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

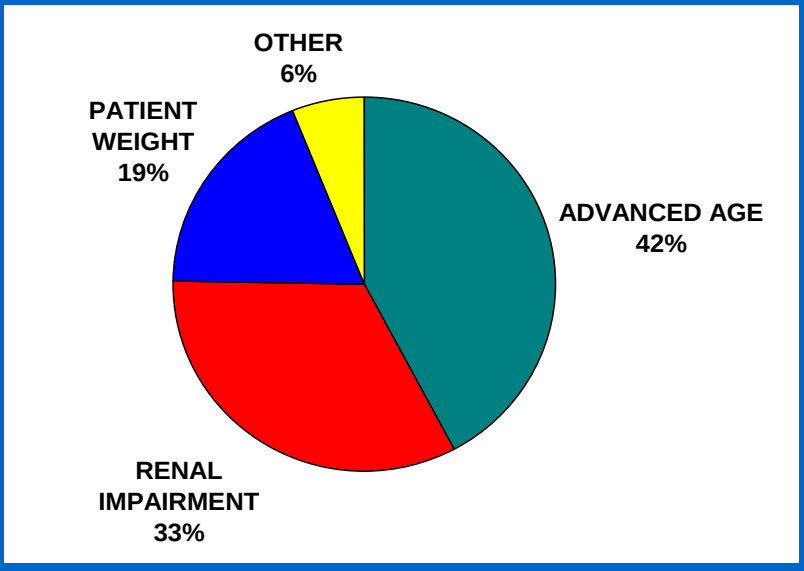
- ***DOSE ADJUSTMENT* in Patients with Renal Impairment**

  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*



* 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%)

* 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

$$CL = \frac{U \times V}{P}$$

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 m^2

***CLEARANCE MARKERS*:**

Inulin

Creatinine

^{125}I-Iothalamate

RENAL BLOOD FLOW:

Normal: 1,209 256 mL/min/1.73 m^2

982 184 mL/min/1.73 m^2

***CLEARANCE MARKER*:**

Para-Aminohippuric Acid

GOALS of Renal Disease Effects Lecture

- **How is renal function assessed?**

***If renal function is stable*, commonly estimated from the *Cockcroft and Gault equation* for creatinine clearance, or the *Modification of Diet in Renal Disease (MDRD) Study equation* for estimating GFR .**

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.
- Not validated in the elderly population

Levey AS et al. *Ann Intern Med. 2006;145:247-254*
Lalonde RL, Wagner JA. *Clin Pharmacol Ther 2009;86:557-561*

Assessment of Renal Function

- **Cockcroft-Gault equation:**
- ***Creatinine Clearance:*** **ml/min**

- **MDRD Study equation:**
- ***eGFR:*** **ml/min/1.73 meter square**

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:

$$C_{SS} = \frac{I}{CL_E}$$

Intermittent Dosing:

