

Course: Drug discovery

Introduction to Pharmacokinetics

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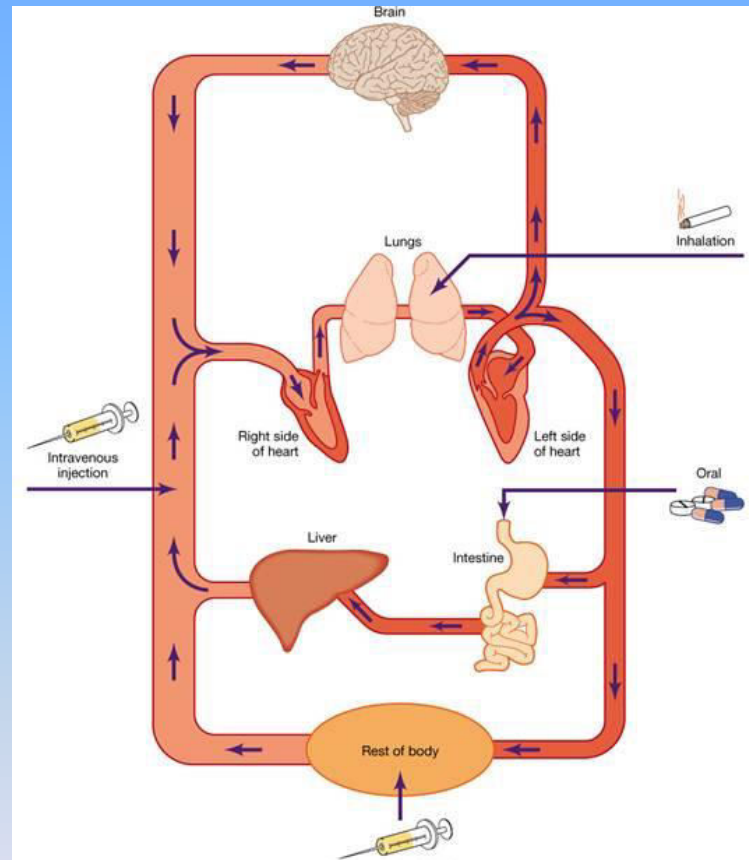
Pharmacokinetics

- Movement of drugs in the body
- Four Processes
 - Absorption
 - Distribution
 - Metabolism
 - Excretion
- Drug concentration at sites of action influenced by several factors, such as:
 - Route of administration
 - Dose
 - Characteristics of drug molecules (e.g., lipid solubility)

Drug Absorption

- Routes of Drug Administration

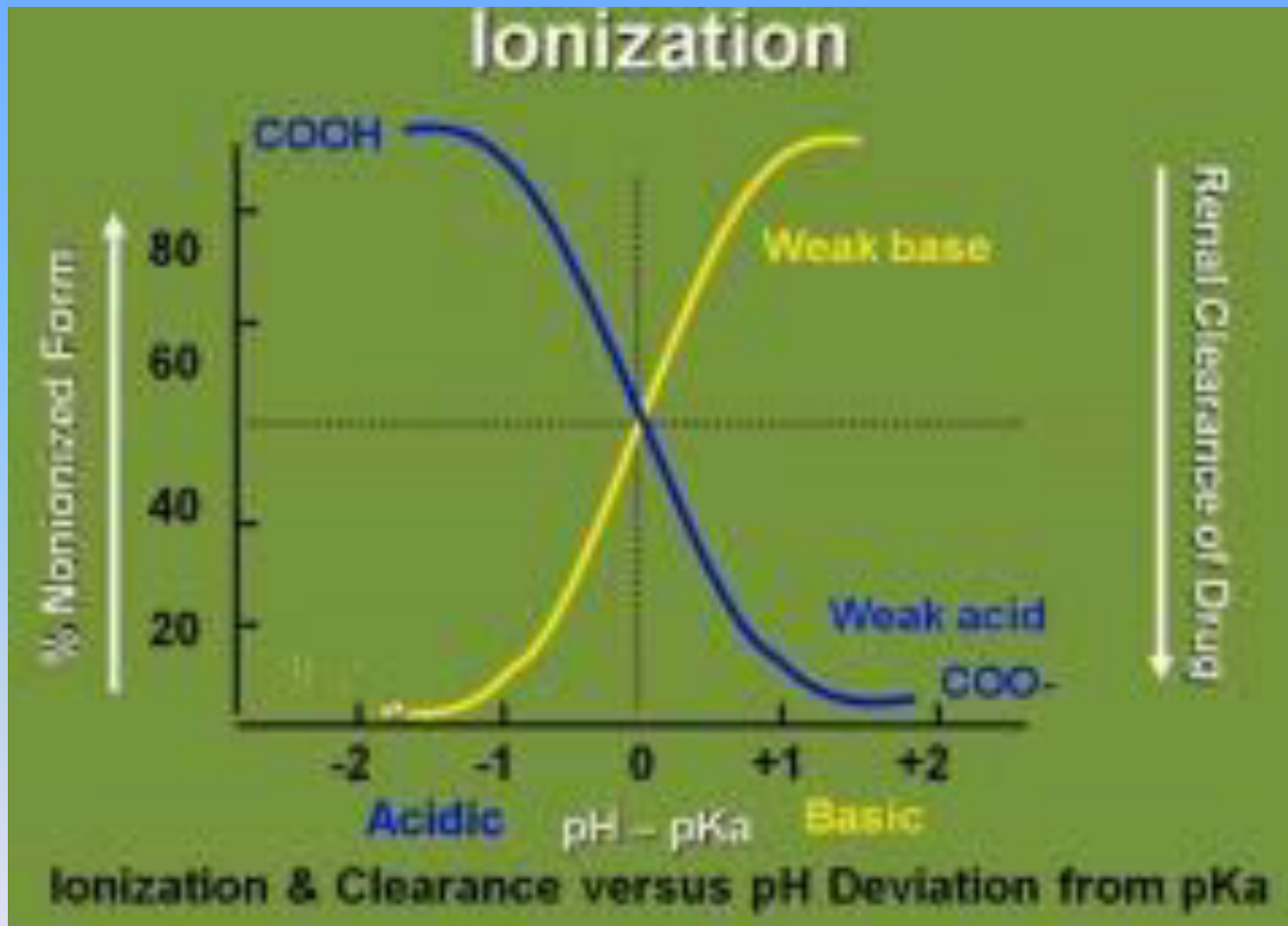
- Oral
 - Vapors, Gases, Smoke
- Inhalation
 - Vapors, Gases, Smoke
- Mucous membranes
 - Intranasal (sniffing)
 - Sublingual
 - Rectal suppositories
- Injection (parenteral)
 - Intravenous (IV)
 - Intramuscular (IM)
 - Subcutaneous (SC)
 - Intraperitoneal (IP; nonhumans only)
- Transdermal



