Hepatic Route of Administration and BCS/BDDCS

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Outline

- Liver physiology
- Perfused liver preparation
- Hepatic distribution
  - Reference markers
- Hepatic elimination
  - Diazepam
  - Diclofenac
- BCS/BDDCS
- Conclusions
Liver Physiology

- Blood flow (1.5 ml/min/g liver)
  - 2/3 from the Portal Vein (PV)
  - 1/3 from the Hepatic Artery (HA)
Functional unit-Hepatic acinus

Arrangement of liver cells

Fenestrated Endothelial cells

SINUSOIDS

Kupffer cells

Stellate cells

Hepatocytes

Microvilli

Tight junctions

Bile cannaliculus

Space of Disse

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September 23-24, Amman-Jordan
Hepatic enzymes and Transporters

Shugarts and Benet, Pharm Res, 26(9):2039-54, 2009
Isolated Liver Perfusion

- The isolated perfused liver preparation is an ideal experimental system that has been widely used to investigate the kinetics of hepatic disposition.

- The perfused liver retains characteristics that are closest to the *in vivo* situation in terms of structural and functional heterogeneity.
Isolated Liver Perfusion

- Single pass perfusion
  - Single (via PV) perfusion
  - Dual (via PV and HA) perfusion

- Recirculation
Isolated Liver Perfusion

- **Single pass mode** permits easy manipulation of the experimental conditions (e.g., perfusate flow, binding, oxygen content, temperature, etc.) without the complicating effects of recirculation.
Isolated Liver Perfusion

- Although the liver has a dual blood supply, hepatic artery (HA) and portal vein (PV), the PV has generally been the sole source of input in the isolated perfused liver preparations studied.

- This modality is unphysiological in the sense that it excludes possible contributions from the arterial input.
Dual perfused rat liver preparation

Outflow cannula

Inferior vena cava

Hepatic artery

Portal vein

Inflow cannula (PV)
**Perfusion system**

P: pump, R: reservoir, HFO: hollow fiber oxygenator, FC: fraction collector

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Hepatic Distributional Spaces

- Total Space
  - Intracellular space (Hepatocytes)
  - Extracellular space
    - Interstitial space (Space of Disse)
    - Intravascular space

- Sinusoids
- Space of Disse
- Hepatocytes
Markers for the hepatic distributional spaces

- **Intravascular Space**: Red blood cells
- **Extracellular Space**: $^{125}\text{I}$-Albumin, $^{14}\text{C}$-Sucrose
- **Total Space**: $^{3}\text{H}$-water, $^{14}\text{C}$-Urea
Reference markers for distributional spaces

- Not metabolized by the liver
- Homogeneous distribution within the space of interest
Parameters for dual perfusion

- **Mean Transit Time (MTT)**
  
  \[ MTT = \frac{\text{AUMC}}{\text{AUC}} \]

- **Volume of distribution (V)**

  - for PV
    
    \[ V_{\text{PV}} = [Q_{\text{PV}} + 0.83 Q_{\text{HA}}] \cdot MTT_{\text{PV}} \]
  
  - for HA
    
    \[ V_{\text{HA}} = Q_{\text{HA}} [MTT_{\text{HA}} - 0.83 MTT_{\text{PV}}] + V_{\text{PV}} \]
Reference markers
Portal vein

![Graph showing reference markers in the Portal vein]
## MTT values (sec)

<table>
<thead>
<tr>
<th>Marker</th>
<th>PV*</th>
<th>HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>8.8 ± 0.5</td>
<td>12.9 ± 0.5</td>
</tr>
<tr>
<td>Albumin</td>
<td>11.6 ± 0.6</td>
<td>15.4 ± 0.6</td>
</tr>
<tr>
<td>Sucrose</td>
<td>12.3 ± 0.9</td>
<td>18.1 ± 0.6</td>
</tr>
<tr>
<td>Urea</td>
<td>34.6 ± 1.9</td>
<td>47.1 ± 1.3</td>
</tr>
<tr>
<td>Water</td>
<td>34.8 ± 2.1</td>
<td>50.3 ± 1.7</td>
</tr>
</tbody>
</table>

Mean ± s.e.m (n=10), *p < 0.001

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Volumes of distribution (ml/g)

* $p < 0.001$

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Pathways of blood flow in the rat liver

Redrawn from Sherman et al., Am J Physiol 271:G201-G210, 1996
**Total hepatic space**

Specific arterial space

**Anatomical**
Peribiliary plexus (~ 5%)

Onori et al., World J Gastrointes Pathophysiol, 1(2): 38-49, 2010
Specific arterial space

 Functional

 Alternate perfusion of sinusoids by HA and PV due to:

 ✓ The angle at which arterioles join the sinusoids (45-90°C)

 ✓ Presence of sphincter activity at the inlet and outlet of sinusoids

 ✓ Kupffer cell migration
Extraction from the common space will be the same whether administered via the HA or PV.

Therefore, any difference in hepatic disposition as a function of route of input could be attributed to the specific space and its enzyme / transporter content.
If the enzyme distribution in this space is the same as in the common space, the route of administration should have no effect on the disposition of a substance within the liver.
If there is no enzyme in this space, up to 17% of the hepatic arterial dose will escape extraction.

