OVERVIEW OF CLINICAL PHARMACOLOGY

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DISCLOSURE

- Most of the slides are from educational materials developed for previous training workshops.
- Special acknowledgements to Mary Pat Knadler, PhD

My background

- Completed basic medical education at the Varna Medical University, Bulgaria
- Post-graduate specialization in Internal Medicine/Clinical Pharmacology at the University College Hospital, Ibadan, Nigeria (2006)
- Obtained an Erasmus Mundus Master of Bioethics (2009)
- 15 years experience teaching medical students and postgraduate residents in Internal Medicine
- Also a Consultant Physician/Clinical Pharmacologist in the associate teaching hospital
- Research and publications in the area of drug utilization and pharmacoepidemiology, pharmacotherapy of chronic diseases etc

LOCATION WITHIN NIGERIA

OBJECTIVES

- To define clinical pharmacology and relate its importance in medical practice
- To highlight important aspects/divisions of clinical pharmacology

WHAT IS CLINICAL PHARMACOLOGY

- "Clinical pharmacology is the science of drugs in humans and their optimal clinical use in patients" – Wikipaedia
- "Clinical pharmacology encompasses all aspects of the relationship between drugs and humans" –British Pharmacological Society
- "It is underpinned by the basic science of pharmacology, with added focus on the application of pharmacological principles and methods in the real world. It has a broad scope, from the discovery of new target molecules, to the effects of drug usage in whole populations"- ASCPT
- "Clinical Pharmacology is a medical specialty with focus on the rational use of medicines" - WHO

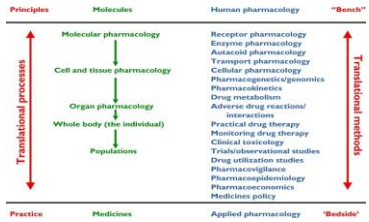
WHO IS A CLINICAL PHARMACOLOGIST

- May differ from country to country
- NHS UK - Clinical pharmacologists are doctors with training in clinical pharmacology and therapeutics (CPT)
- ASCPT - They are physicians, pharmacists, and scientists whose focus is developing and understanding new drug therapies
- WHO - Physicians who are specialists in clinical pharmacology having undergone many years of postgraduate training
- Europe - Health professionals, researchers, biotechnology and pharmaceutical industry professionals and others interested in drug discovery, and in clinical, cost-effectiveness and safety of medicines and related biomarkers

SCOPE OF CLINICAL PHARMACOLOGY

- Bridge between bench and bed
- Main objectives include:
  - Promotion of drug safety
  - Optimal drug effects
  - Reduction in adverse drug reactions

COMPONENTS OF CLINICAL PHARMACOLOGY(Aroson et al- Br J Clin Pharmacol. 2010 Jul; 70(1): 3–13.)

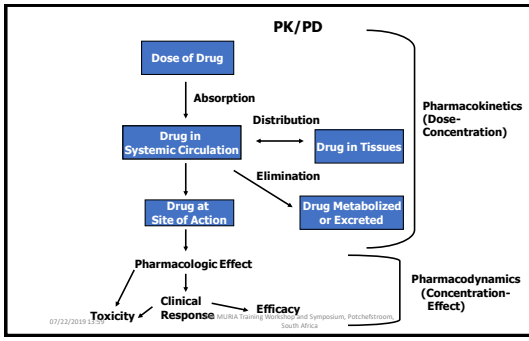


PHARMACOKINETICS

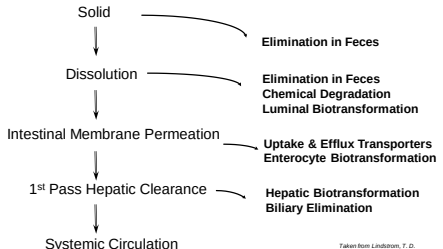
- Pharmacokinetics answers the question : what does the body do to the drug?
- Components include:
  - **Absorption**
  - **Distribution**
  - **Metabolism (biotransformation)**
  - **Excretion**

