Introduction

Pharmacology and Therapeutics

UNIT I: Introduction to Pharmacology and Therapeutics

- This is an introductory unit to understanding pharmacology and therapeutics.
- It gives an overview of the definitions of terms in pharmacology, and considers some of the general principles and concepts in pharmacology and therapeutics

Unit Objectives

- By the end of this unit, you will have achieved the following objectives;
  1. Definitions of terminologies,
  2. Sources of drugs,
  3. General principles and concepts in pharmacology and therapeutics,
  4. Formulations/preparations of drugs,
  5. Classification and naming of drugs,
  6. Routes of drug administration,
  7. The concept of essential drugs and rational use of drugs,
  8. Pharmacy and Poisons Act & Dangerous Drugs Act,
  9. Principles of drug prescribing.

Definition of terms and concepts

Pharmacology and therapeutics

Definitions

- **Pharmacology**
  - The science that deals with drugs. i.e. the study of drugs.
  - The study of substances that interact with living systems through chemical processes especially by binding to regulatory molecules and activating or inhibiting body processes

Definitions…

- **Drug**
  - Is any substance that brings about a change in biologic function through its chemical actions.
  - WHO definition: a drug is any substance or product that is used or intended to e used to modify or explore physiological systems or pathological states for the benefit of the recipient.
  - A drug is any chemical compound that may be used as a medicament to prevent or cure disease.

Definitions…

- **Therapeutics**
  - The branch of medicine concerned with the cure of disease or relief of symptoms, and includes drug treatment.
- **Pharmacy**
  - The science concerned with identification, selection, preservation, standardization, compounding and dispensing of medicinal substances.
- **Pharmacognosy**
  - This is the science of identification of drugs

Definitions…

- **Pharmacokinetics**
  - Is the study of the processes whereby drug concentrations at effecter sites are achieved, maintained, and diminished. i.e. the study of the absorption, distribution, metabolism, and excretion of drugs.
  - It deals with what the body does to drugs.
- **Pharmacodynamics**
  - Is the study of the biological and therapeutic effects of drugs on the body. i.e. actions upon cells, tissues or organs.
  - What the drugs do to the body.

Definitions…

- **Pharmacogenomics (pharmacogenetics)**
  - Is the study of the genetic variations that cause differences in drug response among individuals.
  - The scientific study of the relationship between genetic factors and the nature of response to drugs.

Definitions…

- Pharmacology and genetics…
  - Individuals with inherited diseases have a heritable abnormality in their DNA. It is possible to correct abnormality by gene therapy i.e. insertion of an appropriate healthy gene into somatic cells.
  - Some patients respond to certain drugs with greater than usual sensitivity to standard doses. Increased sensitivity is due to a very small genetic modification that results in decreased activity of a particular enzyme responsible for eliminating that drug.

Definitions …

- **Chemotherapy**
  - This is the use of a specific chemical agent to arrest or eradicate microorganisms and parasites living and multiplying in a living organism without causing irreversible injury to healthy tissues. It also includes the treatment (therapy) of cancer.

Definitions…

- Pharmacopoeia
  - An official code containing a selected list of the established drugs and medicinal preparations with descriptions of their physical properties and tests for their identity, purity and potency.
  - It defines the standards that these preparations must meet, and their average doses for an adult.
  - Every pharmacopoeia also includes a list of drugs added in that particular edition and a list of deleted drugs.
  - Examples of pharmacopoeias:
    - British Pharmacopoeia (B.P)
    - Indian Pharmacopoeia (I.P)
    - United States Pharmacopoeia (U.S.P)

Definitions…

- Toxicology
  - Is the branch of pharmacology which deals with the undesirable effects of chemicals on the living systems from individual cells to complex ecosystems.
  - The science of poisons. Includes measurement and detection of poisons, as well as treatment of poisoning. Many drugs in larger doses act as poisons.

Definitions…

- **Receptor**- specific molecules in biologic system that interact with drug molecule
- **Hormones**-drugs synthesized within the body and released into circulation acting far away from their place of origin
- **Xenobiotics** - drugs/chemicals synthesized outside the body. Chemical substances foreign to animal life, e.g. plant constituents, drugs, pesticides, etc. (xeno =foreign, biotic =pertaining to life)
- **Poisons** - are drugs that have almost exclusively harmful effects
- **Toxins** - are poisons of biologic origin i.e. synthesized by plants or animals

Definitions…

- **Metabolism of drugs**
  - The process of chemical alteration of drugs in the body.
- **Biological lag**
  - This is the time between the administration of a drug and the development of response.

Definitions…

- **Bioavailability of a drug**
  - This is the fraction of the drug dose that reaches the systemic circulation.
- **Biological half-life of a drug**
  - This is the time required to reduce the concentration of a drug in the body compartments by 50%.
- **Drug interactions**
  - The actions of one drug upon the effectiveness or toxicity of another or others.

NB:

- A drug is a single chemical substance that forms the active ingredient of a medicine (a substance or mixture of substances used in restoring or preserving health)
- A medicine may contain many other substances to deliver the drug in a stable form, acceptable and convenient to the patient.
- The terms are often used interchangeably for convenience.

The end.

Thank you.

P.J. Okoth

Sources of Drugs

Sources of drugs

- Drugs are obtained from six major sources:

1. Plant sources
2. Animal sources
3. Mineral sources
4. Microbiological sources (microorganisms)
5. Semi synthetic sources/ Synthetic sources
6. Recombinant DNA technology

Plant Sources

- Plant source is the oldest source of drugs.
- Most of the drugs in ancient times were derived from plants.
- Almost all parts of the plants are used i.e.
  - leaves,
  - stem,
  - bark,
  - fruits and
  - roots.

Plant sources

Leaves:

- a. The leaves of *Digitalis Purpurea* are the source of **Digitoxin** and **Digoxin**, which are cardiac glycosides.
- b. Leaves of Eucalyptus give oil of Eucalyptus, which is important component of cough syrup.
- c. Tobacco leaves give nicotine.
- d. Atropa belladonna gives **atropine**.

Plant sources

Flowers:

- Poppy papaver somniferum gives **morphine** (opioid)
- Vinca rosea gives **vincristine** and **vinblastine**
- Rose gives rose water used as tonic.

Plant sources

Fruits:

- Senna pod gives **anthracine**, which is a **purgative** (used in constipation)
- Calabar beans give **physostigmine**, which is **cholinomimetic** agent.

Seeds:

- Seeds of Nux Vomica give **strychnine**, which is a CNS stimulant.
- Castor oil seeds give castor oil.
- Calabar beans give Physostigmine, which is a cholinomimetic drug.

Plant sources

Roots:

- **Ipecacuanha** root gives **Emetine**, used to induce vomiting as in accidental poisoning. It also has **amoebicidal** properties.
- Rauwolfia serpentina gives **reserpine**, a hypotensive agent. Reserpine was used for hypertension treatment.

Plant sources

Bark:

- **Cinchona** bark gives **quinine** and **quinidine**, which are **antimalarial** drugs. Quinidine also has antiarrythmic properties.
- Atropa belladonna gives **atropine**, which is anticholinergic.
- Hyoscyamus Niger gives **Hyosine**, which is also anticholinergic.

Stem:

- Chondrodendron tomentosum gives **tubocurarine**, which is skeletal muscle relaxant used in general anesthesia.

Pharmacologically active principles in plants

- The pharmacologically active principles in plants include:
  - Alkaloids
  - Glycosides
  - Oils
  - Resins
  - Oleoresins
  - Gums
  - Tannins

Alkaloids

- These are basic substances containing cyclic nitrogen, which are insoluble in water but combine with acids to form well-defined, water-soluble salts, e.g. morphine, atropine, emetine.

Glycosides

- Are ether-like combinations of sugars with other organic structures.
- A glycoside does not form salts with acids but when heated with mineral acids it is hydrolysed to a sugar and a non-sugar component called aglycone or genin e.g. digoxigenin.
- A glycoside which yields glucose on acid hydrolysis is called a glucoside.

Oils

- **Fixed oils** are glycerides of oleic, palmitic and stearic acids. They are fats and may have food value, e.g. peanut oil, coconut oil, and olive oil. Castor oil acts as a purgative.

- **Volatile oils** are volatilized by heat and possess aromas. Chemically, they are not fats and have no caloric value. They contain the hydrocarbon terpene or some polymer of it, which serves as a diluent or solvent for a more active compound, e.g. menthol in peppermint oil.

Oils

- Volatile oils are used as:
  - Carminatives – for expulsion of gas from the stomach e.g. oil of eucalyptus, ginger.
  - Antiseptics – in mouth wash, pastes.
  - Counter-irritants – e.g. turpentine oil
  - Flavoring agents – e.g. oil of peppermint
  - Pain relieving agents – e.g. oil of clove in toothache.

Animal Sources

- Pancreas is a source of Insulin, used in treatment of Diabetes.
- Urine of pregnant women gives human chorionic gonadotropin (hCG) used for the treatment of infertility.
- Sheep thyroid is a source of thyroxin.
- Cod liver is used as a source of vitamin A and D.
- Blood of animals is used in preparation of vaccines.

