FIRST-PASS METABOLISM, BIOAVAILABILITY

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CONTENTS

1. INTRODUCTION
2. PHARMACOKINETICS
3. BIOAVAILABILITY
4. FIRST PASS METABOLISM
5. PRIMARY SYSTEMS EFFECT PRESYSTEMIC METABOLISM
6. HEPATIC ENZYMES
7. DRUG INTERACTIONS INVOLVING DRUG METABOLISM
8. EVIDENCES OF FIRST PASS EFFECT
9. LIVER EXTRACTION RATIO
10. RELATIONSHIP BETWEEN ABSOLUTE BIOAVAILABILITY AND LIVER EXTRACTION
11. ESTIMATION OF REDUCEDS BIOAVAILABILITY DUE TO LIVER METABOLISM & VARIABLE BLOOD FLOW
12. HEPATIC EXTRACTION RATIOS
13. RELATIONSHIP BETWEEN BLOOD FLOW, INTRINSIC CLEARANCE AND HEPATIC CLEARANCE
14. EFFECT OF CHANGING INTRINSIC CLEARANCE & BLOOD FLOW ON HEPATIC EXTRACTION AND ELIMINATION HALF-LIFE AFTER IV & ORAL DOSING

15. EFFECT OF CHANGING BLOOD FLOW ON DRUGS WITH HIGH OR LOW EXTRACTION RATIO

16. PREVENTION OF FIRST PASS METABOLISM

17. CONCLUSIONS

18. REFERENCES
PHARMACOKINETICS

It is concerned with the ADME of drugs as elicited by the plasma drug concentration-time profile and its relationship with the dose, dosage form and frequency and route of administration.
Bioavailability is a measurement of rate and extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action. It is denoted by letter ‘F’
The absolute availability of drug is the systemic availability of a drug after extra vascular administration (e.g., oral, rectal, transdermal, subcutaneous) compared to IV dosing.

The absolute availability of a drug is generally measured by comparing the respective AUCs after extra vascular and IV administration.
Bioavailability = \frac{(AUC)_o}{(AUC)_{iv}}
It is the phenomenon of drug metabolism. Where the concentration of a drug is greatly reduced before it reaches the systemic circulation.
BIOAVAILABILITY

Dose

Destroyed in gut

Not absorbed

Destroyed by gut wall

Destroyed by liver

to systemic circulation
Uptake of orally administered drug proceeds after the stomach passage via the small intestine. In the gut and liver, a series of metabolic transformation occurs.
Primary systems which effect presystemic metabolism

1. Luminal enzymes

2. Gut wall enzymes/ mucosal enzymes

3. Bacterial enzymes

HEPATIC ENZYMES INVOLVED IN DRUG METABOLISM

MIXED FUNCTION OXIDASES (MFO’s)/ MONOOXYGENASES

Requires both molecular oxygen and the reducing agent NADPH

Electron transfer chain consisting 3 components

1. Heme protein ‘cytochrome p-450’
2. Flavoprotein cytochrome p-450 reductase
3. Heat stable lipid component phosphatidylcholine
Cytochrome P450
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Substrates—amitriptyline, imipramine, theophylline (other enzymes also involved); induced by smoking</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine, some quinolones and grapefruit juice are inhibitors</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Substrates—cyclophosphamide, methadone</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Metabolism of S-warfarin and tolbutamide by CYP2C9</td>
</tr>
<tr>
<td></td>
<td>Substrates—NSAIDs—ibuprofen, diclofenac</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole, S-mephenytoin, and Propanolol</td>
</tr>
<tr>
<td></td>
<td>Diazepam (mixed), and imipramine (mixed)</td>
</tr>
<tr>
<td></td>
<td>Inhibitors: cimetidine, fluoxetine, and ketoconazole.</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Many antidepressants, β-blockers are metabolized by CYP2D6</td>
</tr>
<tr>
<td></td>
<td>SRIIs, cimetidine are inhibitors</td>
</tr>
<tr>
<td></td>
<td>Substrates—amitriptyline, imipramine, fluoxetine, antipsychotics (haloperidol, thioridazine)</td>
</tr>
<tr>
<td></td>
<td>Inhibitors—paroxetine, fluoxetine, sertraline, fluvoxamine, cimetidine, haloperidol</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Substrates—acetaminophen, ethanol, halothane</td>
</tr>
<tr>
<td></td>
<td>Induced by INH and disulfiram</td>
</tr>
<tr>
<td>CYP3A4, 5, 6</td>
<td>CYP3A subfamilies are the most abundant cytochrome enzymes in humans and include many key therapeutic and miscellaneous groups:</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole, atorvastatin, lovastatin.</td>
</tr>
<tr>
<td></td>
<td>Azithromycin, clarithromycins, amitriptyline</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines—alprazolam, triazolam, midazolam</td>
</tr>
<tr>
<td></td>
<td>Calcium blockers—verapamil, diltiazam</td>
</tr>
<tr>
<td></td>
<td>Protease inhibitors—ritonavir, saquinavir, indinavir</td>
</tr>
</tbody>
</table>
DRUG INTERACTIONS INVOLVING DRUG METABOLISM

The enzymes involved in the metabolism of drugs may be altered by diet and the co-administration of other drugs and chemicals.

