Effects of Advanced Liver Disease on drug PK

Giovanni Di Perri

Clinica di Malattie Infettive
Università degli Studi di Torino
Ospedale Amedeo di Savoia
• **Pathophysiology of Liver Disease and potential Pharmacokinetic impact**
  Absorption / Protein binding / Distribution / Metabolism / Excretion

• **Evaluation of Liver Function under a Pharmacological Perspective**
  Serum and clinical markers / histology / elastometry / dynamic function tests

• **Antiviral Drugs**
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Pathophysiology of Hepatic Dysfunction and Pharmacokinetic Consequences

- Absorption
- Protein Binding / Distribution
- Elimination

Metabolism

Biliary Excretion
Renal Excretion
Pathophysiology of Hepatic Dysfunction and Pharmacokinetic Consequences

- Absorption
- Protein Binding / Distribution
- Elimination
  - Metabolism
  - Biliary Excretion
  - Renal Excretion
Drugs absorbed from the gastrointestinal tract are exposed to the metabolizing enzymes and bile excretory transport systems of the liver before reaching the systemic circulation.
Dual blood supply consisting of 1500 ml/min:

- Hepatic artery: 25%
- Portal Vein: 75%

Since only 25% of liver blood is of arterial origin, any intervening condition leading to further decrease in pO$_2$ might lead to hepatocellular hypoxia.

The combination of open fenestrae, thin cytoplasm, and lack of an organized basement membrane reduces the distance required for oxygen diffusion and thereby facilitates oxygen delivery to the hepatocyte to compensate for the relatively low pO$_2$ in sinusoidal blood.
The fraction ($F_H$) of an absorbed oral dose escaping first-pass clearance:

$$F_H = 1 - f_H \times E_H = \frac{Q_H + f_u \times CL_{int} (1 - f_H)}{Q_H + f_u \times CL_{int}}$$

- Fraction of the mesenteric blood flow passing through the liver
- Hepatic extraction ratio
- Unbound drug
- Intrinsic clearance of unbound drug
- Hepatic blood flow
- General Circulation
Drugs can be categorized according to the efficiency of the liver in their removal from the circulation:

**High Hepatic Extration Ratio (\(E_H > 0.7\))**

Blood flow limited: rather insensitive to changes in protein binding or enzyme/transporter activity. Significant impact may result from decrease in blood flow and porto-systemic shunting

**Intermediate Hepatic Extration Ratio (0.3 < \(E_H < 0.7\))**

May be influenced by changes in either one of its 3 primary determinants (e.g. hepatic blood flow \([Q_H]\), intrinsic clearance of unbound drug \([CL_{int}]\) and the fraction of unbound drug \([f_u]\) )

**Low Hepatic Extration Ratio (\(E_H < 0.3\))**

Mainly influenced by changes in protein binding and in the intrinsic hepatic clearance \((CL_{int})\). Enzyme/transporter capacity-limited
Systemic Clearance and Oral Clearance:

<table>
<thead>
<tr>
<th>EPATIC EXTRACTION RATIO ((E_H))</th>
<th>SYSTEMIC CLEARANCE ((C_{\text{syst}}))</th>
<th>ORAL CLEARANCE ((C_{\text{or}}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E_H &lt; 0.3)</td>
<td>(f_u \times C_{\text{int}})</td>
<td>(f_u \times C_{\text{int}})</td>
</tr>
<tr>
<td>(0.3 &lt; E_H &lt; 0.7)</td>
<td>(CL_H = Q_H \times \frac{f_u \times C_{\text{int}}}{Q_H + f_u \times C_{\text{int}}})</td>
<td>(f_u \times C_{\text{int}})</td>
</tr>
<tr>
<td>(E_H &gt; 0.7)</td>
<td>(Q_H)</td>
<td>(f_u \times C_{\text{int}})</td>
</tr>
</tbody>
</table>
CIRRHOSIS results in several pathophysiologic changes in the liver that may influence pharmacokinetics.