ROUTES OF ADMINISTRATION

- Intravenous (iv)-No absorption, rapid onset
- Intramuscular (im)-Larger volumes feasible
- Subcutaneous (sc)-Smaller volumes required
- Oral (po)-Most convenient, but first pass effect and enzymes can destroy proteins
- Inhalation –Avoids first pass GI tract, but lung can metabolize/excrete
- Transdermal –Very slow absorption, but no first pass
- Sublingual –Avoids first pass



PROCESSES INVOLVED IN ABSORPTION OF AN ORAL DRUG



Taken from Lindstrom, T. D.

BIOAVAILABILITY

- Fraction of unchanged drug reaching the systemic circulation (F)
- Assumed to be 100% for intravenous route
- Two factors determines
  1) Absorption
  2) First pass effect
- First Pass Effect –After absorption across the gut wall, the portal blood delivers the drug to the liver before entering the systemic circulation and the drug can be removed before it reaches the systemic circulation

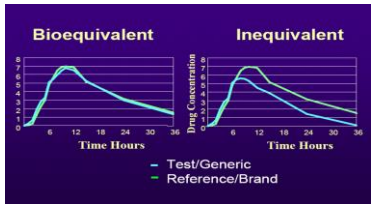
PHARMACOKINETIC PARAMETERS

- **Clearance** – Measure of ability of body to eliminate the drug, most important factor determining systemic drug concentration
  Three factors that influence: Dose, Organ blood flow, Intrinsic function of liver or kidneys
- **Volume of Distribution** –Measure of apparent space in the body available to contain the drug
- **Half-life** –Time required to change amount of drug in the body by 50% during elimination
- **Steady State** – Drug elimination will equal rate of drug availability (amount in = amount out)

BIOEQUIVALENCE

- The **rate and extent of absorption of the active ingredient** or active moiety in pharmaceutical preparation is not significantly different from the reference when administered at the same molar dose under similar conditions in an appropriately designed study
- Determine systemic exposure, rate and extent of absorption
- Comparison of AUC and C_{max} of two preparations

BIOEQUIVALENCE



Slide from CDER presentation by Ted Sherwood

DISTRIBUTION

- High volume of distribution indicates higher concentration in extravascular tissues than vascular space
- Useful to estimate the concentration of drug at a tissue site
- Plasma protein binding –primarily to albumin and alpha -1-acid glycoprotein
- Fat/skeletal muscle mass may affect distribution

FACTORS AFFECTING VOLUME OF DISTRIBUTION

- pK_a of drug
- Degree of plasma protein binding
- Partition coefficient of drug in fat
- Degree of binding to tissues
- Age, gender, body composition
- Diseases such as renal, hepatic, cardiac

METABOLISM

- The process by which the body coverts non-polar, lipophillic drugs and other xenobiotics (foreign chemicals including drugs) into more polar, hydrophilic metabolites that are more readily excreted from the body (via kidneys, bile, etc).
- Biotransformation normally reduces exposure to drugs and thus affects the intensity and/or duration of biological effects.
- Drug-metabolizing systems often have endogenous substrates.
- Drug-metabolizing enzymes exhibit specificity and selectivity for substrates and products, although specificity is often thought to be broad and/or overlapping.

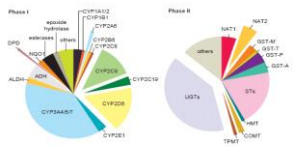
CONSEQUENCES OF METABOLISM

- Drugs undergo metabolism and become:
  1. Inactive – Most drugs
  2. Active (prodrugs);
     Example = lovastatin, simvastatin
  3. More or equally active
     Example = fluoxetine, venlafaxine, imipramine
  4. Toxic (*e.g.,* reactive)
     Example = acetaminophen under certain conditions

PHASES OF METABOLISM

- **Phase 1** metabolism introduces or reveals a polar functional group onto the drug (functionalization). Reactions include: oxidation, reduction, hydrolysis, hydration, dehalogenation
- **Phase 2** metabolism adds a polar endogenous compound like a sugar onto polar functional groups (conjugation). Reactions include: sulfation, glucuronidation, glutathione and amino acid conjugation, acetylation, and methylation.

