Drug Absorption and Bioavailability

Juan J.L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program
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Office of Clinical Research Training and Medical Education
National Institutes of Health
Clinical Center

GOALS of Drug Absorption and Bioavailability Lecture

- Factors Affecting Drug Absorption
- Estimation of Bioavailability
- Clinical Significance of Differences in Bioavailability
- Prediction of Bioavailability in High-Throughput Drug Candidate Screening

Factors Affecting DRUG ABSORPTION

- Biopharmaceutic Factors
  - Tablet compression
  - Coating and Matrix
  - Excipients
- Interactions
  - Food
  - Other Drugs
  - Bacteria
- Physiological Factors
Change in PHENYTOIN Excipients Results in Epidemic Toxicity*  


Factors Affecting DRUG ABSORPTION

• Biopharmaceutic Factors
• INTERACTIONS
  - Food
  - Other Drugs
  - Bacteria
• Physiologic Factors

ENTERIC METABOLISM OF DIGOXIN*

Factors Affecting DRUG ABSORPTION

- Biopharmaceutic Factors
- Interactions
- PHYSIOLOGICAL FACTORS

Drug Absorption

Passive Non-Ionic Diffusion: Primary mechanism for most drugs.

Drug Absorption

- Specialized Transport Mechanisms

Large Neutral Amino Acid Transporter: 
L-Dopa, Methyldopa, Baclofen
Drug Absorption
- Specialized Transport Mechanisms

Oligopeptide Transporter (PEPT-1):
* Amino-beta-lactams
* ACE Inhibitors

Monocarboxylic Acid Transporter:
* Salicylic acid
* Pravastatin

FALLACIES Concerning Gastric Drug Absorption
- Acidic Drugs absorbed in the stomach
- Basic Drugs absorbed in the small intestine
- Gastric pH is always acidic

In Fact, most drug absorption occurs in the SMALL INTESTINE
**ASPIRIN ABSORPTION FROM STOMACH AND SMALL INTESTINE**


**TABLE 1: ASPIRIN (ASA) ABSORPTION FROM SIMULTANEOUSLY PERFUSED STOMACH AND SMALL INTESTINE (3)**

<table>
<thead>
<tr>
<th>pH</th>
<th>ASA ABSORPTION (micromol/100 mg protein/hr)</th>
<th>ASA SERUM LEVEL (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STOMACH</td>
<td>SMALL BOWEL</td>
</tr>
<tr>
<td>3.5</td>
<td>346</td>
<td>469</td>
</tr>
<tr>
<td>6.5</td>
<td>0</td>
<td>424</td>
</tr>
</tbody>
</table>

*Variation in Gastric and Intestinal pH*


**PHYSIOLOGICAL FACTORS Affecting Drug Absorption**

- **Rate of gastric emptying** is a major determinant of initial delay in drug absorption.
- **Intestinal motility** is a determinant of the extent of drug absorption.
PATTERNS OF GASTRIC MOTOR ACTIVITY

FASTING (Cyclical Pattern < 2 HR)
- Phase 1 - Quiescence
- Phase 2 - Irregular Contractions
- Phase 3 - Major Motor Complex Burst
- Phase 4 - Transition Period

Interdigestive Intestinal Motor Activity in Humans*


PATTERNS OF GASTRIC MOTOR ACTIVITY

POST PRANDIAL (Up to 10 hr delay)
- Pylorus constricted
- Antral contractions reduce particle size
GI TRANSIT - SUSTAINED-RELEASE CARBAMAZEPINE FORMULATION*


EXTENT RELEASED
Subject 5: 75%
Subject 6: 56%

Variation in “Peak” Levels ACETAMINOPHEN*


Gastric Emptying Rate Affects ACETAMINOPHEN Absorption*

Factors Affecting RATE and EXTENT of Drug Absorption

RESERVE LENGTH

RESERVE LENGTH is the anatomical length over which absorption of a drug can occur MINUS the length at which absorption is complete.