Histologically, it consists of a diffuse process characterized by fibrosis and a conversion of normal organ architecture into structurally abnormal nodules.

1. Reduction in liver blood flow
2. Intra- and extra-hepatic portal-systemic shunting
3. Reduction in the number and function of hepatocytes
4. Capillarization of the sinusoids

Loss of fenestration, thickening of the cytoplasm, and development of an organized basement membrane is called capillarization.

Impaired synthesis of albumin → edema, ascites → reduced plasma binding of drugs
Four different theories have been proposed to account for the effects of chronic liver disease with cirrhosis on hepatic drug elimination:

1. the sick cell theory;

2. the intact hepatocyte theory;

1. the impaired drug uptake theory;

1. the oxygen limitation theory.

Hepatocytes from **cirrhotic** and **age-matched control rats** were isolated, characterized, and transplanted into the livers of noncirrhotic hosts whose livers permit extensive repopulation with donor cells.

Primary hepatocytes derived from livers with **advanced cirrhosis and compensated function** maintained metabolic activity and the ability to secrete liver-specific proteins, whereas hepatocytes derived from **cirrhotic livers with decompensated function** failed to maintain metabolic or secretory activity. The latter showed signs of replicative senescence and express genes that simultaneously drive both proliferation and apoptosis, with a later effect on metabolism.

Both, however, recovered more than 2 months after transplantation, indicating that either mature hepatocytes or a subpopulation of adult stem cells are capable of full recovery in severe cirrhosis.

Transplantation studies indicate that the state of the host microenvironment is critical to the regenerative potential of hepatocytes, and that a **change in the extracellular matrix** can lead to regeneration and restoration of function by cells derived from livers with end-stage organ failure.
The main effect of chronic liver disease on oral drug availability is thought to result from reduced presystemic drug metabolism.

A. between esophageal veins (portal) and the azygos vein (systemic)
B. between the superior rectal vein (portal) and the lower rectal veins to the IVC (systemic)
C. between the paraumbilical veins (portal) and the abdominal epigastric veins (systemic)
D. between the colic veins (portal) and the retroperitoneal veins (systemic)
CIRRHOSIS may lead to the reduction of:

- PORTO-SYSTEMIC SHUNTS
- DECREASED ACTIVITY OF METABOLIZING ENZYMES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Normal Oral Bioavailability</th>
<th>CIRRHOSIS</th>
<th>Fold Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>0.19</td>
<td>0.83</td>
<td>4.4</td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>0.16</td>
<td>1.16</td>
<td>11.6</td>
</tr>
<tr>
<td>Labetalol</td>
<td>0.33</td>
<td>0.63</td>
<td>1.9</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.48</td>
<td>0.87</td>
<td>1.8</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>0.50</td>
<td>0.84</td>
<td>1.7</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.38</td>
<td>0.76</td>
<td>2.0</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.47</td>
<td>1.01</td>
<td>2.1</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.51</td>
<td>0.91</td>
<td>1.8</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>0.04</td>
<td>0.15</td>
<td>3.8</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>0.18</td>
<td>0.68</td>
<td>3.8</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.36</td>
<td>0.60</td>
<td>1.7</td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.10</td>
<td>0.16</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Pathophysiology of Hepatic Dysfunction and Pharmacokinetic Consequences

- Absorption
- Protein Binding / Distribution
- Elimination
  - Metabolism
    - Biliary Excretion
    - Renal Excretion
CIRRHOSIS also results in changes in protein binding and distribution:

1. Reduced albumin and $\alpha_1$ – acid glycoprotein (AAG)

2. Increase in endogenous compounds (e.g. bilirubin) inhibiting plasma protein binding of several drugs

3. Qualitative changes in albumin and AAG

4. Increase in volume of distribution
Plasma protein (e.g. albumin, $\alpha_{1}$AG)

**Unbound** to plasma proteins

**Bound** to plasma proteins

Free drug, the fraction of total drug to which the therapeutic/toxic actions are attributable
Pathophysiology of Hepatic Dysfunction and Pharmacokinetic Consequences

