

GENERAL PRINCIPLES (11)

Subcommittee:

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Eleven contact hours are recommended at the beginning of the course to provide the foundation for reinforcement and application of these principles throughout the course.

1. Introduction, Roots, and Definition of Terms

a. Definition of Pharmacology

The discipline that is concerned with understanding the interactions of chemical substances with living systems, and the application of this understanding to the practice of medicine.

b. Relation to Other Disciplines

- i. Basis in Chemistry, Physiology, Biochemistry, Immunology and Molecular Biology
- ii. A foundation of medical practice, including historic perspective relationship to Toxicology, Pharmacy and Therapeutics

c. Key Terms and Concepts

- i. Drug - a substance that acts, often by interaction with regulatory molecules, to stimulate or inhibit normal physiologic processes.
- ii. Drug Receptors - molecules with which a drug first interacts to eventually affect biological function. There is often a strict structural requirement for this interaction. Drug targets include receptors for endogenous substances (neurotransmitters, hormones, etc.), enzymes, transport proteins, ion channels, etc. Some pharmacologists prefer the term "drug targets," and reserve the term "receptor" to describe the macromolecules that serve as the initiators of signal transduction for endogenous substances.
- iii. Agonist (full, partial, inverse), antagonist (competitive and non-competitive)
- iv. Drug-receptor interactions – affinity, intrinsic activity
- v. Selectivity of drug action - all drugs have multiple effects, both desirable (beneficial) and undesirable (adverse effects, or "side effects"). Selectivity is partly intrinsic to the nature

of the drug-receptor interaction. The astute physician can maximize selectivity by attention to pharmacologic principles.

- vi. Pharmacodynamics - the study of drug effects on the body. The dose-response relationship(s) and drug-receptor interactions for each drug are of particular importance.
- vii. Pharmacokinetics - the study of the effects of the body on the drug, including its absorption, distribution and elimination by the organism. The understanding of plasma drug concentration as a function of time is of particular importance.
- viii. Time-action relationships - function of dosing schedule and a combination of a drug's pharmacokinetic and pharmacodynamic properties
- ix. Dose-response relationships – graded and quantal
- x. Efficacy, potency
- xi. Long-term effects of drugs (including tolerance, regulation of gene expression)

d. Course Goals

- i. Describe the principles governing drug actions in humans
- ii. Describe the specific knowledge related to the different classes of drugs, and important distinctions among members of each class, in relation to the organ systems they affect, and the diseases for which they are used therapeutically.
- iii. Develop a basis for continued education in medicine
- iv. Establish a foundation on which to build a rational approach to the use of drugs in clinical practice
- v. Develop a foundation to effectively use the medical literature to evaluate new drugs in the context of evidence-based medical practice

2. Pharmacokinetics

a. Chemical Aspects

- i. Weak acids and bases; the Henderson-Hasselbalch equation; relationship between pH and ionization of drugs
- ii. Lipid solubility of drug species; polar and nonpolar drugs
- iii. Properties of biological membranes, mechanisms of drug movement across membranes. Passive and active processes
- iv. Ion trapping of drugs. Specific examples of stomach contents and urine as ion-trapping compartments
- v. Chirality - drugs that exist as mixtures of two or more stereoisomers

b. Absorption

- i. Concept of therapeutic window
- ii. Relationship of lipid solubility, blood flow, and site of drug placement
- iii. Effect of pH; absorption of weak acids and bases from stomach vs. intestine; influence of age; first pass metabolism, factors impairing absorption
- iv. Absorption from oral, IM, SC and other routes
- v. Manipulation of absorption: dosage form, depot preparations, delayed release preparations, transdermal patch
- vi. Special sites of absorption: buccal, pulmonary, rectal, transcutaneous sites
- vii. Systemic absorption of drugs applied for local effects: intraocular, intranasal, dermatologic preparations
- viii. Concept of bioavailability as a function of absorption and first pass metabolism
- ix. Developmental, age-related and disease-related changes in drug absorption

c. Distribution

- i. Plasma protein binding, its effects on distribution
- ii. The lymphatic system and drug distribution
- iii. Factors affecting distribution: tissue perfusion, ease of access, tissue binding and solubility coefficients, pK_a , partition coefficient
- iv. Distribution ("redistribution") as a mode of termination of drug action.
- v. Distribution of drugs into special compartments. Nature of the capillary endothelium at the liver sinusoid, the skeletal muscle and brain. The blood-brain barrier and tight endothelial junctions. Drug penetration across the placenta. Importance of membrane transporters for both entry and efflux.
- vi. Concept of apparent volumes of distribution; relationship to physiological volumes. One and two-compartment drug distribution models.
- vii. Developmental, age-related and disease related changes in drug distribution.