$$\overline{C}_{SS} = \frac{DOSE \,/\, \tau}{CL_E}$$

Professor Luzius Dettli

Clin. Pharmacol. Ther. Nov 2009

Focus: Nephro-pharmacology

ADDITIVITY OF CLEARANCES

$$CL_E = CL_R + CL_{NR}$$

CL_R = RENAL CLEARANCE

CL_{NR} = NON-RENAL CLEARANCE

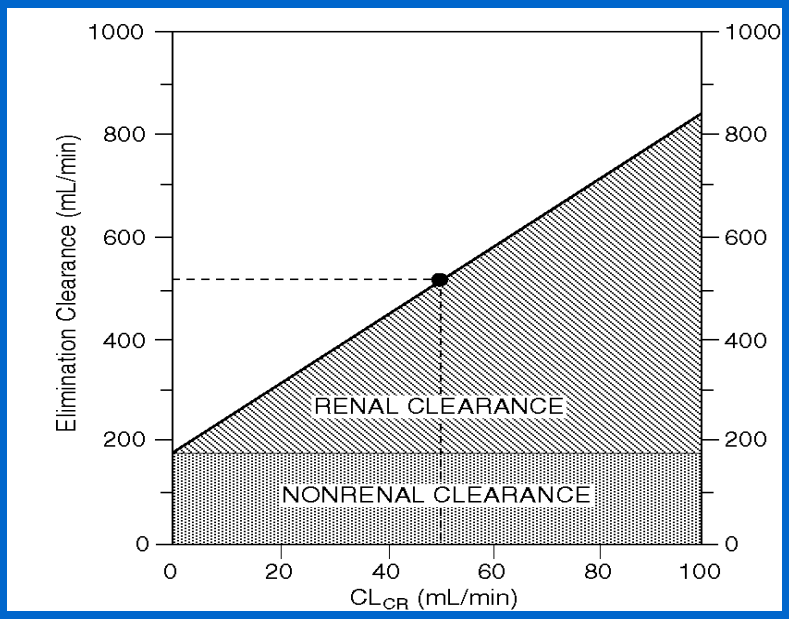
DETTLI Approach*

$$CL_R = \alpha\, CL_{Cr}$$

$$CL_E = CL_R + CL_{NR}$$

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

NOMOGRAM FOR CIMETIDINE DOSING*



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

Key *ASSUMPTIONS* of Dettli Method

- CL_{NR} remains *CONSTANT* when renal function is impaired.
- CL_R declines in *LINEAR FASHION* with CL_{CR}
  - *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 CL_{Cr} < 30 mL/min

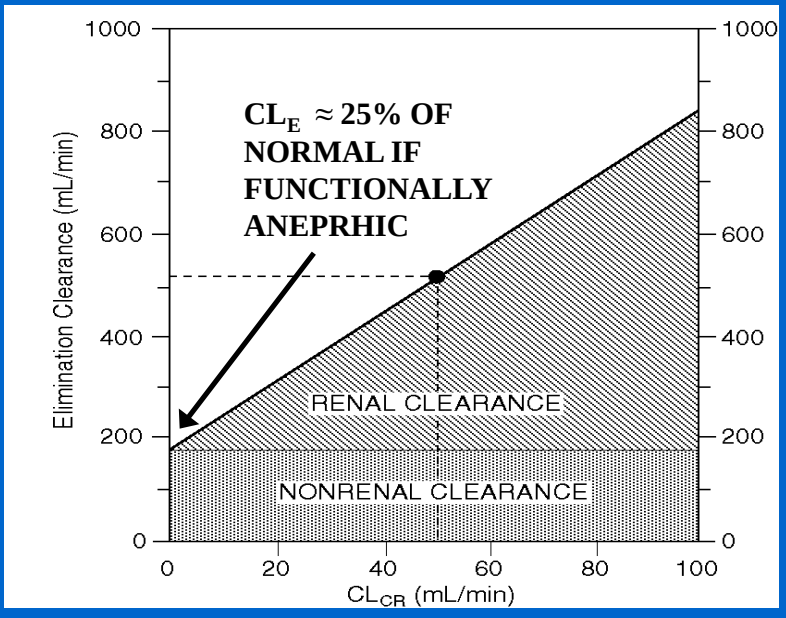
- **PHARMACOKINETICS**

  Following I.V. or I.M. administration in *normal subjects*,

  ~ 75% of drug is recovered from the urine as *parent compound*.

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

NOMOGRAM FOR CIMETIDINE DOSING*



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

DOSE ADJUSTMENT OPTIONS FOR PATIENTS WITH RENAL IMPAIRMENT

$$\overline{C}_{SS} = \frac{DOSE\ /\tau}{CL_E}$$

- MAINTAIN USUAL DOSING INTERVAL BUT *REDUCE DOSE* IN PROPORTION TO $\downarrow CL_E$
- MAINTAIN USUAL DOSE BUT *INCREASE DOSING INTERVAL* IN PROPORTION TO $\downarrow CL_E$
- *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 f_u x [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 • GFR
LIVER: CL = f_U • Cl_{int}

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 = f_U • GFR

LIVER: CL = f_U • 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, CL_{Cr} 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

The influence of chronic renal failure on drug metabolism and transport.

