Effects of Liver Disease on Pharmacokinetics

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Clinical Pharmacology Program
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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

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

ESTIMATED FROM PLASMA LEVEL- VS-TIME CURVE
ESTIMATED FROM RECOVERY OF DRUG IN URINE
ESTIMATED AS CL_E - CL_R
CALCULATION OF $\text{CL}_{\text{H}}$

$$\text{CL}_H = \text{CL}_E - \text{CL}_R$$

ASSUMES $\text{CL}_H = \text{CL}_\text{NR}$

FICK EQUATION

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

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

So

$$\text{Cl} = \text{Q} \cdot \text{E}$$

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

Derivation of ROWLAND EQUATION (I)

Blood Flow ($Q$)

Compartments

$C_v$

Well-Stirred

$C_a$

$\text{fu}$

$\text{CL}_{\text{int}}$

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

$\text{fu} = \text{FRACTION OF DRUG THAT IS UNBOUND}$
Derivation of ROWLAND EQUATION (II)

Blood Flow \( (Q) \)

\[ C_a \]

\[ V \cdot C_v \]

\( f_u \cdot CL_{int} \)

MASS BALANCE EQUATION:

\[ \frac{dC_v}{dt} = Q\left(C_a - C_v - f_u \cdot CL_{int} \cdot C_v \right) \]

Derivation of ROWLAND EQUATION (III)

Blood Flow \( (Q) \)

at steady state:

\[ QC_a - QC_v - f_u \cdot CL_{int} \cdot C_v = 0 \]

so:

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

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

therefore:

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

ROWLAND EQUATION

WELL-STIRRED COMPARTMENT

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

TWO LIMITING CASES:

Restrictively Metabolized Drugs (\( Q \gg f_u \cdot CL_{int} \)):

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

Non-Restrictively Metabolized Drugs (\( f_u \cdot CL_{int} \gg Q \)):

\[ CL_u = Q \]
**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**

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

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

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

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

**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>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_H</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>PORTOSYSTEMIC SHUNTING</td>
<td>↓</td>
<td>↑</td>
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RESTRICTIVELY Metabolized Drugs: Effect of PROTEIN BINDING Changes

$$\bar{c}_{ss} = \frac{\text{DOSE} / \tau}{CL_{Hr}}$$

FOR RESTRICTIVELY ELIMINATED DRUGS:

$$CL_{Hr} = f_u CL_{mf}$$

FREE CONC. = $$\bar{c}_{ss} \cdot f_u = \frac{f_u \text{DOSE}}{\tau}$$

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

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RESTRICTIVELY Metabolized Drugs: Effect of PROTEIN BINDING Changes

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

\[
CL_H = f_u \cdot CL_{int}
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**Role of CYP ENZYMES in Hepatic Drug Metabolism**

- **CYP2D6**: 26%
- **CYP2E1**: 5%
- **CYP2C**: 17%
- **CYP1A2**: 12%
- **CYP3A4-5**: 26%

**% DRUGS METABOLIZED BY CYP ENZYMES**

- **CYP1A2**: 14%
- **CYP2C9**: 14%
- **CYP2C19**: 11%
- **CYP2D6**: 23%
- **CYP2E1**: 5%
- **CYP3A4-5**: 33%

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**RESTRICTIVELY Metabolized Drugs: Effect of CIRRHOSIS on \(CL_{int}\)**

![Graph showing effects of cirrhosis on intrinsic clearance](image)

- **CYP3A4**
- **CYP2D6**
- **GLUCURONIDATION**
- **CYP2C19**
- **CYP1A2**
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>
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<tr>
<td>ENCEPHALOPATHY GRADE</td>
<td>0</td>
<td>1 or 2</td>
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<td>PROTHROMBIN TIME</td>
<td>1 – 4</td>
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CLASSIFICATION OF CLINICAL SEVERITY