d. Metabolism

- i. Importance of drug metabolism for excretion (conversion of non-polar xenobiotics to polar metabolites which can be excreted in the urine).
- ii. Biotransformation: activation vs. inactivation (detoxification) of drugs: prodrugs, toxic metabolites
- iii. Major pathways of metabolism: Phase I vs. Phase II, general properties
 - (1) oxidation, reduction, hydrolysis

- (2) conjugation: glucuronides, glycine, sulfate esters, acetylation, glutathione, mercapturic acids
- iv. The cytochrome P450 system. Liver, other tissues. Major P450s involved in drug metabolism: CYP1A2, CYP2B6, CYP2Cs, CYP2D6, CYP2E1, CYP3A4 and CYP3A5
- v. Enzyme induction: mechanisms, time course, clinical implications, and examples of common inducers (e.g. anticonvulsants, alcohol, rifampin, polycyclic hydrocarbons, environmental factors)
- vi. Enzyme inhibition: clinical implications ((e.g. erythromycin, antifungals, CYP2D6 interactions)
- vii. Developmental, age-related and disease-related changes in drug metabolism. (For isoforms see section on Pharmacogenetics)

e. Excretion

- i. Definition of excretion as the loss of drug molecules from the body; excretion of parent drug vs. excretion of metabolites.
- ii. Major sites of drug excretion: renal, biliary/alimentary, pulmonary (a major route for inhalation agents only). Minor sites of drug excretion: sweat, milk
- iii. Renal excretion: role of filtration, secretion and reabsorption--importance of plasma protein binding, molecular size, polarity, weak acids/bases, urine pH and transporters
- iv. Biliary/alimentary excretion: biliary transport, direct secretion of drugs from blood to intestine, importance of plasma protein binding, molecular size, polarity, weak acids and weak bases. Consequences of enterohepatic circulation.
- v. Developmental, age-related, and disease-related changes in drug and metabolite excretion
- vi. Differentiate excretion from pharmacologic concept of elimination (the sum of metabolism and excretion)
- vii. Clearance as the pharmacologic parameter that characterizes the efficiency of elimination process
 - (1) general definition of clearance: $Cl = \text{rate of elimination}/[C]$
 - (2) additivity of organ clearances, e.g $Cl_{\text{tot}} = Cl_{\text{hepatic}} + Cl_{\text{renal}} + Cl_{\text{other}}$
 - (3) organ clearance--extraction ratio and blood flow $Cl = E \times Q$, high and low extraction ratios and effects of changes in blood flow and plasma protein binding

f. Quantitative Pharmacokinetics

- i. First order, dose-independent kinetics
 - (1) single i.v. bolus dose, one and two compartment systems; noncompartmental model and its clinical utility

- (a) Definition of first order process, explanation of why metabolism and renal elimination are often first order, distribution and elimination phases of log C vs. time plot
 - (b) Pharmacokinetic parameters that determine the plot and can be estimated from it, and their interrelationships: Vd_1 , Vd_{extrap} , Vd_{area} , AUC, k_e , elimination $t_{1/2}$, CI
- (2) Single oral (or other non i.v. dose), one compartment
- (a) effect of k_a , k_e , and dose on C_{max} , t_{max} , and AUC
 - (b) estimation of bioavailability by ratio of AUCs
- (3) constant i.v. infusion, one compartment
- (a) definition of steady state, the plateau principle, $C_{ss} = IR/CI$
 - (b) time to steady state as a function of half-life and effects of stopping infusion or changing infusion rate
 - (c) calculation of loading dose
- (4) repeated dosing one compartment
- (a) drug accumulation and plateau principle: $C_{ss_{av}} = DxF/T \times CI$, independent of k_a
 - (b) peak to trough variation as a function of dose, F, $t_{1/2}$, dosing interval (T), and $k_a:k_e$ ratio
- ii. Deviations from first order (dose-independent) kinetics
- (1) Zero order, dose-dependent and "Michaelis-Menten" elimination kinetics, definition and implications, e.g. phenytoin dosing
 - (2) Saturation of plasma protein binding, implications e.g. salicylate overdose
 - (3) Dose-dependent absorption and bioavailability; intestinal transporters

