Effects of Liver Disease on Pharmacokinetics

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GOALS of Liver Disease Effects Lecture

- Estimation of Hepatic Clearance
- Effect of Liver Disease on Elimination:
  - *RESTRICTIVELY* Eliminated Drugs
  - *NON-RESTRICTIVELY* Eliminated Drugs
- Other Effects of Liver Disease:
  - Renal Function
  - Drug Distribution
  - Drug Response
- Modification of Drug Therapy in Patients with Liver Disease

ADDITIVITY of Clearances

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

- CL_E: ESTIMATED FROM PLASMA LEVEL-VS.-TIME CURVE
- CL_R: ESTIMATED FROM RECOVERY OF DRUG IN URINE
- CL_{NR}: ESTIMATED AS $CL_E - CL_R$

CALCULATION OF CL_H

$$Cl_H = Cl_E - Cl_R$$

ASSUMES $CL_H = CL_{NR}$

FICK EQUATION

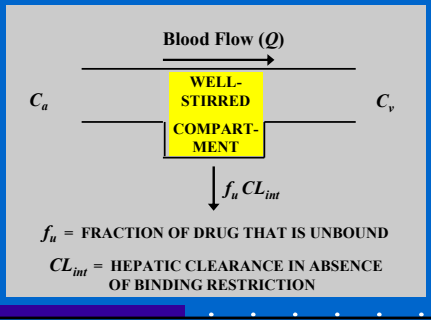
$$Cl = Q \left[\frac{A - V}{A} \right]$$

$$E = \left[\frac{A - V}{A} \right]$$

$$\text{So} \quad Cl = Q \bullet E$$

A = CONCENTRATION ENTERING LIVER
V = CONCENTRATION LEAVING LIVER
Q = HEPATIC BLOOD FLOW

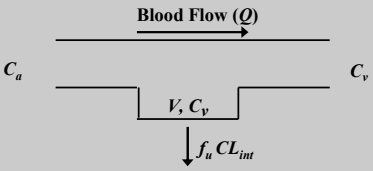
Derivation of *ROWLAND EQUATION (I)*



f_u = FRACTION OF DRUG THAT IS UNBOUND

CL_{int} = HEPATIC CLEARANCE IN ABSENCE OF BINDING RESTRICTION

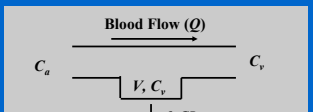
Derivation of *ROWLAND EQUATION (II)*



MASS BALANCE EQUATION :

$$V\frac{dC_v}{dt} = QC_a - QC_v - f_u CL_{int} C_v$$

Derivation of *ROWLAND EQUATION (III)*



at steady state :

$$QC_a - QC_v - f_u CL_{int} C_v = 0$$

so :

$$Q(C_a - C_v) = f_u CL_{int} C_v$$

$$QC_a = (Q + f_u CL_{int}) C_v$$

therefore :

$$ER = \frac{C_a - C_v}{C_a} = \frac{f_u CL_{int}}{Q + f_u CL_{int}}$$

ROWLAND EQUATION
WELL-STIRRED COMPARTMENT

$$CL_H = Q \cdot E = Q \cdot \left[\frac{f_u CL_{int}}{Q + f_u CL_{int}}\right]$$

<u>TWO LIMITING CASES</u>:

RESTRICTIVELY METABOLIZED DRUGS ($Q >> f_t CL_{int}$):

$$CL_H = f_u CL_{int}$$

NON-RESTRICTIVELY METABOLIZED DRUGS ($f_t CL_{int} >> Q$):

$$CL_H = Q$$

RESTRICTIVELY and *NON-RESTRICTIVELY* Eliminated Drugs

RESTRICTIVELY METABOLIZED DRUGS:

Phenytoin
Warfarin
Theophylline

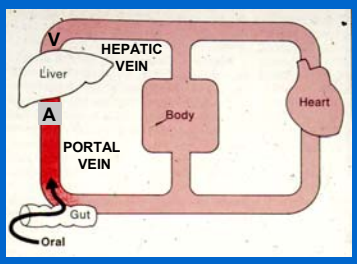
NON-RESTRICTIVELY METABOLIZED DRUGS:

