Drug Absorption and Bioavailability

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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

Guidance for Industry-FDA-CDER

• Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations
  DRAFT GUIDANCE
  March 2014
  Biopharmaceutics
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
- 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**

- Weakly Acidic Drugs absorbed only in the stomach (pH partition hypothesis)
- Weakly Basic Drugs absorbed in the small intestine (pH partition hypothesis)
- Gastric pH is always acidic

*In fact, most drug absorption occurs in the SMALL INTESTINE*

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**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</th>
<th>ASA SERUM LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(micromol/100 mg protein/hr)</td>
<td>(mg/100 ml)</td>
</tr>
<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>

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**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
75% 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 PROPANThELINE on Digoxin Absorption*


Factors Affecting RATE and EXTENT of Drug Absorption

Normal Intestinal Villi

Broad Intestinal Villi in a Patient with SPRUE

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 ± 0.3</td>
<td>0.4 ± 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

Factors Affecting RATE and EXTENT of Drug Absorption

P-GLYCOPROTEIN EFFLUX PUMP

INTESTINAL LUMEN

OUT

MEMBRANE

IN

SLIDE COURTESY OF M. GOTTESMAN

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>METHYLPOPISOLONE</td>
<td>82</td>
<td>ITRACONAZOLE</td>
<td>55</td>
<td>NICARDIPINE</td>
<td>18</td>
</tr>
<tr>
<td>TETRACYCLINE</td>
<td>77</td>
<td>AMITRIPTYLNE</td>
<td>48</td>
<td>SIROLIMUS</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DILTIAZEM</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% BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES

SYSTEMIC CIRCULATION

GUT WALL

100% 100% 100%
50% 50% 50%
P-gp P-gp P-gp
25% 25% 25%
25% UNABSORBED

SMALL BOWEL

75% NET ABSORPTION

EFFECTIVE ABSORBING SURFACE

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
- CYCLOSPORINE*
- ISOPROTERENOL
- LIDOCAINE
- MOPHINE*
- NORTRIPTYLINE
- ORGANIC NITRATES
- PROPRANOLOL
- NORTRIPTYLINE

* 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

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

- $C_{\text{max}}$:
- $t_{\text{max}}$:
- AUC:

<table>
<thead>
<tr>
<th>HOURS AFTER DRUG ADMINISTRATION</th>
<th>[DRUG]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>
**Significance of AUC**

\[ \text{dE} = \text{CL}_E \cdot C \, \text{dt} \]
\[ E = \text{CL}_E \int_0^\infty C \, \text{dt} \]
\[ D \cdot F = \text{CL}_E \cdot \text{AUC} \]

**Calculation of AUC**

Trapezoidal Rule

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

**AUC A > B**

BUT IS A BETTER THAN 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
**RELATIVE Bioavailability**

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

AUC Values have to be **Normalized for Dose**

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**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: \( F \cdot D = E \) and \( E = \left( \frac{\text{CL}_{E}}{\text{CL}_{R}} \right) E_{R} \)

\[ F \cdot D_{\text{oral}} = \left( \frac{\text{CL}_{E}}{\text{CL}_{R}} \right) E_{\text{oral}} \text{ and } D_{\text{IV}} = \left( \frac{\text{CL}_{E}}{\text{CL}_{R}} \right) E_{R(IV)} \]

So: \( \% \) Absorption = \( \frac{D_{\text{IV}} \cdot E_{\text{oral}}}{D_{\text{oral}} \cdot E_{R(IV)}} \times 100 \)
**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**

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

**MODEL Used to Analyze Kinetics of Drug Absorption**

- $k_a$ is absorption rate
- $k_o$ is rate of nonabsorptive loss

- $\text{GI}$
- $V_C$
- $V_P$
- $C_{\text{INR}}$
- $C_{\text{LR}}$
- $C_{\text{IL}}$
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\(_2\)

\(N\)-ACETYLPRAOCAINAMIDE (NAPA-\(^{13}\)C\(_2\))
Simultaneous Administration of Oral NAPA and IV NAPA-C13

MODEL Used to Analyze Oral NAPA and IV NAPA-C13 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

Dose

\[ V_F \]

\[ \text{CL}_F = Q_S (1 - e^{-\beta t}) \]

\[ CL_F \text{ PARTLY REFLECTS SPLANCHNIC BLOOD FLOW} \]

\[ CL_F = CL_S (1 - e^{-\beta t}) \]

\[ CL_S \]

\[ V_S \]

\[ \text{SOMATIC} \]

\[ V_F \]

\[ \text{SPLANCHNIC} \]

Relationship Between CL_F and Extent of NAPA Absorption*

\[ R^2 = 0.8, p = 0.045 \]

Additional Considerations

**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)

**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.

**Standard Bioequivalence Study**

- Two one-sided statistical test procedure – Is the test product less bioavailable relative to a reference product? (80% limit)
  - Is the reference product less bioavailable relative to the test product? (125% limit)*

*All data expressed as a ratio of average AUC and Cmax for test product/reference product (125% reciprocal of 80%)*
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AUC A > B: Therapeutic Significance?

AUC A > B: B Ineffective
AUC A > B:
A and B Equally Effective

AUC A = B:
Equal AUC but Different $K_a$:
B is Ineffective

AUC A = B:
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


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**Three CRITICAL Biopharmaceutical Properties**

- **Drug Solubility Relative to Dose**  
  GOOD = Highest Dose in 250 mL H$_2$O, pH 1.0-7.5

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

- **Intestinal Permeability of Drugs**

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**Correlation of Rates of Drug DISSOLUTION and Oral ABSORPTION**

Three CRITICAL Biopharmaceutical Properties

- Drug Solubility Relative to Dose
- Dissolution Rate of Formulation
- **INTESTINAL PERMEABILITY** of Drug

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### Bioavailability vs. Jejunal Permeability

**MEASUREMENT REQUIRES REGIONAL JEJunal PERFUSION**


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### Bioavailability vs. Caco-2 Cell Permeability $P_{app}$

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*.