

GENERAL PRINCIPLES (11)

Subcommittee:

<u>NAME</u>	<u>SCHOOL</u>
David W. Hein (Chair)	University of Louisville d.hein@Louisville.edu
David B. Bylund	University of Nebraska
William J. Cooke	Eastern Virginia Medical School
Joseph Goldfarb	Mount Sinai School of Medicine
Denis M. Grant	University of Toronto
James R. Halpert	University of Texas Medical Branch, Galveston
Louis S. Harris	Virginia Commonwealth University
John D. Hildebrandt	Medical University of South Carolina
Billy R. Martin	Virginia Commonwealth University
Walter Prozialeck	Midwestern University
Gary O. Rankin	Marshall University
Howard C. Rosenberg	Medical College of Ohio
Daniel Sitar	University of Manitoba
Robert J. Theobald	Kirksville College of Osteopathic Medicine

Twelve 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

Basis in Chemistry, Physiology, Biochemistry, and Molecular Biology

A foundation of medical practice, including historic perspective
Relationship to Toxicology, Pharmacy, Therapeutics

c. Key Terms and Concepts

- 1) Drug - a substance that acts, often by interaction with regulatory molecules, to stimulate or inhibit normal physiologic processes.
- 2) 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 receptors for endogenous substances.
- 3) Agonist (full, partial, inverse), antagonist (competitive and non-competitive)-
- 4) Drug-receptor interactions – affinity, intrinsic activity
- 5) 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.
- 6) 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.
- 7) Pharmacokinetics - the study of the effects of the body on the drug, and its travels through the organism. The understanding of plasma drug concentration as a function of time is of particular importance.
- 8) Time-action relationships - function of dosing schedule and a combination of a drug's pharmacokinetic and pharmacodynamic properties
- 9) Dose-response relationships – graded and quantal
- 10) Efficacy, potency
- 11) Long-term effects of drugs (including tolerance, regulation of gene expression)

d. Course Goals

- 1) Describe the principles governing drug actions in humans
- 2) 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.
- 3) Develop a basis for continued education in medicine
- 4) Establish a foundation on which to build a rational approach to the use of drugs in clinical practice

- 5) Develop a foundation to effectively use the medical literature to evaluate new drugs in the context of evidence-based medical practice

2. Qualitative and Quantitative Pharmacokinetics

a. Chemical Aspects

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

b. Absorption

- 1) Concept of therapeutic window
- 2) Relationship of lipid solubility, blood flow, and site of drug placement
- 3) Effect of pH- absorption of weak acids and bases from stomach vs. intestine - influence of age
- 4) Absorption from oral, IM, SC, and other routes
- 5) Manipulation of absorption - dosage form, depot preparations, delayed release preparations, transdermal patch
- 6) Special sites of absorption; buccal, pulmonary, rectal, transcutaneous sites
- 7) Systemic absorption of drugs applied for local effects: intraocular, intranasal, dermatologic preps
- 8) Concept of bioavailability as a function of absorption and first pass metabolism
- 9) Developmental, age-related, and disease-related changes in drug absorption

c. Distribution

- 1) Plasma protein binding, its effects on distribution
- 2) The lymphatic system and drug distribution
- 3) Factors affecting distribution: Tissue perfusion, ease of access, tissue binding and solubility coefficients

- 4) Distribution ("redistribution") as a mode of termination of drug action.
- 5) Distribution of drugs into special compartments. Nature of the capillary endothelium at the liver sinusoid, the skeletal muscle and brain. Why lipid solubility of a drug is important in the brain but not at the extracellular receptor of the neuromuscular junction. The blood-brain barrier and tight endothelial junctions. Drug penetration across the placenta.
- 6) Concept of apparent volumes of distribution; relationship to physiological volumes. One and two-compartment drug distribution models.
- 7) Developmental, age-related, and disease related changes in drug distribution.