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Liver disease selectively modulates cytochrome P450–mediated metabolism

- 20 patients with different etiologies and severity of liver disease
- 20 age-, sex-, and weight-matched healthy volunteers
- Liver disease severity was categorized by use of the Child-Pugh score
- All participants received a cocktail of 4 oral drugs simultaneously:
  - Caffeine (CYP1A2)
  - Mephenytoin (CYP2C19)
  - debrisoquin (INN, debrisoquine / CYP2D6)
  - Chlorzoxazone (CYP2E1)
- The primary end points were measurements of specific CYP metabolism indexes for each enzyme.
Mean (SE) percentage difference in index of drug metabolism from control group for caffeine, mephenytoin, debrisoquin, and chlorzoxazone in same cohort of patients with compensated (black bars, n = 8) or decompensated (gray bars, n = 12) liver disease. *Section mark, $P < .001$ in comparison with control subjects; #pound sign, $P < .01$ in comparison with control subjects; *asterisk, $P < .05$ in comparison with control subjects.
Relationships between Child-Pugh score and caffeine metabolic ratio ($r = -0.4984, P = .0012$) (A) and mephenytoin hydroxylation ($r = -0.6992, P < .0001$) (B).

The *dashed line* represents the threshold for CYP2C19 poor metabolizer status. Individuals with values below this *line* are considered phenotypic poor metabolizers.

Liver disease selectively modulates cytochrome P450–mediated metabolism
Relationships between Child-Pugh score and debrisoquin recovery ratio ($r = -0.5924$, $P = .0001$) (A) and chlorzoxazone metabolic ratio ($r = -0.4776$, $P = .0024$) (B).

The *dashed line* represents the threshold for CYP2D6 poor metabolizer status. Individuals with values below this line are considered phenotypic poor metabolizers.

Liver disease selectively modulates cytochrome P450–mediated metabolism
Proposed interpretation by the Authors:

“sequential progressive model of hepatic dysfunction”

As an alternative to:

a. The sick cell theory
b. The intact hepatocyte theory

Different aspects of hepatic function are modified in the presence of liver disease, and the order of progression of alteration of each function follows a defined sequence:

<table>
<thead>
<tr>
<th>EARLY STAGE</th>
<th>INTERMEDIATE STAGE</th>
<th>END STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>CYP1A2</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>CyP2D6</td>
<td>CyP2D6</td>
<td>CyP2D6</td>
</tr>
<tr>
<td>CYP 2E1</td>
<td>CYP 2E1</td>
<td>CYP 2E1</td>
</tr>
</tbody>
</table>
CYP enzyme expression with progressive hepatic impairment

Model of hepatic dysfunction and implications for clearance of drugs predominantly metabolized by CYP pathway in liver. Study in healthy volunteers and patients with liver disease

Changes in Nelfinavir PK with Cirrhosis

CYP2C19 is exquisitely sensitive to the presence of liver disease

Conjugation reactions are thought to be less affected than CYP450 reactions in patients with chronic liver disease:

Oxazepam  
Lorazepam  
Temazepam  
mainly cleared by glucuronidation

Diazepam  
Midazolam  
mainly cleared by phase I reactions

NOT reduced in liver cirrhosis  
CLEARANCE  
Reduced in liver cirrhosis

Activation of latent UDP-glucuronyltransferase (UGT) enzymes in liver injury


Increased extra-hepatic metabolism in cirrhosis (e.g. morphine)


In subsequent studies, carried out on patients with more advanced liver disease, impaired glucuronidation was found for drugs like morphine, diflunisal, lormetazepam, oxazepam, lamotrigine, zidovudine and mycophenolate mofetil

Mechanisms for hepatic residence and clearance of drugs

BLOOD

HEPATOCYTES

Pharmacokinetics (PK)
- Genetic/functional variability may translate to variability in plasma PK.
- Inhibition/induction by a “perpetrator” drug may affect PK of a “victim” drug.

