAILABLE AT:
http://www.fda.gov/cder/guidance/index.htm

GOALS of Renal Disease Effects Lecture

• DOSE ADJUSTMENT in Patients with Renal Impairment
  - Statement of the Problem
  - How is renal function assessed?
  - How is drug dose adjusted based on this assessment?

ELIMINATION by Different Routes

<table>
<thead>
<tr>
<th>MEASUREMENTS</th>
<th>RENAL</th>
<th>HEPATIC</th>
<th>DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Flow</td>
<td>+*</td>
<td>+*</td>
<td>+</td>
</tr>
<tr>
<td>Afferent Concentration</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Efferent Concentration</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Eliminated Drug</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

*not actually measured in routine PK studies
RENAL CLEARANCE EQUATION

\[ CL = \frac{U \times V}{P} \]

\( U \) = URINE CONCENTRATION
\( V \) = URINE VOLUME / TIME
\( P \) = PLASMA CONCENTRATION

CLEARANCE TECHNIQUES FOR ASSESSING RENAL FUNCTION

**GLOMERULAR FILTRATION:**
- Normal: 120 – 130 mL/min/1.73 m²

**CLEARANCE MARKERS:**
- Inulin
- Creatinine
- \(^{125}\)I-Iothalamate

**RENAL BLOOD FLOW:**
- Normal: ♂ 1,209 ± 256 mL/min/1.73 m²
  ♀ 982 ± 184 mL/min/1.73 m²

**CLEARANCE MARKER:**
- Para-Aminomhippuric Acid

GOALS of Renal Disease Effects Lecture
- **How is renal function assessed?**
  Commonly estimated from the *Cockcroft and Gault equation* for creatinine clearance if renal function is stable, but the *Modification of Diet in Renal Disease (MDRD) Study equation* for estimating GFR has been used also.
Estimation of GFR

- The MDRD equation to estimate GFR from serum creatinine is the most accurate compared to the (125)I-iothalamate standard.
- However, it is biased and tends to underestimate high GFRs and also overestimates low GFRs.
- Not validated in the elderly population


http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_conn.htm

Renal Clearance of Drugs

- Generally, there is a linear correlation between the clearance of creatinine and the clearance of drugs excreted via the kidneys.
- We take advantage of this correlation when making dose adjustments in patients with impaired renal function.

STEADY STATE CONCENTRATION

Continuous Infusion:

$$C_{\text{ss}} = \frac{I}{CL_e}$$

Intermittent Dosing:

$$C_{\text{ss}} = \frac{\text{DOSE}/\tau}{CL_e}$$
ADDITIVITY OF CLEARANCES

\[ \text{CL}_E = \text{CL}_R + \text{CL}_\text{NR} \]

\( \text{CL}_R = \text{RENALE CLEARANCE} \)
\( \text{CL}_\text{NR} = \text{NON-RENAL CLEARANCE} \)

DETTLI Approach*

\[ \text{CL}_R = \alpha \text{CL}_{\text{Cr}} \]
\[ \text{CL}_E = \text{CL}_R + \text{CL}_\text{NR} \]

* Dettli L. Med Clin North Am 1974;58:977-85
**NOMOGRAM FOR CIMETIDINE DOSING***


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**Key ASSUMPTIONS of Dettli Method**

- $\text{CL}_{\text{NR}}$ remains CONSTANT when renal function is impaired.
- $\text{CL}_{\text{R}}$ declines in LINEAR FASHION with CL$_{\text{CR}}$

  - *Intact Nephron* Hypothesis
  - Some drugs ↓ SECRETION > GFR
    with aging*


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**CIMETIDINE Case History**

A 67-year-old veteran had been functionally anephric, requiring outpatient hemodialysis for several years. He was hospitalized for revision of his arteriovenous shunt and postoperatively complained of symptoms of gastroesophageal reflux. This complaint prompted institution of cimetidine therapy in a dose of 300 mg every 6 hours.
**CIMETIDINE Case History (cont.)**

*Rationale for Prescribed Cimetidine Dose:*

*At that time, 600 mg every 6 hours was the usual cimetidine dose for patients with normal renal function and the Physician’s Desk Reference recommended halving the cimetidine dose for patients “with creatinine clearance less than 30 cc/min”.*

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**CIMETIDINE Case History (cont.)**

Three days later the patient was noted to be confused. The nephrology team reevaluated the patient and agreed to discontinue cimetidine as suggested by the attending internist/clinical pharmacologist. Two days later the patient was alert and was discharged from the hospital to resume outpatient hemodialysis therapy.