3. Pharmacodynamics

a. Receptor Theory

- i. Introduction
 - (1) Historical development
 - (2) Definition of a receptor (signal transduction)
 - (3) Occupancy theory: $E_A/E_M = [A]/([A] + K_A)$
- ii. The log concentration-response relationship

iii. Agonists

- (1) Interpretation of log concentration-response curves
- (2) Potency (ED_{50} and EC_{50}) vs affinity (K_A)
- (3) Intrinsic activity vs efficacy
 - (a) Partial agonists
 - (b) Inverse agonists

iv. Antagonists

- (1) Competitive, reversible, surmountable
- (2) Non-competitive, irreversible, unsurmountable

v. Receptor reserve: EC_{50} not necessarily equal to K_A

b. **Quantal Response Relationships**

- i. ED_{50} (potency) vs LD_{50} or TD_{50}
- ii. Therapeutic indices

c. **Structure-activity relationship (SAR) as a mechanism for modeling receptors, active sites and developing modified drugs.**

d. **Types and subtypes of receptors; therapeutic action vs side effects; receptor superfamilies and mechanisms**

- i. Ligand-gated ion channels
 - (1) Nicotinic ACh receptor
 - (2) GABA-A receptor
- ii. G Protein-coupled receptors
 - (1) Muscarinic ACh receptors
 - (2) Three major types of adrenergic receptors (alpha-1, alpha-2, beta)
 - (3) Guanine nucleotide regulatory binding proteins
- iii. Tyrosine kinase receptors
 - (1) Insulin
 - (2) PDGF
- iv. Transcription factor receptors

(1) Receptors for steroid hormones

e. **Receptor Regulation**

- i. Down-regulation and desensitization: inverse relationship between agonist concentration and receptor levels
- ii. Up-regulation and sensitization

f. **Non-receptor targets as sites of drug action**

- i. Enzymes - acetylcholinesterase
- ii. Nucleic acids as site of action of drugs - actinomycin D
- iii. Target uniqueness as a basis for selective chemotherapy - penicillin

4. **Pharmacogenetics/genomics**

- a. Definition of pharmacogenetics and pharmacogenomics, and their clinical importance.
- b. Genetic polymorphisms include single nucleotide polymorphisms (SNPs), gene deletions, and gene amplifications that determine protein structure, configuration, and/or concentration.
- c. Differentiate haplotype, genotype and phenotype. Discuss methods to determine phenotype and genotype.
- d. Pharmacogenetic polymorphisms affect drug response as well as drug disposition and toxicity. (e.g., NAT2, CYP2D6, beta adrenergic receptors).
- e. Monogenic pharmacogenetic traits often discriminate populations into discrete phenotypes (polymorphic distribution). Polygenic pharmacogenetic traits usually provide monomorphic distributions.
- f. Frequency of pharmacogenetic polymorphisms often differs with ethnicity
- g. Illustrate clinical relevance with selected examples, e.g.: NAT2 (isoniazid, procainamide); CYP2D6 (antidepressants, beta-blockers); CYP2C19 (omeprazole); CYP2C9 (warfarin); serum cholinesterase (succinylcholine), glucose-6-phosphate dehydrogenase (analgesics; antimalarials); thiopurine-S-methyltransferase (6-mercaptopurine); beta-2 adrenergic receptors, (albuterol); dopamine receptors (antipsychotics); malignant hyperthermia (inhalation anesthetics); UGT1A1 (irinotecan), ABCB1 (corticosteroids)

5. **Principles of Drug Interactions**

- a. Prevalence of multi-drug therapy; importance of complete drug history including herbal and other complementary medicine and recreational drugs
- b. Types of interactions by mechanism: pharmacologic, pharmacokinetic, pharmacodynamic; with illustrative examples
- c. Types of interactions by outcome: additivity, synergy, potentiation, antagonism; with illustrative examples

- d. Not all drug interactions are bad: beneficial, planned interactions vs. unintended adverse interactions
- e. Awareness of drug-food interactions, and drug interference with diagnostic tests

6. **Development, Evaluation and Control of Drugs**

- a. Preclinical Development.
- b. Clinical Trials. Placebo effects. Institutional Review Boards. Investigator conflict of interest. FDA requirements for efficacy and safety. Ethics.
- c. Regulatory System. Legal mandates of the FDA and DEA. Classification (scheduling) of drugs with addiction potential. Influence of drug scheduling on medical practice.
- d. Post-Marketing Surveillance of Drugs.
- e. Drug Information for Practitioners. Textbooks, journals, FDA alerts, poison control centers, and electronic databases.
- f. Pharmaceutical Industry: Duration of drug patents; branded versus generic drugs.
- g. Influence of marketing (from sales representatives to television advertising) on medical practice.