DRUG METABOLIZING ENZYMES



From Evans WE and Relling MV. 1999. Science 286:487-491.

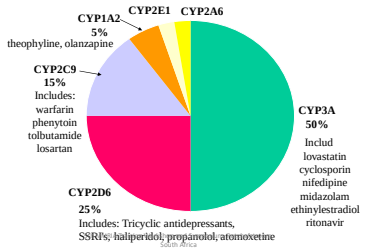
CYP Families

- **Multiple CYP gene families have been identified in humans, and the categories are based upon protein sequence homology**
- **Most of the drug metabolizing enzymes are in CYP 1, 2, & 3 families .**
- **CYPs have molecular weights of 45-60 kDa.**
- **Frequently, two or more enzymes can catalyze the same type of oxidation, indicating redundant and broad substrate specificity.**
- **CYP3A4 is very common to the metabolism of many drugs; its presence in the GI tract is responsible for poor oral availabilty of many drugs**

CYP Nomenclature

- **Families - CYP plus arabic numeral (>40% homology of amino acid sequence, eg. CYP1)**
- **Subfamily - 40-55% homology of amino acid sequence; eg. CYP1A**
- **Subfamily - additional arabic numeral when more than 1 subfamily has been identified; eg. CYP1A2**
- **Comprehensive guide to human Cyps**
  http://drnelson.utmem.edu/human.P450.table.html

Participation of CYPs in Human Drug Metabolism



REACTIVE METABOLITES

- Metabolite or intermediate capable of covalently modifying a macromolecule
- Two main hypothesis for idiosyncratic drug reactions (IDR) invoke the presence of reactive intermediates
- IDRs account for about 25% of all fulminant hepatitis cases
- Drug induced liver injury has been the single most common adverse event which results in drug withdrawal or label restrictions
- Reactive metabolites are implicated in numerous adverse drug reactions
- Small amounts of reactive metabolites can be accommodated and detoxified by the body

PHARMACOGENETICS

- Need to know if enzyme with genetic polymorphism is involved in metabolism
- CYPs with established polymorphism: CYP2D6, CYP2C9, CYP2C19
- CYP1A2 – Some reports of polymorphism in Africans and Chinese women, but not generally considered; smoking induces; males have higher CYP1A2 concentrations than females
- N-acetyltransferase (NAT) – Isoniazid
- Thiopurine methyltransferase (TMT) –Some cytotoxics
- Some hydrolytic enzymes such as cholinesterases
- Different ethnic populations different frequencies of alleles

ELIMINATION

- Liver –A major site of elimination via metabolism or biliary excretion
- Kidney –A major site of elimination via renal excretion; can be site of metabolism, but usually minor
- Other sites of elimination are lung, blood, muscle or other extrahepatic sites of metabolism
- Capacity limited elimination –Saturable, dose or concentration dependent, nonlinear
- Affected by diseases such as renal, hepatic (metabolism or excretion)

RENAL EXCRETION

- Drug/metabolite needs to be water soluble (polar)
- Glomerular filtration, passive reabsorption, or active tubular secretion (transporters)
- pH of urine can affect excretion
- May be able to increase excretion by acidifying or alkalinizing urine –Used in poisonings
- Renal impairment can alter the elimination of drug
- Drug-drug interactions may affect especially if active secretion – competition for transporters
- Dialysis - Does it remove the drug/metabolite?

