Transport of drug through biological membranes. Processes LADME and their parameters

March 2020
Important facts related to drug effect !!!

- There is significant variability in drug response.
- Variability in drug concentration makes a major contribution to the observed variability in pharmacologic effect.
- Pharmacologic response is dependent, in large measure, on the concentration of drug achieved at the site of action.
- There is significant variability in the drug concentration achieved after a standard dose of a drug – importance of LADME system and pharmacokinetic properties of a drug.
Pharmacokinetics
The study of the absorption, distribution, metabolism and elimination of drugs

Pharmacodynamics
The study of the pharmacological effect and clinical response of a drug and their mechanisms of actions
Pharmacokinetics: what the body does to a drug
Pharmacodynamics: what a drug does to the body
REGIMEN SPECIFIC
- Dosage Form
- Frequency
- Route
- Dose

PHARMACOLOGIC EFFECT

DRUG SPECIFIC
- Concentration-effect Relationship
- Site of Biological Effect
- Disposition of the Drug
- Potency of the Drug

PATIENT SPECIFIC
- Environmental Exposure
- Psychological Condition
- Genetic Constitution
- Organ Function
- Enzyme Activity
**Biopharmaceutics**

Drug in dosage form

\[ \text{Liberation} \]

Drug particles in body fluids

\[ \text{Dissolution} \]

Drug in solution

\[ \text{Absorption} \]

GIT

\[ \text{Excretion} \text{ (metabolism and elimination)} \]

Liver/Kidney

**Pharmacokinetics**

**Pharmacodynamics**

Pharmacologic effect

Peripheral Tissues

\[ \text{Distribution} \]

Central Compartment

Free ⇔ Bound
LIBERATION of drug from dosage form.
Kinetic of liberation.

This topic is referred in a following lecture dated on March 30, 2020 !!!
I. ABSORPTION OF DRUGS AND METHODS OF DRUG DELIVERY

- Transport across cell membranes
  - Passive diffusion
  - Active transport/crrier mediated
  - Endocytosis
## Membrane Composition

<table>
<thead>
<tr>
<th>Membrane Type</th>
<th>Phospholipid</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Inner mitochondrial</td>
<td>20-25%</td>
<td>75-80%</td>
</tr>
<tr>
<td>Myelin</td>
<td>75%</td>
<td>25%</td>
</tr>
</tbody>
</table>

**Diagram:**
- Phospholipid:
  - Polar head
  - Non-polar tail
Passive diffusion

a. Passage through lipid cell membrane by dissolution in membrane;
   - rate dependent on concentration gradient and lipid:water partition coefficient of drug;
   - rate markedly higher for unionized form of weak electrolyte because of its higher lipophilicity than the ionized form;
   - obeys first-order kinetics (rate of transport is proportional to concentration gradient at transport site).

b. Filtration through aqueous channels within membranes and between cells.
Active transport

- Passage facilitated by an energy-dependent membrane carrier mechanism such that transport can occur against a concentration gradient;
  - transporters include the family of ATP-dependent proteins, such as
    - the multidrug resistance p-glycoprotein
    - the multidrug resistance-associated proteins

- Exhibits structural selectivity, saturability, competition between structural analogues and genetic variants.

- Sites for drugs in intestinal mucosa (cell to lumen), capillary endothelium of brain and testis (cell to blood), choroid plexus (CSF to blood), proximal renal tubular cell (blood to urine), hepatocyte (blood to bile), tumor cells (efflux pump).

- Obeys Michaelis-Menten kinetics: if drug concentration is high enough to saturate carrier mechanism, kinetics are zero-order (rate of transport is constant).
Endocytosis

- Passage into cell within membrane invagination.
- Important mechanism for particulates and high molecule weight compounds, such as proteins.
Absorption - definitions

- Absorption - the process by which a compound passes into the general circulation.

- Absorption rate constant – the rate constant of the entire process of drug transfer into the body, through all biological membranes.
Factors influencing the absorption of drugs across cell membranes:

- drug solubility in aqueous solution
- drug dissolution rate (if solid)
- surface area of absorption site
- rate of blood flow

Generally:

- absorption involves only the lipophilic, non-ionised form
- dissolution is a rate-limiting factor in absorption
Other factors that modify absorption

- chemical degradation
  drugs can be destroyed by the strong acidity of the stomach – penicillins

- transformation into metabolites
  intestinal bacteria and the enzymes of the mucosa, hepatic enzymes

- complexation
  tetracycline with heavy metals or neomycin with biliary salts

- pathological states
  diarrhoea, gastric ulcers, skin diseases
Bioavailability

- The efficiency of absorption is termed **bioavailability**. It is defined as the fraction of the administered dose that reaches the systemic circulation in an unchanged form.

- It takes into account metabolism and/or excretion that may occur before the drug can go from the point of application to the general circulation.

