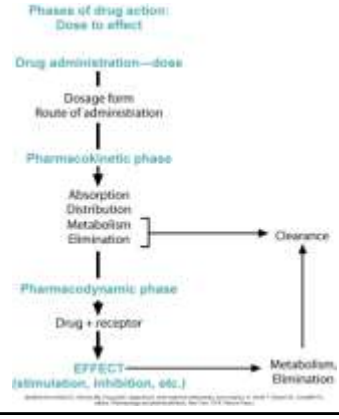
RSPT 2217
Principles of Drug Action
Part 2: The Pharmacokinetic Phase

Gardenhire
Chapter 2; p. 14-25

From the Text

- Common Pathways for Drug Metabolism
  - Box 2-3; page 18
- Plasma Half-lives of Common Drugs
  - Table 2-4; page20
- Factors Increasing the L/T Ratio
  - Box 2-4; page 24



Pharmacokinetic Phase

This phase describes the time course and disposition of a drug in the body, based on its absorption, distribution, metabolism and elimination.

Definitions

- Pharmacokinetics:
  -
- Pharmacodynamics
  -
    -
    -
    -

Absorption

Absorption

- For a drug to be absorbed and used by the body, it must first pass through various anatomical barriers
- For example, an oral dosed drug must first reach the epithelial lining of the stomach or intestine, traverse the lipid membrane barrier of the cells - only then can it be absorbed into the blood for distribution

Absorption

- Inhaled drugs have a similar path
  –
  –
  –
  –
  –
  –

Absorption

- Drugs traverse these barriers by various mechanisms
  –
  –
  –
  –
- In general, drugs must be sufficiently water-soluble to reach a cell membrane and sufficiently lipid-soluble to diffuse across the cell (lipid) barrier

Absorption

- Aqueous diffusion
  – occurs in
  – diffusion is by
  – small pore size
  – most drugs pass into capillaries

Absorption

- Lipid diffusion
  – to diffuse across a lipid layer, a drug must be able to dissolve in a lipid substance
  – another factor that affects lipid solubility
    - lipid insoluble
    - lipid soluble drugs
  – diffusion across cell membranes

Absorption

- Examples
  – thiopental, a barbiturate, is poorly ionized in the bloodstream and will diffuse across cell membranes into the the brain, producing sedation, sleep or anesthesia
  – tubocurarine, a paralyzing agent, is a fully ionized compound which will not reach the brain - a patient paralyzed with tubocurarine cannot move at all, but is fully awake

Absorption

- The degree of ionization of drugs that are weak acids or weak bases is dependent on
  - the drug's pKa
  - the ambient pH which varies
  - whether the drug is a weak acid or base
    - weak acids
    - weak bases

Absorption

- Examples
  - ipratropium bromide (Atrovent) has no capacity for reversible binding of H^+ ions and is permanently positively charged; therefore it is not lipid soluble and does not absorb well from the mouth or lungs - advantage: few, if any, systemic effects/side effects
  - atropine can give up H^+ and become nonionized increasing its absorption and distribution - disadvantage: increased occurrence of side effects

Absorption

- Examples
  - acetylsalicylic acid (aspirin) has a pKa of 3.0 and is 9% ionized at a pH of 2 and 91% ionized at a pH of 4 meaning is is well absorbed from the gastric lining, not so well absorbed from the intestinal tract

Absorption

- In summary
  - consider pKa a reference baseline
  - for a weak acid, there is less ionization in an acidic environment
  - for a weak base, there is more ionization in an acidic environment
- Key principle is: cell membranes are more permeable to the nonionized form of a drug than to the ionized form

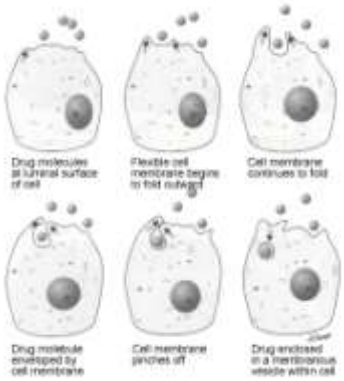
Absorption

- Carrier-mediated (facilitated) transport
  - carrier molecules
  - unlike aqueous diffusion and lipid diffusion
  - since it does not depend on a concentration gradient

Absorption

- Pinocytosis (endocytosis/exocytosis)
  - describes the incorporation of a substance into a cell
  - allows translocation across a membrane barrier

Pinocytosis



Absorption

- Factors affecting absorption
  - primary factor
    - IV offers fastest onset of action
    - oral offers slowest onset of action
    - aerosol is somewhere in between

Absorption

- generally, a trade-off exists
- bioavailability

Absorption

- absorption is also affected by
  -
  -
  -

Distribution

Distribution

- Drug distribution is the process by which a drug is transported to its sites of action, elimination and storage
  -
  -
- Plasma concentration is determined by distribution, absorption and elimination