Mineral Sources

Metallic and Non metallic sources:

- Iron is used in treatment of iron deficiency anemia.
- Zinc is used as zinc supplement. Zinc oxide paste is used in wounds and in eczema.
- Iodine is antiseptic. Iodine supplements are also used.
- Gold salts are used in the treatment of rheumatoid arthritis.

Mineral sources

Miscellaneous Sources:

- Fluorine has antiseptic properties.
- Borax has antiseptic properties as well.
- Selenium as selenium sulphide is used in anti dandruff shampoos.
- Petroleum is used in preparation of liquid paraffin.

Synthetic/ Semi synthetic Sources

Synthetic Sources:

- When the nucleus of the drug from natural source as well as its chemical structure is altered, we call it synthetic.
- Examples include Aspirin, Sulphonamides, Procaine, and Corticosteroids.
- Most of the drugs used nowadays are synthetic forms.

Synthetic and semi-synthetic…

Semi Synthetic Source:

- When the nucleus of a drug obtained from natural source is retained but the chemical structure is altered, we call it semi-synthetic.
- Examples include Apomorphine, Diacetyl morphine, Ethinyl Estradiol, Homatropine, Ampicillin and Methyl testosterone.

Microbiological Sources

- Bacteria and fungi isolated from the soil are important sources of antibacterial substances (antibiotics)
- *Penicillium notatum* is a fungus which gives penicillin. (Also *Penicillium chrysogenum*)
- *Streptomyces griseus* gives Streptomycin.
- Aminoglycosides such as tobramycin and gentamicin are obtained from *Streptomyces* and *Micromonosporas* respectively.

Recombinant DNA technology

- Recombinant DNA technology involves cleavage of DNA by enzyme restriction endonucleases.
- The desired gene is coupled to rapidly replicating DNA (viral, bacterial or plasmid)
- The new genetic combination is inserted into the bacterial cultures which allow production of vast amount of genetic material.
- E.g. human chorionic gonadotropin (usually got from urine of pregnant women or pregnant mares) can be extracted from cultures of genetically modified microbes with recombinant DNA.

Recombinant DNA technology

Advantages:

- Huge amounts of drugs can be produced.
- Drug can be obtained in pure form.
- It is less antigenic.

Disadvantages:

- Well equipped lab is required.
- Highly trained staff is required.
- It is a complex and complicated technique.

Thanks.

The end.

P. J. Okoth

Classification and naming of drugs

Classification

- Drugs may be classified by:

1. **Therapeutic use**
   - Antibacterial
   - Antidiabetic
   - Antihypertensive
   - Analgesic
   - Antifungal
   - Antimalarial

Classification…

2. **Mode or site of action**
   - Molecular interaction
     - Receptor blockers - e.g. beta blockers
     - Enzyme inhibitors – e.g. reverse transcriptase inhibitors
   - Cellular site
     - Loop diuretic
     - Catecholamine uptake inhibitor (imipramine)

Classification…

3. **Molecular structure**
   - Glycoside
   - Alkaloid
   - Steroid
   - Tetracycline
   - Macrolides

Nomenclature (Names)

- Any drug may have names in all three of the following classes/ categories:
  1. The full chemical name
  2. A nonproprietary (official, approved, generic) name
  3. A proprietary (brand) name

Nomenclature (Names)

- Example: one drug – 3 names
  1. 3-(10,11-dihydro-5H-dibenz [b,f]-azepin-5-yl) propyl-dimethylamine
  2. Imipramine
  3. Tofranil (UK), Prodepress, Surplix, Deprinol, etc. (various countries)
- **The full chemical name** describes the compound for chemists. It is obviously unsuitable for prescribing.

Nonproprietary name

- **A nonproprietary name** is given by an official agency, e.g. WHO.
- A prescription for a generic drug formulation may be filled by any officially licensed product that the dispensing pharmacy has chosen to purchase.
- The principal reasons for advocating the habitual use of nonproprietary (generic) names in prescribing are:

Nonproprietary name…

Clarity:

- Because it gives information about the class of the drug, e.g.: -
  - Diazepam, nitrazepam, flurazepam are all benzodiazepines. Their proprietary names are valium, mogadon, and dalmane respectively.
  - Names ending in –olol are adrenoceptor blockers
  - Names ending in –floxacin are quinolone antimicrobials
  - Nortriptyline and amitriptyline are plainly related, but their proprietary names are allegron and laroxyl (lentizol)

Nonproprietary name…

Economy:

- Drugs sold under nonproprietary names are usually, but not always, cheaper than those sold under proprietary names.

Convenience:

- Pharmacists may supply whatever version they stock whereas if a proprietary name is used they are normally obliged to supply that preparation alone.
- International travelers with chronic illnesses will be grateful for recommended international nonproprietary names (rINN)

Proprietary name

- The proprietary name is a trade mark applied to particular formulations of a particular substance by a particular manufacturer.
- Manufacture is confined to the owner of the trade mark or to others licensed by the owner.
- The principal noncommercial reason for advocating the use of proprietary names in prescribing is **consistency** of the product, so that problems of quality, especially of bioavailability, are reduced.

Proprietary name

- When a prescription is written for a proprietary product pharmacists must, under law, dispense that product only, unless they persuade the doctor to alter the prescription, or under law, they have the right to substitute a generic product (generic substitution), or a drug of different molecular structure deemed to be pharmacologically and therapeutically equivalent (therapeutic substitution)

The End.

Thank you.

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Routes of Administration of Drugs

Learning objectives

1. Describe the various routes of drug administration
2. Explain the advantages and disadvantages of each route of drug administration
3. Select a suitable route of drug administration

Main routes of drug administration

- Drugs can be administered:
  1. Locally
  2. Orally or enterally
  3. Parenterally
     - By injection
     - By inhalation

Selection of a suitable route

- Selection of a suitable route is dictated by considerations as follows:
  1. Convenience for the patient
  2. The patient's condition – degree of illness, type of illness
  3. Action required – quick action, local action, systemic action
  4. Achievement and maintenance of an adequate drug concentration at the requisite site, e.g. getting the right concentration of a drug in the meninges.
  5. Drug formulation that is available

Local application of drugs

- This is when a drug is administered directly at the site where it is to produce effects, e.g. of dusting powder, paste, lotion, cream, drops, ointment, vaginal pessaries.

Advantages of local application

- Convenient to the patient
- Encouraging to the patient
- Easy to apply
- Does not require skill
- Acts at site of application
- Self-application is possible
- No gastric irritation

Disadvantages of local application

- May be absorbed and produce adverse systemic effects, especially solutions applied to mucus membranes.
  - Eye drops
  - Nasal sprays
- May be messy on the skin, some might dirty the clothes.

Oral or Enteral route

- This means taking drugs into the body via the alimentary tract.
- It is the most commonly used route of drug administration.
- It includes:
  - Swallowing drugs (oral administration)
  - Sub-lingual administration of drugs
  - Rectal administration of drugs

Oral administration

- Drugs are taken by mouth for absorption in the gastrointestinal tract.

Advantages of oral administration

- Safe
- Convenient to the patient: - self-administered at home
- Economical
- Easy to administer
- Complications of parenteral therapy are avoided

Disadvantages of oral administration

- The onset of drug action is slow
- Irritant and unpalatable drugs cannot be administered by this route
- Route may not be useful in the presence of vomiting
- The route cannot be employed in unconscious patients
- The route cannot be used in uncooperative patients
- Can produce gastric irritation
- Drugs likely to be destroyed by digestive juices cannot be administered by this route (e. g. insulin)

Sub-lingual administration of drugs

- A tablet containing a medicament is placed under the tongue and allowed to dissolve in the mouth.
- The active ingredient thus gets absorbed through the buccal mucous membrane directly into the systemic circulation.

Advantages of sublingual administration

- Rapid onset of action
- Quick termination of drug effect by spitting the tablet
- Degradation of the drug in the stomach is avoided

Disadvantages

- Inconvenience if use has to be frequent
- Irritation of mucous membrane and excessive salivation which promotes swallowing, so losing the advantages of bypassing pre-systemic elimination.

Examples of drugs given sublingually

- Nitro-glycerine tablet in angina pectoris
- Isoprenaline sulphate in bronchial asthma
- Nifedipine in hypertension
- Ergotamine in migraine

Rectal administration of drugs

- The rectum has a rich blood and lymph supply and drugs can cross the rectal mucosa like the other lipid membranes, thus, un-ionized and lipid soluble substances are readily absorbed from the rectum.
- The portion absorbed from the upper rectal mucosa is carried by the superior haemorrhoidal vein into the portal circulation.
- The portion absorbed from the lower rectum enters directly into the systemic circulation via the middle and inferior haemorrhoidal veins.