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**LABELING FOR CIMETIDINE***

- **DOSE ADJUSTMENT**
  1/2 normal dose if CL_{cr} < 30 mL/min

- **PHARMACOKINETICS**
  Following I.V. or I.M. administration in normal subjects,
  ~ 75% of drug is recovered from the urine as parent compound.

**NOMOGRAM FOR CIMETIDINE DOSING**

![Graph showing dosing options for CIMETIDINE based on renal clearance.]


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**DOSE ADJUSTMENT OPTIONS FOR PATIENTS WITH RENAL IMPAIRMENT**

\[ \text{Dose} = \frac{\text{DOSE} \times \tau}{\text{CL}_{\text{E}}} \]

- MAINTAIN USUAL DOSING INTERVAL BUT **REDUCE DOSE** IN PROPORTION TO \( \downarrow \text{CL}_{\text{E}} \)
- MAINTAIN USUAL DOSE BUT **INCREASE DOSING INTERVAL** IN PROPORTION TO \( \downarrow \text{CL}_{\text{E}} \)
- **ADJUST BOTH** DOSE AND DOSING INTERVAL

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**GOALS of Renal Disease Effects Lecture**

- **EFFECT OF RENAL DISEASE ON RENAL DRUG ELIMINATION**
  - **MECHANISMS** OF RENAL DRUG ELIMINATION
  - CONCEPT OF **RESTRICTIVE** VS. **NONRESTRICTIVE** ELIMINATION
MECHANISMS of Renal Drug Elimination

- Glomerular Filtration
- Renal Tubular Secretion
- Reabsorption by Non-Ionic Diffusion
- Active Reabsorption

MECHANISMS OF RENAL ELIMINATION

GLomerular Filtration
- Affects all drugs and metabolites of appropriate molecular size.
- Influenced by protein binding
  \[
  \text{Drug Filtration Rate} = \text{GFR} \times f_u \times [\text{Drug}]
  \]
  \(f_u\) = free fraction

RENal Tubular Secretion
- Not influenced by protein binding
- May be affected by other drugs, etc.

EXAMPLES:
- Active Drugs: ACIDS – Penicillin
  BASES – Procainamide
- Metabolites: Glucuronides, Hippurates, etc.

RESTRICTIVE VS. NONRESTRICTIVE ELIMINATION

RESTRICTIVE:
Clearance DEPENDS on Protein Binding.
- KIDNEY: Drug Filtration Rate = \(f_u \times \text{GFR}\)
- LIVER: \(\text{CL} = f_u \times \text{Cl}_{int}\)

NONRESTRICTIVE:
Clearance INDEPENDENT of Protein Binding
- KIDNEY: \(\text{CL} = Q\) (renal blood flow)

EXAMPLE: PARA-AMINOHIPPURATE CLEARANCE MEASURES RENAL BLOOD FLOW.
INTRINSIC CLEARANCE

*INTRINSIC CLEARANCE* is the elimination clearance that *would be observed in the absence of any protein binding restrictions.*

RESTRICTIVE VS. NONRESTRICTIVE ELIMINATION

**RESTRICTIVE:**
Clearance *DEPENDS* on Protein Binding
KIDNEY: Drug Filtration Rate = $f_U \cdot GFR$
LIVER: $CL = f_U \cdot Cl_{int}$

**NONRESTRICTIVE:**
Clearance *INDEPENDENT* of Protein Binding
KIDNEY: $CL = Q$ (renal blood flow)
LIVER: $CL = Q$ (hepatic blood flow)

Renal REABSORPTION Mechanisms

**REABSORPTION BY NON-IONIC DIFFUSION**
- Affects *weak acids* and *weak bases*.
- Only important if excretion of *free drug* is major elimination pathway.

