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

- 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 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 $pK_a$ of 3.0 and is 9% ionized at a pH of 2 and 91% ionized at a pH of 4 meaning it is well absorbed from the gastric lining, not so well absorbed from the intestinal tract.

Absorption

- **In summary**
  - consider $pK_a$ 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)

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 -

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

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

- 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

- 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

- **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 $T_{1/2}$

- the whole concept of steady-state plasma levels is important because
  - one method often employed to decrease these peaks and valleys
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
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)