Advantages of rectal route

- Gastric irritation is avoided
- By using a suitable solvent the duration of action can be controlled.
- It is a convenient route to use in the long term care of geriatric and terminally ill patients
- Administration of a rectal suppository or a capsule is a simple procedure, which can be undertaken by the unskilled personnel and the patient himself.
- Suitable in vomiting and motion sickness
- Suitable for emergency when intravenous line cannot be quickly established

Disadvantages

- Rectal inflammation may occur in repeated use
- Absorption may be unreliable if the rectum is full of faeces
- Psychological embarrassment

Examples of drugs that can be given rectally

- Indomethacin in rheumatoid arthritis
- Aminophylline for bronchospasm
- Chlorpromazine for vomiting
- Diazepam for convulsions

Enemata

- Administration of a medicament in a liquid form into the rectum is called enema.
- Enemata are of two types:
  1. Evacuant enema
  2. Retention enema

Evacuant enema

- The aim is to remove faecal matter and flatus.
- In soap and water enema, the water stimulates the rectum by distension while the soap acts as a lubricant.
- The quantity of fluid administered at a time is about 600ml.
- An evacuant enema is often administered before delivery, surgical operation, and radiological investigation of the gastrointestinal tract.

Retention enema

- Here the drug incorporated into the enema may act locally or may act systemically after absorption through the mucous membrane.
- The quantity of fluid administered in retention enema is usually 100-120ml.
- It can be used for diagnostic purposes e.g. barium enema.

Enteric coating of pills and tablets

- Sometimes pills and tablets are coated with keratin, salol, or cellulose acid phosphate.
- These substances are not dissolved by the acid juice of the stomach but are dissolved by the intestinal alkaline juices.
- Enteric coating is done:
  - To prevent gastric irritation and alteration of the drug in the stomach
  - To get the desired concentration of the drug in the small intestine
  - To retard the absorption of the drug

Parenteral routes

- These are routes of administration other than the alimentary tract (enteron)

Advantages:

- They can be employed in an unconscious or uncooperative patient
- Useful in cases of vomiting and diarrhoea
- Useful when the patient is unable to swallow
- They avoid drug modification by alimentary juices and liver enzymes
- Drugs that might irritate the stomach or which are not absorbed in the small intestine s can be administered
- Rapid action and economy of dose are ensured

Parenteral routes…

Disadvantages:

- They are less safe
- More expensive
- Inconvenient for the patient
- Self-medication difficult
- Dangers of infection if proper care is not exercised
- Skill is required in administering
- Injections are painful

Inhalation

- By this method drugs are inhaled into the respiratory system.
- **Drugs may be administered as:**
  - Solid particles
  - Nebulized particles from solutions (fine spray)
  - In the form of vapours (e.g. steam inhalation)
  - Fine droplets (aerosols), sprayed and deposited over the mucous membranes, producing local effects.
  - Gases e.g. volatile general anaesthetics.

Inhalation…

- **Advantages:**
  - Quick absorption
  - Produce rapid local and systemic effects
  - Blood levels of volatile general anaesthetics can be conveniently controlled by the law of gases.
  - Self administration is practicable

Inhalation…

- **Disadvantages:**
  - Drugs go directly into the left side of the heart through the pulmonary veins and may produce cardiac toxicity
  - Local irritation may result in an increase in the respiratory tract secretions
  - Obstructed bronchi may cause failure of therapy (mucus plugs in asthma)

Injections

Can be administered:

- Intradermally
- Subcutaneously
- Intramuscularly
- Intravenously
- Intra-arterially
- Intrathecally
- Intraperitoneally
- Intramedullary
- intraarticularly

Injections

Intradermal injection:

- Given in the layers of the skin, e.g. BCG vaccine.
- Only a small quantity can be administered by this route
- The injection is painful
- The route is also employed for studying drug allergy

Injections

Subcutaneous (S/C) injection:

- Drug is injected into the subcutaneous tissue
- Drug absorption is slower than I.M. or I.V. routes
- **Advantages:**
  - The action is sustained and uniform
  - The route is acceptable for self-administration
- **Disadvantages:**
  - Only non-irritant substances can be injected by this route
  - Poor absorption in peripheral circulatory failure
  - Repeated injections in the same area can cause lipoatrophy, leading to erratic absorption.

Injections

Intramuscular (I.M.) injection:

- The drug is injected into the muscles
- **Advantages:**
  - In addition to soluble substances, mild irritants, suspensions and colloids can be injected by this route.
  - Absorption rate is relatively uniform
  - Onset of action is rapid
  - Depot preparations can be used at monthly or longer periods

Injections

I.M. injection…

- **Disadvantages:**
  - Causes local pain
  - May cause abscess
  - May cause nerve irritation or damage if injected very near to or into a nerve causing severe pain or paresis of muscles supplied.
- *NB: the volume of injection should not exceed 10 mls.*

Injections

Intravenous (I.V.) Injection

- Drugs are given directly into a vein
- **Advantages:**
  - Allows rapid modification of dose, i.e. immediate cessation of drug administration is possible if unwanted effects occur during administration.
  - Produce rapid action
  - The desired blood concentration can be obtained with a well-defined dose.
  - Large quantities of solution can be administered by this route.
  - Useful for certain irritant and hypertonic solution (e. g. mannitol and iron) as they are rapidly diluted by blood.

Injections

Intravenous (I.V.) Injection…

- **Disadvantages:**
  - Once a drug has been administered by this route its action cannot be halted
  - Local irritation can lead to venous thrombosis
  - Leakage of the drug outside the vein can produce severe irritation e.g. intravenous iron.
  - Self medication is difficult
  - Infection of the intravenous catheter and the small thrombi on its tip are a risk during prolonged infusions.

Injections

I.V. injection:...

- ***Precautions:***
  - Before injecting ensure that the needle is in the vein
  - The injection should be given slowly in the case of certain drugs such as iron and aminophylline, as sudden high blood concentrations may be dangerous.
  - Only the minimum quantity required to elicit a particular effect should be injected.

Injections

Intra-arterial injection

- In this route a drug is administered through an artery.
- **Danger:**
  - Produces a sudden high concentration in arterial blood and hence, may be harmful locally or dangerous to tissues supplied by the artery.

Injections

Intra-arterial injection…

- **Used in:**
  1. Some diagnostic studies such as angiography
  2. Treatment of peripheral vascular disorders
  3. Treatment of certain localized malignancies where certain anti-malignancy compounds are administered by intra-arterial perfusion.

Injections

Intra-thecal injection:

- This involves the introduction of drugs such as spinal anaesthetics into the subarachnoid space. The drugs act directly on the central nervous system.
- This route is convenient for producing local action on the meninges (e.g. certain antibiotics and corticosteroids)
- Strict aseptic precautions must be observed.

Injections

Intra-peritoneal injection:

- This route is useful in infants for giving fluids like dextrose saline, as the peritoneum offers a large surface from which they are readily absorbed.

Injections

Intramedullary injection:

- This is the introduction of drugs into the bone marrow. It is rare.

Intra-articular injection:

- A drug is administered directly into a joint for local treatment.
- It ensures high local concentration of the drug.

The end.

Thank you.

THE CONCEPT OF ESSENTIAL MEDICINES AND RATIONAL USE OF MEDICINES

Mr. Okoth

Learning objectives

- State the WHO definition of essential medicines
- Explain the importance of the concept of essential medicines
- State the criteria for selection of essential medicines
- State questions to be considered before inclusion of a new drug in the essential medicines list
- Explain the importance of rational drug use
- State the effect of advertising and promotion on rational drug use
- Define first-line treatment

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Essential Medicines

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Essential Medicines

- Essential medicines have been defined by the World Health Organization (WHO) as “those that satisfy the healthcare needs of the population” in a particular country.
- The concept appeared in in the mid-1970s when there was inequitable distribution of resources for health in developing countries.

Selection of essential medicines

- The selection of essential drugs should depend on the health as well as the structure and development of the health services of each country.
- Essential drugs are selected with due regard to their public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.

Essential medicines

- Essential medicines are intended to be available within the context of functioning health systems at all times and in adequate amounts.
- The list of essential drugs should be drawn up locally and reviewed and updated periodically by experts in public health, medicine, pharmacology, pharmacy, and drug management.

Essential medicines

- It has been realized that only a handful of medicines out of the multitude available can meet the health care needs of majority of the people in any country.
- Also, many well tested and cheaper medicines are of equal or better efficacy and comparable safety as their newer more expensive counterparts.
- For optimum utilization of resources, governments in developing countries should concentrate on these medicines by identifying them as **essential medicines**.

Essential medicines

- The concept of essential medicines has not only become recognized as a useful tool for selecting drugs according to needs, but it has also provided a rational basis for drug procurement and for establishing drug requirements in national health care systems.
- Advances in drug therapy or new experiences from current practice should form the basis for the revision of the essential drugs list.

Essential medicines

- The decision to include a new product in the list should consider the following questions:
  - Is the medicine more effective than existing ones on the list?
  - Does the medicine induce lesser side effects than similar medicines currently on the list?
  - Does the medicine have a wider spectrum of action than the listed product it is intended to replace?
  - Is it cheaper than similar existing medicines on the list?