**EXAMPLES:**
- Weak Acids: PHENOBARBITAL
- Weak Bases: QUINIDINE

**ACTIVE REABSORPTION**
- Affects *ions*, not proved for other drugs.

**EXAMPLES:**
- Halides: FLUORIDE, BROMIDE
- Alkaline Metals: LITHIUM
RENAL EXCRETION of DRUGS

INTACT NEPHRON HYPOTHESIS: Provides a basis for dose adjustment when renal excretion of drug is impaired.

- Regardless of mechanism, renal drug elimination declines in parallel with decreases in GFR.
- Therefore, ClCr can be used to assess impact of renal impairment on renal excretion of drugs.

WHAT ABOUT OTHER EXCRETION ROUTES?

GOALS of Renal Disease Effects Lecture

- EFFECT OF RENAL DISEASE ON DRUG METABOLISM and TRANSPORT

CRF – Effects on Drug Metabolism and Transport

Recent Reviews on this topic:

TD Nolin, J Naud, FA Leblond, V Pichette
Emerging Evidence of the Impact of Kidney Disease on Drug Metabolism and Transport
CRF – Effects on Drug Metabolism and Transport

Recent Reviews on this topic:

AW Dreisbach, J JL Lertora
The effect of chronic renal failure on drug metabolism and transport
*Expert Opin. Drug Metab. Toxicol.*
2008;4:1065-1074

Effect of CRF on Non-Renal Drug Clearance in Humans

<table>
<thead>
<tr>
<th>CLNR (%)</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril - 50</td>
<td>TPMT</td>
</tr>
<tr>
<td>Morphine - 40</td>
<td>UGT2B7</td>
</tr>
<tr>
<td>Procainamide - 60</td>
<td>NAT-2</td>
</tr>
<tr>
<td>Verapamil - 54</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Metoclopramide - 66</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Warfarin - 50</td>
<td>CYP2C9</td>
</tr>
</tbody>
</table>

Effect of CRF on Drug Transport

Impaired transport function in renal failure (intestine, liver, kidney)

- P-Glycoprotein
- Organic Anion Transporting Polypeptide (OATP)

*Fexofenadine is a substrate for both*
Effect of CRF on Bioavailability

Studies in human subjects:

- Propranolol +300 % CYP2D6
- Erythromycin +100 % CYP3A4
- Propoxyphene +100 % CYP3A4
- Dyhydrocodeine +70 % CYP2D6

Effects of Uremic Toxins

- Indoxyl sulfate
- CMPF-propanoic acid
- Parathyroid hormone (PTH)
- Cytokines (chronic inflammation)

Inhibition of drug metabolism and transport reversed by hemodialysis

Phase I and Phase II Metabolic Reactions

- Hydroxylation
- Glucuronide conjugation
GOALS of Renal Disease Effects Lecture

- EFFECT OF RENAL DISEASE ON DRUG METABOLISM

- EXAMPLES:
  - PROCAINAMIDE - Acetylation
  - PHENYTOIN - Hydroxylation

PROCAINAMIDE ACETYLATION

PROCAINAMIDE Kinetics in DIALYSIS PATIENTS*

<table>
<thead>
<tr>
<th></th>
<th>Fast</th>
<th>Slow</th>
<th>Fast</th>
<th>Slow</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>2.6</td>
<td>3.5</td>
<td>17.0</td>
<td>12.2</td>
</tr>
<tr>
<td>$C_{L_E}$ (L/kg)</td>
<td>600</td>
<td>809</td>
<td>94</td>
<td>118</td>
</tr>
<tr>
<td>$C_{L_R}$ (L/kg)</td>
<td>357</td>
<td>426</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$C_{L_{inR}}$ (L/kg)</td>
<td>243</td>
<td>383</td>
<td>94</td>
<td>118</td>
</tr>
<tr>
<td>$V_{d_{ss}}$ (L/kg)</td>
<td>1.93</td>
<td>1.95</td>
<td>1.93</td>
<td>1.41</td>
</tr>
</tbody>
</table>

