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?

PATHOPHYSIOLOGIC FACTORS
NOT ACCOUNTED FOR IN DRUG DOSING*

Pie chart showing Advanced age (42%), Renal impairment (33%), Patient Weight (19%), and Other (6%).

***Lesar TS, Briceland L, Stein DS. JAMA 1997;277:312-7.**

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.*

INFORMATION CONTENT
OF CURRENT DRUG LABELS*

CORE INFORMATION CATEGORY	Inclusion of Desirable Data Elements MEAN (95% CI)
MECHANISM OF ACTION	**88% (84% - 93%)**
PHARMACODYNAMICS	**43% (37% - 49%)**
DRUG METABOLISM	**23% (16% - 29%)**
PHARMACOKINETICS	**42% (35% - 49%)**
DOSE ADJUSTMENT	**37% (32% - 42%)**

Chart showing that as of year 2000 desirable data on drug metabolism, pharmacokinetics and dose adjustment were included in only 23%, 42%, and 37% of drug labels, respectively.

*** Spyker DA, et al. Clin Pharmacol Ther 2000;67:196-200.**

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

MEASUREMENTS	RENAL	HEPATIC	DIALYSIS
Blood Flow	+*	+*	+
Afferent Concentration	+	+	+
Efferent Concentration	**0**	**0**	+
Eliminated Drug	+	**0**	+

not actually measured in routine PK studies

RENAL CLEARANCE EQUATION

Clearance is urinary excretion rate divided by plasma concentration.

CLEARANCE TECHNIQUES FOR ASSESSING RENAL FUNCTION

GLOMERULAR FILTRATION:

Normal: 120 – 130 mL/min/1.73 m2

***CLEARANCE MARKERS*:**

Inulin

Creatinine

125I-Iothalamate

RENAL BLOOD FLOW:

Normal: male 1,209 ± 256 mL/min/1.73 m2

female 982 ± 184 mL/min/1.73 m2

***CLEARANCE MARKER*:**

Para-Aminohippuric 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 is now the preferred approach.

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 tends to underestimate high GFRs and also overestimates low GFRs.

Levey AS et al. *Ann Intern Med. 2006;145-247-254*

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

Equations for Continuous Infusion and Intermittent Dosing.

The steady-state concentration is directly related to dosing rate and inversely related to elimination clearance.

ADDITIVITY OF CLEARANCES

Formula showing that total elimination clearance equals the sum of renal and nonrenal clearances.

DETTLI Approach*

Formulas indicating that renal clearance of drugs is proportional to creatinine clearance.

*** Dettli L. Med Clin North Am 1974;58:977-85**

NOMOGRAM FOR CIMETIDINE DOSING*

Chart showing elimination clearance as the sum of nonrenal clearance and renal clearance for cimetidine.

Renal clearance varies as a function of creatinine clearance.

Key *ASSUMPTIONS* of Dettli Method

- CLNR remains *CONSTANT* when renal function is impaired.

- **CLR declines in *LINEAR FASHION* with CLCR**

***Intact Nephron* Hypothesis**

- **Some drugs ↓ *SECRETION* > *GFR* with aging***

*** Reidenberg MM, et al. Clin Pharmacol Ther 1980;28:732-5.**

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".

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.

LABELING FOR CIMETIDINE*

- DOSAGE ADJUSTMENT

1/2 normal dose if CLCr < 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*.

*** Physician's Desk Reference. 58th edition, 2004.**

NOMOGRAM FOR CIMETIDINE DOSING*

Chart showing that **CLE ≈ 25% OF NORMAL IF FUNCTIONALLY ANEPRHIC**

***From: Atkinson AJ Jr, Craig RM. Therapy of peptic ulcer disease.**

DOSE ADJUSTMENT OPTIONS FOR PATIENTS WITH RENAL IMPAIRMENT

Formula for steady-state concentration with intermittent dosing.

- MAINTAIN USUAL DOSING INTERVAL BUT *REDUCE DOSE* IN PROPORTION TO ↓CLE

- MAINTAIN USUAL DOSE BUT *INCREASE DOSING INTERVAL* IN PROPORTION TO ↓CLE

- *ADJUST BOTH* DOSE AND DOSING INTERVAL

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**

  Drug Filtration Rate = GFR x fu x [Drug]

  (fu = 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 = fU x GFR
LIVER: CL = fU x Clint

NONRESTRICTIVE:
Clearance *INDEPENDENT* of Protein Binding
KIDNEY: 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 = fU x GFR
LIVER: CL = fU x Clint

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

<u>INTACT NEPHRON HYPOTHESIS</u>: 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

Clin. Pharmacol. Ther. 2008;83:898-903

CRF – Effects on Drug Metabolism and Transport

Recent Reviews on this topic:

AW Dreisbach, JJL 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

	CL_{NR} (%)	Enzyme
Captopril	- 50	TPMT
Morphine	- 40	UGT2B7
Procainamide	- 60	NAT-2
Verapamil	- 54	CYP3A4
Metoclopramide	- 66	CYP2D6
Warfarin	- 50	CYP2C9

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

Chemical structures of Phenytoin Phase I hydroxylation and Phase II Glucuronide Conjugation.

