Pharmacokinetic Principles

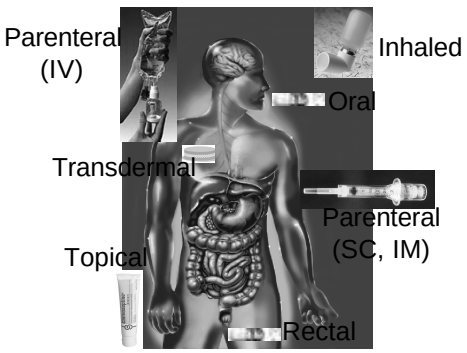
- How drugs get into the body ?
- What happens to them inside the body ?
- And how the body gets rid of them by :
  - Metabolism ?
  - And excretion ?

All these processes affect
1. Onset of drug action
2. Duration & intensity of drug effect

Drug Delivery Systems

- Tablets
- Injections (Syringe)
- Cigarettes
- Beverages
- Patches
- Suppositories
- Candy
- Gum
- Implants
- Gas
- Creams
- Others?
  - Stamps
  - Bandana

Routes of Drug Delivery



Drug Administration

Oral Administration

- Convenient; includes most drugs
- Little absorption until small intestine
  - Are most drugs weak acids or bases?
- Absorption from small intestine
  - Passive transfer dependent on
    - Ionization
    - Lipid solubility
  - Some carrier-mediated transport
    - Levodopa through carrier for phenylalanine
    - Fluorouracil through carrier for pyrimidines
    - Fe, Ca

Drug Administration

- Rates of absorption after oral administration depend on
  - Gi motility
    - Some disorders → gastric stasis
    - Some drugs affect motility (incr or decr)
    - Meals
  - Splanchnic blood flow
  - Drug particle size/formulation
    - Capsules/coated tablets
    - Timed release formulations
  - Physicochemical factors
    - Tetracycline binds Ca → milk prevents abs'n
    - Drug interactions

Drug Administration

- **Sublingual**
  - Important when
    - Rapid response required
    - Drug unstable at gastric pH
    - Drug rapidly metabolized by liver
  - Pass straight into systemic circulation
    - Don't enter liver portal system (so no first-pass effect)
- Ex: glyceryl trinitrate relieves angina

Drug Administration

- **Rectal**
  - Absorption unreliable
  - Often for local action
  - Useful in pts vomiting, unable to take by mouth (infants)
- **Cutaneous**
  - Local effect on skin required
  - Absorption occurs → systemic effects
  - Suitable for lipid-soluble molecules
  - Ex: estrogen patch

Drug Administration

- **Nasal sprays**
  - Absorption through mucosa overlaying lymphoid tissue
  - Important for drugs inactivated in GI
  - Ex: peptide hormone analogs, ADH, calcitonin
- **Inhalation**
  - Large surface area and high blood flow
  - No GI inactivation
  - BUT also route of elimination
  - Ex: volatile, gaseous anesthetics
  - Ex: locally acting drugs
  - Ex: inhaled human insulin being tested

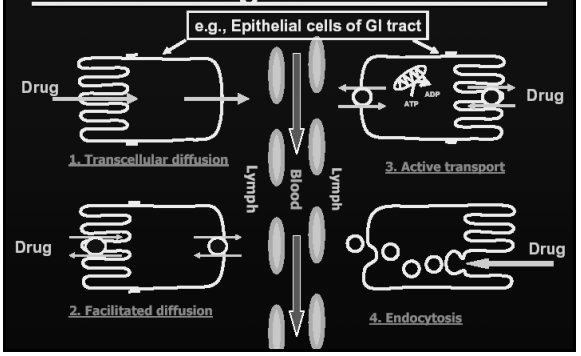
Drug Administration

- **Subcutaneous, intramuscular**
  - Faster than oral
  - Rate absorption depends on site admin, local blood flow
  - Reduction or prolonging systemic action possible by altering drug molecule or preparation or giving with another agent
- **Intravenous (IV)** fastest, most certain
  - Bolus → high concent R heart, lung, systemic circulation
  - Peak concent depends on rate injection
  - Common ex: antibiotics, anesthetics
  - Most uncomplicated to understand distribution, pharmacokinetics

Drug Absorption:

- **Drug absorption refers to the passage of drug from the site of administration into the general circulation** (except for drugs that are applied directly to the target tissue)
- **A drug that is injected intravenously is thus immediately and completely (100%) absorbed.**
- **A drug that is administered orally has several barriers to absorption, so absorption of orally administered drugs is usually delayed and incomplete.**

Main mechanisms of transport across biological membranes :



Passive Diffusion

- **Most important mechanism**
- **Applies to non-polar drugs**
  - **(ie, lipid soluble)**
- **Conc gradient is the driving force**
- **No energy required**

Facilitated Diffusion

- For a few drugs movement occurs faster than predicted
- Appears to depend on an oscillating carrier protein
- Depends on conc gradient
- No energy required
- Sugars & amino acids usual substrates
  - not so important for drugs
  - eg, tetracycline diffusion into bacteria