Procainamide Dosing Nomogram (Fast Acetylators)

**CL\textsubscript{Cr} [mL/min]**

**PA Clearance [mL/min]**

\[ \text{CL}_e = \text{CL}_n + \text{CL}_\text{log} \]

NAPA Elimination Half Life in Functionally Anephric Patients

- **Healthy Subjects:** 6.2 hr
- **Predicted** for Dialysis Patients: 42.8 hr *
- **Measured** in Dialysis Patients: 41.9 hr *

* See Study Problem at end of Chapter 5.

Phenytoin Hydroxylation by P450

Phenytoin \( p - \text{HPPH} \)

CYP2C9: Major, CYP2C19: Minor
Effect of Renal Disease on PHENYTOIN PROTEIN BINDING

[Graph showing % unbound phenytoin vs. serum creatinine, with data points for normals and uremic patients, and symbols for dialed and non-dialized patients.]

Effect of Renal Disease on PHENYTOIN PROTEIN BINDING

<table>
<thead>
<tr>
<th></th>
<th>Normal (N = 4)</th>
<th>Uremic (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Unbound (fu)</td>
<td>12%</td>
<td>26%</td>
</tr>
<tr>
<td>CL_H</td>
<td>2.46 L/hr</td>
<td>7.63 L/hr</td>
</tr>
<tr>
<td>CL_int</td>
<td>20.3 L/hr</td>
<td>29.9 L/hr</td>
</tr>
</tbody>
</table>

CL_H = fu • CL_int, So: CL_int = CL_H/fu


Effect of PROTEIN BINDING Changes on Phenytoin Plasma Concentration

\[ \bar{C}_{\text{SS}} = \frac{\text{DOSE}}{\tau \cdot CL_E} \]

PHENYTOIN > 98% ELIMINATED BY HEPATIC METABOLISM, SO CL_E = CL_H

\[ \bar{C}_{\text{SS, u}} / f_u = \frac{\text{DOSE}}{f_u \cdot CL_{\text{INT}}} \]
FREE AND TOTAL PHENYTOIN LEVELS
(DoSE = 300 MG/DAY)

NORMAL RENAL FUNCTION

FUNCTIONALLY ANEPHRIC

CLH

\[ \text{CLINT} = \text{CLH} \]

\[ \text{BOUND PHENYTOIN} \]

\[ \text{FREE PHENYTOIN} \]

[PHENYTOIN] \( \mu g/mL \)

0 2 4 6 8 10 12

RISK is that TOTAL levels below the usual range of 10 – 20 \( \mu g/mL \) will prompt inappropriate dose adjustment in dialysis patients.

THERAPEUTIC RANGE FOR DIALYSIS PTS:
Based on “Total Levels”: 5 - 10 \( \mu g/mL \)
Based on “Free Levels”: 0.8 - 1.6 \( \mu g/mL \)

GOALS of Renal Disease Effects Lecture

- EFFECT OF RENAL DISEASE ON DRUG DISTRIBUTION
  - PLASMA PROTEIN BINDING
    
    EXAMPLE: PHENYTOIN
  - TISSUE BINDING
    
    EXAMPLE: DIGOXIN
Effect of Renal Disease on Binding to Plasma Proteins*

**BASIC OR NEUTRAL DRUGS:** NORMAL OR SLIGHTLY REDUCED

**ACIDIC DRUGS:** REDUCED FOR MOST


Effect of Binding Changes on Apparent Distribution Volume*

\[ V_d = ECF + \Phi f_u (TBW - ECF) \]

\( \Phi = \text{TISSUE/PLASMA PARTITION RATIO} \)