Hepatic intracellular concentrations (IC)
- Genetic/functional variability may influence IC.
- Inhibition/induction by a “perpetrator” drug may affect IC of a “victim” drug.

Toxicity (hyperbilirubinemia)
- Genetic/functional variability may affect bilirubin uptake, conjugation or apical efflux.
- Inhibition/induction by a drug may affect bilirubin uptake, conjugation or apical efflux.
HCV, liver disease and transporters

<table>
<thead>
<tr>
<th>mRNA levels (amol/µg total RNA)</th>
<th>HCV (-), LC (-)</th>
<th>HCV (+), LC (-)</th>
<th>HCV (-), LC (+)</th>
<th>HCV (+), LC (+)</th>
<th>Ratio [(+), (+)/(-), (-)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT1</td>
<td>16.63 ± 8.91</td>
<td>13.64 ± 9.23</td>
<td>10.70 ± 4.60</td>
<td>8.87 ± 5.56***</td>
<td>0.53</td>
</tr>
<tr>
<td>OCTN2</td>
<td>0.70 ± 0.32</td>
<td>0.83 ± 0.47</td>
<td>0.55 ± 0.24</td>
<td>0.75 ± 0.39</td>
<td>1.07</td>
</tr>
<tr>
<td>OAT2</td>
<td>11.86 ± 7.36</td>
<td>13.37 ± 8.62</td>
<td>10.06 ± 4.03</td>
<td>10.27 ± 5.66</td>
<td>0.87</td>
</tr>
<tr>
<td>OAT7</td>
<td>0.62 ± 0.33</td>
<td>0.56 ± 0.30</td>
<td>0.47 ± 0.19</td>
<td>0.47 ± 0.20</td>
<td>0.76</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>10.55 ± 6.71</td>
<td>8.04 ± 4.78</td>
<td>6.72 ± 2.95</td>
<td>5.91 ± 2.89***</td>
<td>0.56</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>3.83 ± 2.27</td>
<td>2.91 ± 1.95</td>
<td>2.80 ± 1.54</td>
<td>1.98 ± 1.15**</td>
<td>0.52</td>
</tr>
<tr>
<td>OATP2B1</td>
<td>31.20 ± 13.72</td>
<td>32.50 ± 20.18</td>
<td>24.13 ± 10.17</td>
<td>24.36 ± 10.91</td>
<td>0.78</td>
</tr>
<tr>
<td>MATE1</td>
<td>3.14 ± 2.04</td>
<td>2.13 ± 1.27</td>
<td>2.04 ± 0.93</td>
<td>1.34 ± 0.68***</td>
<td>0.43</td>
</tr>
<tr>
<td>PEPT1</td>
<td>1.01 ± 0.55</td>
<td>1.24 ± 0.66</td>
<td>0.81 ± 0.39</td>
<td>0.94 ± 0.32</td>
<td>0.93</td>
</tr>
<tr>
<td>MDR1</td>
<td>1.15 ± 0.52</td>
<td>1.56 ± 0.87</td>
<td>1.07 ± 0.35</td>
<td>1.40 ± 0.43*</td>
<td>1.22</td>
</tr>
<tr>
<td>MRP1</td>
<td>0.25 ± 0.14</td>
<td>0.40 ± 0.26</td>
<td>0.27 ± 0.17</td>
<td>0.51 ± 0.53*</td>
<td>2.04</td>
</tr>
<tr>
<td>MRP2</td>
<td>2.96 ± 1.77</td>
<td>2.44 ± 1.66</td>
<td>1.45 ± 0.68</td>
<td>1.45 ± 0.54***</td>
<td>0.49</td>
</tr>
<tr>
<td>MRP3</td>
<td>2.58 ± 1.31</td>
<td>2.64 ± 1.34</td>
<td>1.68 ± 0.55</td>
<td>2.18 ± 1.09</td>
<td>0.85</td>
</tr>
<tr>
<td>MRP4</td>
<td>0.09 ± 0.05</td>
<td>0.16 ± 0.14</td>
<td>0.11 ± 0.05</td>
<td>0.18 ± 0.13***</td>
<td>2.06</td>
</tr>
<tr>
<td>MRP5</td>
<td>0.07 ± 0.04</td>
<td>0.10 ± 0.06</td>
<td>0.06 ± 0.02</td>
<td>0.11 ± 0.08</td>
<td>1.49</td>
</tr>
<tr>
<td>MRP6</td>
<td>3.41 ± 2.16</td>
<td>3.13 ± 1.76</td>
<td>2.50 ± 1.28</td>
<td>2.33 ± 1.15</td>
<td>0.68</td>
</tr>
<tr>
<td>BCRP</td>
<td>0.57 ± 0.33</td>
<td>0.45 ± 0.25</td>
<td>0.33 ± 0.17</td>
<td>0.31 ± 0.22***</td>
<td>0.53</td>
</tr>
</tbody>
</table>
Fibrosis stage proportional Decreases in mRNA levels of OCT1 and OATP1B1 in cirrhotic patients

