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*

Graph of plasma concentration versus time showing the extent of phenytonin absorption varied greatly with different excipients.

***Bochner F., et al. Proc Aust Assoc Neurol 1973;9:165-70**

Factors Affecting
DRUG ABSORPTION

-Biopharmaceutic Factors

- **INTERACTIONS**
  - **Food**
  - **Other Drugs**
  - **Bacteria**

- **Physiologic Factors**

ENTERIC METABOLISM OF DIGOXIN*

Chemical structure of digoxin and metabolites produced by enteric bacteria.

*** Lindenbaum J, et al. N Engl J Med 1981;305:789-94.**

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 showing Aspirin (ASA) absorption from simultaneously perfused stomach and small intestine. Changes in pH reduce absorption from the stomach but intestinal absorption does not change significantly.

*** From: Hollander D, et al. J Lab Clin Med 1981;98:591-8**

Variation in Gastric and Intestinal pH*

Graph illustrating wide variation in gastric pH.

*** Meldrum SJ, et al. Br Med J 1972;2:104-6.**

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

Phase 1 - Quiescence

Phase 2 - Irregular Contractions

Phase 3 - Major Motor Complex Burst

Phase 4 - Transition Period

Interdigestive Intestinal Motor Activity in Humans*

Chart illustrating gastrointestinal motor activity.

***From: Rees WDW, et al. Dig Dis Sci 1982;27:321-9.**

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**

Illustration of the significant inter-individual variation in extent of carbamazepine absorption.

***From: Wilding IR, et al. Br J Clin Pharmacol 1991;32:573-9.**

Variation in “Peak” Levels
ACETAMINOPHEN*

Chart showing major variability in peak levels of Acetaminophen in patients.

*** Prescott LF. Med Clin N Am 1974;42:907-16.**

Gastric Emptying Rate Affects ACETAMINOPHEN Absorption*

Chart illustrating that metoclopramide accelerates gastric emptying and propantheline delays gastric emptying and the effect of these changes on acetaminophen absorption.

***From: Nimmo J, et al. Br Med J 1973;1:587-9.**

Factors Affecting RATE and EXTENT of Drug Absorption

Illustration showing the impact of intestinal transit time and reserve length on 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*

Graph of Digoxin serum levels showing that metoclopramide causes reduced absorption.

*** From: Manninen V, et al. Lancet 1973;1:398-99.**

Effect of PROPANTHELINE on Digoxin Absorption*

Chart illustrating that propantheline enhances digoxin absorption.

*** From: Manninen V, et al. Lancet 1973;1:398-99.**

Factors Affecting RATE and EXTENT of Drug Absorption

Illustration of the significance of mucosal surface area regarding drug absorption.

Normal Intestinal Villi

Histological section under microscope.

Broad Intestinal Villi in a Patient with SPRUE

Histological section under microscope. Major reduction in absorptive surface.

Digoxin Levels in Patients with INTESTINAL MALABSORPTION*

Chart illustrating reduced digoxin absorption.

*** From: Heizer WD, et al. N Engl J Med 1971;285:257-9.**

Factors Affecting RATE and EXTENT of Drug Absorption

Illustration highlighting the role of transporters in drug absorption.

P-GLYCOPROTEIN EFFLUX PUMP

Intestinal Lumen

Illustration of this drug efflux pump.

Slides courtesy of M. Gottesman.

BIOAVAILABILITY OF SOME
P-GLYCOPROTEIN SUBSTRATES

Chart showing percent of absorption for various substrate drugs.

70% BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES

Illustration of how a large effective absorption surface can compensate for the effect of p-glycoprotein on drug absorption.

FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION

Illustration of the impact of first-pass metabolism on drug absorption.

Sites of FIRST-PASS Elimination

- INTESTINAL MUCOSA

CYP Enzymes

P-Glycoprotein

- LIVER

CYP Enzymes

FIRST-PASS METABOLISM

Illustration of first-pass metabolism and the portal circulation.

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

Illustration of the role of splanchnic circulation on 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

<u>BIOAVAILABILITY</u> 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

Chart showing the area under the serum concentration time-curve after a single oral dose with the Cmax and Tmax. values.

Significance of AUC

Equations illustrating the significance of AUC and its relation to dose and clearance.

Calculation of AUC
Trapezoidal Rule

Graphic illustration of the use of the trapezoidal rule to estimate area under the curve.