Therefore, one might expect higher availabilities following HA injections than PV injections.
Nevertheless, demonstration of any difference in fractional hepatic recovery requires the use of highly cleared compounds (e.g. ones with an extraction ratio in excess 0.90-0.95), because the specific space receives only 17% the HA flow and hence dose.
Hepatic disposition as a function of route of input
Diclofenac

- Highly bound to albumin (> 99%)
- Extensively metabolised (acyl glucuronidation ring hydroxylation by CYP2C9)
- High hepatocyte permeability (220 ml/min/g)
- BCS/BDDCS Class I
Diazepam

- Highly bound the albumin (99%)
- Extensively metabolised
  - C3-hydroxylation by CYP3A2
  - N-demethylation by CYP2C11
  - 4’-hydroxylation by CYP2D1
- High hepatocyte permeability (137ml/min/g)
- BCS/BDDCS Class I
Hepatic disposition of Diclofenac and Diazepam

- **Liver Donor**
  Male Sprague Dawley rats

- **Perfusion medium**
  Krebs bicarbonate (pH 7.4)

- **Flow rate**
  \[ Q_{HA} : 3 \text{ml/min} \]
  \[ Q_{PV} : 12 \text{ml/min} \]

- **Albumin (HSA) concentration for bolus administration**
  0.25%, 0.5%, 1.0%
Mode of administration

- **Bolus administration**
  - Diclofenac
  - Diazepam

- **Steady-state**
  - Diazepam
Parameters

- Hepatic availability (F)
  - **Bolus experiments**
    \[ F = \frac{\text{AUC} \cdot Q}{\text{Dose}} \]
  - **Steady-state experiments**
    \[ F = \frac{C_{\text{out}} \cdot Q_{\text{Tot}}}{C_{\text{in}} \cdot Q_{\text{in}}} \]

\( C \): concentration (\text{in: input} and \text{Out: output})
\( Q_{\text{Tot}} = Q_{\text{HA}} + Q_{\text{PV}} \) and \( Q_{\text{in}} = Q_{\text{HA}} \) (or \( Q_{\text{PV}} \))
Hepatic Clearance \((CL\; ml/min)\)

\[
CL = Q_{in} \cdot E
\]

where \(E = 1 - F\)

\(E:\) hepatic extraction ratio
Diclofenac - Portal vein

fu : 0.006
fu : 0.0123
fu : 0.0246

%1 HSA
%0.5 HSA
%0.25 HSA

Time (s)
f (1/s)

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Diclofenac - Hepatic artery

![Graph showing the concentration of Diclofenac over time for different concentrations of HSA (Hepatic Serum Albumin)].

- %1 HSA
- %0.5 HSA
- %0.25 HSA
**Diclofenac (0.5% Albumin)**

![Graph showing the concentration of diclofenac over time for PV and HA](image)

- **PV**
- **HA**

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Diazepam-Portal vein

1% HSA

0.25% HSA

fu: 0.037

fu: 0.175
Diazepam-Hepatic artery

1% HSA

0.25% HSA

Time (s)

f (1/s)
Diazepam (1% Albumin)
Diazepam – Bolus Experiments

Hepatic Availability (F)

Hepatic Clearance (CL)

$p < 0.01$

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Diazepam – Steady state Experiments

Hepatic Availability (F)*

Hepatic Clearance (CL)**

*p<0.01; **p<0.001
Hepatic route of administration and BCS/BDDCS
Biopharmaceutics Classification System (BCS)

- **Class 1**: High Solubility, High Permeability
  - (Rapid Dissolution for biowaiver)
- **Class 2**: Low Solubility, High Permeability
- **Class 3**: High Solubility, Low Permeability
- **Class 4**: Low Solubility, Low Permeability

Amidon et al., Pharm Res 12: 413-420, 1995
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Biopharmaceutics Drug Disposition Classification System (BDDCS)

Class 1: High solubility, Extensive Metabolism
Class 2: Low Solubility, Extensive Metabolism
Class 3: High solubility, Poor Metabolism
Class 4: Low solubility, Poor Metabolism

Wu and Benet, 2005
## Hepatic extraction as a function of route of input

<table>
<thead>
<tr>
<th></th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyes</strong></td>
<td>Indocyanine green</td>
</tr>
<tr>
<td><strong>Vitamin</strong></td>
<td>Vitamin D&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td>Insulin Epinephrine</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>Acetaminophen Lidocaine Meperidine Phenacetine</td>
</tr>
<tr>
<td>Compound</td>
<td>Hepatic Extraction (from IPRL studies)</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>0.61-0.71 for [3H]-Acetaminophen</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.95 at fub= 1</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.975–0.992 at fub= 1</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>0.997 at &gt;5mg/L</td>
</tr>
<tr>
<td>Meperidine</td>
<td>1.0 to 0.89 at 1 to 19 μg/mL</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>&gt;0.98 for [14C]-phenacetin</td>
</tr>
<tr>
<td>Compound</td>
<td>BCS/BDDCS Class</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>1</td>
</tr>
<tr>
<td>Diazepam</td>
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</tr>
<tr>
<td>Diclofenac</td>
<td>1</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1</td>
</tr>
<tr>
<td>Meperidine</td>
<td>1</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>2</td>
</tr>
</tbody>
</table>
Conclusions

- Based on a literature survey of drug compounds that have been studied in the dual perfused liver preparation, the data suggest that a difference in availability as a function of route of hepatic administration (PV vs. HA) is more likely to be observed for highly extracted BCS/BDDCS Class 1 and Class 2 compounds.
The possibility that there are differences in enzyme and transporter activities or passive permeabilities between the arterial and portal spaces, which will be manifest in a difference in clearance as a function of hepatic input, has yet to be explored.
Currently no experimental data exist for BCS/BDDCS Class 3 or 4 compounds. However, given that these have low permeabilities and hence tend toward low hepatic extraction ratios, an influence of route of hepatic input on hepatic availability is not expected.
Acknowledgements

- Prof. Malcolm Rowland
Diclofenac results published in J PHARM SCI, 102 (9), 3220-3227, 2013 special Issue: DEDICATED TO PROFESSOR LESLIE Z. BENET
Thank you

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