- Since intravenous administration (IV) of a drug directly deposits the drug into the systemic circulation, the bioavailability of a drug administered IV is defined as 100%.

- **Bioavailability by other routes** is often less than 100% due to incomplete absorption or metabolism before the drug reaches the systemic circulation.
First-Pass Effect

- Following absorption across the gut wall, the portal circulation delivers the drug to the liver prior to entry to the systemic circulation.

- Liver is the major site of drug metabolism, so depending on the nature of the drug a significant amount of drug can be eliminated by metabolism before reaching the systemic circulation. This so-called "first-pass effect" is a major determinant of bioavailability.

*For example*, approximately 66% of morphine absorbed from the gut is metabolized by first-pass metabolism, markedly reducing its bioavailability.
The first-pass effect represents a loss of drug through metabolism before its entry into general circulation.

- It is not solely hepatic but may also be gastric, intestinal (lumen and mucosa), pulmonary, tissueous (injection site), vascular (endothelium), cutaneous or blood - dependent.

- In order to understand better the nature of first-pass effect is important to consider the **route of drug administration.**
Routes of administration

- There are two general categories of administrative routes: **enteral**, which utilizes the GI tract, and **parenteral**, which does not.

- Parenteral administration has the potential advantage of avoiding early contact with hepatic metabolizing enzymes, and thus having a higher bioavailability.

- However, unlike enteral administration, it is usually not possible to remove the drug once delivered if toxic signs appear.
Parenteral Routes I

- **Intravenous:**
  - maximum bioavailability is achieved
  - continuous infusion to achieve constant drug level is possible
  - potential for irritation of vascular walls
  - increased risk for blood borne infections

- **Subcutaneous:**
  - less painful than IV
  - self-administration is possible
  - circulation at the injection site is important for delivery

- **Intramuscular:**
  - injection site can serve as a depot for slow delivery of the drug
  - all of the drug is not absorbed instantly, so can get slow release
  - depends on rate of blood flow; exercising injected muscle will increase delivery
  - self-administration is possible
Parenteral Routes II

- **Topical/transdermal:**
  - absorption depends on the lipid solubility of the drug or its vehicle
  - some topically applied drugs may be irritants
  - can get slow absorption

- **Pulmonary:**
  - technically a topical application
  - result is usually local with little systemic absorption (bronchodilators)
  - in cases of anesthesia, can finely control the depth of anesthesia

- **Intrathecal:**
  - administration of drug to cerebrospinal fluid
  - commonly used to produce selective spinal blockade.
Enteral routes

- **Oral:**
  - the most common form of administration
  - generally the most economical and convenient method
  - disadvantages include GI tract irritation, potential for first-pass metabolism

- **Rectal:**
  - delivered via suppository
  - often used for patients who are vomiting or unable/unwilling to swallow pills

- **Sublingual:**
  - absorbed drug travels directly into the head/neck venous drainage
  - avoids first-pass metabolism

- **Buccal:**
  - dosage form is placed in the check
  - absorption is similar to sublingual
# ROUTES OF ADMINISTRATION & BIOAVAILABILITY

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>Bioavailability (%)</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>100 (by definition)</td>
<td>most rapid onset</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>75-100</td>
<td>large volumes often feasible</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>75-100</td>
<td>smaller volumes than IM</td>
</tr>
<tr>
<td>Oral</td>
<td>5-99</td>
<td>most convenient, but 1st-pass effect may be significant</td>
</tr>
<tr>
<td>Rectal</td>
<td>30-99</td>
<td>less 1st-pass effect than oral</td>
</tr>
<tr>
<td>Inhalation</td>
<td>5-99</td>
<td>often rapid onset of action</td>
</tr>
<tr>
<td>Transdermal</td>
<td>80-100</td>
<td>very slow absorption kinetics; no 1st-pass effect; prolonged duration of action</td>
</tr>
</tbody>
</table>
II. KINETICS OF DRUG DISTRIBUTION AND ELIMINATION

- Once a drug has been absorbed, the processes of distribution and elimination begin.

- **Distribution** refers to the movement of the drug from the systemic circulation to other tissues, while **elimination** refers to the process of removing the drug from the systemic circulation by either excretion or metabolism to an inactive metabolite.

- The **drug concentration time course** will define both the extent and duration of drug action.

- This, in turn, determines both the **dosage level and the dosage regimen** that needs to be employed in the use of pharmacological agents.
**Tissue distribution** is the process whereby a drug is transported to all tissues and organs.

The parameter used to define the process of distribution is the **volume of distribution**. This is the theoretical volume in which the drug would have to be distributed in order to give the same concentration as that of the plasma.

The larger the volume of distribution, the more extensive the distribution: it rarely has a physiological significance.