\( f_u = \text{FRACTION NOT BOUND TO PLASMA PROTEINS} \)

FOR PHENYTOIN: \( \Phi = 10.4 \)


Phenytoin Distribution in Dialysis Patients*

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Uremic Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Unbound ((f_u))</td>
<td>12%†</td>
<td>26%</td>
</tr>
<tr>
<td>(V_d) (AREA)</td>
<td>0.64 L/kg</td>
<td>1.40 L/kg</td>
</tr>
</tbody>
</table>

† USUAL VALUE IN NORMAL SUBJECTS ~ 9%

GOALS OF RENAL DISEASE EFFECTS LECTURE

• EFFECT OF RENAL DISEASE ON DRUG DISTRIBUTION
  - PLASMA PROTEIN BINDING
    EXAMPLE: PHENYTOIN
  - TISSUE BINDING
    EXAMPLE: DIGOXIN

IMPAIRED RENAL FUNCTION REDUCES DIGOXIN DISTRIBUTION VOLUME*

\[ V_d = 3.84 \times \text{wt (kg)} + 3.12 \times \text{CL}_{\text{Cr}} \text{(mL/min)} \]


CRITERIA FOR NORMAL ABSORPTION OF 25 GRAM D-XYLOSE DOSE

- 5-hr URINE RECOVERY \( > 4 \text{ g} \)
- [SERUM] 1 hr AFTER DOSE \( \geq 0.2 \text{ mg/mL} \)
- % DOSE ABSORBED \( > 42\% \)
- \( k_a > 0.37 \text{ hr}^{-1} \)
**EFFECT OF RENAL DISEASE ON D-XYLOSE ABSORPTION**

<table>
<thead>
<tr>
<th>PATIENT GROUP</th>
<th>$k_{s}$ (hr⁻¹)</th>
<th>$k_{a}$ (hr⁻¹)</th>
<th>% DOSE ABSORBED</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMALS</td>
<td>1.03 ± 0.33</td>
<td>0.49 ± 0.35</td>
<td>69.4 ± 13.6</td>
</tr>
<tr>
<td>MODERATE</td>
<td>0.64 ± 0.28</td>
<td>0.19 ± 0.15</td>
<td>77.4 ± 14.8</td>
</tr>
<tr>
<td>DIALYSIS</td>
<td>0.56 ± 0.42</td>
<td>0.67 ± 0.61</td>
<td>48.6 ± 13.3</td>
</tr>
</tbody>
</table>


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**FUROSEMIDE**

![Furomide molecule](image)

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**BIOPHARMACEUTIC CLASSIFICATION OF FUROSEMIDE**

BIOPHARMACEUTIC DRUG CLASSIFICATION OF FUROSEMIDE *

CLASS IV:  
LOW SOLUBILITY-LOW PERMEABILITY  

- *in vitro – *in vivo correlation poor  
- good bioavailability not expected  


Biopharmaceuticals Classification System (BCS)  

- Class I (high S, high P)  
  *Enzyme effects* predominate  
- Class II (low S, high P)  
  *Both* enzymes and transporters  
- Class III (high S, low P)  
  *Transporter effects* predominate  


FDA GUIDANCE FOR INDUSTRY  

*PHARMACOKINETICS IN PATIENTS WITH IMPAIRED RENAL FUNCTION* – Study  
Design, Data Analysis, and Impact on Dosing and Labeling  

AVAILABLE AT:  
http://www.fda.gov/cder/guidance/index.htm
BASIC “FULL” STUDY DESIGN

Effects of Hemodialysis

Advanced CRF:
Stage IV (GFR 15-29 ml/min)
Stage V (GFR 0-15 ml/min)

Hemodialysis may reverse the inhibition of drug metabolizing enzymes and transporters

FDA GUIDANCE FOR INDUSTRY

• A revision of this guidance document is currently under way (2008).
• A concept paper/draft guidance has been posted by the FDA regarding revised recommendations for PK studies in patients with impaired renal function.


(document pages 57-73)