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

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
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 (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


**POST PRANDIAL (Up to 10 hr delay)**
- Pylorus constricted
- Antral contractions reduce particle size

**Interdigestive Intestinal Motor Activity in Humans**

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. GOTTFESMAN

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>METHYLREDNISOLONE</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>AMITRIPTYLINE</td>
<td>95</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>ITRACONAZOLE</td>
<td>95</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>CHLORPROMAZINE</td>
<td>93</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>CYCLOSPORINE</td>
<td>92</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>TACROLIMUS</td>
<td>90</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>90</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>VERAPAMIL</td>
<td>80</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>NICARDIPINE</td>
<td>75</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>ATORVASTATIN</td>
<td>70</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>DOKORUBICIN</td>
<td>65</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

> 70% BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES
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

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

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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
**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**

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

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

Comparison here is between 2 ORAL Formulations

---

**RELATIVE Bioavailability**

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 $E = \frac{CL_D}{CL_{\text{r}}} \cdot E_{\text{r}}$

$F \cdot D_{\text{oral}} = \left( \frac{CL_D}{CL_{\text{r}}} \right) E_{\text{r \(oral\)}}$ and $D_{\text{IV}} = \left( \frac{CL_D}{CL_{\text{r}}} \right) E_{\text{r \(IV\)}}$

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

ABSORPTION        DISPOSITION          DRUG IN PLASMA
G(t)  ≠  H(t)  =  X(t)

IV DOSE
ORAL DOSE

MODEL Used to Analyze Kinetics of Drug Absorption

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

\text{N-ACETYLPROCAINAMIDE (NAPA-^{13}C_2)}

Simultaneous Administration of Oral NAPA and IV NAPA-C^{13}O

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

- Drug Table or Capsule
- Stomach Contents
- Gastric Emptying Time
- Intestinal Peristalsis
- Luminal pH
- First-Pass Effect
- Portal Vein
- Hepatic Extraction
- CYP450 Enzyme System
- Protein Binding
- Renal Excretion
- Metabolism
NAPA PK Model After IV Dose

\[ V_c = \frac{Q_s}{1 - e^{-t/V_s}} \]

\[ CL_F = Q_s (1 - e^{-t/V_s}) \]

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

\[ V_F \text{ SPLANCHNIC} \]

\[ V_S \text{ SOMATIC} \]

Relationship Between \( CL_F \) and Extent of NAPA Absorption*

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

\[ 65 \ 70 \ 75 \ 80 \ 85 \ 90 \]

\[ 0.8 \ 1 \ 1.2 \ 1.4 \ 1.6 \ 1.8 \ 2 \]

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


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 Kₐ: 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
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

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*.