Criteria for selection of essential medicines

- In principle, essential medicines selected for any country are those which meet the health care needs of the majority of the population.
- They are supposed to be available at all times, in sufficient amounts and in the required dosage forms.
- The world health organization (WHO) has laid down criteria to guide selection of an essential medicine:

Criteria for selection of essential medicines

The choice depends on:

- Pattern of prevalent diseases in the country
- Availability of treatment facilities
- Availability of trained personnel
- Available financial resources
- Demographic and environmental factors

Criteria for selection of essential medicines

The choice depends on:

- Adequate data on its efficacy and safety should be available from clinical studies
- The medicine being available in a form in which quality, including bioavailability and stability on storage can be assured.

Criteria for selection of essential medicines

The choice depends on:

- In the case of two or more similar medicines, choice should be made on the basis of their relative efficacy, safety, quality, price and availability.
- Comparative pharmacokinetic properties and local facilities for manufacture and storage.

Criteria for selection of essential medicines

- Most essential medicines should be single compounds.
- Fixed ratio combination products should be included only when dosage of each ingredient meets the requirements of a defined population group, and when the combination has a proven advantage in the therapeutic effect, safety, patient compliance, or in reducing the emergence of drug resistance.

Criteria for selection of essential medicines

- Selection of essential medicines should be a continuous process which should take into account the changing priorities for public health action, epidemiological conditions as well as availability of better drugs/ formulations and advancement in pharmacological knowledge.
- Selection of essential medicines is also based on rationally developed treatment guidelines.

16

Rational use of drugs

P.J. Okoth

Rational use of drugs

- The rational use of drugs requires that an appropriate drug be prescribed, that it be available at the right time at a price which is affordable, that it be dispensed correctly, that it be taken in the right dose at the prescribed intervals and for the correct length of time.
- The appropriate drug must be safe, effective and of acceptable quality.

Rational use of drugs

- Rational drug use is an essential component in the implementation of national drug policies.
- Education and training are essential components of the rational use of drugs
- Appropriate training is given so as to ensure that drugs are prescribed, dispensed and used rationally.

Rational use of drugs

- Education and training should be provided for:
  - Doctors
  - Dentists
  - Clinical Officers
  - Pharmacists / Pharmaceutical technologists
  - Nurses and others who offer healthcare services
- Emphasis should be made on the importance of rational drug use.

Rational use of drugs

- Objective and unbiased information about the correct handling and use of drugs should be provided to health workers at all levels and to the public.
- Guidance for rational prescribing and dispensing of drugs should be made available to health workers in all units.

Rational use of drugs

- Patients should be appropriately advised on correct drug use, how to recognize and report adverse drug reactions.
- Patients should be made to understand the purpose as well as the effects of the drugs they are taking.
- Supply of drugs without medical judgment, over-prescription and polypharmacy should be evaluated periodically to reduce unnecessary consumption.

P. J.

Advertising and promotion

- Ethical drug promotion and advertisement can support improvement of health care through rational drug use
- Advertisement of drugs must be based on proven scientific evidence and must be objective and in line with pharmaceutical legislation
- Where the advertisement is directed to the public for over the counter (OTC) products it must be educational in purpose

Advertising and promotion

- Drug promotions must always comply with national regulations which reflect the national health policy.
- Promotional activities are responsible for influencing both the purchasing of OTC drugs by the public and prescribing drugs by clinicians.
- As a result, drugs are commonly overused, misused or even abused.

First-line treatment / therapy

- A first-line treatment or first-line therapy is a medical therapy recommended for the initial treatment of a disease, sign or symptom, usually on the basis of **empirical** evidence for its efficacy.
- This evidence typically suggests the recommended therapy is most likely to have an effect for the given condition.

First-line treatment

- First-line treatment usually consists of drugs in the essential drugs list.
- Second-line drugs are alternative drugs for use in case the first line drug is ineffective / contraindicated in the treatment of a disease.

THE END!

Thanks

DISTRIBUTION OF A DRUG

Pharmacokinetics

Distribution

- Distribution of a drug is the transfer of a drug from one location to another within the body.
- Once a drug enters the systemic circulation by absorption or direct administration, it must be distributed into various body fluid compartments and tissues.
- The rate of entry of a drug into a tissue depends on the rate of blood flow to the tissue, tissue mass, and partition characteristics between blood and tissue.

Body fluid compartments through which a drug is distributed

- After absorption, a drug enters or passes through the various body fluid compartments such as:
  1. Plasma
  2. Interstitial fluid compartment
  3. Cellular (intracellular) fluid compartment
  4. Transcellular fluid compartment, e.g. fluids in the gut, bronchi and cerebrospinal fluid.

Body fluid compartments…

- Some drugs pass into the cell, some remain in the cell membrane, and some remain extracellular.
- However, a drug can penetrate into and exist in more than one compartment.
- The rate of passage of a drug through a membrane is dependent upon the pH of the drug's environment and the dissociation constant (pKa) of the drug, the pH at which the non-ionized and ionized drug concentrations are equal.

Body fluid compartments…

- Non-ionized lipid-soluble drugs that readily cross membranes are distributed throughout all fluid compartments.
- Drugs that do not readily cross membranes are restricted in their distribution.
- The extent of distribution of a drug depends on its lipid solubility, ionization at physiological pH, extent of binding to plasma and tissue proteins and differences in regional blood flow.

Plasma concentration of a drug

- Depends upon the rate of absorption, distribution, metabolism and excretion of the drug.
- After absorption, the drug circulates in the blood in two forms:
  1. In the free form
  2. Bound to plasma proteins

Significance of plasma protein and tissue binding

- Binding of drugs to plasma proteins **assists in absorption**.
- Diffusion across the intestinal wall continues as long as the concentration within the gut exceeds that of the unbound portion in the portal capillaries.
- The free portion of drug is pharmacologically active.
- The protein-bound component is a **reservoir of drug** that is inactive because of this binding.

Significance of plasma protein and tissue binding…

- Protein binding reduces diffusion of the drug into the cell and thereby **delays its metabolism** (breakdown)
- Protein binding also reduces the amount of drug available for filtration at the glomeruli and hence **delays its excretion.**
- Free and bound fractions are in equilibrium and free drug removed from the plasma by metabolism is replaced by drug released from the bound fraction.

Significance of plasma protein and tissue binding…

- Since it is the diffusible portion of the drug that determines its activity, highly protein-bound drugs may have too low concentrations in interstitial fluid, CSF and tissue cells to combat dangerous infections.
- Some drugs are extensively tissue-bound. This delays elimination from the body and accounts for the long half-life.

Apparent volume of distribution

- Presuming that the body behaves as a single homogenous compartment with volume V into which drug gets immediately and uniformly distributed:
- $V = \frac{\text{dose administered I.V.}}{\text{Plasma concentration}}$
- This is only an apparent volume of distribution which can be defined as: “the volume that would accommodate all the drug in the body, if the concentration throughout was the same as in plasma”.
- Thus, it describes the amount of drug present in the body as a multiple of that contained in a unit volume of plasma.

Volume of distribution…

- The apparent volume of distribution is the theoretical volume of fluid into which the total drug administered would have to be diluted to produce the concentration in plasma.
- For a drug that is highly tissue-bound, very little drug remains in the circulation; thus, plasma concentration is low and volume of distribution is high.
- Drugs that remain in the circulation tend to have a low volume of distribution.

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The end

Thank you.

Pharmacokinetics

METABOLISM (BIOTRANSFORMATION) OF DRUGS

Learning objectives

- Define metabolism of drugs
- State the three possible fates of drugs after absorption
- State the two major ways in which metabolism changes drugs
- Discuss how metabolism reduces lipid solubility
- Discuss how metabolism alters biological activity of a drug
- State the reactions that bring about metabolic changes
- Describe the two phases of metabolism

Definition

- Metabolism is the process of chemical alteration of drugs in the body.
- i.e. the chemical alterations that occur to the drug within the body.

Fate of drugs after absorption

- The three possible fates of drugs after absorption are:

1. They could be metabolized by enzymes
2. They could change spontaneously into other substances without the intervention of enzymes
3. They could be excreted unchanged.

Ways in which metabolism changes drugs

- The processes of metabolism change drugs in two major ways:
  1. By reducing lipid solubility
  2. By altering biological activity

Reducing lipid solubility

- Metabolic reactions tend to **make a drug molecule more water-soluble** and so favour its **elimination** in the urine.
- Drug metabolism often converts **lipophilic** chemical compounds into more readily excreted **hydrophilic** products.
- Products of lipid soluble drugs are thus more water soluble and more readily excreted by the kidneys.

Altered biological activity

- Drugs are metabolized by enzymes with resultant:
  - Activation
  - Inactivation
  - Modification
- The end result of metabolism is the **abolition of biological activity**.

Altered biological activity

- Steps in drug metabolism:

1. Conversion of a pharmacologically active to an inactive substance. This applies to most drugs.
2. Conversion of a pharmacologically active to another active substance. This has the effect of prolonging drug action.
3. Conversion of a pharmacologically inactive to an active substance, i.e. prodrugs.

Organs of metabolism

- The liver is the most important organ for drug metabolism.
- Other tissues also contribute:
  - Kidneys
  - Gut mucosa
  - Lungs
  - Skin
  - Plasma

Organs of metabolism…

- The liver has special drug metabolizing enzyme system. Therefore:
  - In liver disease drugs may be poorly metabolized, hence drug excretion is reduced.
  - In a diseased liver, use of drugs may aggravate the illness.
  - In neonates the liver microsomal enzyme system that metabolizes drugs is poorly developed and thus drug metabolism is slow, hence excretion is slower than in adults.

