Xenobiotic Bioavailability: Role of Intestinal Disposition

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Bioavailability and Fraction Dose Absorbed

• Bioavailability ($F$) – measurement of the rate and extent of therapeutically active drug that reaches the systemic circulation and is available at the site of action (Shargel & Yu, 1999)

• Fraction Dose Absorbed ($f_a$ – fraction of oral) dose that traverses the intestine intact
Intestinal Disposition

- Intestinal permeability, metabolism, solubility, stability and dissolution of a xenobiotic
- Inhibition of membrane transporters and/or metabolizing enzymes
- Modulation of the expression of membrane transporters and/or metabolizing enzymes
Factors Affecting Oral Bioavailability

**Physicochemical**
- Solubility
- Ionization
- Dissolution Rate
- Chemical Stability
- Diffusion (intra-lumenal)

**Physiological**
- GI Transit
- Bile Secretion
- Transport Mechanisms
- Metabolism
- Regional Effects
- Polymorphism of Transporters/Enzymes
Oral Bioavailability Comparison

G. Grass
Fa – Permeability Comparison

Permeability – Permeability
Comparison

Intestinal Transport and Metabolism

Figure from *Eur J Pharm Sci* 21: 25, 2004
Proteins Involved in Intestinal Disposition

- **Influx Transporters**
  - Peptide, bile acid, nucleoside, amino acid, etc.

- **Efflux Transporters**
  - P-gp, MRP2, BCRP, etc.

- **Metabolizing Enzymes**
  - Phase I — CYP isoforms (primarily 3A4, 2D6, etc.)
  - Phase II — GSTs, UGTs, sulfotransferases

- **Nuclear Hormone Receptors**
  - CAR, PXR, PPAR, RXR, etc.
Intestinal Disposition

- Permeability
- Metabolism

Also
- Inhibition
- Induction

figure from Drug Metab Dispos 31: 1507, 2003
Biopharmaceutical Classification System

- **Permeability**
  - High
  - Low

- **Solubility**
  - High
    - Class 1: Dissolution Rate Limited
    - Class 3: Permeability Limited
  - Low
    - Class 2: Solubility Limited
    - Class 4: Mixed
Factors affecting rate and extent of oral absorption

BCS

Xenobiotic in systemic circulation

Metabolism in liver

Metabolism in the gut wall

Efflux

Transit

Release from dosage form

Rate of dissolution

Permeability across the membrane

Decomposition

Xenobiotic in solution in GI tract

S. Agrawal
## Clinical Intestinal Metabolism Drug Interactions

![Table of Clinical Intestinal Metabolism Drug Interactions](image)

Preclinical Methods for Intestinal Disposition

- Intestinal permeability studies
  - Perfusion
  - Diffusion chamber (excised tissue or cultured cells)
  - Everted gut sac
  - PAMPA
- Intestinal metabolism
  - Perfusion
  - Microsomes
- Oral PK studies
  - P-gp, CYP inhibitors
  - Knockout animals
Chlorpyrifos

- Organophosphate pesticide
- Potential exposure routes
- Limited human bioavailability studies
- Goals
  - Determine intestinal permeability as a function of region and concentration
  - Determine effect of chlorpyrifos on expression and function of membrane transporters
Chlorpyrifos

- Single-pass Intestinal Perfusion (SPIP)
  - Regional permeability as a function of concentration
- Exposure studies in Caco-2 cells
  - Competitive PCR assay for MDR1
  - Effect on membrane efflux function
Single Pass Intestinal Perfusion

- Permeability determined by loss from perfusate

\[ P_{eff} = \frac{-Q}{2\pi rl} \ln \left( \frac{C_{out}}{C_{in}} \right) \]

- Correct for adsorption, stability, accumulation

Figure from: Salphati, et al, JPP 2001, 53: 1007–1013
Results – Permeability

Results – Effect of CPF on MDR1 Expression in Caco-2 Cells

## Results

### Effect of CPF on Efflux Function in Caco-2 Cells

<table>
<thead>
<tr>
<th></th>
<th>VL</th>
<th>VC</th>
<th>VH</th>
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<tbody>
<tr>
<td>Control</td>
<td>2.87</td>
<td>3.40</td>
<td>4.44</td>
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<tr>
<td>8 hr CPF pre-incubation</td>
<td>3.65</td>
<td>4.18</td>
<td>5.01</td>
</tr>
<tr>
<td>Increase</td>
<td>27%</td>
<td>23%</td>
<td>13%</td>
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Sulforaphane

- Isothiocyanate from cruciferous vegetables
- Potential chemopreventive agent
- Mechanism of action
  - Induction of Phase II metabolizing enzymes and efflux transporters, e.g., MRP2
- Goal: Determine intestinal disposition and effect of SFN on expression of Phase II enzymes and MRP2 in intestine
SPIP-MV

- Permeability Determination
  - Lumenal
  - Blood
- Bioanalytical

**Fig. 1.** Illustration of the experimental setup for single-pass intestinal perfusion with mesenteric cannulation and continuous infusion of blood through the jugular vein.

Figure from Cummings, et al, *JPET*, **305**:306, 2003.
SFN and SFN-GLU in Mesenteric Blood

Permeability of SFN and Metabolites

Effect of SFN on GST Expression in Rat Ileum

Model of SFN Intestinal Disposition

Relevance

• Depends on:
  • Metabolic pathways
  • Therapeutic index of drug
  • Toxicity of xenobiotic
  • Variability in intestinal metabolism

• Xenobiotic – Drug Interactions
  • Induction of expression
  • Relative affinity for transporter/enzyme
  • Concentration, etc
  • Exposure
Summary

• Intestinal disposition is critical for the bioavailability of orally administered compounds (*but may not be the limiting factor*)
• Interactions with transporters/enzymes (modulation of expression and/or function) should be considered
• Dietary factors (e.g., grapefruit juice) can contribute to variability in oral drug bioavailability
• “Baseline” expression of patients may change based on dietary factors
• Potential contribution of unidentified transporters/enzyme isoforms
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