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

AUC A > B

A chart illustrating this concept with 2 hypothetical drugs.

ABSOLUTE Bioavailability

The formula for estimating absolute bioavailability is shown.

Comparison here is between an ORAL and an IV Formulation.

RELATIVE Bioavailability

The formula for estimating relative bioavailability is shown.

The comparison here is between 2 ORAL Formulations.

Old Ad for Bayer Timed-Release aspirin entitled, “How to keep salicylate blood levels up…even when your arthritis patient isn’t.”

Illustrates why the dose administered needs to be considered when comparing the relative bioavailability of drug formulations.

Example of misleading advertisement.

RELATIVE Bioavailability

The formula for relative bioavailability is shown.

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?
  - **TMAX**
  - **Integrated Pharmacokinetic Analysis of Absolute Bioavailability.**

Extent of Absorption from Renal Excretion of Unchanged Drug

Formulas illustrating how to estimate absolute bioavailability from urinary recovery data after oral and intravenous administration.

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?

- **TMAX**
- **Integrated Pharmacokinetic Analysis of Absolute Bioavailability.**

INTERACTION OF DRUG ABSORPTION AND DISPOSITION PROCESSES

Illustration of these processes and the combination of absorption and disposition functions.

THE OPERATION OF CONVOLUTION

Equations that illustrate this concept.

MODEL Used to Analyze Kinetics of Drug Absorption

Graphic illustration of this model.

Calculation of Bioavailability from First-Order Absorption Model

Mathematical formula.

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-$^{13}C_2$

Chemical structure for N-Acetylprocainamide.

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

Chart illustrating their pharmacokinetic profile.

*** From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.**

MODEL Used to Analyze Oral NAPA and IV NAPA-C^{13} Kinetics*

Illustration of a 3-compartment model.

*** From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.**

BIOAVAILABILITY Estimates From Kinetic Analysis and URINE RECOVERY

Chart showing good agreement between percent predicted bioavailability by kinetic analysis and the actual percent of NAPA recovery in urine.

Factors Affecting RATE and EXTENT of Drug Absorption

Illustration of the factors affecting rate and extent of drug absorption that highlights splanchnic blood flow.

NAPA PK Model After IV Dose

Illustration of 3-compartment model emphasizing the fast intercompartmental clearance term.

Relationship Between CL_F and Extent of NAPA Absorption*

Graph of experimental data illustrating this relationship.

*** From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.**

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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- **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?

Chart illustrating this concept.

AUC A > B: B Ineffective

Illustration of this concept when drug B does not achieve therapeutic concentrations.

AUC A > B:
A and B Equally Effective

Illustration of this concept when drug B achieves therapeutic concentrations in spite of a lower AUC.

Equal AUC but Different K_a: B is Ineffective

Chart illustrating that drug B has slower absorption that renders it ineffective.

Equal AUC but Different K_a: A is Toxic

Chart illustrating this concept and rapid absorption of drug A results in toxicity.

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

*** From: Amidon GL, et al. Pharm Res 1995;12:413-20**

Three CRITICAL
Biopharmaceutical Properties

- **Drug Solubility *Relative* to Dose**
  GOOD = Highest Dose in 250 mL H20, 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

Chart showing this correlation.

From Rackley RJ. In Young D, Devane JG, Butler J, eds. In vitro-in vivo correlations. p. 1-15.

Three Critical Biopharmaceutical Properties

- **Drug Solubility Relative to Dose**

- **Dissolution Rate of Formulation**

- **Intestinal Permeability of Drug**

Bioavailability vs. Jejeunal Permeability*

Chart illustrating this comparison for several prototype drugs.

*** From Amidon GL et al. Pharm Res 1995;12:413-20.**

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

Chart illustrating this in vitro-in vivo correlation.

***From Arturson P, Karlsson J. Biochem Biophys Res Commun 1991;175:880-5**

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

From: Amidon GL, et al. Pharm Res 1995;12:413-20

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**

From: Amidon GL, et al. Pharm Res 1995;12:413-20

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.**

*** From: Amidon GL, et al. Pharm Res 1995;12:413-20**

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS IV:
LOW SOLUBILITY-LOW PERMEABILITY

- ***in vitro – in vivo*** **correlation poor**
- **good bioavailability not expected**

*** From: Amidon GL, et al. Pharm Res 1995;12:413-20**

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.**