Effect of METOCLOPRAMIDE on Digoxin Absorption*

Effect of PROPANTHEL  ELINE on Digoxin Absorption*

Factors Affecting RATE and EXTENT of Drug Absorption

Normal Intestinal Villi

Digoxin Levels in Patients with Intestinal Malabsorption

<table>
<thead>
<tr>
<th></th>
<th>CONTROLS</th>
<th>MALABSORPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>[DIGOXIN] (ng/mL)</td>
<td>$1.3 \pm 0.3$</td>
<td>$0.4 \pm 0.3$</td>
</tr>
<tr>
<td>Urine D-XYLOSE Excretion (gm/5 hr)</td>
<td>$5 – 8^+$</td>
<td>$1.1 – 4.1$</td>
</tr>
</tbody>
</table>

$^+$ NORMAL RANGE

BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES

<table>
<thead>
<tr>
<th>Drug</th>
<th>F %</th>
<th>Drug</th>
<th>F %</th>
<th>Drug</th>
<th>F %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>100</td>
<td>Digoxin</td>
<td>70</td>
<td>Cyclosporine</td>
<td>28</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>99</td>
<td>Indinavir</td>
<td>65</td>
<td>Tacrolimus</td>
<td>25</td>
</tr>
<tr>
<td>Methadone</td>
<td>92</td>
<td>Cimetidine</td>
<td>60</td>
<td>Morphine</td>
<td>24</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90</td>
<td>Clarithromycin</td>
<td>55</td>
<td>Verapamil</td>
<td>22</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>92</td>
<td>Itraconazole</td>
<td>55</td>
<td>Nicardipine</td>
<td>18</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>77</td>
<td>Amitriptyline</td>
<td>48</td>
<td>Sirolimus</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diltaizem</td>
<td>38</td>
<td>Saquinavir</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin</td>
<td>35</td>
<td>Atorvastatin</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chlorpromazine</td>
<td>32</td>
<td>Doxorubicin</td>
<td>5</td>
</tr>
</tbody>
</table>

> 70% ABSORPTION | 30% - 70% ABSORPTION | < 30% ABSORPTION

SYSTEMIC CIRCULATION

GUT WALL

SMALL BOWEL

EFFECTIVE ABSORBING SURFACE

75% NET ABSORPTION

25% UNABSORBED
FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION

Sites of FIRST-PASS Elimination

• INTESTINAL MUCOSA
  - CYP Enzymes
  - P-Glycoprotein

• LIVER
  - CYP Enzymes

FIRST-PASS METABOLISM
First-Pass Metabolism
P-Glycoprotein Transport

ALDOSTERONE   MORPHINE*
CYCLOSPORINE* NORTRIPTYLINE
ISOPROTERENOL ORGANIC NITRATES
LIDOCAINE     PROPRANOLOL

* Known P-Glycoprotein Substrates

Factors Affecting RATE and EXTENT of Drug Absorption

GOALS of Drug Absorption and Bioavailability Lecture

- Factors Affecting Drug Absorption
- ESTIMATION OF BIOAVAILABILITY
- Clinical Significance of Differences in Bioavailability
- Prediction of Bioavailability
BIOAVAILABILITY is the RELATIVE AMOUNT ($F$) of a drug dose that reaches the systemic circulation unchanged and the RATE at which this occurs.

**Serum Concentration-Time Curve after a Single Oral Dose**

**Significance of AUC**

$$dE = CL_E \cdot C \, dt$$

$$E = CL_E \int_0^\infty C \, dt$$

$$D \cdot F = CL_E \cdot AUC$$
Calculation of AUC
Trapezoidal Rule

From: Rowland M, Tozer TN. Clinical Pharmacokinetics. p 470.

AUC A > B

ABSOLUTE Bioavailability

\[
\% \text{ Absorption} = \frac{D_{\text{IV}} \cdot AUC_{\text{oral}}}{D_{\text{oral}} \cdot AUC_{\text{IV}}} \times 100
\]

Comparison here is between an ORAL and an IV Formulation
### RELATIVE Bioavailability

\[
\% \text{ Relative B.A.} = \frac{D_{\text{Ref.}} \cdot AUC_{\text{Test}}}{D_{\text{Test}} \cdot AUC_{\text{Ref.}}} \times 100
\]

Comparison here is between 2 ORAL Formulations

AUC Values have to be Normalized for Dose
**ASSESSMENT of Bioavailability**

- AUC Estimates can be used to estimate Extent of Drug Absorption.
- Recovery of Parent Drug in Urine can be used to estimate Extent of Drug Absorption.
- How is ABSORPTION RATE assessed?
  - $T_{\text{MAX}}$
  - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.

