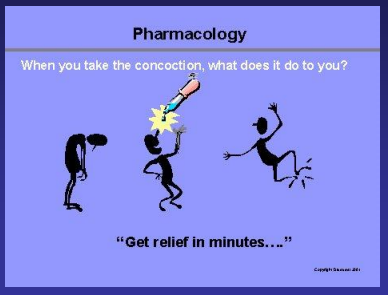
Introduction to Pharmacology



What is Pharmacology?

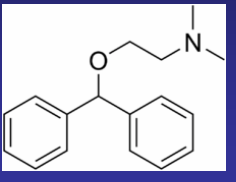
- Study of Drugs
  - Actions
  - Effects in a living system
- Medications
  - Legal
  - Illegal
  - Over-the-counter
- Safe Administration
  - Dose
  - Route of administration
  - Indications
  - Side effects
  - Adverse reactions
  - Drug interactions
  - Contraindications
  - Monitoring techniques
  - Interventions

Key Terms to Remember

- Drug- any substance used in diagnosis, cure, treatment or prevention of a disease or condition
- Chemical name- precise description of drug's chemical composition and molecular structure

Chemical Name

- Benadryl
  - 2-[di(phenyl)methoxy]-N,N-dimethylethanamine



Key Terms Continued...

- Generic name- official name listed in pharmacopeia given by manufacturer
  - **Diphenhydramine**
- Prescription (legend) drug- requires legal prescription
- Nonprescription (OTC) drug- may be purchased without a prescription

Key Terms Continued...

- Indication- basis for initiation of treatment
- Toxicology- science of poisons and toxicity
- Inert ingredients- components that provide bulk, prevent disintegration in bottle, prevent sticking, facilitate disintegration in GI tract

Key Terms Continued...

- Adverse Reaction- undesirable or unwanted consequence of a drug, procedure or regimen
  - rare and unforeseen bodily responses
  - always unintended and harmful even on a correct dosage
- Side Effects- results of drug or other therapy in addition to or in extension of the desired therapeutic effect
  - may be unwanted but natural and anticipated consequences of taking a particular medication

Key Terms Continued...

- Pharmacokinetics- concentration of drugs within biological systems, as affected by uptake, distribution, binding, elimination
- Pharmacodynamics- relating to drug action

Sources of Drugs

- Plants
  - digitalis, colchicine, Quinine
- Animals and humans
  - epinephrine, insulin (hormones)
- Minerals or mineral products
  - iron, iodine, epsom salt
- Synthetic or chemical substances
  - sodium bicarbonate, sulfonamides

Pharmaceutical Preparations

- Drug products suitable for administration of a specific dose of a drug to a patient by a particular route of administration.

Example: Tablets/ Capsules
- inert ingredients
- enteric coating
- sustained release/ extended release
- hard/ soft capsules

Drug Approval Process

Investigational New Drug (IND)

1) Filed after preclinical animal testing
2) Sponsor must submit:
   - toxicity data
   - pharmacokinetic/ pharmacologic profile of drug
   - therapeutic index
3) Forwarded to 1 of 9 divisions
4) 30 days for review

Phase 1 Trials

After approval of IND

1) Clinical pharmacology studies
2) Done in 20-80 patients
3) Last an average of 6 months- 1 year
4) Purpose: to determine safety

Phase 2 Trials

1) Controlled studies in disease specific pts
2) Involve 100-200 patients
3) Average 2 years duration
4) Purpose: determine efficacy

Phase 3 Trials

1) Multicenter, controlled and open trials
2) Involve 600-1000 patients
3) Average 3 years in duration
4) Pivotal studies- get drug approved by FDA
5) Purpose: establishes safety and efficacy

New Drug Application (NDA)

NDA includes:

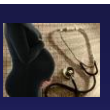
- preclinical data
- clinical data (phase I, II, III)
- manufacturing methods
- product quality assurance information
- relevant foreign market experience or testing
- all published reports of experience with drug
- proposed package insert

Phase IV
(Post-marketing Surveillance)

1) Conducted based on the approval indication
2) May evaluate:
   – new doses
   – effects of extended therapy
   – safety in populations not previously represented

Time to Approval

Average time from synthesis to approval = 100 months



Pregnancy Categories

- **Category A:** controlled studies fail to demonstrate risk to fetus in first trimester + no evidence of risk in later trimesters; FETAL HARM APPEARS REMOTE
- **Category B:** (1) animal reproductive studies not demonstrated a fetal risk but no studies in women or (2) animal reproductive studies have shown adverse effect not confirmed in controlled studies on women in 1st trimester.

Pregnancy Categories

- **Category C:** (1) studies in animals revealed AE on fetus and no controlled studies in women, or (2) studies in women and animals not available. GIVE ONLY IF POTENTIAL BENEFIT JUSTIFIES RISK TO FETUS.
- **Category D:** (+) evidence of human fetal risk, but the benefits may be acceptable despite risk. An appropriate statement must appear in the "warnings" section of the label of these drugs.