The volume of distribution is influenced by:
- physiological states (age, pregnancy, obesity)
- pathological states (renal, hepatic or cardiac insufficiency)
DISTRIBUTION - The reversible transfer of drug from one location in the body to another

**Extent of Distribution**

Determined by:

- partitioning across various membranes
- binding to tissue components
- binding to blood components (RBC, plasma protein)
- physiological volumes

![Components of Total Body Water Table]
Consequently, a drug will be better distributed if it:
- is poorly bound to plasma proteins
- has high affinity for tissue proteins
- is highly lipophilic

Moreover, distribution is faster in organs and tissues that are well perfused.

There are two specific mechanisms of tissue distribution:
- diffusion into the central nervous system
- foetoplacental diffusion
CNS DISTRIBUTION

Three compartments in the CNS:

- blood
- brain
- cerebrospinal fluid (CSF)

Three anatomical barriers

- blood-brain barrier
- blood-CSF barrier
- CSF-brain barrier
Mechanisms of Blood-Brain Barrier Biotransport

Transport Systems for the CNS

- **Carrier-Mediated**
  - glucose, amino acids, lactic acid, thyroid hormone nucleosides

- **Receptor-Mediated**
  - angiotensin II, insulin, transferrin

- **Plasma Protein-Mediated**
  - corticosteroids, androgens, propranolol, estradiol, bupivicaine
### Factors that may influence placental transfer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental blood flow</td>
<td>increased delivery of drug to placental membrane</td>
</tr>
<tr>
<td>Molecular size of drug</td>
<td>decreased transfer as size increases</td>
</tr>
<tr>
<td></td>
<td>impermeable to drugs MW&gt;1000</td>
</tr>
<tr>
<td></td>
<td>permeable to drugs MW&lt;600</td>
</tr>
<tr>
<td>Lipid solubility of drug</td>
<td>increased transfer as lipid solubility increases</td>
</tr>
<tr>
<td>pKa of drug</td>
<td>ion trapping on either side</td>
</tr>
</tbody>
</table>
The single compartment model, in which the body is modeled as a single compartment to which a drug can be introduced into and eliminated from.

We will consider the case of instantaneous delivery of a bolus of drug such as might be seen for an acute IV administration.

The drug is eliminated from the compartment, and the rate of elimination is proportional to the concentration of the drug, $C$, in the compartment (i.e., a first-order kinetic process): 

$$ \text{Rate of elimination} = -k_e C $$

Where $k_e$ is the elimination rate constant.
the time course of drug concentration:

\[ C(t) = C_0 \exp(-k_c t) \]

Where \( C_o \) is the concentration at \( t=0 \).
The **half-life**, which is the time it takes for the concentration at any one time to get to 50% of that value. It is related to the elimination rate constant by:

\[ t_{1/2} = \frac{0.693}{k_e} \]

The **volume of distribution** relates the concentration of drug in the compartment (the plasma) to the amount of drug introduced:

\[ V_d = \frac{\text{dose}}{C_0} \]

Where the dose is given in weight, and \( C_0 \) is the concentration at \( t=0 \). (100 in the figure shown above)
## PHYSICAL VOLUMES OF VARIOUS BODY COMPARTMENTS

<table>
<thead>
<tr>
<th>Compartment and Volume (l/kg)</th>
<th>Representative Drug Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body water = 0.6 l/kg</td>
<td>small water-soluble drugs. e.g., ethanol</td>
</tr>
<tr>
<td>Extracellular water = 0.2 l/kg</td>
<td>larger water-soluble molecules, e.g., gentamicin</td>
</tr>
<tr>
<td>Blood = 0.08 l/kg</td>
<td>large molecules (e.g., heparin) and strongly plasma protein-bound</td>
</tr>
<tr>
<td>Plasma = 0.04 l/kg</td>
<td></td>
</tr>
<tr>
<td>Fat = 0.2-0.35 l/kg</td>
<td>highly lipid soluble molecules, e.g., DDT</td>
</tr>
<tr>
<td>Bone = 0.07 l/kg</td>
<td>certain ions like F⁻ and Pb⁺</td>
</tr>
</tbody>
</table>
Clearence

The final parameter we can obtain is the clearance (CL). CL is the factor that relates the rate of elimination to the plasma concentration:

$$\text{Elimination rate} = \text{CL} \cdot C$$

And has units of ml/min/kg (or some other set of similar units) and is related to the other parameters by:

$$t\frac{1}{2} = \frac{0.693V_d}{CL}$$

Thus, knowing any two parameters allows one to determine the third.
Pharmacokinetic models

- Instantaneous delivery of a bolus of drug
- Non-instantaneous delivery
- Constant infusion
- More than one compartment
- Multiple dosing
Non-instantaneous delivery

- Many drugs are delivered by means where absorption may not be instantaneous (oral, intramuscularly, transdermal, etc.).

- We handle this by adding an absorption rate constant, $k_a$.