Reactions that bring about metabolic changes (biotransformation reactions)

NON-SYNTHETIC REACTIONS

1. Oxidation
2. Reduction
3. Hydrolysis
4. Cyclization
5. Decyclization

SYNTHETIC REACTIONS

1. Glucuronide conjugation
2. Acetylation
3. Methylation
4. Sulphate conjugation
5. Glycine conjugation
6. Glutathione conjugation
7. Ribonucleoside/ nucleotide synthesis

Non-synthetic or phase I reactions

- Phase I reactions may occur by oxidation, reduction, hydrolysis, cyclization, and decyclization.
- If the metabolites of phase I reactions are sufficiently polar, they may be readily excreted at this point.
- However, many phase I products are not eliminated rapidly and undergo a subsequent reaction in which an **endogenous substrate** combines with the newly incorporated functional group to form a highly **polar conjugate.**

Non-synthetic or phase I reactions

- A common Phase I oxidation involves conversion of a C-H bond to a C-OH.
- This reaction sometimes converts a pharmacologically inactive compound (a **prodrug**) to a pharmacologically active one.

Non-synthetic reactions

Oxidation:

- Involves addition of oxygen/ negatively charged radical or removal of hydrogen / positively charged radical.
- Oxidations are the most important drug metabolizing reactions
- Oxidation results in loss of electrons from the drug.
- Oxidation reactions include:
  - Hydroxylation
  - Oxygenation at C, N or S atoms
  - N- or O-dealkylation
  - Oxidative deamination

Non-synthetic reactions

Reduction:

- This is the converse of oxidation (and involves cytochrome P-450 enzymes working in opposite direction)
- Cytochrome P450 enzymes are housed in the smooth endoplasmic reticulum of the cell.

Hydrolysis:

- This is cleavage of drug molecule by taking up a molecule of water.
- Hydrolysis occurs in liver, intestines, plasma and other tissues.

Non-synthetic reactions

Cyclization:

- This is formation of ring structure from a straight chain compound. E.g. proguanil.

Decyclization:

- This is opening up of ring structure of the cyclic drug molecule, e.g. barbiturates and phenytoin.

Synthetic reactions

- These involve **conjugation** of the drug or its phase I metabolite with an endogenous substrate, to form a **polar**, highly ionized organic acid, which is **easily excreted** in urine or bile.
- Conjugation reactions have high energy requirement.

Synthetic reactions

Glucuronide conjugation:

- This is the most important synthetic reaction.
- Occurs in the hepatocyte cytoplasm
- The attachment of an ionized group makes the metabolite more water soluble.
- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose. E.g. chloramphenicol, aspirin, morphine, metronidazole.

Synthetic reactions

Acetylation:

- Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A. e.g.
  - Sulphonamides
  - Isoniazid
  - Paraaminosalicylic acid
  - hydralazine

Synthetic reactions

Methylation:

- The amines and phenols can be methylated. E.g. adrenaline, histamine.

Sulphate conjugation:

- The phenolic compounds and steroids are sulfated by sulfokinases. E.g. chloramphenicol, adrenal and sex steroids.

Phases of metabolism

- There are two phases of metabolism:
  1. **Phase I metabolism**
     - Nonsynthetic reactions
  2. **Phase II metabolism**
     - Synthetic/ conjugation reactions

Phase I metabolism

- This phase brings about a change in the drug molecule by oxidation, reduction or hydrolysis.
- Oxidation, reduction and hydrolysis introduce polar groups such as hydroxyl, amino, carboxyl into drugs, which are consequently made water-soluble, and pharmacologically less active.

Phase I metabolism…

- The new metabolite may retain biological activity but have different pharmacokinetic properties, e.g. a shorter half-life.
- The most important single group of reactions is oxidation, in particular those undertaken by the so-called **mixed-function (microsomal) oxidases.** These are capable of metabolizing a variety of compounds.

Phase I metabolism…

- Phase I oxidation of some drugs results in formation of **epoxides**, which are short-lived and highly reactive metabolites.
- Epoxides are important because they can bind irreversibly through covalent bonds to cell constituents; indeed this is one of the principal ways in which drugs are toxic to body tissues.
- **Glutathione** is a tripeptide that combines with epoxides, rendering them inactive. Its presence in the liver is part of an important defense mechanism against hepatic damage by halothane and paracetamol.

Phase II metabolism

- This involves union of the drug with one of several polar endogenous molecules to form a water-soluble conjugate which is readily eliminated by the kidney or if the molecular weight exceeds 300, in bile.
- Morphine, paracetamol and salicylates form conjugates with glucuronic acid.
- Oral contraceptive steroids form sulphates
- Isoniazid, phenelzine and dapsone are acetylated.
- Phase II metabolism almost invariably terminates biological activity.

Enzyme induction

- Enzyme induction is a process by which enzyme activity is enhanced, usually because of **increased enzyme synthesis** (or, less often, reduced enzyme degradation).
- The capacity of the body to metabolize drugs can be altered by certain medicinal drugs themselves or other substances that induce enzyme activity.
- These stimulate the microsomal enzyme systems (enzyme induction) accelerating biotransformation of drugs.

Enzyme induction…

Relevance of Enzyme induction to drug therapy:

- *Clinically important drug reactions may result* , e.g. failure of oral contraceptives or loss of anticoagulant control.
- *Disease may result* ; e.g. antiepilepsy drugs increase the breakdown of dietary and endogenously formed vitamin D, producing an inactive metabolite – in effect vitamin D deficiency state, which can result in osteomalacia.
  - The accompanying hypocalcemia can increase the tendency to fits and a convulsion may lead to fracture of the demineralized bones.

Enzyme induction…

Relevance of enzyme induction…

- *Tolerance to drug therapy* may result in and provide an explanation for sub-optimal treatment, e.g. with an antiepilepsy drug.
- *Variability in response to drugs* : enzyme induction caused by heavy alcohol drinking or heavy smoking may be an unrecognized cause for failure of an individual to achieve the expected response to a normal dose of a drug.

Enzyme induction…

Relevance of enzyme induction…

- *Drug toxicity may be more likely* . A patient who becomes enzyme-induced by taking rifampicin is more likely to develop liver toxicity after paracetamol overdose by increased production of a hepatotoxic metabolite.

Substances that cause enzyme induction

- Barbiturates
- Barbequed meats
- Carbamazepine
- Ethanol
- Griseofulvin
- Phenytoin
- Rifampicin
- Tobacco smoke

Enzyme inhibition

- Some drugs inhibit enzyme activity thereby inhibiting metabolism of other drugs.
- Consequences of inhibiting drug metabolism can be more profound than those of enzyme induction.
- Enzyme inhibition is more selective and offers more scope for therapy.

Examples of enzyme inhibition

- Acetazolamide inhibits carbonic anhydrase and is used for the treatment of glaucoma.
- Allopurinol inhibits xanthine oxidase and is used for the treatment of gout.
- Disulfiram inhibits aldehyde dehydrogenase and is used for treatment of alcoholism.
- Enalapril inhibits angiotensin-converting enzyme and is used for treatment of hypertension and cardiac failure.

Thanks.

The end.

BIOLOGICAL HALF-LIFE OF DRUGS

AND ITS SIGNIFICANCE

Learning objectives

- Define *biological half-life* of a drug
- Explain its importance
- Explain *exponential kinetics* (first-order kinetics) in relation to drug elimination
- Describe the *steady state concentration* of a drug
- Show how the plasma half-life of a drug can be used to know when the steady state concentration of a drug has been reached
- Distinguish *zero-order kinetics* from first-order kinetics

Biological half-life

- ***Biological half-life*** of a drug is the time required to reduce its concentration in the body compartments by 50%.
- The***biological*** half-life of a drug is an estimate of the time it takes for the concentration or amount in the***body*** of that drug to be reduced by exactly one half (50%).
- It may also be called the elimination half life.
- The symbol for half-life is T½.

Biological half-life

Importance:

- It gives a measure of drug elimination
- It guides drug therapy
- It may be used to predict the manner in which plasma concentration alters in response to starting, altering or ceasing drug administration.

Biological half-life

Importance …

- Drugs that have a shorter half-life tend to act very quickly, but their effects wear off rapidly, and thus they usually need to be taken several times a day to have the same effect.
- Drugs with a longer half-life may take longer to start working, but their effects persist for longer, and they may only need to be dosed once a day, once a week, once a month, or even less frequently.

Plasma half-life

- The ***plasma*** half-life of a drug is an estimate of the time it takes for the concentration or amount of that drug in the ***plasma*** to be reduced by exactly one half (50%).
- This can be **different from the biological or elimination half-life** of a drug because it depends on: -
  - How well the drug is distributed in the body,
  - whether it binds to proteins,
  - Whether it reaches a saturation point.