Pregnancy Categories

- **Category X:** studies in animals or humans have demonstrated fetal abnormalities, evidence of fetal risk based on human experience or both; Risk of using the drug in pregnant women clearly outweighs any benefit. CONTRAINDICATED in women who are or may become pregnant. Statement MUST appear in the "contraindications" section of labeling of drugs in this category.

Controlled Substances Act (CSA)

- Also known as Comprehensive Drug Abuse Prevention and Control Act of 1970
- Places all federally regulated substances into one of five schedules
- Enforced by Drug Enforcement Agency (DEA)
- Most follow most stringent law- either federal or state

Schedule of Controlled Substances

- *Schedule I*- high abuse potential, no accepted medical use
- *Schedule II*- high abuse potential, accepted medical uses, may lead to severe dependence
- *Schedule III*- less abuse potential than schedule I or II, may lead to moderate or low physical dependence
- *Schedule IV*- lower abuse potential than schedule III, may lead to limited dependence

*Federal law prohibits transfer of these drugs other than to the prescribed patient

Accounting for Controlled Substances

- Responsible for accounting for inventory
- Records indicate:
  - balance on hand
  - supplies added to stock
  - doses administered to patients
  - each dose accounted for even if wasted
  - storage in locked cabinets

Narrow Therapeutic Index Drugs

Less than 2-fold difference in minimum toxic concentration and minimum effective concentration in the blood

Or

Those drug formulations that exhibit limited or erratic absorption, formulation dependent bioavailability and wide intrapatient pharmacokinetics requiring monitoring

Narrow Therapeutic Index Drugs

- Carbamazapine
- Digoxin
- Levothyroxine sodium
- Lithium
- Phenytoin
- Theophylline
- Warfarin

Refill using only same drug product and manufacturer

Close lab monitoring necessary

Toxicity more common than with other medications

Generic Drug Nomenclature
Rules of Thumb

Drugs ending in “pine”	=	CCBs
Drugs ending in “pril”	=	ACEI
Drugs ending in “lol”	=	Beta Blockers
Drugs ending in “artan”	=	A_2RBs
Drugs ending in “statin”	=	HMG CoA Reductase Inhibitors

Generic Drug Nomenclature
Rules of Thumb

Drugs ending in “apam”	=	Benzodiazapines
Drugs ending in “vir”	=	Antivirals
Drugs ending in “acin”	=	Fluoroquinolones
Drugs ending in “cycline”	=	Tetracyclines
Drugs ending in “azole”	=	Proton pump inhibitors

Pharmacokinetic Phases
“ADME”

1) Absorption into body
2) Distribution to sites of action or storage
3) Metabolism to breakdown or form active metabolites
4) Excretion by various routes

A
D
M
E

Absorption

- *Passive diffusion*- proportional to drug concentration gradient across the barrier and surface area available
  - Lipid diffusion- drug dissolves in the lipid components of the cell membranes.
  - Aqueous diffusion- passage through the aqueous pores in cell membranes.
- *Facilitated diffusion*- active transport

Absorption Influences

1) Nature of absorbing surface
2) Blood flow to site of administration
3) Solubility of drug
4) pH
5) Drug concentration and form
6) Enzymatic activity
7) First-pass metabolism

Absorption of Preparations

Liquids, elixirs, syrups — fastest
Suspension solutions
Powders
Capsules
Tablets
Coated tablets
Enteric-coated tablets — slowest

Routes of Administration

- Enteral Route
- Parenteral Route
- Inhalational Route
- Transdermal Route
- Topical Route




Distribution

- Once inside the circulatory system, drugs are distributed to body tissues
- Most drugs pass early into target cells and have a rapid onset
- Protein bound drugs have a slower onset
- Blood brain barrier protects the brain from some compounds
- Placental barrier protects the fetus from some compounds

Distribution Variables

- Organ blood flow
- Protein binding
- Tissue binding
- Molecular size
- Lipid solubility

Key Terms Continued...

- Volume of Distribution- volume of fluid in which a drug would need to be dissolved in order to have the same concentration in that volume as it does in plasma
- Receptor- reactive cellular site with which drug interacts to produce a pharmacologic response
- Half-life ($t_{1/2}$)- time required to reduce the amount by 1/2 of unchanged drug in the body

Biotransformation / Metabolism

- Conversion of one chemical species to another
- Inactive water-soluble metabolites
- Active metabolites
- Sites of biotransformation
  - *Liver*
  - Kidney
  - Lung

Role of Drug Biotransformation

- Primary Purpose: inactivate and detoxify
  - More water soluble than parent compound
    - more readily excreted
  - Some metabolites active, others metabolites inactive
- Prodrugs: agents administered as inactive and biotransformed to active metabolites.

