Effects of Liver Disease on Pharmacokinetics

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Clinical Pharmacology Program
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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
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 $\text{CL}_H$

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

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

\[ V, C_v = \text{FRACTION OF DRUG THAT IS UNBOUND} \]

\[ \frac{C_a}{C_v} = f_u \cdot CL_{\text{int}} \]

- Blood Flow \((Q)\)
- \(C_a\) and \(C_v\) in a WELL-STIRRED COMPARTMENT
- \(f_u \cdot CL_{\text{int}}\)
- \(f_u = \text{FRACTION OF DRUG THAT IS UNBOUND}\)
- \(CL_{\text{int}} = \text{HEPATIC CLEARANCE IN ABSENCE OF BINDING RESTRICTION}\)
Derivation of *ROWLAND EQUATION (II)*

**MASS BALANCE EQUATION:**

\[ V \frac{dC}{dt} = QC_a - QC_v - f_u CL_{int} C_v \]
Derivation of **ROWLAND EQUATION (III)**

- Blood Flow ($Q$)

\[ C_a \quad V, C_v \quad C_r \]

\[ f_u \cdot CL_{\text{int}} \]

- at steady state:

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

- so:

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

\[ QC_a = Q + f_u \cdot CL_{\text{int}} \cdot C_v \]

- therefore:

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

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

TWO LIMITING CASES:
RESTRICTIVELY METABOLIZED DRUGS \((Q >> f_u \cdot CL_{int})\):
\[ CL_H = f_u \cdot CL_{int} \]
NON-RESTRICTIVELY METABOLIZED DRUGS \((f_u \cdot CL_{int} >> Q)\):
\[ CL_H = Q \]
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 \( E = 0 \): \( V = A \)
\[ \text{Cl}_H = Q = Q \cdot ER \]

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></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

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

FOR RESTRICTIVELY ELIMINATED DRUGS:

\[ CL_H = f_u CL_{int} \]

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

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

[PHENYTOIN] [μg/mL]

0 2 4 6 8 10 12

NORMAL RENAL FUNCTION

BOUND [PHENYTOIN]
FREE [PHENYTOIN]

FUNCTIONALLY ANEPHRIC
RESTRICTIVELY Metabolized Drugs: Effect of PROTEIN BINDING Changes

Graph showing:
- Prolithrombin Time (sec) vs Days
  - 3 Days
  - 14 Days
- Warfarin Concentration (µg/mL) vs Days
  - Total
  - Free
  - Displacing Drug

Days:
- 3 Days
- 14 Days
- 7 Days

Concentration Levels:
- 10.0
- 1.0
- 0.1
**RESTRICTIVELY Metabolized Drugs:**

**Effects of LIVER DISEASE**

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

<table>
<thead>
<tr>
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<th>FREE CONC.</th>
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<tr>
<td>PORTOSYSTEMIC SHUNTING</td>
<td>↓</td>
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</tbody>
</table>
Role of CYP ENZYMES in Hepatic Drug Metabolism

- **RELATIVE HEPATIC CONTENT OF CYP ENZYMES**
  - CYP2D6: 2%
  - CYP2C: 17%
  - CYP 1A2: 12%
  - CYP 3A4-5: 26%
  - OTHER: 36%

- **% DRUGS METABOLIZED BY CYP ENZYMES**
  - CYP 1A2: 14%
  - CYP 2C9: 14%
  - CYP 2C19: 11%
  - CYP2D6: 23%
  - CYP 2E1: 5%
  - CYP 3A4-5: 33%
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</td>
<td>1 – 4</td>
<td>4 – 10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

(Seconds > control)

<table>
<thead>
<tr>
<th>CLASSIFICATION OF CLINICAL SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL SEVERITY</td>
</tr>
<tr>
<td>MILD</td>
</tr>
<tr>
<td>MODERATE</td>
</tr>
<tr>
<td>SEVERE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOTAL POINTS</th>
<th>5 – 6</th>
<th>7 – 9</th>
<th>&gt; 9</th>
</tr>
</thead>
</table>

- **CLINICAL SEVERITY MILD MODERATE SEVERE**
- **TOTAL POINTS 5 – 6 7 – 9 > 9**
- **ASSESSMENT PARAMETERS 1 POINT 2 POINTS 3 POINTS**
- **ENCEPHALOPATHY GRADE 0 1 or 2 3 or 4**
- **ASCITES ABSENT SLIGHT MODERATE**
- **BILIRUBIN (mg/dL) 1 – 2 2 – 3 > 3**
- **ALBUMIN (gm/dL) > 3.5 2.8 – 3.5 < 2.8**
- **PROTHROMBIN TIME 1 – 4 4 – 10 > 10 (seconds > control)**
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*


<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>
</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>( 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, 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>Condition</th>
<th>CL&lt;sub&gt;H&lt;/sub&gt;</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ALBUMIN</td>
<td>NO CHANGE*</td>
<td>NO CHANGE</td>
</tr>
<tr>
<td>↓ CL&lt;sub&gt;int&lt;/sub&gt;</td>
<td>“NO CHANGE”</td>
<td>“NO CHANGE”</td>
</tr>
<tr>
<td>↓ HEPATIC PERFUSION</td>
<td>↓</td>
<td>↑↑</td>
</tr>
</tbody>
</table>
**Effects of Hepatic Shunting on Rowland Equation**

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

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

### 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 $CL_H$</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 extent of drug absorption (F)
**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>
</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.
HEPATOURENAL 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
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

A method for assessing the severity of liver disease by assigning points to various clinical parameters and classifying the total points into mild, moderate, or severe categories.

<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>
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**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>
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</table>
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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>CL&lt;sub&gt;E&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>↑ 213%</td>
<td>↓ 59%</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>
</tr>
<tr>
<td>CARDIOVASC. DRUGS</td>
<td>CHANGE IN CIRRHOSIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>CL_E</td>
<td></td>
</tr>
<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>
<td></td>
</tr>
</tbody>
</table>
Drugs Requiring ≥ 50% *Dose Reduction* in Patients with MODERATE CIRRHOSIS

<table>
<thead>
<tr>
<th>OTHER DRUGS</th>
<th>CHANGE IN CIRRHOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>↑ 75%</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↑ 33%</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