Effects of Liver Disease on Pharmacokinetics
Juan J.L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program
October 29, 2015
National Institutes of Health
Clinical Center

GOALS of Effects of Liver Disease 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

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.
**FDA-approved Drug Labels: Dosing Guidance in Liver Disease**

*Evaluation of hepatic impairment dosing recommendations in FDA-approved * product labels.*
Chang Y, Burckart GJ, Lesko LJ, Dowling TC

* January 2004-December 2011 (67/157 NMEs)

---

**ADDITIVITY of Clearances**

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

- Estimated from plasma level vs. time curve
- Estimated from recovery of drug in urine
- Estimated as \( \text{CL}_{IE} \cdot \text{CL}_R \)

---

**CALCULATION OF CL_H**

\[ \text{CL}_H = \text{CL}_E - \text{CL}_R \]

Assumes \( \text{CL}_H = \text{CL}_{NR} \)
**FICK EQUATION**

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

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

So \( \text{Cl} = Q \cdot E \)

- \( A \) = CONCENTRATION ENTERING LIVER
- \( V \) = CONCENTRATION LEAVING LIVER
- \( Q \) = HEPATIC BLOOD FLOW

---

**Derivation of ROWLAND EQUATION (I)**

Blood Flow (Q)

\( C_a \) \leftarrow \text{WELL-STIRRED COMPARTMENT} \rightarrow \( C_v \)

\( f_u \cdot \text{CL}_{int} \)

\( f_u = \text{FRACTION OF DRUG THAT IS UNBOUND} \)

\( \text{CL}_{int} = \text{HEPATIC CLEARANCE IN ABSENCE OF BINDING RESTRICTION} \)

---

**Derivation of ROWLAND EQUATION (II)**

Blood Flow (Q)

\( C_a \) \leftarrow \text{WELL-STIRRED COMPARTMENT} \rightarrow \( C_v \)

\( V \cdot C_v \)

\( f_u \cdot \text{CL}_{int} \)

**MASS BALANCE EQUATION:**

\[ V \frac{dC_v}{dt} = QC_a - QC_v - f_u \cdot \text{CL}_{int} \cdot C_v \]
Derivation of ROWLAND EQUATION (III)

Blood Flow ($Q$)

\[ C_u \frac{V_c}{f_u CL_{\text{int}}} C_v \]

at steady state:

\[ QC_u - QC_v - f_u CL_{\text{int}} C_v = 0 \]

so:

\[ Q(C_u - C_v) = f_u CL_{\text{int}} C_v \]

\[ QC_u = (Q + f_u CL_{\text{int}}) C_v \]

therefore:

\[ \frac{C_u - C_v}{C_u} = \frac{f_u CL_{\text{int}}}{Q + f_u CL_{\text{int}}} \]

ROWLAND EQUATION
WELL-STIRRED COMPARTMENT

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

TWO LIMITING CASES:

RESTRICTIVELY METABOLIZED DRUGS ($Q >> f_u CL_{\text{int}}$):

\[ CL_u = f_u CL_u \]

NON-RESTRICTIVELY METABOLIZED DRUGS ($f_u CL_{\text{int}} >> Q$):

\[ CL_u = Q \]

RESTRICTIVELY and NON-RESTRICTIVELY Eliminated Drugs (examples)

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 \cdot 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

\[ CL_H = f_u \cdot CL_{int} \]

<table>
<thead>
<tr>
<th>Change</th>
<th>( CL_H )</th>
<th>FREE CONC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ALBUMIN</td>
<td>↑</td>
<td>NO CHANGE</td>
</tr>
<tr>
<td>↓ ( CL_{int} )</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>PORTOSYSTEMIC SHUNTING</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

RESTRICTIVELY Metabolized Drugs: Effect of PROTEIN BINDING Changes

\[ \bar{C}_{ss} = \frac{DOSE / \tau}{CL_n} \]

FOR RESTRICTIVELY ELIMINATED DRUGS:

\[ CL_n = f_u \cdot CL_{int} \]

FREE CONC. = \( \bar{C}_{ss} \cdot f_u = \frac{f_u \cdot DOSE / \tau}{f_u \cdot CL_{int}} \)
**FREE and TOTAL PHENYTOIN Levels (DOSE = 300 MG/DAY)**

![Graph showing FREE and TOTAL PHENYTOIN Levels]

**RESTRICTIVELY Metabolized Drugs: Effect of PROTEIN BINDING Changes**

![Graph showing effect of protein binding changes]

**RESTRICTIVELY Metabolized Drugs: Effects of LIVER DISEASE**

\[ CL_H = f_u \cdot CL_{int} \]

<table>
<thead>
<tr>
<th>Condition</th>
<th>CL_{int}</th>
<th>FREE CONC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ALBUMIN</td>
<td>↑</td>
<td>NO CHANGE</td>
</tr>
<tr>
<td>↓ CL_{int}</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>PORTOSYSTEMIC SHUNTING</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
**Role of CYP Enzymes in Hepatic Drug Metabolism**