Lidocaine
Propranolol
Morphine

HEPATIC *FIRST-PASS* METABOLISM

$$E = \frac{A - V}{A}$$

IF E = 1: V = 0
IF E = 0: V = A



NON-RESTRICTIVELY Eliminated Drugs

$$Cl_H = Q = Q \bullet ER$$

$$FOR: ER = \left[\frac{A - V}{A}\right] \Rightarrow 1, \; V \Rightarrow 0$$

$$BUT: F = 1 - ER, \; So \; F \Rightarrow 0$$

THESE DRUGS HAVE EXTENSIVE FIRST-PASS METABOLISM

ACUTE VIRAL HEPATITIS

- Acute inflammatory condition
- Mild and *transient changes* related to extent of disease in most cases. Infrequently severe and fulminant
- *May become chronic* and severe
- Changes in drug disposition less than in chronic disease
- *Hepatic elimination returns to normal* as disease resolves

CHRONIC LIVER DISEASE

- Usually related to chronic alcohol use or viral hepatitis
- *Irreversible* hepatocyte damage
  - Decrease in *SERUM ALBUMIN* concentration
  - Decrease in *INTRINSIC CLEARANCE* of drugs
  - Intrahepatic and extrahepatic *shunting* of blood from functioning hepatocytes
  - *FIBROSIS* disrupts normal hepatic architecture
  - *NODULES* of regenerated hepatocytes form

RESTRICTIVELY Metabolized Drugs:

Effects of LIVER DISEASE

$$CL_H = f_u\, CL_{int}$$

	CL_H	FREE CONC.
↓ ALBUMIN	↑	NO CHANGE
↓ CL_{int}	↓	↑
PORTOSYSTEMIC SHUNTING	↓	↑

RESTRICTIVELY Metabolized Drugs: Effect of PROTEIN BINDING Changes

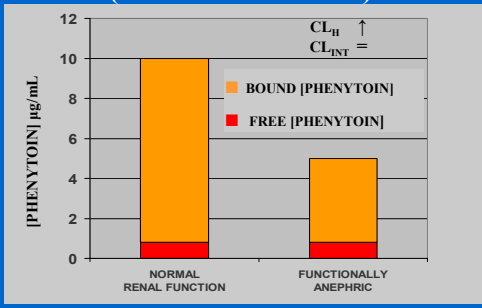
$$\bar{C}_{ss} = \frac{\text{DOSE}/\tau}{CL_H}$$

FOR RESTRICTIVELY ELIMINATED DRUGS :

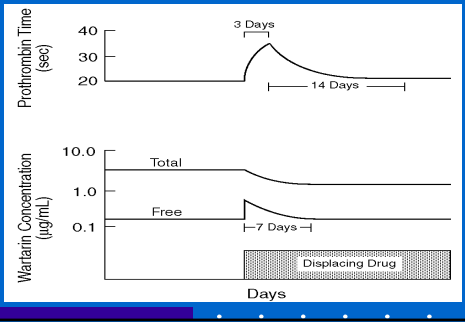
$$CL_H = f_u CL_{int}$$

$$\text{FREE CONC.} = \bar{C}_{ss} \cdot f_u = \frac{f_u \,\text{DOSE}/\tau}{f_u \; CL_{int}}$$

FREE and *TOTAL* PHENYTOIN Levels (DOSE = 300 MG/DAY)



