Drug Absorption and Bioavailability

Juan J.L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program
September 30, 2010

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

Drug Absorption
- Specialized Transport Mechanisms

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
**Table 1**: Aspirin (ASA) Absorption from Simultaneously Perfused Stomach and Small Intestine (3)

<table>
<thead>
<tr>
<th>pH</th>
<th>Stomach ASA Absorption (micromol/100 mg protein/hr)</th>
<th>Small Bowel ASA Absorption (micromol/100 mg protein/hr)</th>
<th>ASA Serum Level (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>346</td>
<td>469</td>
<td>20.6</td>
</tr>
<tr>
<td>6.5</td>
<td>0</td>
<td>424</td>
<td>19.7</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.

Variation in Gastric and Intestinal pH*
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*


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 PROPANTHELING 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>DOSE FOR BOTH GROUPS = 0.25 mg/day.</th>
<th>CONTROLS</th>
<th>MALABSORPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>[DIGOXIN] (ng/mL)</td>
<td>1.3 ± 0.3</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>URINE D-XYLOSE EXCRETION (g/m 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>&gt; 70% Absorption F%</th>
<th>30% - 70% Absorption F%</th>
<th>&lt; 30% Absorption F%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>100</td>
<td>70</td>
<td>28</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>99</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>Methadone</td>
<td>92</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90</td>
<td>55</td>
<td>22</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>82</td>
<td>55</td>
<td>18</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>77</td>
<td>48</td>
<td>15</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>100</td>
<td>70</td>
<td>28</td>
</tr>
<tr>
<td>Digoxin</td>
<td>65</td>
<td>55</td>
<td>18</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>92</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>90</td>
<td>55</td>
<td>22</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>82</td>
<td>55</td>
<td>18</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>77</td>
<td>48</td>
<td>15</td>
</tr>
<tr>
<td>Diltilazem</td>
<td>38</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>55</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>32</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Methadone</td>
<td>99</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>Digoxin</td>
<td>70</td>
<td>55</td>
<td>22</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>60</td>
<td>55</td>
<td>18</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>55</td>
<td>55</td>
<td>18</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>48</td>
<td>48</td>
<td>15</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>38</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>Diltilazem</td>
<td>55</td>
<td>55</td>
<td>13</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>35</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>32</td>
<td>32</td>
<td>12</td>
</tr>
</tbody>
</table>

### > 70% Bioavailability of Some P-Glycoprotein Substrates

- Systemic Circulation
  - GUT Wall: 100% → 50% → 25%
  - SMALL BOWEL: 100% → 50% → 25%
- 75% Net Absorption
- Effective Absorbing Surface: 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**

\[
\begin{align*}
\frac{dE}{dt} &= \text{CL}_E \cdot C dt \\
E &= \text{CL}_E \int_0^\infty C dt \\
D \cdot F &= \text{CL}_E \cdot \text{AUC}
\end{align*}
\]
Calculation of AUC
Trapezoidal Rule

AUC A > B

ABSOLUTE Bioavailability

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

Comparison here is between an ORAL and an IV Formulation

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

---

Even when your arthritis patient isn't...
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.

Extent of Absorption from Renal Excretion of Unchanged Drug

\[
\begin{align*}
F \cdot D &= E \\
E &= \left( \frac{CL_e}{CL_R} \right) E_R \\
F \cdot D_{\text{oral}} &= \left( \frac{CL_e}{CL_R} \right) E_{R(\text{oral})} \\
D_{\text{oral}} &= \left( \frac{CL_e}{CL_R} \right) E_{R(\text{oral})} \\
S &= \frac{D_{\text{oral}} \cdot E_{R(\text{oral})}}{D_{\text{oral}} \cdot E_{R(\text{oral})}} \cdot 100
\end{align*}
\]

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)                           H(t)                                X(t)

IV DOSE

ABSORPTION FUNCTION

THE OPERATION OF CONVOLUTION

INTEGRAL FORM :  \[ X(t) = \int_0^t G(\tau) \cdot H(t - \tau) \, d\tau \]

TIME DOMAIN :  \[ X(t) = G(t) \cdot H(t) \]

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

\( V_C \)
\( V_P \)
\( C_L \)
\( C_{INR} \)
\( C_R \)
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$_2$
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
Factors Affecting RATE and EXTENT of Drug Absorption

NAPA PK Model After IV Dose

Dose

\[ V_F = \text{SPLANCHNIC} \]

\[ V_S = \text{SOMATIC} \]

\[ CL_F = Q_F/(1 - e^{-Q_F/\theta}) \]

\[ CL_S = Q_S/(1 - e^{-Q_S/\theta}) \]

Relationship Between CL_F and Extent of NAPA Absorption*

\[ \text{R}^2 = 0.8, p = 0.045 \]

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 H₂O, 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

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*.