Clin. Pharmacol. Ther. 2009;86:553-556

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:

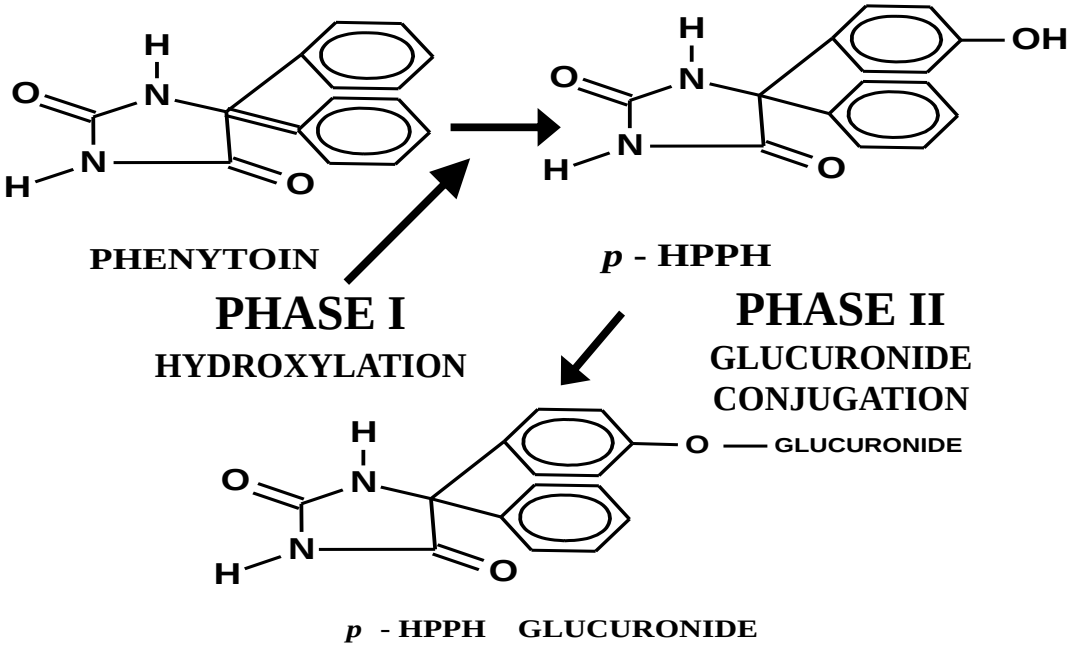
Propranolol	**+300 %**	**CYP2D6**
Erythromycin	**+100 %**	**CYP3A4**
Propoxyphene	**+100 %**	**CYP3A4**
Dyhydrocodeine	**+70 %**	**CYP2D6**

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



GOALS of Renal Disease Effects Lecture

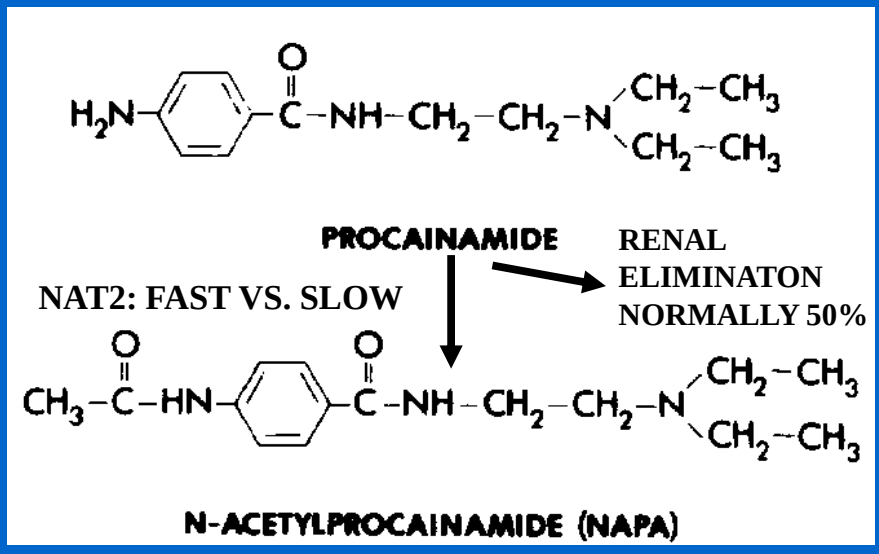
- **EFFECT OF RENAL DISEASE ON *DRUG METABOLISM***