...may prevent the accumulation of endogenous and exogenous toxic compounds in damaged hepatocytes...

Upregulation of MRP4 mRNA in patients with HCV-associated cirrhosis
(Also reported in
✓ PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS,
✓ PRIMARY BILIARY CIRRHOSIS
✓ ACETAMINOPHEN-INDUCED ACUTE LIVER FAILURE)

...may serve to prevent further damage to hepatocytes through the increased efflux of potentially toxic compounds, like bile acids......

Both support the general hypothesis of activation of multiple detoxifying mechanisms
**Biliary Excretion**

- Reduced formation or secretion of bile into the duodenum leads to a decreased clearance of both endogenous and exogenous substances that are eliminated by biliary excretion (e.g. ampicillin, piperacillin, several cephalosporins, clindamycin, ciprofloxacin)
- Hepatocellular damage from biliary obstruction (e.g. changes in the membrane and cytoskeleton of biliary canaliculi)
- Role of transporters

**Renal Excretion**

- Advanced liver disease is often complicated by impaired renal function – **hepatorenal syndrome**, such as unexplained progressive renal failure occurring in patients with chronic liver disease without other causes of renal failure
- Conventional creatinine-based GFR measurements often inadequate:
  - Reduced muscle mass
  - Impaired metabolism of creatine to creatinine
  - Increased fractional tubular secretion of creatinine
- Pathophysiology of Liver Disease and potential Pharmacokinetic impact
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- Antiviral Drugs
### Child-Pugh classification and scoring of liver diseases

<table>
<thead>
<tr>
<th>Clinical/Biochemical Indicator</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2 - 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8 – 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prothrombine time (s &gt; control)</td>
<td>&lt; 4</td>
<td>4 - 6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>none</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>
</tbody>
</table>

Points are summed, and the total score is classified according to severity as follows:

**GROUP A** (mild) = 5 – 6 points

**GROUP B** (moderate) = 7 – 9 points

**GROUP C** (severe) = 10 – 15 points
## Staging of fibrosis in chronic viral hepatitis

<table>
<thead>
<tr>
<th>Definition</th>
<th>IASL</th>
<th>Metavir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Fibrosis</td>
<td>F0</td>
</tr>
<tr>
<td></td>
<td>Mild Fibrosis</td>
<td>F1</td>
</tr>
<tr>
<td></td>
<td>Moderate Fibrosis</td>
<td>F2</td>
</tr>
<tr>
<td></td>
<td>Severe Fibrosis</td>
<td>F3</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis</td>
<td>F4</td>
</tr>
</tbody>
</table>