d. Metabolism

- 1) Importance of drug metabolism for excretion (conversion of non-polar xenobiotics to polar metabolites which can be excreted in the urine).
- 2) Biotransformation: activation vs. inactivation (detoxification) of drugs: prodrugs, toxic metabolites
- 3) Major pathways of metabolism:
Phase I vs. Phase II, general properties
 - a) oxidation, reduction, hydrolysis
 - b) conjugation -glucuronides, glycine, sulfate esters, acetylation, glutathione, mercapturic acids
- 4) The cytochrome P450 system. Liver, other tissues. Major P450s involved in drug metabolism: CYP1A2, CYP2B6, CYP2Cs, CYP2D6, CYP2E1, CYP3A4. (For isoforms see section on Pharmacogenetics)
- 5) Enzyme induction: mechanisms, time course, clinical implications, and examples of common inducers (e.g. phenobarbital, rifampin, polycyclic hydrocarbons, environmental factors)
- 6) Enzyme inhibition: clinical implications
- 7) Developmental, age-related, and disease-related changes in drug metabolism

e. Excretion

- 1) Definition of excretion as the loss of drug molecules from the body; excretion of parent drug vs. excretion of metabolites.
- 2) Major sites of drug excretion: renal, biliary/alimentary, pulmonary (a major route for inhalation agents only). Minor sites of drug excretion: sweat, milk

- 3) Renal excretion: role of filtration, secretion and reabsorption-
-importance of plasma protein binding, molecular size, polarity, weak acids and weak bases, urine pH
- 4) 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.
- 5) Developmental, age-related, and disease-related changes in drug and metabolite excretion
- 6) Differentiate excretion from pharmacologic concept of elimination (the sum of metabolism and excretion)
- 7) Clearance as the pharmacologic parameter that characterizes the efficiency of elimination process
 - a) general definition of clearance: $Cl = \text{rate of elimination}/[C]$
 - b) additivity of organ clearances, e.g $Cl_{tot} = Cl_{hepatic} + Cl_{renal} + Cl_{other}$
 - c) 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

- 1) First order, dose-independent kinetics
 - a) single IV bolus dose, one and two compartment systems
 - i. 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
 - ii. 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 $t_{1/2}$, Cl
 - b) single oral (or other non IV dose), one compartment
 - i. effect of k_a , k_e , and dose on C_{max} , t_{max} , and AUC
 - ii. estimation of bioavailability by ratio of AUCs
 - c) constant IV infusion, one compartment
 - i. definition of steady state, the plateau principle, $C_{ss} = IR/Cl$
 - ii. time to steady state as a function of half-life and effects of stopping infusion or changing infusion rate
 - iii. calculation of loading dose
 - d) repeated dosing one compartment

- i. drug accumulation and plateau principle: $C_{ss_{av}} = D \times F / T \times Cl$, independent of k_a
 - ii. peak to trough variation as a function of dose, F , $t_{1/2}$, dosing interval(T), and $k_a:k_e$ ratio
- 2) Deviations from first order (dose-independent) kinetics
 - a) Zero order and "Michaelis-Menten" elimination kinetics, definition, and implications (dose-dependent kinetics)
 - b) Saturation of plasma protein binding, implications
 - c) Dose-dependent absorption and bioavailability

3. Pharmacodynamics - Relationship of Distributional Factors and Protein Binding, to Concentration of Drug at the Receptor Site

- a. Receptor Theory
 - 1) Introduction
 - a) Historical development
 - b) Definition of a receptor (signal transduction)
 - c) Occupancy theory: $E_A/E_M = [A]/([A] + K_A)$
 - 2) The log concentration-response relationship
 - 3) Agonists
 - a) Interpretation of log concentration-response curves
 - b) Potency (ED50 and EC50) vs affinity (K_A)
 - c) Intrinsic activity vs efficacy
 - i. Partial agonists
 - ii. Inverse agonists
 - 4) Antagonists
 - a) Competitive, reversible, surmountable
 - b) Non-competitive, irreversible, unsurmountable
 - 5) Receptor reserve
- b. Quantal Response Relationships
 - 1) ED50 (potency) vs LD50 or TD50
 - 2) 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
 - 1) Receptor superfamilies and mechanisms
 - a) Ligand-gated ion channels
 - i. Nicotinic ACh receptor
 - ii. GABA-A receptor