- ***EXAMPLES:***

  PROCAINAMIDE - Acetylation

  PHENYTOIN - Hydroxylation

PROCAINAMIDE *ACETYLATION*

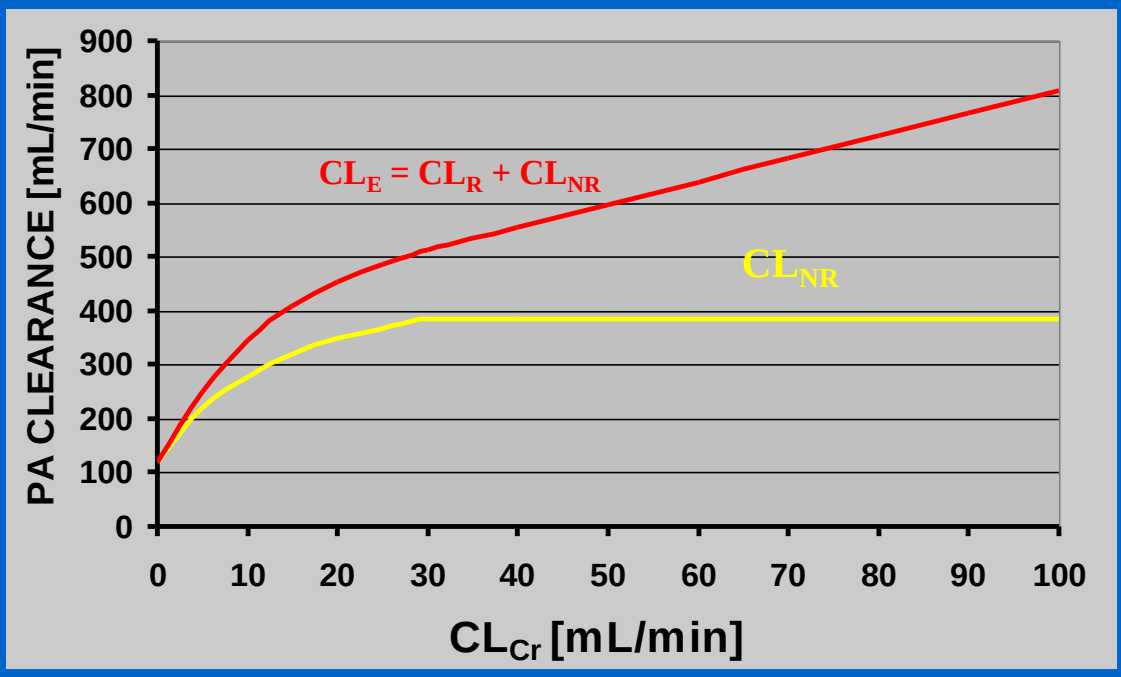


Procainamide Kinetics in *DIALYSIS PATIENTS**

	NORMALS		*FUNCTIONALLY ANEPHRIC PATIENTS*	
	Fast	Slow	Fast	Slow
$T_{1/2}$ (hr)	2.6	3.5	12.2	17.0
CL_E (L/kg)	809	600	118	94
CL_R (L/kg)	426	357	0	0
CL_{NR} (L/kg)	383	243	118	94
$V_{d(ss)}$ (L/kg)	1.95	1.93	1.41	1.93

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

Procainamide Dosing Nomogram
(*FAST ACETYLATORS*)

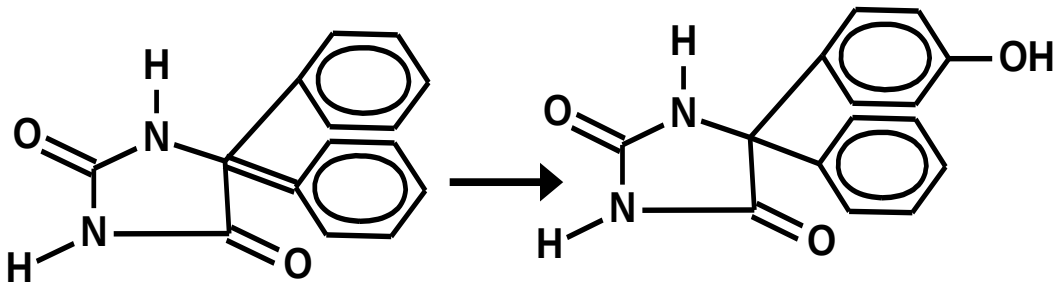


NAPA ELIMINATION HALF LIFE IN *FUNCTIONALLY ANEPHRIC* PATIENTS

- 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.