**Fibrous Portal Expansion**
- Few Bridges or Septa
- Numerous Bridges or Septa

**Cirrhosis**

Metavir score by liver stiffness assessed with transient elastography (Fibroscan®)

<table>
<thead>
<tr>
<th>Metavir score</th>
<th>Liver stiffness (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>&lt; 5.0</td>
</tr>
<tr>
<td>F1</td>
<td>5.1-7</td>
</tr>
<tr>
<td>F2</td>
<td>7.1-9.5</td>
</tr>
<tr>
<td>F3</td>
<td>9.6-12.5</td>
</tr>
<tr>
<td>F4</td>
<td>&gt;12.5</td>
</tr>
</tbody>
</table>

DYNAMIC LIVER FUNCTION TESTS (1)

In order to better predict individual drug handling in patients with hepatic dysfunction

Oral or IV administration

Exogenous substance mostly or exclusively eliminated by the liver

Determination of:

a) the plasma disappearance of the probe or
b) the appearance of a metabolite

Exogenous substances used as model substrates can be classified as:

1. **Blood-flow-limited** (high extraction ratio)
2. **Capacity-limited** (low-extraction ratio)
Based on test principles, the measurement of hepatic extraction of blood-flow dependent probes (e.g. indocyanine green and sorbitol) will give an estimate of the degree of sinusoidal and vascular shunting.

It is not clear how concurrent alteration of hepatic-uptake mechanisms might affect the hepatic clearance of these high extraction ratio molecules.

**LIDOCAINE** \((E_H > 0.7)\) transformation into MONOETHYLGLYCINEXYLIDIDE (MEGX) CYP3A AND CYP1A2. The test was shown to correlate with Child-Pugh scores.

Metabolic dysfunction of liver cells can be assessed by low extraction ratio substances, whose clearance should be minimally dependent upon alterations in hepatic blood flow and the presence of portal-systemic shunts.

**ANTIPYRINE**: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP3A4

**CAFFEINE**: CYP1A2

Ratios of PARAXANTHINE (a caffeine metabolite) to CAFFEINE are reduced in patients with liver disease and correlate linearly with Child-Pugh scores.

**MIDAZOLAM**: CYP3A4

In order to by-pass intestinal CYP3A4 activity and thus using it as a marker for hepatic CYP3A4 MIDAZOLAM should be administer IV – Midazolam is not a Pgp substrate.
DYNAMIC LIVER FUNCTION TESTS (3)

$^{14}\text{CO}_2$ BREATH TESTS:

**AMINOPYRINE** (CYP2D6, CYP2C9, CYP2C19, CYP1A2)

**ERYTHROMYCIN** (CYP3A probe, Pgp substrate)

**CAFFEINE** (CYP1A2)

No demonstration has been so far provided on the superiority of these dynamic liver function tests over Child-Pugh classification.

In addition, several studies found a significant correlation in the same group of patients between tests using a low-extraction drug and tests using a high-extraction drug.

Clinicians rely more on the Child-Pugh score which is more easily available and consists of parameters to which they are more accustomed.
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  Absorption / Protein binding / Distribution / Metabolism / Excretion

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• Antiviral Drugs
ANTIRETROVIRALS IN LIVER DISEASE, HCV AND/OR HBV CO-INFECTED PATIENTS

**AZT** > 1st pass effect by glucuronyltransferase > 63% oral bioavailability (although glucuronidation seems not to be altered in liver disease, AZT appears to be an exception)  
< 63-70% decrease in oral clearance in cirrhosis patients

**NNRTIs** CYP3A, CYP2B6, non-significant tendency to PK increase

**NFV** > CYP3A4 and CYP2C19  
Reduced oral clearance of NFV and reduced generation of the M8 metabolite in cirrhosis patients: M8/NFV ratio decreased by 80%

