RSPT 2317
Principles of Drug Action
Part 2: The Pharmacokinetic Phase

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:
  - describes what the body does to a drug
- Pharmacodynamics
  - describes what the drug does to the body

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
  - airway surface liquid
  - epithelial cells
  - basement membrane
  - interstitium
  - capillary vascular network
  - and eventually to the smooth muscle or glands of the airway where it is intended to work

Absorption

- Drugs traverse these barriers by various mechanisms
  - aqueous diffusion
  - lipid diffusion
  - carrier-mediated transport
  - pinocytosis
- 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 the aqueous compartments
  - diffusion is by
  - small pore size
  - most drugs pass into capillaries because of larger pores

Absorption

- Lipid diffusion
  - to diffuse across a lipid layer
  - another factor that affects lipid solubility is ionization
    - lipid insoluble drugs tend to be ionized or polar
    - 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:

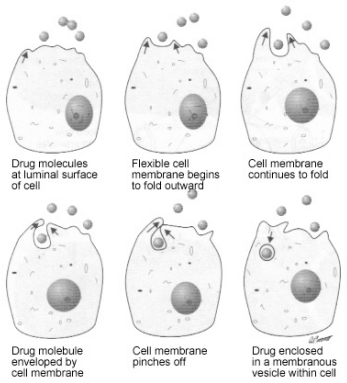
Absorption

- 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)

Pinocytosis



Absorption

- Factors affecting absorption
  - primary factor is route of administration which affects time to onset of action, peak effect and duration of action
    - IV
    - oral
    - aerosol

Absorption

- generally, a trade-off exists between onset of action and duration of action
- bioavailability is another factor affecting absorption -
  - example -

Absorption

- absorption is also affected by
  -
  -
  -

Distribution

Distribution

- Drug distribution
  - protein binding
- Plasma concentration is determined by
  - if delivery exceeds absorption and elimination
  - drug doses must be adjusted

Metabolism

Metabolism

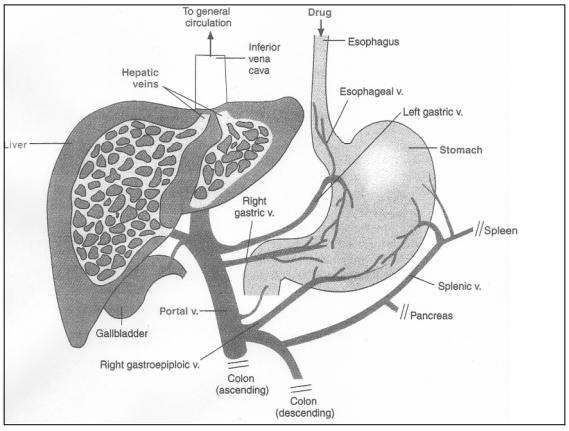
- Major site of drug metabolism is the liver
  - contains microsomal enzymes

Metabolism

- Enzyme induction
  - chronic administration or abuse of drugs
    - 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 must be known

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

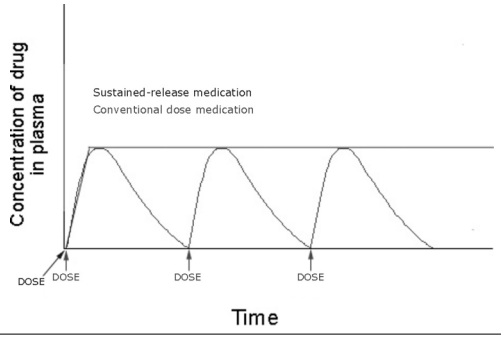
Elimination

- Plasma half-life ($T_{1/2}$)
  - $T_{1/2}$
  - may be more important in terms of understanding
  - 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
  - one method often employed to decrease these peaks and valleys

Elimination



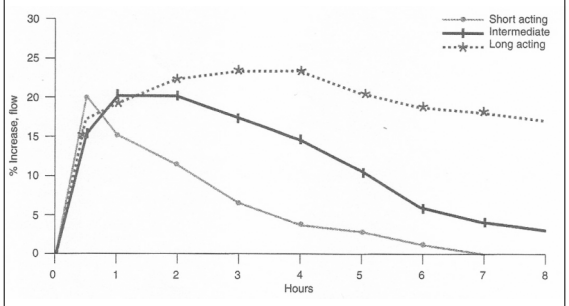
Elimination

- 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
- useful when determining how a drug will be used
  -
  -
  -
- therapeutic effect should be one of the primary factors

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
  - 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

Pharmacokinetics of Inhaled Drugs

- Pharmacokinetics of Inhaled Drugs
  - a portion of all inhaled aerosols
  - a 1981 study
  - the airway proportion can vary

Pharmacokinetics of Inhaled Drugs

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

Pharmacokinetics of Inhaled Drugs

- Lung availability/total systemic availability ratio (L/T)
  –