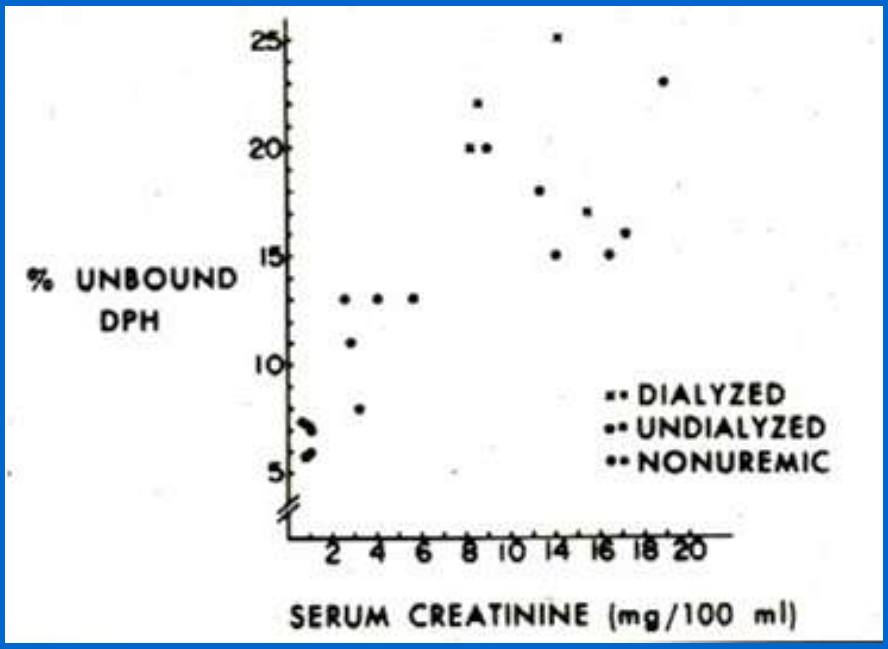
PHENYTOIN *HYDROXYLATION* BY P450



PHENYTOIN *p* - HPPH

CYP2C9: Major, CYP2C19: Minor

Effect of Renal Disease on *PHENYTOIN PROTEIN BINDING*



PHENYTOIN
*KINETICS IN DIALYSIS PATIENTS**

	NORMALS (N = 4)	UREMIC PATIENTS (N = 4)	
% UNBOUND (f_u)	12%	26%	
CL_H	2.46 L/hr	7.63 L/hr	
CL_{int}	20.3 L/hr	29.9 L/hr	NS

$$CL_H = f_u \bullet Cl_{int}, \quad \text{So: } Cl_{int} = CL_H/f_u$$

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

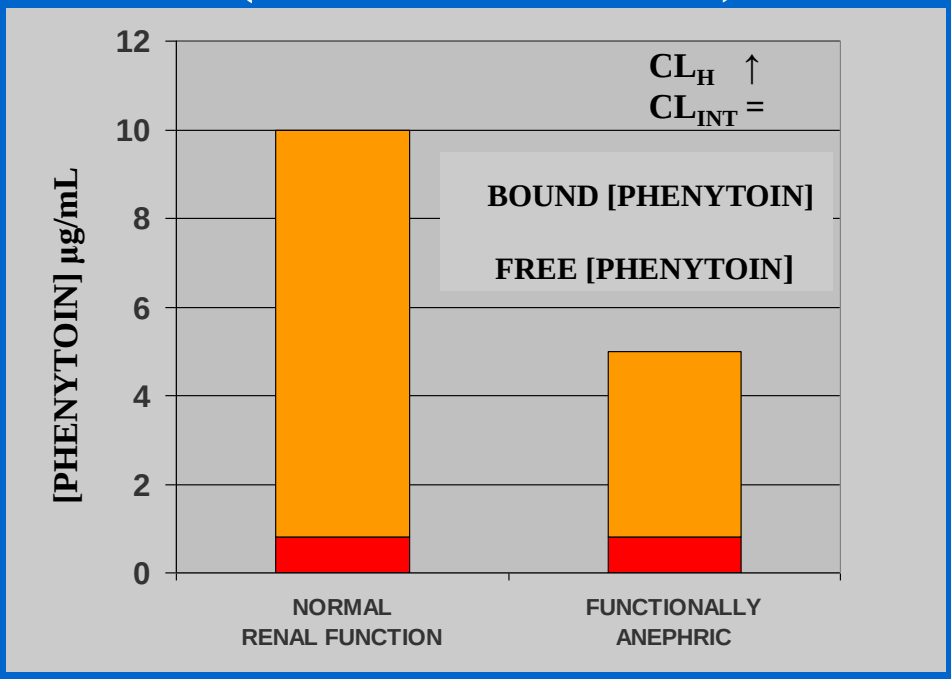
Effect of *PROTEIN BINDING Changes* on Phenytoin Plasma Concentration

$$\overline{C}_{SS} = \frac{DOSE/\tau}{CL_E}$$

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

$$\overline{C}_{ss,u}/f_u = \frac{DOSE/\tau}{f_u\ CL_{INT}}$$

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



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**
  - **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**

