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

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
**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>
</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>


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

- **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** 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>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 (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

ATP

ATP

+ +

SLIDE COURTESY OF M. GOTTESMAN

BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>&gt; 70% ABSORPTION</th>
<th>30% - 70% ABSORPTION</th>
<th>&lt; 30% ABSORPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG</td>
<td>F %</td>
<td>DRUG</td>
<td>F %</td>
</tr>
<tr>
<td>PHENOBARBITAL</td>
<td>100</td>
<td>CYCLOSPORINE</td>
<td>25</td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>99</td>
<td>TACROLIMUS</td>
<td>25</td>
</tr>
<tr>
<td>METHADONE</td>
<td>92</td>
<td>MORPHINE</td>
<td>24</td>
</tr>
<tr>
<td>PHENYTIN</td>
<td>90</td>
<td>VERAPAMIL</td>
<td>22</td>
</tr>
<tr>
<td>METHYLPREDNISOLONE</td>
<td>82</td>
<td>NICARDIPINE</td>
<td>18</td>
</tr>
<tr>
<td>TETRACYCLINE</td>
<td>77</td>
<td>SIROLIMUS</td>
<td>15</td>
</tr>
<tr>
<td>AMITRIPTYLINE</td>
<td>48</td>
<td>DILTIAZEM</td>
<td>13</td>
</tr>
<tr>
<td>ERYTHROMYCIN</td>
<td>35</td>
<td>SAQUINAVIR</td>
<td>12</td>
</tr>
<tr>
<td>CHLORPROMAZINE</td>
<td>32</td>
<td>ATORVASTATIN</td>
<td>5</td>
</tr>
</tbody>
</table>

30% - 70% 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 MORAINE *
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**

**BIOAVAILABILITY** is the *RELATIVE AMOUNT* (F) of a drug dose that reaches the systemic circulation *unchanged* and the *RATE* at which this occurs.

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

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**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

BUT IS A BETTER THAN B?

ABSOLUTE Bioavailability

% Absorption $= \frac{D_{\text{IV}} \bullet AUC_{\text{oral}}}{D_{\text{oral}} \bullet AUC_{\text{IV}}} \times 100$

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: \( F \times D = E \) and \( E = \left( \frac{CL_k}{CL_R} \right) E_R \)

\( F \times D_{\text{oral}} = \left( \frac{CL_k}{CL_R} \right) E_{R(oral)} \) and \( D_{IV} = \left( \frac{CL_k}{CL_R} \right) E_{R(IV)} \)

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

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**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

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

\[ \text{IV DOSE} \quad \text{ORAL DOSE} \]

THE OPERATION OF CONVOLUTION

INTEGRAL FORM: \( X(t) = \int_{0}^{t} G(\tau) \ast H(t - \tau) \, d\tau \)

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

SUBSIDIARY EQUATION: \( x(s) = g(s) \ast h(s) \)

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-\textsuperscript{13}C\textsubscript{2}

\[ \text{\textit{N}}\text{-ACETYLPROCAINAMIDE (NAPA-}^{13}\text{C}_2) \]
Simultaneous Administration of Oral NAPA and IV NAPA-C^{13}\*  


MODEL Used to Analyze Oral NAPA and IV NAPA-C^{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 66.1</td>
<td>65.9</td>
<td></td>
</tr>
<tr>
<td>2 92.1</td>
<td>92.1</td>
<td></td>
</tr>
<tr>
<td>3 68.1</td>
<td>69.9</td>
<td></td>
</tr>
<tr>
<td>4 88.2</td>
<td>73.1</td>
<td></td>
</tr>
<tr>
<td>5 75.7</td>
<td>75.6</td>
<td></td>
</tr>
</tbody>
</table>

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

NAPA PK Model After IV Dose

\[ \text{ICL}_F = Q_F (1 - e^{-Q_F/\text{CL}_F}) \]

\[ \text{ICL}_S = Q_S (1 - e^{-Q_S/\text{CL}_S}) \]

\text{ICL}_F \text{ PARTLY REFLECTS SPLANCHNIC BLOOD FLOW}

Relationship Between CLF and Extent of NAPA Absorption

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

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)

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• 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:**
  - **A** and **B** equally effective.

- **AUC A > B:**
  - **A** more effective than **B**.

- **AUC A > B:**
  - **B** ineffective.
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

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


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


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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


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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


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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*