RESTRICTIVELY Metabolized Drugs : Effect of PROTEIN BINDING Changes

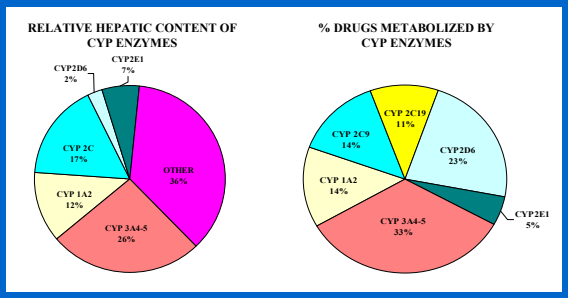


RESTRICTIVELY Metabolized Drugs: Effects of LIVER DISEASE

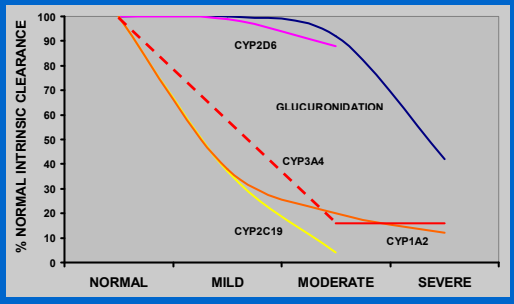
$$CL_H = f_u\, CL_{int}$$

	CL_H	FREE CONC.
↓ ALBUMIN	↑	NO CHANGE
↓ CL_{int}	↓	↑
PORTOSYSTEMIC SHUNTING	↓	↑

Role of *CYP ENZYMES* in Hepatic Drug Metabolism



RESTRICTIVELY Metabolized Drugs: Effect of CIRRHOSIS on CL_{int}



PUGH-CHILD CLASSIFICATION Of Liver Disease Severity

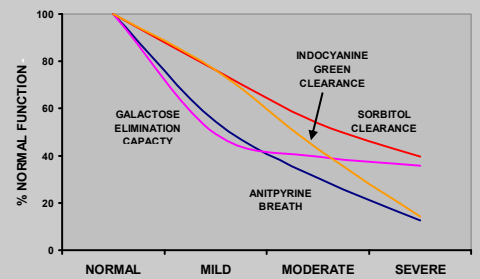
ASSESSMENT PARAMETERS	ASSIGNED SCORE 1 POINT	2 POINTS	3 POINTS
ENCEPHALOPATHY GRADE	0	1 or 2	3 or 4
ASCITES	ABSENT	SLIGHT	MODERATE
BILIRUBIN (mg/dL)	1 – 2	2 – 3	> 3
ALBUMIN (gm/dL)	> 3.5	2.8 – 3.5	< 2.8
PROTHROMBIN TIME (seconds > control)	1 – 4	4 – 10	> 10
CLASSIFICATION OF CLINICAL SEVERITY			
CLINICAL SEVERITY	MILD	MODERATE	SEVERE
TOTAL POINTS	5 – 6	7 – 9	> 9

Correlation of Lab Test Results with Impaired CYP Enzyme Function

The Central Problem:

***There is no laboratory test of liver function that is as useful for guiding drug dose adjustment in patients with liver disease* as is the estimation of creatinine clearance in patients with impaired renal function.**

Correlation of *SPECIAL TESTS* of Liver Function with *CHILD-PUGH SCORES**



* Data from Herold C, et al. Liver 2001;21:260-5.

"*PITTSBURGH COCKTAIL*" Approach*

DRUG	ENZYME
CAFFEINE	CYP 1A2
CHLORZOXAZONE	CYP 2E1
DAPSONE	CYP 3A + NAT2
DEBRISOQUIN	CYP 2D6
MEPHENYTOIN	CYP 2C19

* From: Frye RF, et al. Clin Pharmacol Ther 1997;62:365-76

RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

$$CL_H = f_u\, CL_{int}$$

	CL_H	FREE CONC.
↓ ALBUMIN	↑	NO CHANGE
↓ CL_{int}	↓	↑
PORTOSYSTEMIC SHUNTING	↓	↑

Effects of *HEPATIC SHUNTING* on ROWLAND EQUATION*

$$CL_H = \left(\frac{Q_P}{Q_T}\right)\left(\frac{Q_T\, f_u\, CL_{int}}{Q_T + f_u\, CL_{int}}\right)$$

Q_T = TOTAL BLOOD FLOW TO LIVER
Q_P = BLOOD FLOW PERFUSING LIVER
$Q_T - Q_P$ = SHUNT BLOOD FLOW

* From: McLean A, et al. Clin Pharmacol Ther 1979;25:161-6.