Active Transport

- Can proceed against a conc gradient
- Requires energy
- can become saturated
- Specific organs
  - Liver, kidney, bbb, gut epithelium

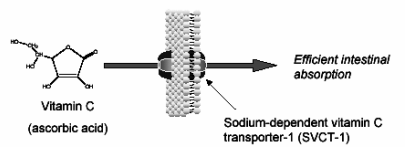
Allows cell to :

1. Accumulate compounds essential for growth (eg sugars,amino acids,vitamins & drugs such as methotrexate, glucuronides)
2. Remove waste products
3. Protects against toxins

Active Transport

Compared to passive diffusion:

- Not common for drugs
- Requires energy expenditure and specific transport proteins
- Saturable
- Effectively transports highly polar compounds
- Transport against a concentration gradient



Endocytosis

- Internalisation of large molecule by cell
- Mainly for drugs with MW > 1000
  - Eg, cytokines, hormones, growth factors, immunoglobulins
- 3 steps involved :
  - Substrate binds to receptor
  - Invagination of receptor-substrate complex
  - Budding off & delivery of vesicle into cell

Other Physiological Factors Affecting Oral Drug Absorption

1) Gastrointestinal Motility

- Decreased stomach emptying slows onset and/or rate of drug absorption
- Can be decreased by food, disease, drugs (opioids)

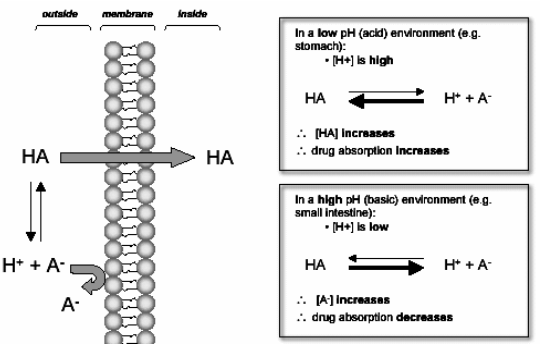
2) Metabolism and Efflux

- Many drugs are metabolized in the intestinal wall
- Many drugs are effluxed from enterocytes to gut lumen by transport proteins

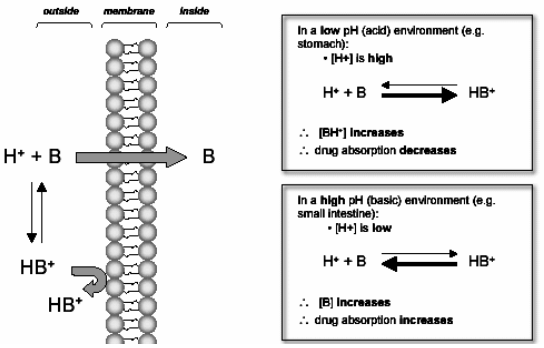
3) Changes in pH of Gastrointestinal Tract

- Affects ionization of drug
- Can be altered by food, disease, other drugs (e.g. antacids)

Effect of pH on Absorption of Acidic Drugs



Effect of pH on Absorption of Basic Drugs



Drug Absorption - Summary

- Most drug absorption occurs through passive absorption
- Lipid soluble drugs are more readily absorbed than non-lipid soluble drugs
- Non-polar drugs are more readily absorbed than polar drugs
- Non-ionized drugs are more readily absorbed than ionized drugs
- Basic drugs are more readily absorbed in the small intestine than acid drugs; acid drugs in the stomach
- Overall, the majority of drug absorption occurs in the small intestine, especially the duodenum

Drug Distribution

- Process by which a drug reversibly leaves the site of administration and is distributed throughout the tissues of the body
- Extent is dependent upon various factors
  - – Blood flow (lung, kidney, liver, brain, skeletal muscle, adipose, bone)
  - – Ability of drug to traverse biological membranes
  - – Degree of binding to blood proteins (e.g. serum albumin)
- Distribution of drug to target organ/site is a critical requirement for achieving a therapeutic benefit

Drug Distribution

- **The tissue that receives more blood receives more drug**
- **Rate of distribution to tissues depends on relative blood flow :**
  - **– Heart, lungs, brain, liver & kidney receive drug very rapidly**
  - **– Slower rate to less well perfused organs, such as muscle, skin & fat**

Volume of Distribution (Vd)

Volume of Distribution is the apparent volume of fluid into which an administered drug is dispersed

- Determined from measurement of blood (plasma) drug levels
- "Apparent" because assumes equal partitioning throughout body (i.e plasma concentration is equal to that of all other volumes)

$$Vd = \frac{Q}{Cp}$$

Vd = volume of distribution
Q = total amount of drug in body (dose)
Cp = plasma concentration

Factors Influencing Bioavailability

- **Decomposition in acidic gastric juices**
- **Decomposition by hydrolytic gut enzymes (eg, proteases, lipases)**
- **Degradation by gut microorganisms**
- **Food in the gut may alter absorption rate and amount (eg interact or form a complex)**
- **Metabolism by gut wall enzymes**
- **Metabolism by liver enzymes prior to reaching the systemic circulation**