**Enzyme induction** is a drug- or chemical-stimulated increase in enzyme activity, usually due to an increase in the amount of enzyme present.

**Enzyme inhibition** may be due to substrate competition or due to direct inhibition of drug-metabolizing enzymes, particularly one of several of the cytochrome P-450 enzymes.

**Diet also affects drug-metabolizing enzymes.** For example, plasma theophylline concentrations and theophylline clearance in patients on a high-protein diet are lower than in subjects whose diets are high in carbohydrates.
Drug- Grapefruit Juice Interaction
Villus

Enterocytes

Drug

70%

FC

100%

Drug

30%

Nucleus

CYP3A4
<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>felodipine</td>
<td>~ 3 fold</td>
</tr>
<tr>
<td>cisapride</td>
<td>~ 1.4 fold</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>~ 1.5 fold</td>
</tr>
<tr>
<td>saquinavir</td>
<td>~ 2 fold</td>
</tr>
<tr>
<td>terfenadine</td>
<td>~ 2.5 fold</td>
</tr>
<tr>
<td>buspirone</td>
<td>~ 9 fold</td>
</tr>
<tr>
<td>lovastatin/simvastatin</td>
<td>~ 10 fold</td>
</tr>
</tbody>
</table>
over 90% of saquinavir is metabolized by the cytochrome P450 isozyme CYP3A4. Saquinavir is thought to undergo extensive first-pass metabolism and is rapidly metabolized to a variety of inactive mono- and di-hydroxylated compounds.
HEPATIC ELIMINATION OF DRUGS

HEPATIC CLEARANCE

It is the measure of drug elimination by the liver.

may be defined as volume of blood that perfuses the liver and is cleared of drug per unit of time

\[ Cl_h = Cl_T - Cl_R \]
EVIDENCES OF FIRSTPASS EFFECTS

For drugs that undergo first-pass effects $AUC_\infty \ 0$, oral is smaller than $AUC_\infty \ 0$, IV and $F < 1$. Drugs such as propranolol, morphine, and nitroglycerin have F values less than 1 because these drugs undergo significant first-pass effects.

$$F = \frac{[AUC]_\infty \text{ oral}}{[AUC]_\infty \text{ IV}} \div \frac{D_0 \text{ oral}}{D_0 \text{ IV}}$$

Eq. 1
The liver extraction ratio (ER) provides a direct measurement of drug removal from the liver after oral administration of a drug.

\[
ER = \frac{C_a - C_v}{C_a}
\]

Eq. 2

where \(C_a\) is the drug concentration in the blood entering the liver and \(C_v\) is the drug concentration leaving the liver.
Relationship between Absolute Bioavailability and Liver Extraction

\[ F = 1 - ER - F'' \]  
Eq. 3

where \( F \) is the fraction of bioavailable drug, \( ER \) is the drug fraction extracted by the liver, and \( F'' \) is the fraction of drug removed by nonhepatic process.

If \( F'' \) is assumed to be negligible

\[ F = 1 - ER \]  
Eq. 4

After substitution of Equation 1 in 4

\[ ER = 1 - \frac{[AUC]_{\infty, \text{oral}} / D_{0, \text{oral}}}{[AUC]_{\infty, \text{IV}} / D_{0, \text{IV}}} \]  
Eq. 5
Estimation of Reduced Bioavailability Due to Liver Metabolism and Variable Blood Flow

\[ F' = 1 - \frac{Cl_h}{Q} = 1 - ER \]

where \( Cl_h \) is the hepatic clearance of the drug and 
\( Q \) is the effective hepatic blood flow. 
\( F' \) is the bioavailability factor obtained from estimates of liver blood flow and hepatic clearance, \( ER \).

The usual effective hepatic blood flow is 1.5 L/min, but it may vary from 1 to 2 L/min depending on diet, food intake, physical activity or drug intake.

