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  DRAFT GUIDANCE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

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

Monocarboxylic Acid Transporter:
- Salicylic acid
- Pravastatin
Drug Absorption
- Specialized Transport Mechanisms

Organic Anion Transporting Polypeptide:
Sulfasalazine (OATP2B1)
Fexofenadine (OATP1A2)

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

ASPIRIN Absorption From STOMACH and SMALL INTESTINE*

<table>
<thead>
<tr>
<th>pH</th>
<th>ASA ABSORPTION (micromol/100 mg protein/hr)</th>
<th>ASA SERUM LEVEL (mg/100 ml)</th>
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</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>
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</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**

**Variation in “Peak” Levels ACETAMINOPHEN*\(^\text{1}\)**

- Levels measured 1-hour post dose


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**Gastric Emptying Rate Affects ACETAMINOPHEN Absorption*\(^\text{2}\)**

- With metoclopramide
- Alone
- With propantheline


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**Factors Affecting RATE and EXTENT of Drug Absorption**

- Various factors influencing absorption
- Diagram illustrating the process

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**RESERVE LENGTH**

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

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**Effect of METOCLOPRAMIDE on Digoxin Absorption**


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**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>
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<tbody>
<tr>
<td>PHENOBARBITAL</td>
<td>100</td>
<td>DIGOXIN</td>
<td>70</td>
<td>CYCLOSPORINE</td>
<td>26</td>
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<tr>
<td>LEVOFLOXACIN</td>
<td>99</td>
<td>INDINAVIR</td>
<td>65</td>
<td>TACROLIMUS</td>
<td>25</td>
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<tr>
<td>METHADONE</td>
<td>92</td>
<td>CIMETIDINE</td>
<td>60</td>
<td>MORPHINE</td>
<td>24</td>
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<td>PHENYTIN</td>
<td>90</td>
<td>CLARITHROMYCIN</td>
<td>55</td>
<td>VERAPAMIL</td>
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<tr>
<td>METHYLPREDNISOLONE</td>
<td>82</td>
<td>ITRACONAZOLE</td>
<td>55</td>
<td>NICARDIPINE</td>
<td>18</td>
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<td>TETRACYCLINE</td>
<td>77</td>
<td>AMITRIPTYLINE</td>
<td>48</td>
<td>SIROLIMUS</td>
<td>15</td>
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<td></td>
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<td>DILTIAZEM</td>
<td>38</td>
<td>SAQUINAVIR</td>
<td>13</td>
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<td></td>
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<td>ERYTHROMYCIN</td>
<td>35</td>
<td>ATORVASTATIN</td>
<td>12</td>
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<td>CHLORPROMAZINE</td>
<td>32</td>
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FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION

12
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
- MORPHINE*
- NORTRIPTYLINE
- ORGANIC NITRATES
- PROPRANOLOL

* Known P-Glycoprotein Substrates
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

\[ dE = \text{CL}_E \cdot C \, dt \]

\[ E = \text{CL}_E \int_0^\infty C \, dt \]

\[ D \cdot F = \text{CL}_E \cdot \text{AUC} \]

Calculation of AUC
Trapezoidal Rule

From: Rowland M, Tozer TN. Clinical Pharmacokinetics. p 470.
AUC A > B

**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**

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

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.
Extent of Absorption from Renal Excretion of Unchanged Drug

Since: \( F \cdot D = E \) and \( E = \left( \frac{C_{L_E}}{C_{L_R}} \right) E_R \)

\[
F \cdot D_{oral} = \left( \frac{C_{L_E}}{C_{L_R}} \right) E_{R(oral)} \quad \text{and} \quad D_{IV} = \left( \frac{C_{L_E}}{C_{L_R}} \right) E_{R(IV)}
\]

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

ASSESSMENT of Bioavailability

- AUC Estimates Can Be Used to Estimate Extent of Drug Absorption.
- HOW IS ABSORPTION RATE ASSESSED?
  - \( T_{MAX} \)
  - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.

INTERACTION OF DRUG ABSORPTION AND DISPOSITION PROCESSES

\( G(t) * H(t) = X(t) \)
MODEL Used to Analyze Kinetics of Drug Absorption

Calculation of Bioavailability from First-Order Absorption Model

\[ F = \frac{k_a}{k_a + k_0} \]

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
Simultaneous Administration of Oral NAPA and IV NAPA-\textsuperscript{13}C


MODEL Used to Analyze Oral NAPA and IV NAPA-\textsuperscript{13}C 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>
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<tr>
<td>3</td>
<td>68.1</td>
<td>69.9</td>
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<td>4</td>
<td>88.2</td>
<td>73.1</td>
</tr>
<tr>
<td>5</td>
<td>75.7</td>
<td>75.6</td>
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</tbody>
</table>

* Corrected for absorption lag time.

Factors Affecting RATE and EXTENT of Drug Absorption

NAPA PK Model After IV Dose

\[
\begin{align*}
C_{Lr} &= Q_s \left( 1 - e^{-\alpha t/\theta_s} \right) \\
C_{Lp} &= Q_s \left( 1 - e^{-\alpha t/\theta_p} \right)
\end{align*}
\]

\[V_F = \text{SPLANCHNIC} \]

\[V_S = \text{SOMATIC} \]
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

• Single-dose, two-way, crossover design – *Usually in healthy subjects.*
• 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%)

GOALS of Drug Absorption and Bioavailability Lecture

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

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


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

**BIOPHARMACEUTICAL 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*.