RESTRICTIVELY Metabolized Drugs: Effects of Hepatic Shunting*

SEVERITY	Q_T (mL/min)	Q_P (mL/min)	Q_P/Q_T (%)	ANTIPYRINE CL_H (mL/min)
MODERATE	1.26	0.92	73	27.1
SEVERE	0.72	0.20	28	10.3
SEVERE/ MODERATE	0.57	0.22	0.38	0.38

* From: McLean A, et al. Clin Pharmacol Ther 1979;25:161-6.

NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

$$CL_H = Q$$

	CL_H	F
↓ ALBUMIN	NO CHANGE*	NO CHANGE
↓ CL_{int}	"NO CHANGE"	"NO CHANGE"
↓ HEPATIC PERFUSION	↓↓	↑↑

* HOWEVER, NOTE THAT FREE CONCENTRATION IS ↑

NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

$$CL_H = Q$$

	CL_H	F
↓ ALBUMIN	NO CHANGE*	NO CHANGE
↓ CL_{int}	"NO CHANGE"	"NO CHANGE"
↓ HEPATIC PERFUSION	↓↓	↑↑

HOWEVER, $f_u CL_{int}$ MAY NO LONGER BE >> Q

NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

$$CL_H = Q$$

	CL_H	F
↓ ALBUMIN	NO CHANGE*	NO CHANGE
↓ CL_{int}	"NO CHANGE"	"NO CHANGE"
↓ HEPATIC PERFUSION	↓↓	↑↑

Effects of Hepatic Shunting on Rowland Equation*

$$CL_H = \left(\frac{Q_P}{Q_T}\right)\left(\frac{Q_T\, f_u\, CL_{int}}{Q_T + f_u\, CL_{int}}\right)$$

Q_T = TOTAL BLOOD FLOW TO LIVER
Q_P = BLOOD FLOW PERFUSING LIVER
$Q_T - Q_P$ = SHUNT BLOOD FLOW

* From: McLean A, et al. Clin Pharmacol Ther 1979;25:161-6.

NON-RESTRICTIVELY Metabolized Drugs: Effects of Decreased Liver Perfusion*

SEVERITY	Q_T (mL/min)	Q_P (mL/min)	Q_P/Q_T (%)	ICG CL_H (mL/min)
MODERATE	1.26	0.92	73	766
SEVERE	0.72	0.20	28	182
SEVERE/ MODERATE	0.57	0.22	0.38	0.24

* From: McLean A, et al. Clin Pharmacol Ther 1979;25:161-6.

Influence of *PORTOSYSTEMIC SHUNTING* on Oral Bioavailability (F)

RESTRICTIVELY **Eliminated Drugs:**

Little change

NON-RESTRICTIVELY **Eliminated Drugs:**

SHUNTING **may markedly increase extent of drug absorption (F)**

CIRRHOSIS Affects Exposure to Some *NON-RESTRICTIVELY* Metabolized Drugs

	ABSOLUTE BIOAVAILABILITY		RELATIVE EXPOSURE CIRRHOTICS/CONTROL	
	CONTROLS (%)	CIRRHOTICS (%)	IV	ORAL
MEPERIDINE	48	87	1.6	3.1
PENTAZOCINE	18	68	2.0	8.3
PROPRANOLOL	38	54	1.5*	2.0*

* THIS ALSO INCORPORATES 55% INCREASE IN PROPRANOLOL f_u

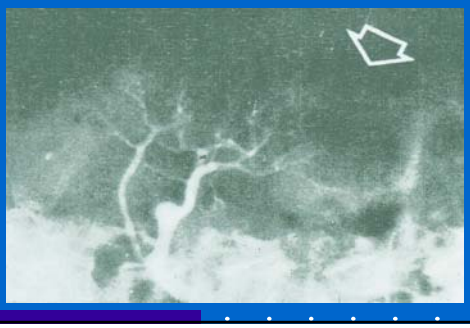
CIRRHOSIS Affects Renal Function: The Hepatorenal Syndrome

- *Risk* in Patients with Cirrhosis, Ascitis, and GFR > 50 mL/min:
  - 18% within 1 year
  - 39% within 5 years
- *Predictors* of Risk:
  - Small liver
  - Low serum albumin
  - High plasma renin
- Cockcroft and Gault Equation may *overestimate* renal function

CIRRHOSIS Affects Renal Function: The Hepatorenal Syndrome

- The Syndrome has a *FUNCTIONAL* rather than an Anatomical Basis.