Exponential (First-order) Kinetics

- Drugs taken into the body are subject to processes of absorption, distribution, metabolism and excretion.
- In the majority of instances, the rates at which these processes occur are directly proportional to the concentration of the drug.
- Transfer of drug across a cell membrane or formation of a metabolite is high at high concentrations and falls in direct proportion to be low at low concentrations.

Exponential (First-order) Kinetics...

- This is because the processes follow the **law of mass action**, which states that the rate of reaction is directly proportional to the active masses of reacting substances.
- In other words, at high concentrations, there are more opportunities for crowded molecules to interact with each other or to cross cell membranes than at low, uncrowded concentrations.

Exponential (First-order) Kinetics...

- Elimination of most drugs follows exponential kinetics. i.e.: -
- A **constant fraction** of the drug in the body disappears in each equal interval of time - usually reflected in the rate of lowering of the plasma concentration.

Exponential (First-order) Kinetics...

- The drug is removed from the body not at a constant rate but at a rate proportional to its plasma concentration; so that **a constant fraction of the drug is eliminated in unit time**.
- Processes for which rate is proportional to concentration are said to undergo ***first-order (exponential) kinetics***.

Exponential kinetics…

- For example, if 100mg of a drug with a half-life of 60 minutes is taken, the following is estimated:
  1. 60 minutes after administration, 50mg remains
  2. 120 minutes after administration, 25mg remains
  3. 180 minutes after administration, 12.5mg remains
  4. 240 minutes after administration, 6.25mg remains
  5. 300 minutes after administration, 3.125mg remains.
- Observe that after 300 minutes, almost 97% of this drug is expected to have been eliminated. Most single dose drugs are considered to have a negligible effect after four-to-five half-lives.

Exponential (First-order) Kinetics...

- With drugs whose elimination is exponential, the biological half-life is independent of:
  - The dose
  - The rate of administration and
  - The plasma concentration
- However, the actual quantity of the drug removed per unit time is smaller at lower plasma concentrations and larger at higher plasma concentrations.

How plasma concentration increases after dosing begins

- When a drug is given at a constant rate the amount in the body and with it the plasma concentration rise until a state is reached at which the rate of administration of drug to the body is exactly equal to the rate of elimination.
- This is called the **steady state** and when it is attained the amount of drug in the body remains constant; the plasma concentration is on a **plateau**.

Increase in plasma conc. with dosing…

- If a drug is given by intermittent oral or intravenous dose, the plasma concentration will fluctuate between peaks and troughs, but in time all the troughs will be of equal length.
- This is also called a steady-state concentration, since the mean concentration is constant.

How the plasma half-life of a drug can be used to know when the steady state concentration of a drug has been reached:

- Certain simple and valuable calculations are dependent on knowing the plasma half-life of a drug: -
  - Estimation of time taken to eliminate a drug
  - Construction of dosing schedules
  - Prediction of the time to achieve steady state plasma concentration.

Plasma half-life and steady-state concentration...

- It is important to know when the steady state concentration of a drug has been reached, for maintaining the same dosing schedule will ensure a constant amount of the drug action and the patient will experience neither toxicity nor decline of effect.

Prediction of steady state concentration…

- The t ½ provides the answer:
  - With the passage of each t ½ period of time, the plasma concentration rises by *half the difference between the current concentration and the ultimate steady state (100%) concentration.*
  - The significant fact is that when a drug is given at a constant rate the time to reach the steady state depends only on the plasma half-life.
  - For all practical purposes, after 5 t ½s the amount of drug in the body will be constant and the plasma concentration will be at a plateau.

Rise in plasma concentration of a drug administered by constant I.V. infusion

- In 1 x t ½ the concentration will reach 100/2 = 50%
- In 2 x t ½ the concentration will reach 50+50/2 = 75%
- In 3 x t ½ the concentration will reach 75+25/2 = 87.5%
- In 4 x t ½ the concentration will reach 87.5+12.5/2 = 93.75%
- In 5 x t ½ the concentration will reach 93.75+6.25/2 = 96.875% of the ultimate steady state.

Zero-order Kinetics

- As the amount of drug in the body rises, those processes that have limited capacity become saturated, i.e. the rate of the process reaches a maximum at which it stays constant.
- For example, due to limited amount of enzyme, where further increase in rate is impossible despite an increase in the dose of the drug.

Zero-order kinetics…

- Clearly, these are circumstances in which the rate of reaction is not proportional to dose and processes that exhibit this type of kinetics are described as:
  - *Rate limited* or
  - *Dose dependent* or
  - *Zero order* or as showing
  - *Saturation kinetics*

Zero-order kinetics…

- In practice enzyme mediated metabolic reactions are the most likely to show rate-limitation because the amount of enzyme present is finite and can become saturated.
- Examples:
  - Alcohol and Phenytoin initially show first-order kinetics but as the amount of drug in the body increases their elimination becomes zero-order.

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The end.

Thank you.

EXCRETION OF DRUGS

Pharmacokinetics

Learning objectives

- Define excretion of drugs
- Name the organs of drug excretion
- Describe the processes which contribute to drug elimination from the kidneys
- Explain how *ionisation of a drug* and *pH of urine* affects drug elimination
- Discuss biliary excretion of drugs

Introduction

- Excretion of drugs is the process through which drugs are removed from the body.
- Drugs are removed from the body after being partly or wholly *converted to water-soluble metabolites* or, in some cases, without being metabolised.

Organs of drug excretion

- The ***kidney*** is the major organ of drug excretion.
- Others are:
  - Biliary tract
  - Intestines e.g. those not absorbed
  - Saliva
  - Skin through sweat or hairs falling off (e.g. heavy metals like mercury and arsenal)
  - Breast milk
  - Lungs e.g. volatile general anaesthetics

Principal organs involved:

- Kidneys (Renal Excretion)
- Bile (Biliary Excretion)
- Lungs (Pulmonary Excretion)
- Saliva (Salivary Excretion)
- Milk (Mammary Excretion)
- Sweat (Skin Excretion)

Renal Elimination

Processes which contribute to drug elimination

1. Passive glomerular filtration
2. Active tubular secretion
3. Passive diffusion across the tubules (renal tubular re-absorption)

Passive glomerular filtration

- Substances with molecular weight less than 10,000 (includes almost all drugs) pass easily through the pores of the glomerular membrane.
- Those that have a molecular weight in excess of 50,000 are excluded from the glomerular filtrate.

Passive glomerular filtration

- **Ionised** drugs, which are poorly absorbed, are excreted almost entirely by glomerular filtration and are **not reabsorbed**.
- **Unionised** drugs, which are well absorbed, are filtered at the glomerulus, but they can **diffuse back** from the lumen of the renal tubule into the cells lining the tubules.

Active tubular secretion

- Some drugs are actively secreted into the renal tubules by the system responsible for the transfer of naturally occurring substances like uric acid.
- Cells of the proximal renal tubule actively transfer strongly charged molecules from the plasma to the tubular fluid. There are two such systems, one for acids, e.g. penicillin, frusemide, and one for bases, e.g. amiloride, amphetamine.

Active tubular secretion…

- Metabolic inhibitors can block this mechanism.
- For example, excretion of penicillin can be competitively inhibited by Probenecid.
- This leads to the prolongation of the half-life of the drug and higher concentration in blood for longer periods.

Passive diffusion

- This is a bi-directional process and drugs may diffuse across the tubules in either direction depending upon the drug concentration and the pH.

Ionisation of a drug and pH of tubular fluid

- Since the tubular epithelium has the properties of a lipid membrane, the extent to which a drug diffuses back into the blood will depend on its lipid solubility, i.e. on its dissociation constant and on the pH of the tubular fluid.

Passive diffusion…

- If the fluid becomes more alkaline, an acidic drug ionises, becomes less lipid soluble, and its re-absorption diminishes, but a basic drug becomes un-ionised (and therefore more lipid soluble) and its re-absorption increases.
- Therefore, the *pH of urine* (tubular fluid) exerts an influence on the excretion of certain weak acids and bases.

Passive diffusion…

- *Weak acids are quickly eliminated in alkaline urine*
  - e.g. barbiturates and salicylates.
- *Weak bases are rapidly excreted in acidic urine*
  - e.g. pethidine, amphetamine.

Passive diffusion…

Importance :

- May be used to enhance the elimination of drugs in overdose (poisoning) with either weak acids or weak bases e.g. phenobarbitone or aspirin.
  - Sodium bicarbonate is given to treat overdose with aspirin.

Biliary excretion of drugs

- Some drugs are *excreted actively* by liver cells into bile.
- In the liver there is one active transport system for acids and one for bases, and in addition, there is a system that transports un-ionised molecules e.g. digoxin into the bile.
- Small molecules tend to be reabsorbed by the bile canaliculi and in general only compounds that have a molecular weight greater than 300 are excreted in bile.
- Impaired liver functions lead to decreased liver secretion.

Examples of drugs excreted through the biliary tract

- Erythromycin
- Doxycycline
- Minocycline
- Chlortetracycline
- Chloramphenicol
- Phenolphthalein
- Novobiocin
- Oral contraceptives
- Ampicillin
- Rifampicin
- Some of these drugs are reabsorbed in the intestines (enterohepatic cycling) and ultimately excreted in urine.

