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.
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 \( \text{CL}_E - \text{CL}_R \)
CALCULATION OF $CL_H$

$CL_H = CL_E - CL_R$

Assumes $CL_H = CL_{NR}$
FICK EQUATION

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

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

So \[ Cl = Q \cdot E \]

A = CONCENTRATION ENTERING LIVER
V = CONCENTRATION LEAVING LIVER
Q = HEPATIC BLOOD FLOW
Derivation of ROWLAND EQUATION (I)

\[ V \cdot C_v = \text{fraction of drug that is unbound} \]

\[ CL_{int} = \text{hepatic clearance in absence of binding restriction} \]

Blood Flow \((Q)\)

\[ f_u \cdot CL_{int} \]

\( f_u = \text{fraction of drug that is unbound} \)

\( CL_{int} = \text{hepatic clearance in absence of binding restriction} \)

WELL-STIRRED COMPARTMENT
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:

\[ Q \left( C_a - C_v \right) = f_u \, CL_{int} \, C_v \]

\[ QC_a = \left( Q + f_u \, CL_{int} \right) C_v \]

Therefore:

\[ ER = \frac{C_a - C_v}{C_a} = \frac{f_u \, CL_{int}}{Q + f_u \, CL_{int}} \]
ROWLAND EQUATION
WELL-STIRRED COMPARTMENT

\[ \text{CL}_H = Q \cdot E = Q \cdot \left[ \frac{f_u \text{CL}_{int}}{Q + f_u \text{CL}_{int}} \right] \]

TWO LIMITING CASES:

RESTRICTIVELY METABOLIZED DRUGS (Q >> f_uCL_{int}):

\[ \text{CL}_H = f_u \text{CL}_{int} \]

NON-RESTRICTIVELY METABOLIZED DRUGS (f_uCL_{int} >> Q):

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

\[ \text{Cl}_H = Q = Q \cdot \text{ER} \]

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

\[ \text{BUT: } F = 1 - \text{ER}, \ \text{So } F \Rightarrow 0 \]

**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
• 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

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

<table>
<thead>
<tr>
<th></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

\[ \overline{C}_{ss} = \frac{\text{DOSE}}{\tau} \frac{1}{CL_H} \]

FOR RESTRICTIVELY ELIMINATED DRUGS:

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

FREE CONC. = \( \frac{f_u \cdot \text{DOSE}}{f_u \cdot CL_{int}} \)
FREE and TOTAL PHENYTOIN Levels (DOSE = 300 MG/DAY)

\[ \text{CL}_\text{H} \uparrow \]
\[ \text{CL}_\text{INT} = \]

[PHENYTOIN] mg/L

BOUND [PHENYTOIN]
FREE [PHENYTOIN]

[0 2 4 6 8 10 12]

NORMAL RENAL FUNCTION
FUNCTIONALLY ANEPHRIC
RESTRICTIVELY Metabolized Drugs: Effect of PROTEIN BINDING Changes

Prolactin Time (sec)

Warfarin Concentration (µg/mL)

Total

Free

Displacing Drug

3 Days

14 Days

7 Days
RESTRICTIVELY Metabolized Drugs:
Effects of LIVER DISEASE

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

<table>
<thead>
<tr>
<th>Condition</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>
Role of CYP ENZYMES in Hepatic Drug Metabolism

Relative Hepatic Content of CYP Enzymes
- CYP2D6: 2%
- CYP2C19: 11%
- CYP2C9: 14%
- CYP1A2: 12%
- CYP3A4-5: 26%
- CYP2E1: 5%
- Other: 36%

% Drugs Metabolized by CYP Enzymes
- CYP2D6: 23%
- CYP2C9: 11%
- CYP2C19: 14%
- CYP1A2: 14%
- CYP3A4-5: 33%
- CYP2E1: 5%
RESTRICTIVELY Metabolized Drugs: Effect of CIRRHOSIS on CL_{int}
# 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>
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>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**

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

<table>
<thead>
<tr>
<th></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>
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

## 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 $CL_H$ (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**

\[ CL_H = Q \]

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

\[ CL_H = Q \]

<table>
<thead>
<tr>
<th>( CL_H )</th>
<th>( F )</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ALBUMIN</td>
<td>NO CHANGE*</td>
</tr>
<tr>
<td>↓ ( CL_{int} )</td>
<td>“NO CHANGE”</td>
</tr>
<tr>
<td>↓ HEPATIC PERFUSION</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

HOWEVER, \( f_u CL_{int} \) MAY NO LONGER BE >> \( Q \)
**NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease**

\[ CL_H = Q \]

<table>
<thead>
<tr>
<th>Change in</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>
Effects of Hepatic Shunting on Rowland Equation*

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

\( Q_T \) = 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_T ) (mL/min)</th>
<th>( Q_P ) (mL/min)</th>
<th>( Q_P/Q_T ) (%)</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>AbsolutePath Bioavailability</th>
<th>Relative Exposure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONTROLS (%)</td>
<td>CIRRHOTICS (%)</td>
<td>IV</td>
<td>ORAL</td>
</tr>
<tr>
<td>MEPERIDINE</td>
<td>48</td>
<td>87</td>
<td>1.6</td>
<td>3.1</td>
</tr>
<tr>
<td>PENTAZOCINE</td>
<td>18</td>
<td>68</td>
<td>2.0</td>
<td>8.3</td>
</tr>
<tr>
<td>PROPRANOLOL</td>
<td>38</td>
<td>54</td>
<td>1.5*</td>
<td>2.0*</td>
</tr>
</tbody>
</table>

* 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*

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>ANALGESIC DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
</tr>
<tr>
<td>Morphine</td>
<td>↑ 213%</td>
</tr>
<tr>
<td>Meperidine</td>
<td>↑ 94%</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>↑ 318%</td>
</tr>
<tr>
<td>CARDIOVASC. DRUGS</td>
<td>CHANGE IN CIRRHOSIS</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Propafenone</td>
<td>↑ 257%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>↑ 136%</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>↑ 78%</td>
</tr>
<tr>
<td>Losartan</td>
<td>↑ 100%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>OTHER DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$F$</td>
<td>$CL_E$</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

### Assessment Parameters

<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*