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**Extent of Absorption from Renal Excretion of Unchanged Drug**

Since: $F = D = E$ and $E = \frac{\text{CL}_E}{\text{CL}_R} E_R$

$F \times D_{\text{oral}} = \left( \frac{\text{CL}_E}{\text{CL}_R} \right) E_{\text{oral}}$ and $D_{\text{IV}} = \left( \frac{\text{CL}_E}{\text{CL}_R} \right) E_{\text{IV}}$

So: $\% \text{ Absorption} = \frac{D_{\text{IV}} \times E_{\text{oral}}}{D_{\text{oral}} \times E_{\text{IV}}} \times 100$

---

**ASSESSMENT of Bioavailability**

- AUC Estimates Can Be Used to Estimate Extent of Drug Absorption.
- **HOW IS ABSORPTION RATE ASSESSED?**
  - $T_{\text{MAX}}$
  - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.
INTERACTION OF DRUG ABSORPTION AND DISPOSITION PROCESSES

**ABSORPTION**                **DISPOSITION**           **DRUG IN PLASMA**

\[ G(t) \ast H(t) = X(t) \]

IV DOSE

ORAL DOSE

THE OPERATION OF CONVOLUTION

**INTEGRAL FORM:** \( X(t) = \int G(\tau) \cdot H(t-\tau) d\tau \)

**TIME DOMAIN:** \( X(t) = G(t) \ast H(t) \)

**SUBSIDIARY EQUATION:** \( x(s) = g(s) \cdot h(s) \)

MODEL Used to Analyze Kinetics of Drug Absorption

\( k_a \) is absorption rate
\( k_o \) is rate of nonabsorptive loss
Calculation of **Bioavailability** from First-Order Absorption Model

\[ F = \frac{k_a}{k_a + k_o} \]

**Methods for Assessment of **ABSOLUTE BIOAVAILABILITY**

- **CONVENTIONAL:**
  - IV and ORAL doses given on **two separate occasions**.
  - Requires two study sessions
  - Requires two sets of blood samples
  - Assumes no change in disposition parameters between studies
- **STABLE ISOTOPE:**
  - One study and set of blood samples
  - Special synthesis requirements
  - Mass Spectrometer Assay required

**NAPA-\(^{13}\)C\(_2\)**

\[
\begin{array}{c}
\text{H}_3\text{C}^{13}\text{C}N\text{C}NH\text{CH}_2\text{CH}_2\text{N} \text{CH}_2\text{CH}_3 \\
\text{CH}_2\text{CH}_3 \\
\end{array}
\]

\(N\text{-ACETYLPРОCAINAMIDE (NAPA-}\(^{13}\)C\(_2\))\)
Simultaneous Administration of Oral NAPA and IV NAPA-C\textsuperscript{13}


MODEL Used to Analyze Oral NAPA and IV NAPA-C\textsuperscript{13} Kinetics


BIOAVAILABILITY Estimates From Kinetic Analysis and URINE RECOVERY

<table>
<thead>
<tr>
<th>PATIENT NUMBER</th>
<th>KINETIC ANALYSIS (%)</th>
<th>NAPA RECOVERY IN URINE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66.1</td>
<td>65.9</td>
</tr>
<tr>
<td>2</td>
<td>92.1</td>
<td>92.1</td>
</tr>
<tr>
<td>3</td>
<td>68.1</td>
<td>69.9</td>
</tr>
<tr>
<td>4</td>
<td>88.2</td>
<td>73.1</td>
</tr>
<tr>
<td>5</td>
<td>75.7</td>
<td>75.6</td>
</tr>
</tbody>
</table>

* Corrected for absorption lag time.
Factors Affecting RATE and EXTENT of Drug Absorption

NAPA PK Model After IV Dose

Relationship Between CLF and Extent of NAPA Absorption*

THOUGHTS About Absolute Bioavailability Studies

• Absolute Bioavailability is usually studied in Healthy Subjects, NOT in the Patient Population for whom the drug is intended.

