Effects of Liver Disease on Pharmacokinetics

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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

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

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

ADDITIVITY of Clearances

\[
CL_E = CL_R + CL_{NR}
\]

CALCULATION OF \(CL_H\)

\[
CL_H = CL_E - CL_R
\]

ASSUMES \(CL_H = CL_{NR}\)
FICK EQUATION

\[ C_{I} = Q \left( \frac{A - V}{A} \right) \]

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

\[ So \cdot C_{I} = Q \cdot E \]

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

Derivation of ROWLAND EQUATION (I)

Blood Flow (Q)

\[ C_{a} \quad \text{WELL-STIRRED} \quad C_{v} \]

\[ f_{u} \cdot \text{CL}_{int} \]

\[ f_{u} = \text{FRACTION OF DRUG THAT IS UNBOUND} \]

\[ \text{CL}_{int} = \text{HEPATIC CLEARANCE IN ABSENCE OF BINDING RESTRICTION} \]

Derivation of ROWLAND EQUATION (II)

Blood Flow (Q)

\[ C_{a} \quad \text{V, } C_{v} \quad C_{v} \]

\[ f_{u} \cdot \text{CL}_{int} \]

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)**

\[ C_a \quad \frac{V, C_v}{f_u \cdot CL_u} \quad C_v \]

at steady state:

\[ C_a - C_v = f_u \cdot CL_u \cdot C_v = 0 \]

so:

\[ Q \left( C_a - C_v \right) = f_u \cdot CL_u \cdot C_v \]

\[ Q \cdot C_a = \left( Q + f_u \cdot CL_u \right) \cdot C_v \]

therefore:

\[ ER = \frac{C_a - C_v}{C_a} = \frac{f_u \cdot CL_u}{Q + f_u \cdot CL_u} \]

ROWLAND EQUATION

**WELL-STIRRED COMPARTMENT**

\[ CL_u = Q \cdot E = Q \cdot \left( \frac{f_u \cdot CL_u}{Q + f_u \cdot CL_u} \right) \]

**TWO LIMITING CASES:**

RESTRICTIVELY METABOLIZED DRUGS (\( Q \gg f_u \cdot CL_u \)):

\[ CL_u = f_u \cdot CL_u \]

NON-RESTRICTIVELY METABOLIZED DRUGS (\( f_u \cdot CL_u \gg Q \)):

\[ CL_u = Q \]

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**

\[ C_I_H = Q = Q \cdot ER \]

For: \( ER = \left[ \frac{A - V}{A} \right] \Rightarrow 1, V \Rightarrow 0 \)

But: \( F = 1 - ER, \) So \( F \Rightarrow 0 \)

**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>Effect</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>

\[ \bar{C}_{bs} = \frac{DOSE/\tau}{CL_{H}} \]

FOR RESTRICTIVELY ELIMINATED DRUGS:

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

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

![Graph showing FREE and TOTAL PHENYTOIN levels under different renal function conditions.]

- **CLH**↑
- **CLINT** =

- BOUND [PHENYTOIN]
- FREE [PHENYTOIN]

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

![Graph showing the effect of protein binding changes on drug clearance.]

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

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>CLH</th>
<th>FREE CONC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ALBUMIN</td>
<td>↑</td>
<td>NO CHANGE</td>
</tr>
<tr>
<td>↓ CLINT</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:
- CYP2D6: 12%
- CYP2C9: 17%
- CYP2C19: 11%
- CYP2E1: 7%
- CYP1A2: 12%
- CYP2C18: 5%
- CYP3A4-5: 26%

% Drugs Metabolized by CYP Enzymes:
- CYP2D6: 36%
- CYP2C18: 14%
- CYP2C19: 14%
- CYP1A2: 14%
- CYP3A4-5: 33%
- CYP2E1: 5%

Restrictively Metabolized Drugs: Effect of Cirrhosis on CLint

Pugh-Child Classification of Liver Disease Severity

<table>
<thead>
<tr>
<th>Assessment Parameters</th>
<th>1 Point</th>
<th>Assigned Score</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 (s)</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>

Normal MILD MODERATE SEVERE
Correlation of SPECIAL TESTS of Liver Function with CHILD-PUGH SCORES*


```
0 20 40 60 80 100
NORMAL MILD MODERATE SEVERE

% NORMAL FUNCTION

GALACTOSE ELIMINATION CAPACITY
ANTIPYRINE BREATH
INDOCYANINE GREEN CLEARANCE
SORBITOL CLEARANCE
```

“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>DAPSONE</td>
<td>CYP 3A + NAT2</td>
</tr>
<tr>
<td>DEBRISOQUIN</td>
<td>CYP 2D6</td>
</tr>
<tr>
<td>MEPHENYTOIN</td>
<td>CYP 2C19</td>
</tr>
</tbody>
</table>


RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease

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

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

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

- \( Q_T \) = 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>( CL_{H_{int}} ) (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>38</td>
<td>0.38</td>
</tr>
</tbody>
</table>


**NON-RESTRICTIVELY** Metabolized Drugs: Effects of Liver Disease

\[ CL_H = Q \]
**NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease**

\[ CL_H = Q \]

<table>
<thead>
<tr>
<th></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, \( f_CL_{int} \) MAY NO LONGER BE \( \gg Q \)**

**Effects of Hepatic Shunting on Rowland Equation**

\[ CL_H = Q \]

\[ \frac{Q_P \left( Q_T f_CL_{int} \right)}{Q_T + f_CL_{int}} \]

\( Q_T = \) 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_T (mL/min)</th>
<th>Q_P (mL/min)</th>
<th>Q_P/Q_T (%)</th>
<th>ICG CL_H (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 CIRRHOTICS/CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONTROLS (%)</td>
<td>CIRRHOTICS (%)</td>
</tr>
<tr>
<td>MEPERIDINE</td>
<td>48</td>
<td>87</td>
</tr>
<tr>
<td>PENTAZOCINE</td>
<td>18</td>
<td>68</td>
</tr>
<tr>
<td>PROPRANOLOL</td>
<td>38</td>
<td>54</td>
</tr>
</tbody>
</table>

* THIS ALSO INCORPORATES 55% INCREASE IN PROPRANOLOL f_a
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

- 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*


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 $\geq 50\%$ Dose Reduction in Patients with MODERATE CIRRHOSIS

<table>
<thead>
<tr>
<th>ANALGESIC DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>CL&lt;sub&gt;E&lt;/sub&gt;</td>
</tr>
<tr>
<td>Morphine</td>
<td>$\uparrow$ 213%</td>
<td>$\downarrow$ 59%</td>
</tr>
<tr>
<td>Meperidine</td>
<td>$\uparrow$ 94%</td>
<td>$\downarrow$ 46%</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>$\uparrow$ 318%</td>
<td>$\downarrow$ 50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIOVASC. DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>CL&lt;sub&gt;E&lt;/sub&gt;</td>
</tr>
<tr>
<td>Propafenone</td>
<td>$\uparrow$ 257%</td>
<td>$\downarrow$ 24%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>$\uparrow$ 136%</td>
<td>$\downarrow$ 51%</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>$\uparrow$ 78%</td>
<td>$\downarrow$ 60%</td>
</tr>
<tr>
<td>Losartan</td>
<td>$\uparrow$ 100%</td>
<td>$\downarrow$ 50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>CL&lt;sub&gt;E&lt;/sub&gt;</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>$\uparrow$ 75%</td>
<td>$\downarrow$ 89%</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>$\uparrow$ 33%</td>
<td>$\downarrow$ 72%</td>
</tr>
</tbody>
</table>
**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 – 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*