HEPATIC/BILIARY EXCRETION

- Drug or metabolites excreted in feces
- Transporters involved
- Saturation of excretory capacity is possible
- Interactions may occur if have competition for excretion pathways/transporters
- Enterohepatic cycling –Drug is excreted into bile and then reabsorbed from intestine
- Bacteria in GI tract may convert an inactive metabolite back to the active drug which can then be reabsorbed (i.e., some glucuronide conjugates)
- Hepatic impairment has a much greater effect on drug metabolism than excretion

FACTORS AFFECTING DRUG DISPOSITION

Internal (Intrinsic)
- Species
- Genetics (strain)
- Age
- Sex
- Hormones
- Disease (i.e. hepatic, renal, cardiac)
- Body weight/ composition

External (Extrinsic)
- Diet
- Environment
- Other Drugs
- Smoking
- Alcohol
- Pollutants
- Herbals, supplements

DRUG INTERACTIONS

- The effects of a drug are altered by the presence of another drug, food, herbs or environment
- Adverse drug reactions (ADR) secondary to a drug-drug interaction increases with the number of medications a patient is taking (polypharmacy)
- Drug interactions can occur due to effects on absorption, distribution, metabolism or elimination
- Drug interactions can be classified as either pharmacodynamic or pharmacokinetic
- The primary mechanism of of drug-drug interactions is modulation of CYP mediated metabolism
- Drug-drug interactions can often be managed, but need to know all medications, OTC and herbal products a patient is taking as well as an understanding of clinical pharmacology

PHARMACODYNAMICS

- Drug actions at receptor sites and the physiological effects produced by these actions
- A receptor is the component of a cell or organism that interacts with a drug and initiates the chain of events leading to the drug's observed effects.
- The concepts of dose-response curve, agonist/antagonist, potency and therapeutic index are found under this umbrella

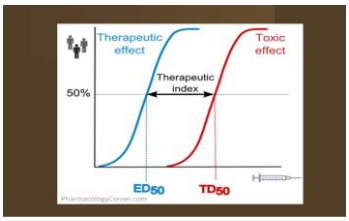
THERAPEUTIC INDEX

- A quantitative measurement of the relative safety of a drug

TD50/ED50

- Clinical importance:
  - Low TI – caution (Warfarin, Lithium, Aminoglycosides)
  - High TI – good safety profile (Penicillins)

THERAPEUTIC INDEX



MECHANISM OF DRUG ACTION

- Usually drug targets are proteins, enzymes or cell receptors
- Typically the "free" or unbound drug interacts with the target
- Drugs in the body can be "free" or bound to proteins or other constituents; drugs can bind to plasma proteins
- Proteins and antibodies are used as drugs

POTENCY AND EFFICACY

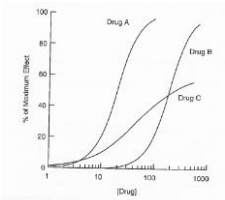
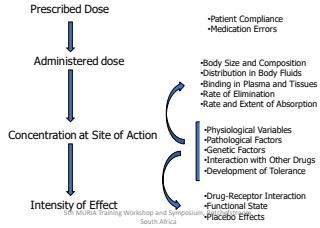


FIGURE 16.8 Evaluation of the relative potency and efficacy of drugs that produce the same pharmacological effect. Drug A is more potent than is Drug B, and Drugs A and B are more efficacious than is Drug C.

RELATIONSHIP BETWEEN PRESCRIBED DOSE AND EFFECT



DRUG-RECEPTOR INTERACTION

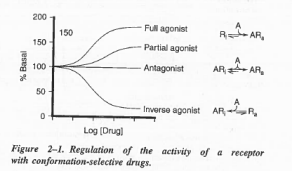


Figure 2–1. Regulation of the activity of a receptor with conformation-selective drugs.