Phases of Biotransformation

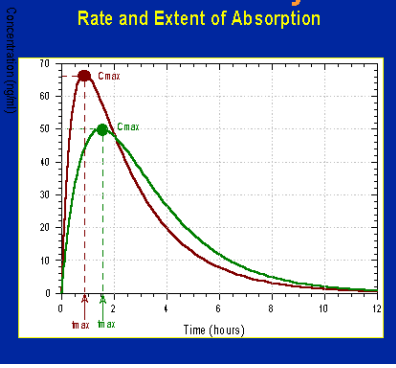
- PHASE I
  - oxidative reactions
    - most common, Cyt P450 system
  - hydrolytic reactions
  - reductive reactions
- PHASE II
  - conjugation reactions
    - acetylation, glucuronide formation, sulfation

Key Terms Continued...

- Bioavailability- percentage of active drug substances absorbed and available to reach target after administration
- Bioequivalence- drug containing biologically equivalent concentrations in blood and tissue at similar times

Bioavailability

Rate and Extent of Absorption



Biotransformation Variables

- Nutrition state
- Present hepatic function
- Cardiac or renal impairment
- Concomitant medications

Excretion

Excreted unchanged or converted to metabolites

- *Renal excretion*
- Biliary and fecal excretion
- Pulmonary excretion
- Breast milk excretion
- Quantitatively unimportant excretion
  - Sweat, saliva, tears
  - Hair and skin

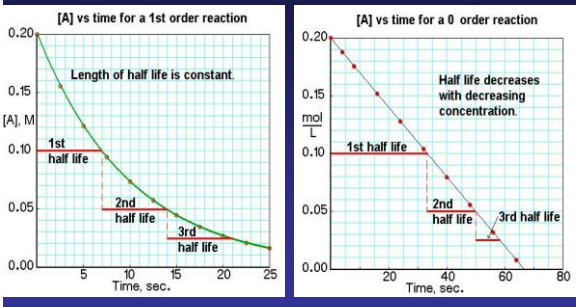
Renal Drug Excretion

- Glomerular Filtration
  - free drug enters renal tubule as dissolved solute
- Active Tubular Secretion
  - free drug actively transported across renal tubule (weak acids/bases)
- Passive Tubular Secretion
  - dependent on lipid solubility/ ionized more rapidly excreted than nonionized

Renal clearance = renal excretion rate / plasma drug concentration

Pharmacokinetic Calculations

- First-order kinetics:
  - most drugs exhibit first-order kinetics
  - elimination rate declines as the plasma concentration declines (proportional)
- Zero-order kinetics:
  - rate of drug elimination is constant



Pharmacodynamic Key Terms

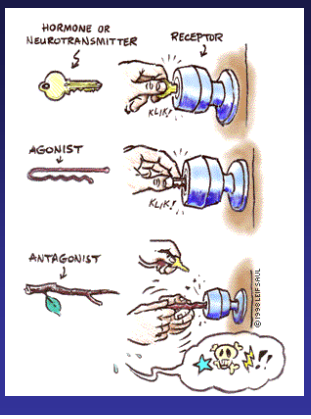
- Onset of Action: interval between time of administration to effect
- Duration of Action: interval between onset to end of measurable response
- Potency: dose required to produce a defined magnitude of drug effect

Key Terms Continued...

- Toxic level- concentration producing serious adverse effects
- Minimal effective concentration- lowest concentration producing desired effect
- Therapeutic range- range of concentration producing desired effect without toxicity

Pharmacodynamics: Signal Transduction

- Drug-Receptor Complex
- Receptor States
- Receptor Families
  - Ligand-gated ion channels
  - G-protein coupled receptors
  - Enzyme-linked receptors
  - Intracellular receptors



Types of agonist

- Full agonists: ability to produce maximal response obtainable in a tissue
  - direct - directly bind and activate
  - indirect - increase levels without binding
- Partial agonists: ability to produce only submaximal response

Types of antagonists

- Competitive antagonists: binds REVERSIBLY to a receptor
- Noncompetitive antagonists: binds to the receptor in a way that reduces the ability of the agonist to elicit a response

Factors Altering Drug Response

- Age
- Body Mass
- Gender
- Environment
- Time of Administration
- Genetic Factors
- Pathologic State
- Psychologic Factors

Review of Common Abbreviations

OU=	Each eye
po=	by mouth
tsp=	teaspoon
OD=	right eye
gtt=	drop
ac=	before meals
bid=	twice daily
tid=	three times daily
kg=	kilogram
hs=	bedtime
q4h=	every 4 hours

Review of Drug Abbreviations

NSAID=	Nonsteroidal antinflammatory drug
PCN=	Penicillin
HCTZ=	Hydrochlorothiazide
Fe=	Iron
D5W=	5% dextrose in water
APAP=	Acetaminophen
ASA=	Aspirin
NTG=	Nitroglycerin
KCl=	Potassium chloride


Questions?