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

Effect of Binding Changes on *APPARENT DISTRIBUTION VOLUME**

$$V_d = ECF + \phi f_u (TBW - ECF)$$

Φ = TISSUE/PLASMA PARTITION RATIO

f_u = FRACTION NOT BOUND TO PLASMA PROTEINS

FOR PHENYTOIN: Φ = 10.4

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

PHENYTOIN *DISTRIBUTION* IN *DIALYSIS* PATIENTS*

	NORMALS	UREMIC PATIENTS
% UNBOUND (f_u)	12%†	26%
$V_{d(AREA)}$	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**

$$V_d = 3.84 \bullet wt\ (kg) + 3.12\ CL_{Cr}\ (mL/min)$$

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

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

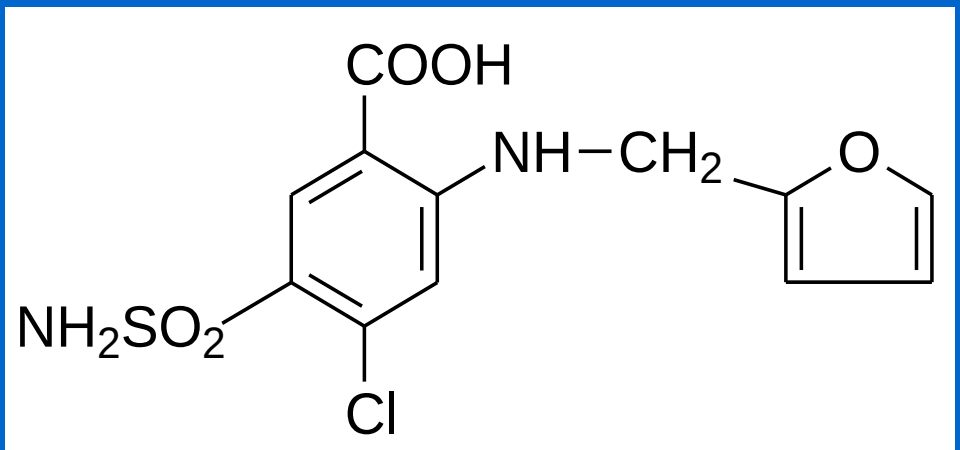
5-hr URINE RECOVERY	> 4 g
[SERUM] 1 hr AFTER DOSE	≥ 0.2 mg/mL
% DOSE ABSORBED	> 42%
k_a	> 0.37 hr^{-1}

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

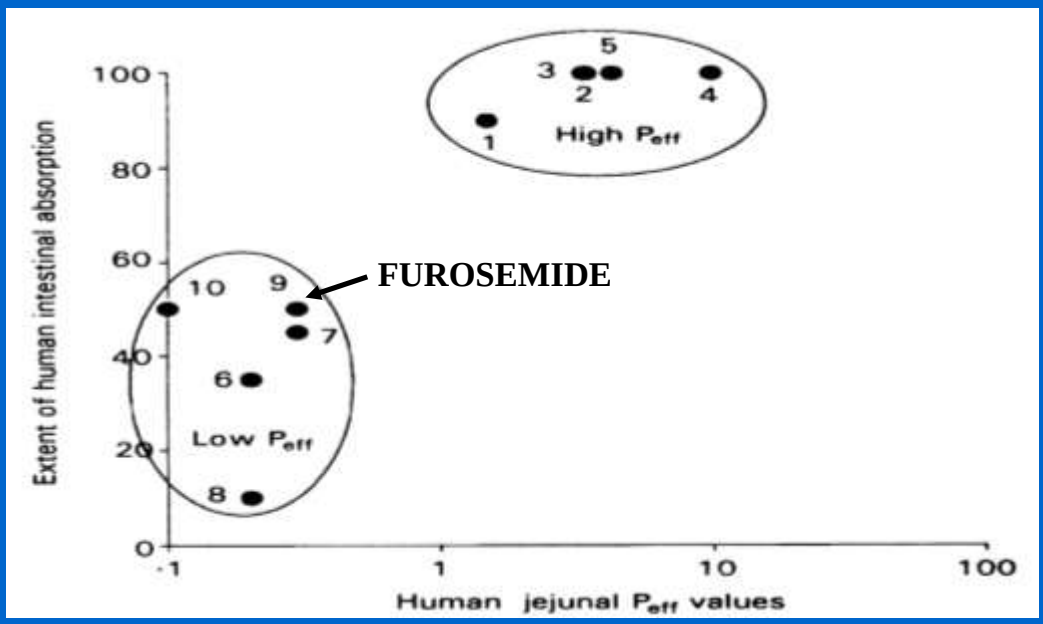
PATIENT GROUP	k_a (hr^{-1})	k_o (hr^{-1})	% DOSE ABSORBED
NORMALS	1.03 ± 0.33	0.49 ± 0.35	69.4 ± 13.6
MODERATE	0.64 ± 0.28	0.19 ± 0.15	77.4 ± 14.8
DIALYSIS	0.56 ± 0.42	0.67 ± 0.61	48.6 ± 13.3