- In our original formulation, $k=\infty$, and we get the nice single exponential decay.
If absorption becomes slow enough to be measurable, then we observe the following (the slow absorption curve is filled in red, while the instantaneous absorption is the solid black line):

\[ V_d = \frac{\text{dose}}{(k_e \text{AUC})} \]

where AUC is area under the curve.
Constant infusion

- In some cases (i.e. anesthesia) it is desirable to maintain a constant plasma drug level for a prolonged time.

- In order to maintain a steady-state concentration $C_{ss}$, the delivery rate must equal the elimination rate. Therefore, the dosing rate is given by:

\[
\text{Dosage rate} = CL \times C_{ss}
\]

- Generally, it takes at least 4 half-lifes to reach steady state.
More than one compartment

- We assume that some tissues have different accessibility to various drugs and are not in rapid equilibrium with the plasma.

![Diagram of drug compartment model]

Plasma, liver, kidney
The time course of the plasma drug concentration can be described by a two-exponential decay:

\[ C(t) = A \exp(-\alpha t) + B \exp(-\beta t) \]
Multiple dosing

- The figure below shows plasma drug profiles for three different regimens designed to maintain a therapeutic level - constant infusion and two multiple dosing approaches.
For the multiple dosage regimen, each bolus of drug raises the plasma concentration ($\Delta C$) and the concentration decays with a half-life.

$$\Delta C = \frac{\text{dose}}{V_d}$$
III. BIOTRANSFORMATION REACTIONS AND EXCRETION

Once the drug has reached the general circulation and been distributed, the body will activate a number of mechanism in order to eliminate this foreign substance.

Two possibilities exist:

- **transformation** of the drug into other products called metabolites, which are more polar and easily eliminated.
- **direct elimination** of the drug by **excretion** through:
  - the kidney
  - the bile
The self purification by the body may be quantified by a parameter called **clearance**.

- **Total blood clearance or body clearance**
  - the volume of blood completely cleared of a drug per unit time
  - the body capacity to eliminate a drug after it has reached the general circulation

- **Organ clearance**
  - the volume of blood or plasma completely cleared of a drug by the organ per unit time
  - renal and extrarenal clearance (primary hepatic)

- **Extraction ratio**
  - the fraction of a drug extracted by an organ from the general circulation during a single transit
The overall goal of biotransformation reactions is to convert active, lipophilic molecules to (hopefully) less active, polar molecules that can be subsequently excreted.

- Biotransformation reactions are broken down into two broad categories:
  - **Phase I**: convert parent drug to a more polar metabolite by introducing or unmasking a polar functional group (-OH, -NH$_2$, -SH)
  - **Phase II**: polar substances or polar functional groups acquired during Phase I reactions are conjugated to endogenous polar substrates such as glucuronic acid, sulfuric acid, acetic acid, or glycine
Phase I reactions

- Phase I reactions usually increase the polarity of a drug, and thus its water solubility. In addition, they always change the pharmacological activity of the drug. This usually means a reduction or loss of activity.
  - Some of the products may be completely inactive, while in others the metabolite will have some activity, although weaker than the parent drug.

- There are examples of inactive drugs that are converted to active metabolites:
  - enalapril (an inactive "prodrug") is converted to enalaprilat (an ACE inhibitor) by deesterification

- The majority of Phase I reaction are catalysed by enzymes located on microsomes. Two microsomal enzymes play a key role: NADPH-cytochrome P450 reductase and cytochrome P450, an oxidase.
Phase II reactions produce highly polar compounds with high water solubility, increasing excretion of the metabolized drug. Almost all conjugated products are completely inactive.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Relative Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>100</td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
</tr>
<tr>
<td>Kidney</td>
<td>8</td>
</tr>
<tr>
<td>Intestine</td>
<td>6</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
</tr>
<tr>
<td>Brain</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Excretion of drugs

- Once a drug has been metabolised to a more water-soluble form, it can be excreted from the body.

- They are two major routes of excretion: renal and biliary
Renal excretion

- The kidney are the major site of excretion, and **three separate transport mechanism** are involved:

- Glomerular filtration
- Passive tubular absorption
- Active tubular secretion
Biliary excretion

- Following conjugation in the liver, biotransformation products are frequently excreted into the biliary tract and subsequently enter the bowel, where they may be excreted.
- However, bowel flora contain enzymes (especially glucuronidases) which can cleave off the conjugate, and the drug may be reabsorbed if it is sufficiently lipid-soluble. This is termed **enterohepatic recirculation**.
DRUG RESPONSE

DRUG CONCENTRATION

DISTRIBUTION

ELIMINATION

BILIARY EXCRETION

METABOLISM

GENETICS

ENVIRONMENTAL EXPOSURE

PHYSIOLOGICAL VARIATIONS

ABSORPTION

RENAL EXCRETION

DISEASE
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