Pulmonary Excretion

- Gases and other volatile substances such as general anesthetics that enter the body primarily through the respiratory tract can be expected to be excreted by this route.
- No specialized transport systems are involved in the loss of substances in expired air; simple diffusion across cell membranes is predominant.
- The rate of loss of gases is not constant; it depends on the rate of respiration and pulmonary blood flow.

- The degree of solubility of a gas in blood also will affect the rate of gas loss.
- Gases such as nitrous oxide, which are not very soluble in blood, will be excreted rapidly, that is, almost at the rate at which the blood delivers the drug to the lungs.
- Ethanol, which has a relatively high blood gas solubility, is excreted very slowly by the lungs.

Salivary excretion

- The pH of saliva varies between 5.8 and 8.4
- Unionized lipid soluble drugs are excreted passively
- The bitter taste in the mouth of a patient is indicative of drug excretion through saliva
- Compounds excreted in saliva include caffeine, phenytoin and theophylline.

Mammary Excretion

Milk consists of lactic secretions which is rich in fats and proteins.

- Excretion of drug in milk is important as it gains entry in breast feeding infants.
- pH of milk varies from 6.4 to 7.6. Free un-ionized and lipid soluble drugs diffuse passively.
- Highly plasma bound drug like Diazepam is less secreted in milk.

EXCRETION PATHWAYS, TRANSPORT MECHANISMS & DRUG EXCRETED.

Excretory route	Mechanism	Drug Excreted
Urine	GF, ATS, PTR	Free, hydrophilic, unchanged drugs/ metabolites of MW< 300
Bile	Active secretion	Hydrophilic, unchanged drugs/ metabolites/ conjugates of MW >500
Lung	Passive diffusion	Gaseous &volatile, blood & tissue insoluble drugs
saliva	Passive diffusion Active transport	Free, unionized, lipophilic drugs. Some polar drugs
Milk	Passive diffusion	Free, unionized, lipophilic drugs (basic)
Sweat	Passive diffusion	Free, unionized lipophilic drugs

The end.

Thank you

PRESCRIPTION OF DRUGS

P.J. Okoth

Prescription of drugs

- The treatment of a sick person includes many aspects, and administration of drugs is one of them.
- In certain patients drugs are of the greatest importance while in others they have only a minor role to play.

Prescription of drugs

- **Before prescribing drugs one should know:**
  1. Pharmacological actions and toxicity of the drug he uses
  2. The natural course of the disease he is treating
  3. Reasons for choosing a particular preparation, more so if it is a costly one
  4. The possible interactions when several drugs are administered simultaneously
  5. The cost of the therapy
  6. Benefits versus risks of using the drug
  7. Availability of the drug

Components of a prescription

A prescription should include the following:

1. Date of prescription
2. Patient information:
    1. Name of the patient
    2. Age of the patient – especially important in children to allow for the pharmacist to check the correctness of the dose
    3. Sex of the patient
    4. Patient's number (OP or IP) where necessary
3. Superscription: take thou of (Rx symbol)

Components of a prescription

4. **Inscription**:
   - The name of the drug
   - The form in which the drug is to be supplied – syrup, tablet, capsule, injection, cream, suppository, pessary, etc.
5. **Subscription**: instructions to the pharmacist or dispenser to compound medications. It indicates the quantity of medication (number of capsules, tablets) or the size of bottle to be dispensed (5ml, 10ml, 15ml).

Components of a prescription

6. **Transcription**: instructions to the pharmacist or dispenser indicating how the patient should use the medication.
   - The dose (amount of drug)
   - The frequency
   - The duration of the therapy
   - The route of administration
   - The manner in which the drug is to be taken e.g. chew, swallow whole, take with meals, after meals or on an empty stomach
7. **Signature** of the licensed practitioner or prescriber.

ABBREVIATIONS IN PRESCRIPTION WRITING

P. J. Okoth

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
a.c.	ante cibum	before meals
ad lib.	ad libitum	use as much as one desires; freely
a.m.	ante meridiem	morning, before noon
amp		ampoule
aq	aqua	water
b.i.d.	bis in die	twice daily
bol.		bolus as a large single dose (usually intravenously

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
cap., caps.	capsula	capsule
c	cum	with (usually written with a bar on top of the "c")
comp.		compound
elix.		elixir
emuls.	emulsum	emulsion
g		gram
gtt(s)	gutta(e)	drop(s)

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
h, hr	hora	hour
h.s.	hora somni	at bedtime
ID		intradermal
IM		intramuscular (with respect to injections)
inj.	injectio	injection
IP		intraperitoneal
IV		intravenous

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
lin	linimentum	liniment
mcg		microgram
mg		milligram
mist.	mistura	mixture
mL		millilitre
nocte	nocte	at night

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
non rep. (non repet.)	non repetatur	no repeats (not to be repeated)
NS		normal saline (0.9%)
per	per	by or through
p.c.	post cibum	after meals
p.m.	post meridiem	evening or afternoon
prn	pro re nata	as needed (as need arises)
p.o.	per os	by mouth or orally

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
p.r.	Per rectum	by rectum
q	quaque	every
q.h.	quaque hora	every hour
q.h.s.	quaque hora somni	every night at bedtime
q.1h	quaque 1 hora	every 1 hour; (can replace "1" with other numbers)
q.d.	quaque die	every day
q.i.d.	quater in die	four times a day

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
repet.	repetatur	Repeats (to be repeated)
s	sine	without (usually written with a bar on top of the "s")
U		Units
MU		Mega units
IU		International units
x		for
OD		Once a day

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
SC		subcutaneous
SL		sublingually, under the tongue
sol	solutio	solution
stat	statim	immediately
supp	suppositorium	suppository
susp		suspension
syr	syrupus	syrup

Abbreviations in prescription writing

Abbreviation	From the Latin	Meaning
tab	tabella	tablet
t.i.d.	ter in die	three times a day
t.d.s.	ter die sumendum	three times a day
t.i.w.		three times a week
top.		topical
T.P.N.		total parenteral nutrition
tinc., tinct.		tincture

Prescription writing

Practice prescription writing using correct format and abbreviations:

1. Septrin tablets, two to be taken twice daily for five days.
2. Intramuscular injection of chlorpromazine, fifty milligrams immediately, then tablets twenty-five milligrams orally twice daily.
3. Methyldopa tablets, two hundred and fifty milligrams to be taken three times daily for two weeks.

Prescription writing…

4. Frusemide tablets, forty milligrams once daily for one month.
5. Omeprazole capsules twenty milligrams once daily for four weeks.
6. Paracetamol tablets one gram three times a day for three days.
7. Intravenous ceftriaxone four grams immediately, then two grams once daily for ten days.

Prescription writing…

8. Piriton tablets four milligrams three times a day for four days.
9. Cetirizine tablets ten milligrams once daily for five days.
10. Norfloxacin tablets four hundred milligrams twice daily for five days.
11. Adrenaline injection 0.5 milliliters subcutaneously, immediately. Repeat same dose after half an hour.

Prescription writing…

12. Tetracycline capsules five hundred milligrams every six hours for five days.
13. Actal tablets, chew two when the need arises.
14. Erythromycin syrup, five milliliters four times a day for one week.
15. Intravenous fifty per cent dextrose, twenty milliliters immediately as a bolus.
16. Crystapen injection two mega units intravenously, six hourly for forty-eight hours, then review.

The end.

Thank you.

PHARMACOKINETICS

DRUG MOVEMENT ACROSS CELL MEMBRANES

Introduction

- Pharmacokinetics is the process whereby drug concentrations at effecter sites are achieved, maintained and diminished; that is, the study of the absorption, distribution, metabolism and excretion of drugs in the intact animal or human.
- The quantitative study of drug movement in, through and out of the body.

Importance

- Pharmacokinetics quantifies the component parts of drug disposition to determine:
  - Absorption
  - Distribution
  - Metabolism
  - Elimination

Importance

- It helps to know the:
  - Optimum routes
  - Absorption rates
  - Timing of drug administration
- Regimes of drug administration are determined from pharmacokinetic studies.

Importance…

- Pharmacokinetics is concerned with the rate at which drug molecules cross cell membranes to enter the body, to distribute within it and to leave the body, as well as with the structural changes (metabolism) to which they are subject within it.