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

FUROSEMIDE



BIOPHARMACEUTIC CLASSIFICATION OF FUROSEMIDE*



* 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

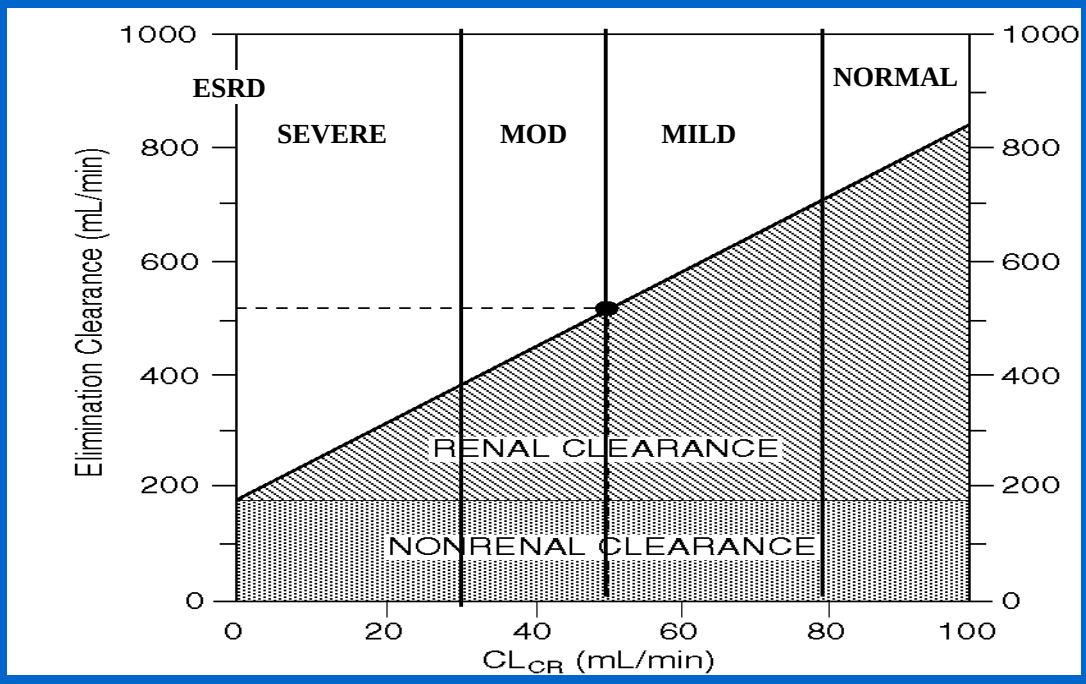
Sun H, et al (2006)
Amidon GI, et al (1995)

FDA *GUIDANCE FOR INDUSTRY*

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

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 (initiated in 2008).
- A ***concept paper/draft guidance*** has been posted by the FDA regarding revised recommendations for PK studies in patients with ***impaired renal function***.

US FDA Perspective:

S-M Huang, R Temple, S Xiao, L Zhang, LJ Lesko

Clin. Pharmacol. Ther. 2009;86:475-479