HEPATORENAL SYNDROME *ANTEMORTEM* Arteriogram



HEPATORENAL SYNDROME *POSTMORTEM* Arteriogram

CIRRHOSIS Affects Renal Function: The Hepatorenal Syndrome

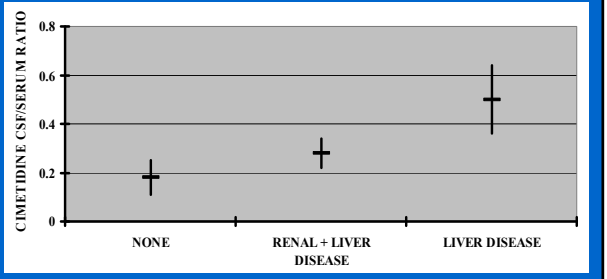
- Therapy with some drugs *may precipitate* Hepatorenal Syndrome

  ACE Inhibitors
  NSAIDs
  Furosemide (High Total Doses)

CIRRHOSIS May Affect *Drug Distribution*

- Increased *Free Concentration* of *NON-RESTRICTIVELY* Eliminated Drugs (e.g. PROPRANOLOL)
- Increased Permeability of *Blood:CNS Barrier* (e.g. CIMETIDINE)

CIRRHOSIS Affects Drug Distribution: Increased CNS Penetration of Cimetidine*



* From Schentag JJ, et al. Clin Pharmacol Ther 1981;29:737-43

CIRRHOSIS may affect *PHARMACODYNAMICS*

- Sedative response to ***BENZODIAZEPINES*** is exaggerated
- Response to ***LOOP DIURETICS*** is reduced

Drug Dosing in Patients with LIVER DISEASE

The Central Problem:

There is no laboratory test of liver function that is as useful for guiding drug dose adjustment in patients with liver disease as is the estimation of creatinine clearance in patients with impaired renal function.

PUGH-CHILD CLASSIFICATION of Liver Disease Severity

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Drugs *CONTRAINDICATED* in Patients with Severe Liver Disease

- *May precipitate renal failure*:
  - NSAIDs
  - ACE Inhibitors
- *Predispose to bleeding*:
  - β-LACTAMS with *N*-Methylthiotetrazole Side Chain (e.g. CEFOTETAN)

Drug Requiring ≥ 50% *Dose Reduction* in Patients with MODERATE CIRRHOSIS

	CHANGE IN CIRRHOSIS	
	F	CL_E
ANALGESIC DRUGS		
Morphine	↑ 213%	↓ 59%
Meperidine	↑ 94%	↓ 46%
Pentazocine	↑ 318%	↓ 50%

Drugs Requiring ≥ 50% *Dose Reduction* in Patients with MODERATE CIRRHOSIS

	CHANGE IN CIRRHOSIS	
	F	CL_E
CARDIOVASC. DRUGS		
Propafenone	↑ 257%	↓ 24%
Verapamil	↑ 136%	↓ 51%
Nifedipine	↑ 78%	↓ 60%
Losartan	↑ 100%	↓ 50%

Drugs Requiring ≥ 50% *Dose Reduction* in Patients with MODERATE CIRRHOSIS

	CHANGE IN CIRRHOSIS	
	F	CL_E
OTHER DRUGS		
Omeprazole	↑ 75%	↓ 89%
Tacrolimus	↑ 33%	↓ 72%

Recommended Evaluation of Pharmacokinetics in Liver Disease Patients*

REDUCED Study Design:

- Study Control Patients and Patients with *Child-Pugh Moderate Impairment*
- Findings in Moderate Category *Applied to Mild* Category; *Dosing Prohibited in Severe* Category

FULL Study Design:

- Study Control Patients and Patients in *All Child-Pugh Categories*
- Population PK Approach

* FDA Clinical Pharmacology Guidance, May 2003