**IDV** > CYP3A4  
Higher incidence of nephrolytiasis and higher [c] in HCV and/or HBV HIV-coinfected patients

**RTV** > CYP3A  
60% lower AUC and Cmax but similar Cmin in cirrhosis vs controls
LPV/r > CYP3A
Higher exposure (Cmin > 73%), unbound LPV from 0.69 to 0.91,

AMP > CYP3A
AUC increase 146-351% (correlated with Child-Pugh score)
Dose estimation to be equivalent to the 1200 mg dose of a patient without liver disease:
  Child-Pugh scores 5-8: 450 mg, Child-Pugh ≥ 9: 300 mg

ATV > CYP3A and UGT1A1
42% increase in AUC, T/2 from 6.4 h to 12.1 h

Although relevant PK changes may be seen with PIs in patients with liver disease/cirrhosis, with the exception of drugs whose administration is today minimal (e.g. IDV), no relevant efficacy/toxicity issues result from liver disease-associated PK alterations of antiretrovirals
# Reference Concentrations ($C_{\min}$) for Efficacy & Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cmin (ng/mL) Efficacy</th>
<th>Cmin (ng/mL) Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir</td>
<td>100</td>
<td>8000 - 10000</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>2100</td>
<td>2100</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>150</td>
<td>850</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>100 - 2200 – 3000 *</td>
<td>4000</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>1000 – 4300 **</td>
<td>6000</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>15000 – 20000 #</td>
<td>35000</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>-</td>
<td>100 - 140</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>50</td>
<td>600</td>
</tr>
</tbody>
</table>

* after NVP failure  **prior failures of NRTIs  # in case of triple drug failure
SVR by Advanced Fibrosis/Cirrhosis in Patients Receiving BOC + PegIFN/RBV

- **Recommendation:** All cirrhotic patients receiving BOC + PR should receive 48 weeks of therapy\(^1\,^2\)

---

**Subgroup Analysis of SPRINT-2\(^3\)**

<table>
<thead>
<tr>
<th></th>
<th>F0/1/2</th>
<th>F3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR48</td>
<td>38/123</td>
<td>38/9</td>
</tr>
<tr>
<td>BOC RGT</td>
<td>67/213</td>
<td>67/211</td>
</tr>
<tr>
<td>BOC/PR48</td>
<td>67/319</td>
<td>52/313</td>
</tr>
</tbody>
</table>

**Subgroup Analysis of RESPOND-2\(^4\)**

<table>
<thead>
<tr>
<th></th>
<th>F0/1/2</th>
<th>F3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR48</td>
<td>23/14</td>
<td>68/81</td>
</tr>
<tr>
<td>BOC RGT</td>
<td>66/77</td>
<td>68/81</td>
</tr>
<tr>
<td>BOC/PR48</td>
<td>44/14</td>
<td>68/31</td>
</tr>
</tbody>
</table>

---

# Effect of Mild and Moderate Hepatic Impairment on Telaprevir Pharmacokinetics

Adiwijaya B, et a.

6th International Workshop on Clinical Pharmacology of Hepatitis Therapy

22 – 23 June 2011, Cambridge, MA, USA

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>1st dose (day 1, 750 mg QD)</th>
<th>1st dose (day 1, 750 mg QD)</th>
<th>Multiple doses (days 2-5, 750 mg q8h)</th>
<th>Multiple doses (days 2-5, 750 mg q8h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(C_{\text{Max}})</td>
<td>(\text{AUC}_{\text{8h}})</td>
<td>(C_{\text{Max}})</td>
<td>(\text{AUC}_{\text{8h}})</td>
</tr>
<tr>
<td><strong>No</strong> (n = 10) hepatic impairment</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Mild</strong> (n = 10) hepatic impairment</td>
<td>0.82 (0.62 – 1.08)</td>
<td>0.89 (0.66 – 1.22)</td>
<td>0.90 (0.73 – 1.10)</td>
<td>0.85 (0.70 – 1.02)</td>
</tr>
<tr>
<td><strong>Moderate</strong> (n = 10) hepatic impairment *</td>
<td>0.59 (0.45 – 0.78)</td>
<td>0.63 (0.47 – 0.86)</td>
<td>0.51 (0.41 – 0.63)</td>
<td>0.54 (0.43 – 0.66)</td>
</tr>
</tbody>
</table>