Metabolism

Metabolism

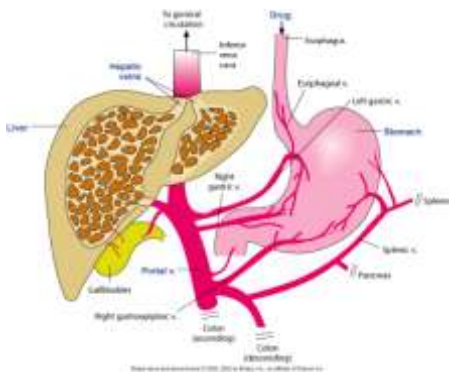
- Major site of drug metabolism is the liver
  - contains microsomal enzymes
  - metabolites

Metabolism

- Enzyme induction
  - chronic administration or abuse of drugs that are metabolized by enzymes can increase or decrease enzyme levels - this can affect drug dosages
    - example – rifampin
    - dosages of affected drugs

Metabolism

- First-pass effect
  - when a drug is given orally
  - if the drug is metabolized by liver enzymes



Metabolism

- solution is to increase the oral dose or administer via routes that circumvent this first-pass metabolism e.g.

injection	transdermal
buccal	rectal
sublingual	inhalational

- these routes allow the drug to be distributed throughout the body before being circulated through the liver

Elimination

Elimination

- Primary site of drug excretion is the kidney
  -
  -
- Function of both the liver and kidneys

Elimination

- Clearance
  - a measure of the body's ability to rid itself of a drug
  - usually expressed as total systemic clearance or plasma clearance
  - plasma clearance is arguably theoretical at best, but could be used to help define a maintenance dose

Elimination

- Maintenance dose
  - To achieve constant level
  - Many drugs start with a loading dose
  - Subsequent administration
  - Maintenance doses depend on several factors and must be carefully titrated

Elimination

- Plasma half-life ($T_{1/2}$)
  - $T_{1/2}$
  - may be more important in terms of understanding how quickly a drug can accumulate and reach a steady-state plasma level
  - drugs with a short $T_{1/2}$
  - drugs with a long $T_{1/2}$

Elimination

  - the whole concept of steady-state plasma levels is important because it helps to decrease the peaks and valleys of a drug's effect
  - one method often employed to decrease these peaks and valleys is to administer a sustained-release form of a drug

Elimination

Elimination

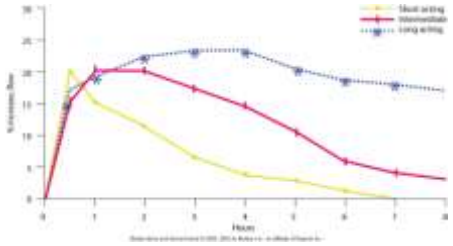
- with inhaled aerosol bronchodilators, the $T_{1/2}$ is measured by the effect on peak expiratory flow rates (PEF), or by the effect on the forced expiratory volume in the first second of expiration (FEV_1)
  - example – pre-bronchodilator PEF = 30 L/min and maximum post-bronchodilator PEF = 60 L/min, then the $T_{1/2}$ would be the time required for the PEF to drop to 45 L/min
  - since the total increase = 30 L/min, the $T_{1/2}$ represents the time it takes to lose one half of that increase, or 15 L/min

Elimination

- with inhaled aerosol drugs, it is also important to look at time-effect curves
- these curves show

- useful when determining how a drug will be used
  - is rapid onset required? ("rescue drug")
  - is a longer duration desirable? (maintenance drug)
  - is patient compliance a factor? (device, timing)
-

Time-effect curves



Pharmacokinetics of Inhaled Drugs

Pharmacokinetics of Inhaled Drugs

- Local versus systemic effect
  - inhaled aerosols are deposited on the surface of the airways and so are considered topical drugs
  - may be used for both local and systemic effects
    - local effect examples
    - systemic effect examples

Pharmacokinetics of Inhaled Drugs

- Inhaled aerosols in pulmonary disease
  - most inhaled aerosol drugs are intended for a local effect
    -
    -
    -
    -
  - inhalational route is used to maximize lung deposition and effect and minimize systemic absorption, effect and side effects

Pharmacokinetics of Inhaled Drugs

- Pharmacokinetics of Inhaled Drugs
  - a portion of all inhaled aerosols is swallowed due to impaction in the mouth and oropharynx
  -
  -

Pharmacokinetics of Inhaled Drugs

- Pharmacokinetics of Inhaled Drugs
  - oral portion
    -
    -
  - airway portion
    -
    -

Pharmacokinetics of Inhaled Drugs

- Lung availability/total systemic availability ratio (L/T)
  - The portion of a drug available from the lung out of the total systemically available drug
  - Quantifies the efficiency of aerosol drug delivery to the lung and is based on the distribution to the airway and GI tract
  - The therapeutic effect of a bronchoactive drug comes from the inhaled drug deposited in the lung
  - The systemic side effects are the result of the amount of drug absorbed into the system