• The Stable Isotope Method is ideally suited for studies in Special Populations (e.g. Pediatrics, Pregnant Women, other)

GOALS of Drug Absorption and Bioavailability Lecture

• Factors Affecting Drug Absorption
• Estimation of Bioavailability
• Clinical Significance of Differences in Bioavailability
• Prediction of Bioavailability

RELATIVE Bioavailability Terms

Bioequivalence: AUC and Cmax within 80% - 125% of reference compound.

Bioinequivalence: Greater difference in bioavailability.

Therapeutic Equivalence: Similar clinical effectiveness and safety.

Therapeutic Inequivalence: Important clinical difference in bioavailability.
AUC A > B: Therapeutic Significance?

- AUC A > B: B Ineffective

- AUC A > B: A and B Equally Effective
Equal AUC but Different $K_a$: B is Ineffective

Equal AUC but Different $K_a$: A is Toxic

RELATIVE BIOAVAILABILITY

CONCLUSIONS

• BIOEQUIVALENCE = THERAPEUTIC EQUIVALENCE

• BIOINEQUIVALENCE NOT NECESSARILY = THERAPEUTIC INEQUIVALENCE
GOALS of Drug Absorption and Bioavailability Lecture

• Factors Affecting Drug Absorption
• Estimation of Bioavailability
• Clinical Significance
• PREDICTION of Bioavailability as part of High-Throughput Drug Candidate Screening

WHY DRUG DEVELOPMENT FAILS

• Unsuitable Biopharmaceutical Properties
• Unsuitable Clinical Pharmacokinetics
• Pharmacology (PD) Doesn’t Work in Humans
• Unexpected Toxicity is Encountered

* Ronald E. White, Bristol-Myers Squibb (From Good Ligands to Good Drugs, AAPS-NIGMS Symposium, February 19-21, 1998)

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS I:
High Solubility-High Permeability
CLASS II:
Low Solubility-High Permeability
CLASS III:
High Solubility-Low Permeability
CLASS IV:
Low Solubility-Low Permeability
Three CRITICAL Biopharmaceutical Properties

- Drug Solubility Relative to Dose
  GOOD = Highest Dose in 250 mL H_2O, pH 1.0-7.5

- Dissolution Rate of Formulation
  GOOD = 85% Dissolution in 15 min

- Intestinal Permeability of Drugs

CORRELATION of Rates of Drug DISSOLUTION and Oral ABSORPTION

% Absorption vs % Dissolution graph

\[ y = -8.6 + 1.07x \]
\[ R^2 = 0.970 \]


Three CRITICAL Biopharmaceutical Properties

- Drug Solubility Relative to Dose

- Dissolution Rate of Formulation

- INTESTINAL PERMEABILITY of Drug
**Bioavailability vs. Jejunal Permeability**


**Bioavailability vs. Caco-2 Cell Permeability**


**Evaluation of Caco-2 Cell Model**

- **ADVANTAGES**
  - *In Vitro* Method
  - Suitable for High-Throughput
- **DISADVANTAGES**
  - ↓ Paracellular Permeability
  - ↓ Drug Metabolizing Enzymes and Transporters
  - No Hepatic First-Pass Metabolism
BIOPHARMACEUTIC DRUG CLASSIFICATION

CLASS I: HIGH SOLUBILITY-HIGH PERMEABILITY
- *in vitro*–*in vivo* correlation generally good
- *but* no way to account for 1st pass metabolism


BIOPHARMACEUTIC DRUG CLASSIFICATION

CLASS II: LOW SOLUBILITY-HIGH PERMEABILITY
- rate of absorption limited by dissolution rate
- *in vitro*–*in vivo* correlation tenuous since many factors may affect dissolution


BIOPHARMACEUTIC DRUG CLASSIFICATION

CLASS III: HIGH SOLUBILITY-LOW PERMEABILITY
- Intestinal reserve length is marginal.
- If dissolution is rapid, bioavailability will reflect intestinal permeability and transit time.

BIOPHARMACEUTIC DRUG CLASSIFICATION

CLASS IV:
LOW SOLUBILITY-LOW PERMEABILITY

- in vitro – in vivo correlation poor
- good bioavailability not expected


THE BOTTOM LINE

CLASS I DRUGS:
HIGH SOLUBILITY-HIGH PERMEABILITY

- Preferred as development candidates
- FDA may waive repeat in vivo testing if initial formulation has good bioavailability*.