VARIATION IN DRUG RESPONSIVENESS

- Idiosyncratic – Unusual response; Possible metabolic or immunologic mechanisms
- Hypo-reactive – Decreased responsiveness
- Hyper-reactive – Increased responsiveness
- Tolerance – Responsiveness decreases with continued drug administration

MECHANISMS CONTRIBUTE TO VARIATION IN RESPONSE

- Alterations in the concentration of drug that reaches the receptor
- Alterations in the concentrations of an endogenous receptor or ligand
- Alterations in the number or function of a receptor
- Changes in post receptor processes

FACTORS AFFECT DRUG RESPONSIVENESS

- Age
- Sex
- Body size
- Disease state
- Genetics
- Concomitant drugs
- Propensity to produce tolerance
- Adaptive responses

CLINICAL TRIALS

- A clinical trial is one important aspect of drug research and development
- The cost of getting a new drug from the lab to the market has skyrocketed from 318 to 802 million USD between 1991-2003 (Di Masi et al, 2003)
- The average cost of clinical trials have risen to about 60% of R&D cost compared to just 30% in the 80s (www.pfizer.com)
- 70% of the 46.4 billion USD spent on R&D (2010) by PhRMA was on clinical trials (Pierre A, 2004)

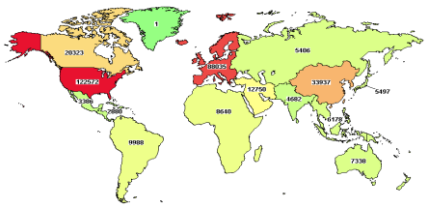
CLINICAL TRIALS

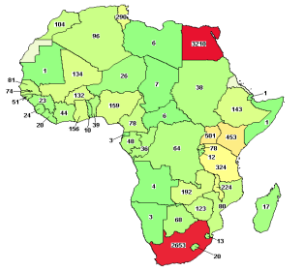
- A ***clinical trial*** : prospectively planned experiment for the purpose of evaluating potentially beneficial therapies or treatments
- In general, these studies are conducted under as many controlled conditions as possible so that they provide definitive answers to pre-determined, well-defined questions

BENEFITS OF CLINICAL TRIALS

- Prevention and treatment of disease
- Accelerated introduction of drugs into the community
- Capacity building for healthcare workers
- Health awareness in the community
- Infrastructure development
- Provision of employment

PHASES OF CLINICAL TRIALS





ROLE OF CLINICAL PHARMACOLOGISTS AS EDUCATORS

- Undergraduate and postgraduate level
- Emphasis on rational prescribing
  - Reduction in adverse drug reactions
  - Drug interactions
  - Reduction in cost
  - Decrease antimicrobial resistance
- Delivery of relevant undergraduate/postgraduate curriculum
- Continuing medical /professional education

CLINICAL PHARMACOLOGISTS IN CLINICAL PRACTICE

- Improving rational use of medicines
- Drug issues in special populations
- Participating in Drugs and Therapeutics Committee and Antimicrobial Stewardship Programs
- Collaboration with pharmacists in establishing Drug Information Services
- Therapeutic Drug Monitoring
- Pharmacovigilance and Pharmacogenetics

CLINICAL PHARMACOLOGISTS AS RESEARCHERS

- Develop strategies towards improvement of rational use of medicines
- Usually interdisciplinary and translational
- Leading Role in Clinical Trials
- Pharmacovigilance
- Pharmacoepidemiology
- Pharmacoeconomics

CLINICAL PHARMACOLOGISTS IN THE POLICY ARENA

- Development of National Drug Policy
- Development of Treatment Guidelines
- Working on policies to ensure quality, safety and efficacy of medicines
- Working as regulators in relevant agencies

CONCLUSIONS

- Clinical Pharmacology is important in determining the disposition of drugs and assessing the safety and efficacy profile (the risk to benefit ratio)
- Understanding the clinical pharmacology of a drug leads to appropriate dosing regimens administered to the appropriate individuals
- Pharmacokinetics and pharmacodynamics can help explain patient variability