**Relative Hepatic Content of CYP Enzymes**

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>2%</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>7%</td>
</tr>
<tr>
<td>CYP2C</td>
<td>17%</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>12%</td>
</tr>
<tr>
<td>CYP3A4-5</td>
<td>26%</td>
</tr>
<tr>
<td>OTHER</td>
<td>36%</td>
</tr>
</tbody>
</table>

**Percentage of Drugs Metabolized by CYP Enzymes**

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>23%</td>
</tr>
<tr>
<td>CYP3A4-5</td>
<td>33%</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>5%</td>
</tr>
<tr>
<td>OTHER</td>
<td>36%</td>
</tr>
</tbody>
</table>

**Restrictively Metabolized Drugs: Effects of Cirrhosis on CL**

- Normal
- Mild
- Moderate
- Severe

**Pugh-Child Classification of Liver Disease Severity**

<table>
<thead>
<tr>
<th>Assessment Parameters</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy Grade</td>
<td>0</td>
<td>1-2</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1-2</td>
<td>2-3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prothrombin Time (seconds &gt; control)</td>
<td>1-4</td>
<td>4-10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

**Classification of Clinical Severity**

<table>
<thead>
<tr>
<th>Clinical Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Points</td>
<td>5-6</td>
<td>7-9</td>
<td>&gt; 9</td>
</tr>
</tbody>
</table>
Correlation of SPECIAL TESTS of Liver Function with CHILD-PUGH SCORES*


“PITTSBURGH COCKTAIL” Approach*

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ENZYME</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAFFEINE</td>
<td>CYP 1A2</td>
</tr>
<tr>
<td>CHLORZOXAZONE</td>
<td>CYP 2E1</td>
</tr>
<tr>
<td>DAPSOONE</td>
<td>CYP 3A + NAT2</td>
</tr>
<tr>
<td>DEBRIXOQUIN</td>
<td>CYP 2D6</td>
</tr>
<tr>
<td>MEPHENYTOIN</td>
<td>CYP 2C19</td>
</tr>
</tbody>
</table>


RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

\[ CL_H = f_u \times CL_{int} \]

<table>
<thead>
<tr>
<th>( f_u )</th>
<th>FREE CONC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ALBUMIN</td>
<td>↑ NO CHANGE</td>
</tr>
<tr>
<td>↓ ( CL_{int} )</td>
<td>↑</td>
</tr>
<tr>
<td>PORTOSYSTEMIC SHUNTING</td>
<td>↓ ↑</td>
</tr>
</tbody>
</table>
Effects of HEPATIC SHUNTING on ROWLAND EQUATION*

\[ \text{CL}_H = \left( \frac{Q_P}{Q_T} \right) \left( \frac{Q_T f_u \text{CL}_{int}}{Q_T + f_u \text{CL}_{int}} \right) \]

- \( Q_T \) = TOTAL BLOOD FLOW TO LIVER
- \( Q_P \) = BLOOD FLOW PERFUSING LIVER
- \( Q_T - Q_P \) = SHUNT BLOOD FLOW


Restrictively Metabolized Drugs: Effects of Hepatic Shunting*

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>( Q_T ) (mL/min)</th>
<th>( Q_P ) (mL/min)</th>
<th>( Q_P/Q_T ) (%)</th>
<th>ANTIPYRINE CLH (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODERATE</td>
<td>1.26</td>
<td>0.92</td>
<td>73</td>
<td>27.1</td>
</tr>
<tr>
<td>SEVERE</td>
<td>0.72</td>
<td>0.20</td>
<td>28</td>
<td>10.3</td>
</tr>
<tr>
<td>SEVERE/MODERATE</td>
<td>0.57</td>
<td>0.22</td>
<td>0.38</td>
<td>0.38</td>
</tr>
</tbody>
</table>


Non-Restrictively Metabolized Drugs: Effects of Liver Disease

\[ \text{CL}_H = Q \]

- ↓ ALBUMIN: NO CHANGE*
- ↓ CLint: "NO CHANGE"*
- ↓ HEPATIC PERFUSION: ↓↓

* HOWEVER, NOTE THAT FREE CONCENTRATION IS ↑
**NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease**

\[ CL_H = Q \]

<table>
<thead>
<tr>
<th>Effect</th>
<th>( CL_H )</th>
<th>( F )</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ALBUMIN</td>
<td>NO CHANGE*</td>
<td>NO CHANGE</td>
</tr>
<tr>
<td>↓ ( CL_{int} )</td>
<td>&quot;NO CHANGE&quot;</td>
<td>&quot;NO CHANGE&quot;</td>
</tr>
<tr>
<td>↓ HEPATIC PERFUSION</td>
<td>↓</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

HOWEVER, \( f \cdot CL_{int} \) MAY NO LONGER BE >> \( Q \)

