1. Pharmacokinetics and Pharmacodynamics

- 1.1. Pharmacokinetics
  - The study (or kinetics) of drug absorption, distribution, metabolism, and excretion (ADME) is known as Pharmacokinetics.
  - The processes of drug distribution and elimination (*metabolism and excretion*) are also known as drug disposition.
  - The processed of drug metabolism and excretion are called drug elimination.
  - What the body does to the drug.

Absorption (Part 1) Outline

- 1. Pharmacokinetics and Pharmacodynamics
- 2. Absorption and Bioavailability
- 3. Drug Absorption Mechanisms
- 4. Four Primary Factors influence Drug Absorption

1.2. Pharmacokinetics include ADMET
1.2. Pharmacokinetics include ADMET (Con’t)

- **ADME**
  - Absorption (A): drug is absorbed from site of administration to systemic circulation.
  - Distribution (D): drug is distributed from circulation to other tissues.
  - Metabolism (M): drug is metabolized in liver or other tissues by metabolizing enzymes.
  - Excretion (E): drug is excreted from kidney or other organs.

- **ADMET**
  - T: Transporters

1.3. Methods to Study of Pharmacokinetics

- **Experimental approaches:**
  - biological sampling techniques
  - analytical methods for the measurement of drugs and metabolites in biological matrix
  - procedures that facilitate data collection and analysis

- **Theoretical approaches:**
  - development of pharmacokinetic models that predict drug absorption and disposition after administration

1.4. Application of Pharmacokinetics

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually.
3. Estimate the possible accumulation of drugs and/or metabolites.
4. Correlate drug concentration with pharmacologic or toxicological activity.
5. Evaluate differences in the rate and extent of availability between different formulations
6. Describe how changes in physiology or disease affect absorption, distribution, or elimination.
7. Explain drug interactions.
1.5. Pharmacodynamics

- Pharmacodynamics is the study of the effects of the drug, their mechanism of action, and relationship between drug concentrations at the site of action (receptor) as well as the intensity of pharmacologic effect.

- What the drug does to the body.

1.5. Pharmacodynamics (Con’t)

- The relationship between dose and effect can be plotted and results in a hyperbolic curve with maximum effect at the plateau.

2. Absorption and Bioavailability

Absorption:
Drug entry into systemic circulation from site of administration

2.1. Drug absorption and Bioavailability
2.2. Mass Balance of a Drug

\[ \text{Rate of change of drug in body} = \text{Rate of absorption} - \text{Rate of elimination} \]

2.3. Bioavailability

\[ F = F_a \cdot F_g \cdot F_h \]

- \( F \): bioavailability
- \( F_a \): fraction of drug absorbed
- \( F_g \): fraction of drug escaped from gut wall metabolism
- \( F_h \): fraction of drug escaped from liver metabolism
- First pass effect
  - The drug loss as it passes, for the first time, through sites of elimination, such as in GI membranes and the liver

2.3. Bioavailability (Con’t)

CFR 21.320.1 (Definitions)

Bioavailability means “the rate and extent to which the active drug ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by the measurements intended to reflect the rate and extent to which active ingredient or active moiety becomes available at the site of action.”

3. Drug Absorption Mechanisms

Types of Intestinal Membrane Transport:
3. Drug Absorption Mechanisms (Con't)

- 3.1. Passive diffusion
- 3.2. Carrier-mediated processes (active transporters)
- 3.3. Paracellular tight junction
- 3.4. Endocytosis

3.2. Membrane Transporters

A Few hundreds of transporters have been studied in human body

<table>
<thead>
<tr>
<th>Intestinal lumen</th>
<th>Apical membrane</th>
<th>Basal membrane</th>
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</tr>
<tr>
<td>GLUT5</td>
<td>GLUT2</td>
<td>?</td>
</tr>
</tbody>
</table>
3.3. Paracellular Tight Junctions

Functions:
- Prevent passage of molecules and ions between cells (MW < 300-1000 pass through)
- Block the movement of integral membrane proteins
  - heregulin and erbB
  - bronchitis, asthma, and cystic fibrosis
- Cell-cell adhesion

3.4. Endocytosis

3.5. Which routes dominate (control) drug absorption?
- Drug absorption (or movement through membrane) include passive, active, paracellular, and endocytosis routes.
  - Fastest process dominates (control) drug absorption (movement across membrane)
    - Lipophilic compounds (passive diffusion)
    - Carrier substrates (active transport)
    - Small polar molecules with MW < 300 (paracellular)
    - Nanoparticles (endocytosis/transcytosis)
4. Four Primary Factors influence drug absorption

4.1. Permeability
- Physiological properties of membrane
4.2A. Solubility
- Physiochemical properties of drug molecules
4.2B. Dissolution
- Dosage form variables
4.2C. Dose

4.1. Factors influence drug permeability
- Passive diffusion permeability (cm/s)
  - Partition coefficient (K)
  - Diffusion coefficient (D, cm²/s)
  - Membrane thickness (h, cm)
- Active transporter permeability
  - Substrate specificity (Km)
  - Concentration (C)
  - Drug flux (J)
- Paracellular permeability
  - Molecular size, 300-1000 Da
  - polarity

Permeability Across Lipid Bilayer
4.2. Solubility, Dissolution, and Dose
Governing Drug absorption

- Solid drug $\rightarrow$ Drug Solution $\rightarrow$ Blood
  - Disintegration
  - Dissolution
  - Solubility---ionization
  - Aqueous transport
  - Membrane transport

4.2. Solubility, Dissolution, and Dose Governing
Drug absorption (Con’t)

- 2A. Solubility
  - Extent of ionization (pH-partition hypothesis)
  - Oil / water partition coefficient ($K_{o/w}$)
- 2B. Dissolution (Extent and Rate)
  - Dosage forms
- 2C. Dose
  - Small dose: easy to be dissolved.
  - Large dose: Difficult to be dissolved.

Summary

- 1. Pharmacokinetics and Pharmacodynamics
  - PK (ADMET): What the body does to the drug
  - PD (Efficacy vs. dose): What the drug does to the body
- 2. Absorption and Bioavailability
  - $F = F_a, F_g, F_h$
- 3. Drug Absorption Mechanisms
  - Passive diffusion
  - Active transporters
  - Paracellular tight junction
  - Endocytosis
- 4. Four Primary Factors influence Drug Absorption
  - Permeability, solubility, dissolution, dose.