Drug Absorption

- Lipid solubility
- $pK_a = pH$ at which 50% of drug molecules are ionized (charged)
 - Only uncharged molecules are lipid soluble.
 - The pK_a of a molecule influences its rate of absorption through tissues into the bloodstream.
 - pH varies among tissue sites
 - e.g., stomach: 3-4, intestines: 8-9

pKa and Lipid Solubility



Routes of Drug Administration

- Oral Drug Administration
 - Advantages:
 - relatively safe, economical, convenient, practical
 - Disadvantages:
 - Blood levels are difficult to predict due to multiple factors that limit absorption.
 - Some drugs are destroyed by stomach acids.
 - Some drugs irritate the GI system.

Routes of Drug Administration

- Advantages of Injection Routes
 - Absorption is more rapid than with oral administration.
 - Rate of absorption depends on blood flow to particular tissue site (I.P. > I.M. > S.C.).
- Advantages specific to I.V. injection
 - No absorption involved (inject directly into blood).
 - Rate of infusion can be controlled.
 - A more accurate prediction of dose is obtained.

Routes of Drug Administration

- Disadvantages/Risks of Injection
 - A rapid onset of action can be dangerous in overdosing occurs.
 - If administered too fast, heart and respiratory function could collapse.
 - Drugs insoluble in water or dissolved in oily liquids can not be given I.V.
 - Sterile techniques are necessary to avoid the risk of infection.

Drug Distribution

- Cell Membranes
- Capillaries
 - Drug affinities for plasma proteins
 - Bound molecules can't cross capillary walls
- Blood Brain Barrier
 - Tight junctions in capillaries
 - Less developed in infants
 - Weaker in certain areas, e.g. area postrema in brain stem
 - Cerebral trauma can decrease integrity
- Placenta
 - Not a barrier to lipid soluble substances.

Termination of Drug Action

- Biotransformation (metabolism)
 - Liver microsomal enzymes in hepatocytes transform drug molecules into less lipid soluble by-products.
 - Cytochrome P450 enzyme family

Termination of Drug Action

- Elimination
 - Two-stage kidney process (filter, absorption)
 - Metabolites that are poorly reabsorbed by kidney are excreted in urine.
 - Some drugs have active (lipid soluble) metabolites that are reabsorbed into circulation (e.g., pro-drugs)
 - Other routes of elimination: lungs, bile, skin

Termination of Drug Action

- Kidney Actions
 - excretes products of body metabolism
 - closely regulates body fluids and electrolytes
 - The human adult kidney filters approx. 1 liter of plasma per minute, 99.9% of fluid is reabsorbed.
 - Lipid soluble drugs are reabsorbed with the water.

Termination of Drug Action

- Factors Influencing Biotransformation
 - Genetic
 - Environmental (e.g., diet, nutrition)
 - Physiological differences (e.g., age, gender differences in microsomal enzyme systems)
- Drug Interactions
 - Some drugs increase or decrease enzyme activity
 - e.g., carbamazepine stimulates CYP-3A3/4
 - e.g., SSRIs inhibit CYP-1A2, CYP-2C

Drug Time Course

- Time Course Studies important for
 - predicting dosages/dosing intervals
 - maintaining therapeutic levels
 - determining time to elimination
- Elimination Half-Life
 - time required for drug blood levels to be reduced by 50%
 - Approx. 6 half-lives to eliminate drug from body
 - With repeated regular interval dosing, steady-state concentration reached in approx. 6 x half-life

Therapeutic Drug Monitoring

- TDM important for clinical decisions
- Plasma levels rough approximation of tissue/receptor concentrations
- TDM goals
 - assess medication compliance
 - avoid toxicity
 - enhance therapeutic response

Tolerance & Dependence

- Mechanisms of Tolerance
 - Metabolic (Pharmacokinetic, Dispositional)
 - Cellular-Adaptive (Pharmacodynamic)
 - Behavioral Conditioning
- Dependence
 - Abstinence Syndrome
 - Not all addictive drugs produce physical dependence.
 - Some nonaddictive therapeutic drugs (e.g. SSRIs) can produce physical dependence.

THANK YOU