- 2) G Protein coupled receptors
 - a) Muscarinic ACh receptors
 - b) Three major types of adrenergic receptors (alpha-1, alpha-2, beta)
 - c) Guanine nucleotide regulatory binding proteins
 - 3) Tyrosine kinase receptors
 - a) Insulin
 - b) PDGF
 - 4) Transcription factor receptors
 - a) Receptors for steroid hormones
- e. Receptor Regulation
- 1) Down-regulation and desensitization
 - a) Inverse relationship between agonist concentration and receptor levels
 - 2) Up-regulation and sensitization
- f. Non-receptor targets as sites of drug action
- 1) Enzymes - acetylcholinesterase
 - 2) Nucleic acids as site of action of drugs - actinomycin D
 - 3) Target uniqueness as a basis for selective chemotherapy - penicillin

4. **Pharmacogenetics/genomics**

- a. Pharmacogenetics is the genetic basis for differences among the human population in drug therapeutic response and/or toxicity. Pharmacogenomics is the application of genomic information towards the discovery and development of drugs with new and more specific targets. Rational, individualized selection of drug and/or drug dose based on patient's genetic information will increasingly replace the paradigm of one drug and/or one dose fits all. The pharmacogenetics knowledge base is expanding exponentially since the publication of the human genome. The "idiosyncratic" drug response will increasingly be predictable, preventable, and unacceptable (i.e., considered malpractice). Effective drugs previously discarded because of a high incidence of toxicity will be useful when targeted to patients of appropriate genetic profile.
- b. All proteins are gene products and many (perhaps most) exhibit genetic polymorphism. Single nucleotide polymorphisms (SNPs), gene deletions, gene amplifications determine protein structure, configuration, and/or concentration. When a protein is important

in drug action or disposition, then genetic differences between individuals in that drug's action or disposition are expected.

- c. Differentiate genotype and phenotype. Discuss methods to determine phenotype and genotype. Discuss polymerase chain reaction, restriction fragment length polymorphism; allele-specific amplification; DNA microarrays.
- d. Pharmacogenetic polymorphisms affect drug response as well as drug disposition and toxicity. Examples should be provided illustrating both drug disposition and toxicity (i.e., NAT2, CYP2D6) and drug action (i.e. 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 ethnic group. Polymorphisms are genetic differences in germ-line DNA and are not "mutations." Individuals with polymorphisms are healthy and are not "aberrant" or "abnormal" unless challenged with inappropriate drug or drug dose.
- g. Illustrate clinical relevance with examples such as:
 - 1) NAT2; isoniazid, procainamide
 - 2) CYP2D6; debrisoquine, codeine
 - 3) CYP2C19; mephenytoin
 - 4) CYP2C9; warfarin
 - 5) Serum cholinesterase; succinylcholine
 - 6) Glucose-6-phosphate dehydrogenase; analgesics; antimalarials
 - 7) Thiopurine-S-methyltransferase; 6-mercaptopurine
 - 8) Beta-2 adrenergic receptors; albuterol
 - 9) Dopamine receptors; antipsychotics
 - 10) Malignant hyperthermia; inhalation anesthetics

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--pharmaceutic, 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. The goal is to develop therapeutic agents with known mechanism(s) of action, maximal therapeutic indices, and favorable pharmacokinetic properties. Drugs emerge from both rational design as well as serendipity. Rational drug design involves structure-activity considerations, modeling, and computational chemistry. Advantages and limitations of *in vitro* and *in vivo* screening. Difficulty of extrapolating animal toxicity studies to humans. FDA criteria for clinical trials approval.
- b. Clinical Trials. Sequential trials and outcomes. Rigorous requirements for clinical trials. Controls including concurrent versus historical controls. Placebo effects. Institutional Review Boards - informed consent and patient confidentiality. Investigator conflict of interest. FDA requirements for efficacy and safety.
- 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. Adverse drug reaction reporting mechanism. Problems with subpopulations such as children, the elderly, the mentally impaired, pregnant or lactating women. Limitations of statistical analysis.
- e. Drug Information for Practitioners. Textbooks, journals, FDA alerts, poison control centers, and electronic databases.
- f. Pharmaceutical Industry: Duration of drug patents; branded verses generic drugs.

Influence of marketing (from sales representatives to television advertising) on medical practice.