* Volunteers with CPB had significantly lower average albumin levels compared to volunteers with CPA and healthy volunteers; therefore, a positive correlation was observed between albumin levels and telaprevir exposure.
Impact of Hepatic Impairment on Telaprevir PK

- Reduced Absorption
- Increased clearance due to reduced protein binding

GLS Mean Ratio (90% CI)

<table>
<thead>
<tr>
<th>Condition</th>
<th>$C_{\text{max}}$</th>
<th>$AUC_{8h}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPA</td>
<td>0.90 (0.72, 1.10)</td>
<td>0.85 (0.70, 1.02)</td>
</tr>
<tr>
<td>CPB</td>
<td>0.51 (0.41, 0.63)</td>
<td>0.54 (0.43, 0.66)</td>
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</table>

- Reduced Absorption
- Increased clearance due to reduced protein binding

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
Telaprevir

<table>
<thead>
<tr>
<th>Clinical/Biochemical Indicator</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2 - 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8 – 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prothrombine time (s &gt; control)</td>
<td>&lt; 4</td>
<td>4 - 6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>none</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>
</tbody>
</table>

**GROUP A (mild) = 5 – 6 points**
Patients with hepatic impairment (mild [n = 6], moderate [n = 6], severe [n = 6] and healthy controls [n = 6]) received a single dose of boceprevir (400 mg) on day 1, and whole blood was collected at selected timepoints up to 72 hours postdose to measure plasma drug concentrations.

In the hepatic impairment study, there was a trend toward increased mean maximum (peak) plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) of boceprevir with increasing severity of liver impairment.

GMR for Cmax ranged from 100% in patients with mild hepatic impairment to 161% in patients with severe hepatic impairment, relative to healthy subjects.

GMR for AUC ranging from 91% in patients with mild hepatic impairment to 149% for patients with severe hepatic impairment, relative to healthy subjects.
Impact of Hepatic Impairment on Boceprevir PK

# Boceprevir

**Clinical/Biochemical Indicator**

<table>
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**GROUP A (mild) = 5 – 6 points**

Torino, data on file, 2013
Daclatasvir Unbound Concentrations Unchanged in Hepatic Impairment

Total concentrations appear lower, but free amount is unchanged.

Bifano, M. 62nd AASLD 2011
Asunaprevir Increased with Moderate and Severe Hepatic Impairment

- Metabolized by CYP3A, substrate for OATP1B1 and OATP2B1

Figure 3. Mean ASV Plasma Concentrations in Hepatic Impairment Groups and Controls at Day 7 (0-12 hr)

- AUC ↑ 9.8-fold and 32-fold in moderate and severe impairment

Eley T et al. AASLD 2012, #1873
What are the pharmacokinetic goals for HCV therapy?
Do plasma concentrations reflect intra-hepatic concentrations?

The Pravastatin Story

• The systemic bioavailability of pravastatin is decreased by 60% (!) when administered at bedtime compared to a morning dose.
  – Already low at approximately 18%.

• Despite this decrease in systemic bioavailability, the efficacy of pravastatin is marginally more effective when given at bedtime (as measured by reduction in total cholesterol) than when given in the morning.

• Does this reflect better hepatic uptake after an evening dose?

  
  see Bellosta et al., Circulation 2004;109:III-50
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ROMA:
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Emanuele Nicastrini
Giuseppe Ippolito

and to Charlie Flexner....