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<th>MILD</th>
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<tr>
<td>TOTAL POINTS</td>
<td>5 – 6</td>
<td>7 – 9</td>
<td>&gt; 9</td>
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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*
**“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></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>
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**Effects of HEPATIC SHUNTING on ROWLAND EQUATION**

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

- \( Q_T = \) 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_T/Q_T ) (%)</th>
<th>( \text{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/</td>
<td>0.57</td>
<td>0.22</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>MODERATE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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### 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_{in} )</td>
<td>&quot;NO CHANGE&quot;</td>
</tr>
<tr>
<td>↓ HEPATIC PERFUSION</td>
<td>↓↓</td>
</tr>
</tbody>
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* HOWEVER, NOTE THAT FREE CONCENTRATION IS ↑

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

\[ CL_H = Q \]

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<th>( CL_{in} )</th>
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<td>↓ HEPATIC PERFUSION</td>
<td>↓↓</td>
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HOWEVER, \( f_{CL_{in}} \) MAY NO LONGER BE >> \( Q \)
**NON-RESTRICTIVELY Metabolized Drugs: Effects of Liver Disease**

\[ CL_{\text{H}} = Q \]

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

**Effects of Hepatic Shunting on Rowland Equation**

\[
CL_{\text{H}} = \left( \frac{Q_{p}}{Q_{T}} \right) \left( \frac{Q_{T} f_{L} CL_{\text{int}}}{Q_{T} + f_{L} CL_{\text{int}}} \right)
\]

\( Q_{p} = \) 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} )</th>
<th>( Q_{p} )</th>
<th>( Q_{p}/Q_{T} )</th>
<th>ICG ( CL_{\text{H}} )</th>
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<tr>
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<td>1.26</td>
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<td>766</td>
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<td>182</td>
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<td>0.38</td>
<td>0.24</td>
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Influence of \textit{PORTOSYSTEMIC SHUNTING} on Oral Bioavailability (F)

\textbf{RESTRICTIVELY Eliminated Drugs:}
Little change

\textbf{NON-RESTRICTIVELY Eliminated Drugs:}
\textit{SHUNTING} may markedly increase extent of drug absorption (F)

\textbf{CIRRHOSIS Affects Exposure to Some NON-RESTRICTIVELY Metabolized Drugs}

<table>
<thead>
<tr>
<th>Drug</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>
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* THIS ALSO INCORPORATES 55\% INCREASE IN PROPRANOLOL f

\textbf{CIRRHOSIS Affects Renal Function: The Hepatorenal Syndrome}

- \textit{Risk} in Patients with Cirrhosis, Ascitis, and GFR > 50 mL/min:
  - 18\% within 1 year
  - 39\% within 5 years
- \textit{Predictors} of Risk:
  - Small liver
  - Low serum albumin
  - High plasma renin
- Cockcroft and Gault Equation may \textit{overestimate} renal function
CIRRHOSIS Affects Renal Function: The Hepatorenal Syndrome

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

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

<table>
<thead>
<tr>
<th>ANALGESIC DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
<th>( F )</th>
<th>( CL_E )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>↑ 213%</td>
<td>↓ 50%</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>↑ 94%</td>
<td>↓ 46%</td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td>↑ 318%</td>
<td>↓ 50%</td>
<td></td>
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<thead>
<tr>
<th>CARDIOVASC. DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
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<th>( CL_E )</th>
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<tbody>
<tr>
<td>Propafenone</td>
<td>↑ 257%</td>
<td>↓ 24%</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>↑ 136%</td>
<td>↓ 51%</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>↑ 78%</td>
<td>↓ 60%</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>↑ 100%</td>
<td>↓ 50%</td>
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Drugs Requiring ≥ 50% Dose Reduction in Patients with MODERATE CIRRHOSIS

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<th>OTHER DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
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<tr>
<td>Omeprazole</td>
<td>( \uparrow 75% )</td>
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<tr>
<td>Tacrolimus</td>
<td>( \uparrow 33% )</td>
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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