GOALS of Renal Disease Effects Lecture

- EFFECT OF RENAL DISEASE ON *DRUG METABOLISM*

- ***EXAMPLES:***
  PROCAINAMIDE - Acetylation
  PHENYTOIN - Hydroxylation

PROCAINAMIDE *ACETYLATION*

Chemical structure of procainamide acetylation to NAPA.

Procainamide Kinetics in *DIALYSIS PATIENTS**

	NORMALS		*FUNCTIONALLY ANEPHRIC PATIENTS*	
	Fast	**Slow**	**Fast**	**Slow**
T1/2 (hr)	**2.6**	**3.5**	**12.2**	**17.0**
CLE (L/kg)	**809**	**600**	**118**	**94**
CLR (L/kg)	**426**	**357**	**0**	**0**
CLNR (L/kg)	**383**	**243**	**118**	**94**
Vd(ss) (L/kg)	**1.95**	**1.93**	**1.41**	**1.93**

*** From: Gibson TP. Kidney Int 1977;12:422-9.**

Procainamide Dosing Nomogram
(*FAST ACETYLATORS)*

Chart showing PA renal and nonrenal clearance (mL/min) with increasing levels of Clcr[mL/min]

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

Chemical structure of phenytoin hydroxylation

CYP2C9: Major, CYP2C19: Minor

Effect of Renal Disease on
PHENYTOIN PROTEIN BINDING

Chart showing increasing % of unbound DPH with increasing serum Creatinine (mg/100 ml).

PHENYTOIN

*KINETICS IN DIALYSIS PATIENTS**

	NORMALS (N = 4)	UREMIC PATIENTS (N = 4)
% UNBOUND (fu)	12%	26%
CLH	2.46 L/hr	7.63 L/hr
CLint	20.3 L/hr	29.9 L/hr

Formulas for intrinsic clearance

***From: Odar-Cederlöf I, Borgå O: Eur J Clin Pharmacol 1974;7:31-7.**

Effect of *PROTEIN BINDING Changes* on Phenytoin Plasma Concentration

Formula

PHENYTOIN > 98% ELIMINATED BY HEPATIC METABOLISM, SO CLE = CLh

Formula

FREE AND *TOTAL* PHENYTOIN LEVELS
(DOSE = 300 MG/DAY)

Chart illustrating these levels.

The free fraction of phenytoin is increased but the free drug concentration is the same in functionally anephric patients.

THERAPEUTIC RANGE of Phenytoin Levels in *Dialysis Patients*

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

THERAPEUTIC RANGE FOR DIALYSIS PTS:

Based on "Total Levels": 5 - 10 µg/mL

Based on "Free Levels": 0.8 - 1.6 µg/mL

GOALS of Renal Disease Effects Lecture

EFFECT OF RENAL DISEASE ON DRUG DISTRIBUTION

- **PLASMA PROTEIN BINDING**

  ***EXAMPLE*: PHENYTOIN**

- **ISSUE 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**

*** From: Reidenberg MM, Drayer DE: Clin Pharmacokinet 1984;9(Suppl. 1):18-26.**

Effect of Binding Changes on *APPARENT DISTRIBUTION VOLUME**

Formula to estimate phenytoin VD

*** Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.**

PHENYTOIN *DISTRIBUTION* IN *DIALYSIS* PATIENTS*

	NORMALS	UREMIC PATIENTS
% UNBOUND (fu)	**12%†**	**26%**
Vd(AREA)	**0.64 L/kg**	**1.40 L/kg**

† USUAL VALUE IN NORMAL SUBJECTS ~ 9%

*** From: Odar-Cederlöf I, Borgå O: Eur J Clin Pharmacol 1974;7:31-7.**

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**

Formula to estimate digoxin VD as a function of creatinine clearance.

*** Sheiner LB, et al. J Pharmacokinet Biopharm 1977;5:445-79.**

CRITERIA FOR NORMAL *ABSORPTION* OF 25 GRAM D-XYLOSE DOSE

5-hr URINE RECOVERY	**>**	**4 g**
[SERUM] 1 hr AFTER DOSE		**≥ 0.2 mg/mL**
% DOSE ABSORBED		**> 42%**
ka		**> 0.37 hr-1**

EFFECT OF RENAL DISEASE ON D-XYLOSE *ABSORPTION**

Chart comparing normals, moderates and dialysis patients showing the % of dose absorbed for each group. Absorption is impaired in dialysis patients.

*** From: Worwag EM et al. Clin Pharmacol Ther 1987;41:351-7.**

FUROSEMIDE

Chemical structure of Furosemide, a loop diuretic.

BIOPHARMACEUTIC CLASSIFICATION OF FUROSEMIDE*

Chart illustrating that furosemide has low permeability for intestinal absorption.

*** From: Lenneräs. J Pharm Pharmacol 1997;49:627-38.**

BIOPHARMACEUTIC DRUG CLASSIFICATION OF FUROSEMIDE *

CLASS IV:
LOW SOLUBILITY-LOW PERMEABILITY

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

*** From: Lenneräs, et al. Pharm Res 1995;12:S396/**

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**

Sun H, et al (2006)
Amidon GI, et al (1995)

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

Chart showing reductions in creatinine clearance with increasing severity of renal disease.

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)