For the drug propoxyphene hydrochloride, \( F' \) has been calculated from hepatic clearance (990 ml/min) and an assumed liver blood flow of 1.53 L/min:

\[ F' = 1 - \frac{0.99}{1.53} = 0.35 \]
<table>
<thead>
<tr>
<th>Extraction Ratios</th>
<th>Hepatic Extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low (&lt;0.3)</strong></td>
<td><strong>Intermediate (0.3–0.7)</strong></td>
</tr>
<tr>
<td>Amobarbital</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
</tr>
<tr>
<td>Digitoxin</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td></td>
</tr>
<tr>
<td>Salicylic acid</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
</tr>
</tbody>
</table>
Relationship between Blood Flow, Intrinsic Clearance, and Hepatic Clearance

The ER may vary from 0 to 1.0. An ER of 0.25 means that 25% of the drug was removed by the liver.
If both the ER for the liver and the blood flow to the liver are known, then hepatic clearance may be calculated by the following expression:

\[ ER = \frac{C_a - C_v}{C_a} \]

Eq. 7

\[ Cl_h = \frac{Q (C_a - C_v)}{C_a} = Q \times ER \]

Eq. 8

For some drugs (such as isoproterenol, lidocaine, and nitroglycerin), the extraction ratio is high (greater than 0.7),

For drugs with very high extraction ratios, the rate of drug metabolism is sensitive to changes in hepatic blood flow. Thus, an increase in blood flow to the liver will increase the rate of drug removal by the organ.
**INTRINSIC CLEARANCE**

**Intrinsic clearance (Cl_{int})** is used to describe the total ability of the liver to metabolize a drug in the absence of flow limitations, reflecting the inherent activities of the mixed-function oxidases and all other enzymes.

\[
Cl_h = \frac{Cl_{int}}{Q + Cl_{int}}
\]

Eq. 9

Hepatic clearance changes with blood flow and the intrinsic clearance of the drug, as described in Equation 9.

For drugs with low extraction ratios (e.g., theophylline, phenylbutazone and procainamide), the hepatic clearance is less affected.
The relationship between liver blood flow and total hepatic clearance for drugs with varying extraction rates (ER).
Effect of Changing Intrinsic Clearance after IV and Oral Dosing

- **Blood concentration (μg/mL)**
  - **Time (hours)**
  - **Blood concentration (μg/mL)**

- **ER**
  - 0.100
  - 0.180

- **C_{int}**
  - 0.167
  - 0.334 liters/min

- **Cl**
  - 0.150
  - 0.273 liters/min

- **ER**
  - 0.90
  - 0.95

- **C_{int}**
  - 13.70
  - 27.00 liters/min

- **Cl**
  - 1.35
  - 1.42 liters/min
Effect of Changing Blood Flow on Drugs with High or Low Extraction Ratio

\[
\begin{align*}
\text{Blood concentration [\mu g/mL]} & \quad \text{Blood concentration [\mu g/mL]} \\
\text{Time (hours)} & \quad \text{Time (hours)} \\
\hline
0 & 0.1 \quad 0.05 \\
10 & 0.01 \quad 0.01 \\
20 & 0.001 \quad 0.001 \\
30 & 0.0001 \quad 0.0001 \\
\end{align*}
\]

**Legend:**
- **ER =** 0.100 0.180
- **Q =** 1.500 0.750 liters/min
- **Cl =** 0.150 0.135 liters/min
- **ER =** 0.90 0.95
- **Q =** 1.50 0.75 liters/min
- **Cl =** 1.35 0.71 liters/min
PREVENTION OF FIRSTPASS METABOLISM

1. Route of drug administered may be changed

Various transmucosal non invasive routes of drug administration to bypass presystemic elimination in GIT / Liver

Like ocular delivery
  - nasal delivery
  - pulmonary delivery
  - buccal/sublingual delivery
  - rectal delivery
  - vaginal delivery
2. Alternative routes of administration like suppository, intravenous, intramuscular, inhalation aerosol avoid the first pass effect because they allow drugs to be allowed directly into systemic circulation.

3. Another way to overcome the first pass effect is to either enlarge the dose or change the drug product to a more rapidly absorbable dosage form.

4. Prodrugs
   - e.g. sulfasalazine
CONCLUSIONS

Drugs given parenterally, transdermally or by inhalation may distribute within the body prior to metabolism by the liver.

But the drugs that are highly metabolized by the liver or by the intestinal mucosal cells demonstrate poor systemic availability when given orally.

In drug design drug candidates may have good drug likeness but fail on first pass metabolism, because it is biochemically selective.
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WEBSITES
WWW.GOOGLE.COM
Thank you