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
### 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*

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

Subject 5

8.6

1.6

6.8

3.4

4.4

5.0

Subject 6

2.9

2.0

2.5

1.6

2.9

2.0

0.5

1.6

6.8

5.9

3.4

3.9

4.4

9.5

4.9

3.4

3.9

4.4

9.5

EXTENT RELEASED

75% 56%

Variation in “Peak” Levels

ACETAMINOPHEN*

LEVELS MEASURED 1-HOUR POST DOSE

ACETAMINOPHEN (μg/mL)

PATIENTS

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></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

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>Phenobarbital</td>
<td>100 F%</td>
<td>Digoxin 70 F%</td>
<td>Cyclosporine 28 F%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>99 F%</td>
<td>Indinavir 65 F%</td>
<td>Tacrolimus 25 F%</td>
</tr>
<tr>
<td>Methadone</td>
<td>92 F%</td>
<td>Cimetidine 60 F%</td>
<td>Morphine 24 F%</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90 F%</td>
<td>Clarithromycin 55 F%</td>
<td>Verapamil 22 F%</td>
</tr>
<tr>
<td>Methyprednisolone</td>
<td>82 F%</td>
<td>Itraconazole 55 F%</td>
<td>Nicardipine 18 F%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>77 F%</td>
<td>Amitriptyline 48 F%</td>
<td>Sirolimus 15 F%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diltiazem 38 F%</td>
<td>Saffinavir 13 F%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin 35 F%</td>
<td>Atorvastatin 12 F%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chlorpromazine 32 F%</td>
<td>Doxorubicin 5 F%</td>
</tr>
</tbody>
</table>
> 70% BIOAVAILABILITY OF SOME P-GLYCOProTEIN SUBSTRATES

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

- Stomach
  - Gastric Emptying Time
  - Acid Hydrolases

- Drug Tablet or Capsule
  - Disintegration
  - Drug in Small Particles

- Drug in Solution
  - Dissolution

- Portal Vein
  - Site of Maximal Absorption

- Small Intestine
  - Transit Time
  - Mucosal Surface Transporters
  - 1st-Pass Metabolism

- Liver
  - 1st-Pass Metabolism

- Splanchnic Circulation
  - Splanchnic Blood Flow

- Somatic Circulation
  - Muscle, Fat, Etc.

- Heart

- Spleen

- Colon
  - Transit Time
  - Bacterial Metabolism

- Absorption Complete

- Reserve Length
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

Area
(0-16 hours)

A = 29.8 $\text{mcg/mL} \times \text{hours}$

B = 14.0 $\text{mcg/mL} \times \text{hours}$

Average Serum Concentration (mcg/mL)

Time After Drug Administration (hours)
ABSOLUTE Bioavailability

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

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
How to keep salicylate blood levels up
...even when
your arthritis
patient isn't.

Bayer Timed-Release
Aspirin

The main "hit" in arthritis therapy
with Bayer Timed-Release Aspirin is
the longer-acting analgesic and
anti-inflammatory properties of
Timed-Release Aspirin. Bayer
Timed-Release Aspirin provides a
sustained release of aspirin, which
keeps the body from making
salicylates, the active ingredient in
aspirin. This sustained release
means that the body is not exposed
to sudden, sharp peaks in salicylate
levels that can cause side effects.

TOTAL SALICYLATES IN PLASMA (mg %)

... Pixels

[Graph showing total salicylates in plasma over time for Bayer Timed-Release Aspirin]

Formulation and release data for Bayer Timed-Release Aspirin were obtained from the studies listed below:

**RELATIVE** Bioavailability

% 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 beNormalized 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 \( E = \left( \frac{CL_E}{CL_R} \right) E_R \)

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

So: \% Absorption = \[
\frac{D_{\text{IV}} \cdot E_{R(\text{oral})}}{D_{\text{oral}} \cdot E_{R(\text{IV})}} \times 100
\]
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.
INTERACTION OF DRUG ABSORPTION AND DISPOSITION PROCESSES

\[ G(t) \ast H(t) = X(t) \]
THE OPERATION OF CONVOLUTION

INTEGRAL FORM: \[ X(t) = \int_{0}^{t} G(\tau) \cdot H(t - \tau) d\tau \]

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

SUBSIDIARY EQUATION: \[ x(s) = g(s) \cdot h(s) \]
MODEL Used to Analyze Kinetics of Drug Absorption

$\text{ GI }$  \hspace{2cm} $\text{ ORAL }$  \hspace{2cm} $\text{ INTRAVENOUS }$

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

$V_C$  \hspace{2cm} $V_P$

$C_l_I$  \hspace{2cm} $C_l_{NR}$  \hspace{2cm} $C_l_R$
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$_2$

$N$-ACETYLPRAOCAINAMIDE (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

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

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

\( CL_F \) PARTLY REFLECTS SPLANCHNIC BLOOD FLOW

\( V_F \) SPLANCHNIC

\( V_S \) SOMATIC
Relationship Between CL_F 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?

![Graph showing comparison of two curves with AUC calculation](image)
AUC A > B: B Ineffective
AUC A > B: A and B Equally Effective

![Graph showing drug concentration over time with areas under the curve (AUC) for A and B and their respective concentrations and time points.](image-url)
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

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

Three CRITICAL Biopharmaceutical Properties

• Drug Solubility *Relative* to Dose

• Dissolution Rate of Formulation

• *INTESTINAL PERMEABILITY* of Drug
Bioavailability vs. Jejeunal Permeability


**MEASUREMENT**
**REQUIRES**
**REGIONAL**
**JEJEUNAL**
**PERFUSION**

Bioavailability vs. *Caco-2 Cell Permeability* 

\[ \text{P}_{\text{app}} \]

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

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

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*.

*Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, CDER Guidance for Industry, August 2000.*