Effects of Liver Disease on Pharmacokinetics

Juan J.L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program
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National Institutes of Health
Clinical Center

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

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

CALCULATION OF CL_H

Equation showing that hepatic clearance is estimated as the total clearance minus the renal clearance, assuming that it equals non-renal clearance.

FICK EQUATION

Defines clearance as liver blood flow times the extraction ratio A-V/A.

Derivation of Rowland Equation (I)

Diagram of hepatic capillary blood flow, fraction of unbound drug and intrinsic clearance with the “well-stirred” model.

Derivation of Rowland Equation (II)

The same diagram now including volume and concentration terms and a mass balance equation for hepatic drug clearance.

Derivation of Rowland Equation (III)

The same diagram with a derivation of an extraction ratio term that includes unbound fraction, intrinsic clearance, and liver blood flow.

Rowland Equation

WELL-STIRRED COMPARTMENT

Rowland Equation for hepatic clearance.

Two limiting cases:

Restrictively metabolized drugs (influenced by protein binding)

Non-restrictively metabolized drugs (blood flow-dependent)

RESTRICTIVELY AND NON-RESTRICTIVELY
ELIMINATED DRUGS

RESTRICTIVELY METABOLIZED DRUGS:

Phenytoin
Warfarin
Theophylline

NON-RESTRICTIVELY METABOLIZED DRUGS:

Lidocaine
Propranolol
Morphine

HEPATIC *FIRST-PASS* METABOLISM

Equation for the extraction ratio A-V/A.

Illustration of hepatic first-pass metabolism and the portal and systemic circulations.

NON-RESTRICTIVELY Eliminated Drugs

These drugs have extensive first-pass metabolism.

Equation showing that hepatic clearance is a function of liver blood flow.

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

Equation showing that hepatic clearance equals unbound fraction times the intrinsic clearance.

Chart showing that hepatic clearance increases if albumin decreases, and decreases if intrinsic clearance decreases.

RESTRICTIVELY METABOLIZED DRUGS: EFFECT OF PROTEIN BINDING CHANGES

Equations showing that free drug concentration at steady-state is a function of dosing rate and intrinsic hepatic clearance.

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

Chart showing that total Phenytoin concentration is lower than normal in functionally anephric patients but free Phenytoin concentration is the same.

RESTRICTIVELY METABOLIZED DRUGS: EFFECT OF PROTEIN BINDING CHANGES

Chart showing a protein binding interaction with Warfarin. There is a transient increase in free Warfarin concentration and prothrombin time.

RESTRICTIVELY METABOLIZED DRUGS:
EFFECTS OF LIVER DISEASE

Equation showing that hepatic clearance equals unbound fraction times the intrinsic clearance.

Chart showing that hepatic clearance increases if albumin decreases, and decreases if intrinsic clearance decreases.

ROLE OF CYP ENZYMES IN HEPATIC DRUG METABOLISM

Pie chart showing relative hepatic content of CYP enzymes and pie chart showing % of drugs metabolized by CYP enzymes.

RESTRICTIVELY METABOLIZED DRUGS: EFFECT OF CIRRHOSIS ON Clint

Chart illustrating % of normal intrinsic clearance for normal, mild, moderate, and severe cirrhosis, and the impact on glucuronidation and CYP2D6, CY3A4, CYP2C19, and CYP1A2.

PUGH-CHILD CLASSIFICATION
OF LIVER DISEASE SEVERITY

Chart showing assessment parameters and assigned scores in addition to classification of clinical severity of mild, moderate and severe.

CORRELATION OF LAB TEST RESULTS WITH
IMPAIRED CYP ENZYME FUNCTION

<u>The Central Problem</u>:
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*

Chart showing changes in indocyanine green and sorbitol clearances, and the galactose elimination and the antipyrine breath tests.

*** 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

Equation showing that hepatic blood flow equals unbound fraction times the intrinsic clearance.

Chart showing that hepatic clearance increases if albumin decreases, and decreases if intrinsic clearance decreases.

Portosystemic shunting reduces total hepatic clearance and increases free drug concentration.

EFFECTS OF HEPATIC SHUNTING ON ROWLAND EQUATION*

Modified Rowland Equation accounting for shunt blood flow.

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

RESTRICTIVELY METABOLIZED DRUGS: EFFECTS OF HEPATIC SHUNTING*

Chart showing liver disease severity, QT, QP, QP/QT, and Antipyrine CLH

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

NON-RESTRICTIVELY METABOLIZED DRUGS: EFFECTS OF LIVER DISEASE

Equation for hepatic clearance = blood flow showing that changes in protein binding and intrinsic clearance have no impact on hepatic clearance for these drugs.

Chart

* However, note that free concentration is ↑

NON-RESTRICTIVELY METABOLIZED DRUGS: EFFECTS OF LIVER DISEASE

Equation for CLH =Q

Equation for hepatic clearance = blood flow showing that changes in protein binding and intrinsic clearance have no impact on hepatic clearance for these drugs.

HOWEVER, *fuCLint* MAY NO LONGER BE >> *Q*

NON-RESTRICTIVELY METABOLIZED DRUGS: EFFECTS OF LIVER DISEASE

Equation for CLH = Q

Equation for hepatic clearance = blood flow showing that changes in protein binding and intrinsic clearance have no impact on hepatic clearance for these drugs.

Decreased hepatic perfusion results in increased oral bioavailability (F).

EFFECTS OF HEPATIC SHUNTING ON ROWLAND EQUATION*

Modified Rowland Equation

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

NON-RESTRICTIVELY METABOLIZED DRUGS: EFFECTS OF DECREASED LIVER PERFUSION*

Chart showing liver disease Severity, QT, QP, QP/QT, and ICG CLH (clearance of indocyanine green)

*** 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

Chart showing increased Absolute Bioavailability and relative exposure cirrhotics/control of Meperidine, Pentazocine, and Propranolol.

*** THIS ALSO INCORPORATES 55% INCREASE IN PROPRANOLOL fu**

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

There is no renal perfusion.

HEPATORENAL SYNDROME
POSTMORTEM Arteriogram

Renal perfusion appears normal.

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*

Chart showing cimetidine CSF/serum ratio from normal to renal + liver disease to liver disease

*** 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

<u>The Central Problem</u>:
***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

Chart showing assessment parameters with assigned score and classification of clinical severity of mild, moderate and severe.

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	**CLE**
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	**CLE**
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	**CLE**
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**