**Effects of Hepatic Shunting on Rowland Equation**

\[
CL_H = \left( \frac{Q_P}{Q_T} \right) \left( \frac{Q_T f_u \cdot CL_{int}}{Q_T + f \cdot CL_{int}} \right)
\]

\( Q_T = \) TOTAL BLOOD FLOW TO LIVER

\( Q_P = \) BLOOD FLOW PERFUSING LIVER

\( Q_T - Q_P = \) SHUNT BLOOD FLOW

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

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>(Q_r) (mL/min)</th>
<th>(Q_p) (mL/min)</th>
<th>(Q_r/Q_p) (%)</th>
<th>ICG CLH (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODERATE</td>
<td>1.26</td>
<td>0.92</td>
<td>73</td>
<td>766</td>
</tr>
<tr>
<td>SEVERE</td>
<td>0.72</td>
<td>0.20</td>
<td>28</td>
<td>182</td>
</tr>
<tr>
<td>SEVERE/MODERATE</td>
<td>0.57</td>
<td>0.22</td>
<td>0.38</td>
<td>0.24</td>
</tr>
</tbody>
</table>


Influence of PORTOSYSTEMIC SHUNTING on Oral Bioavailability (F)

RESTRICTIVELY Eliminated Drugs:
Little change

NON-RESTRICTIVELY Eliminated Drugs:
SHUNTING may markedly increase oral bioavailability (F) due to reduced first-pass metabolism (drug bypasses hepatocytes)

CIRRHOSIS Affects Exposure to Some NON-RESTRICTIVELY Metabolized Drugs

<table>
<thead>
<tr>
<th></th>
<th>ABSOLUTE BIOAVAILABILITY</th>
<th>RELATIVE EXPOSURE</th>
<th>CIRRHOTICS/CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONTROLS (%)</td>
<td>CIRRHOTICS (%)</td>
<td>IV</td>
</tr>
<tr>
<td>MEPERIDINE</td>
<td>48</td>
<td>87</td>
<td>1.6</td>
</tr>
<tr>
<td>PENTAZOCINE</td>
<td>18</td>
<td>68</td>
<td>2.0</td>
</tr>
<tr>
<td>PROPRANOLOL</td>
<td>38</td>
<td>54</td>
<td>1.5*</td>
</tr>
</tbody>
</table>

* THIS ALSO INCORPORATES 55% INCREASE IN PROPRANOLOL f,
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.

HEPATURENAL 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*


CIRRHOSIS may affect PHARMACODYNAMICS

• Sedative response to BENZODIAZEPINES is exaggerated

• Response to LOOP DIURETICS is reduced

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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>CHANGE IN CIRRHOSIS</th>
<th>F</th>
<th>CLₜₜE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANALGESIC DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>↑ 213%</td>
<td></td>
<td>↓ 59%</td>
</tr>
<tr>
<td>Meperidine</td>
<td>↑ 94%</td>
<td></td>
<td>↓ 46%</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>↑ 318%</td>
<td></td>
<td>↓ 50%</td>
</tr>
<tr>
<td><strong>CARDIOVASC. DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>↑ 257%</td>
<td></td>
<td>↓ 24%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>↑ 136%</td>
<td></td>
<td>↓ 51%</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>↑ 78%</td>
<td></td>
<td>↓ 60%</td>
</tr>
<tr>
<td>Losartan</td>
<td>↑ 100%</td>
<td></td>
<td>↓ 50%</td>
</tr>
<tr>
<td><strong>OTHER DRUGS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>↑ 75%</td>
<td></td>
<td>↓ 89%</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↑ 33%</td>
<td></td>
<td>↓ 72%</td>
</tr>
</tbody>
</table>

---

**Note:** The table above lists drugs that require a ≥ 50% dose reduction in patients with moderate cirrhosis. The changes in clearance (CLₜₜE) are indicated for each drug, showing the increased or decreased clearance due to the liver condition.
**Pugh-Child Classification**

of Liver Disease Severity

<table>
<thead>
<tr>
<th>ASSESSMENT PARAMETERS</th>
<th>1 POINT</th>
<th>2 POINTS</th>
<th>3 POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENCEPHALOPATHY GRADE</td>
<td>0</td>
<td>1 or 2</td>
<td>3 or 4</td>
</tr>
<tr>
<td>ASCITES</td>
<td>ABSENT</td>
<td>SLIGHT</td>
<td>MODERATE</td>
</tr>
<tr>
<td>BILIRUBIN (mg/dL)</td>
<td>1 – 2</td>
<td>2 – 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>ALBUMIN (gm/dL)</td>
<td>&gt; 3.5</td>
<td>2.8 – 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>PROTHROMBIN TIME (seconds &gt; control)</td>
<td>1 – 4</td>
<td>4 – 10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

**Classification of Clinical Severity**

<table>
<thead>
<tr>
<th>CLINICAL SEVERITY</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL POINTS</td>
<td>5 – 6</td>
<td>7 – 9</td>
<td>&gt; 9</td>
</tr>
</tbody>
</table>

---

**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