Drug movement across cell membranes

Pharmacokinetics

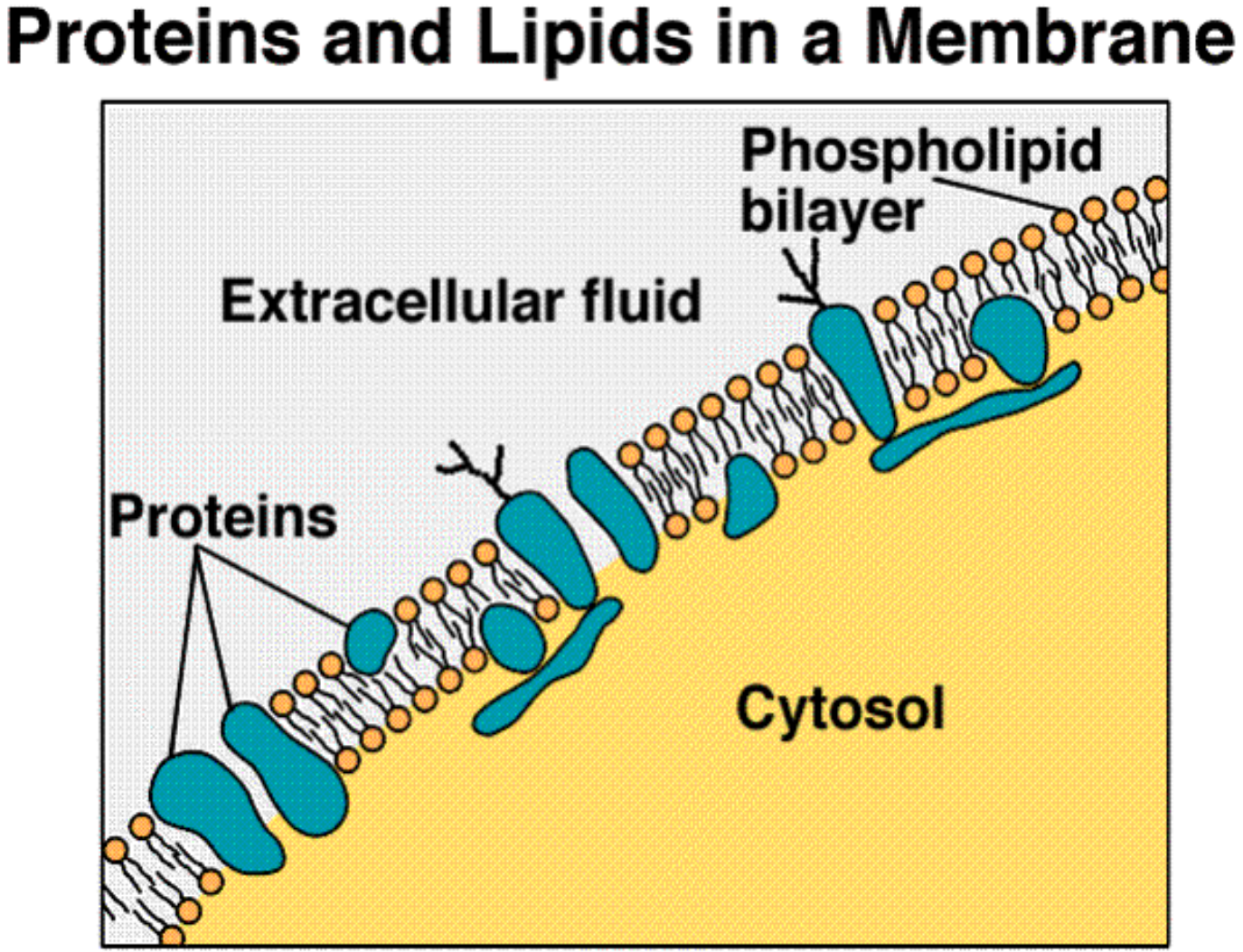
Learning objectives

- Describe the components of a cell membrane
- Explain how passage across cell membranes affects drug use
- Describe the processes through which drugs cross cell membranes
- Describe the physicochemical classification of drugs and explain its relationship to drug passage across cell membranes
- Explain the clinical relevance of drug passage across cell membranes

Structure of cell membrane

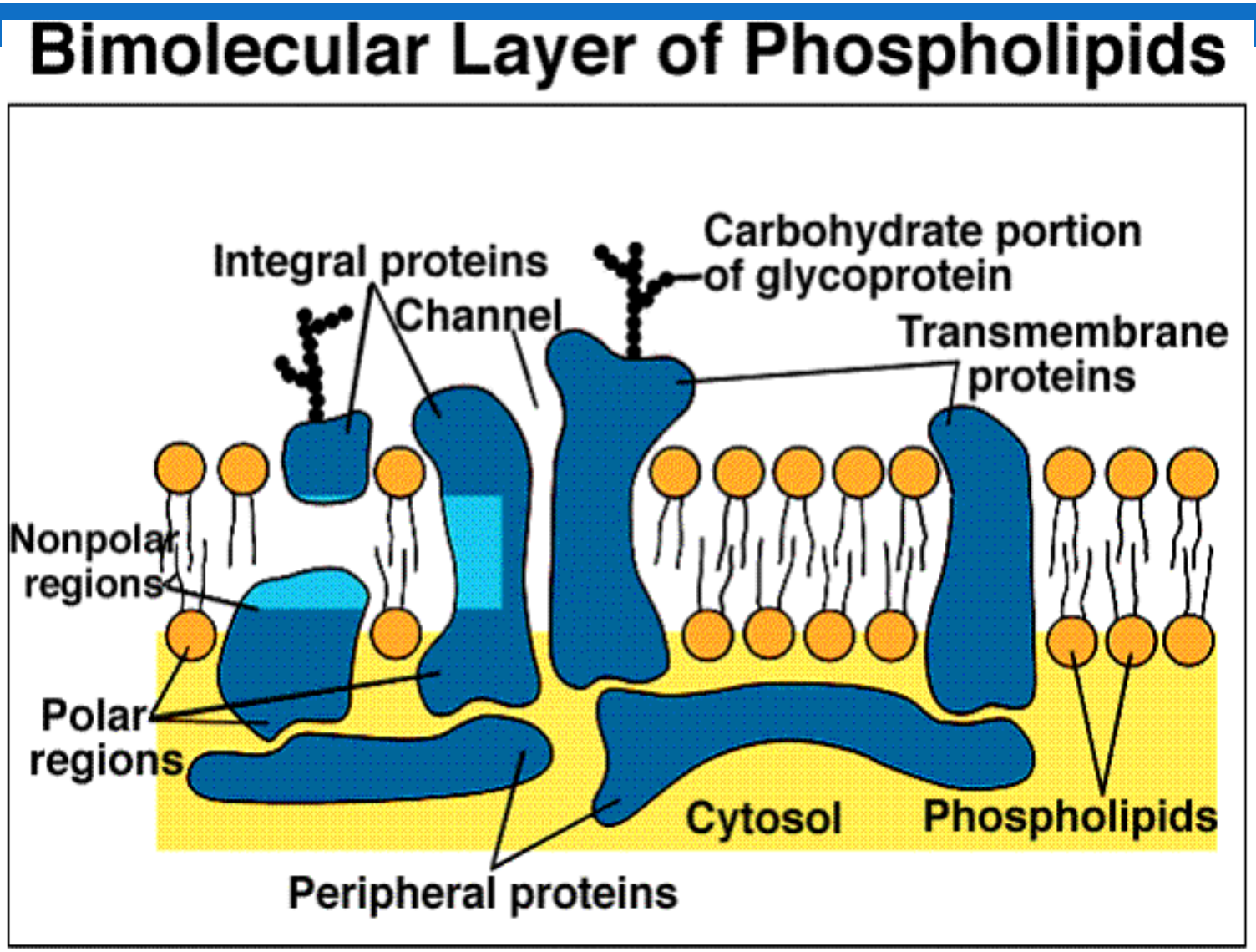
- Cell membranes are essentially bilayers of lipid molecules with ‘islands’ of protein.
- The hydrophilic ends of the lipids orientate themselves at both the inner and outer surfaces, while the hydrophobic portions occupy the center of the membrane.

Cell membrane…



Mr. Okoth

Cell membrane…



Cell membrane structure…

- Integral proteins extend the full length of the membrane and show a predominance of either hydrophilic or hydrophobic groups at their surfaces – contiguous to the corresponding lipids according to their depth within the membrane.
- Peripheral proteins are attached either to integral proteins at the inner side of the membrane and are predominantly hydrophilic or to the hydrophilic ends of lipids at either surface.

Cell membrane structure…

- Some of the integral proteins, which extend through the full thickness of the membrane, surround fine aqueous pores.
- Carbohydrates – glycoproteins or glycolipids are formed on the outer surface of the membrane by the attachment of different polymeric arrangements of monosaccharides.

Relationship with drug use

- The extent to which a drug can cross epithelia is fundamental to its clinical use.
- It is the major factor that determines whether a drug can be taken orally for systemic effect and whether within the glomerular filtrate it will be reabsorbed or excreted in the urine.
- Lipid-soluble substances diffuse readily into cells and therefore throughout body tissues.

Relationship with drug use

- Adjacent epithelial or endothelial cells are joined by tight junctions, some of which contain water-filled channels through which water-soluble substances of small molecular size may filter.
- The **jejunum** and **proximal renal tubules** contain many such channels and are called **leaky epithelia**.
- The tight junctions in the **stomach** and **urinary bladder** do not have these channels and water cannot pass; they are termed **tight epithelia**.
- Special protein molecules within the lipid bilayer allow specific substances to enter or leave the cell preferentially (carrier proteins)

Processes through which drugs pass across membranes

- The passage of drugs across cell membranes is determined by the natural processes of:
  1. Filtration
  2. Carrier-mediated transport
  3. Diffusion

Filtration

- Aqueous channels in the tight junctions between adjacent epithelial cells (paracellular spaces) allow the passage of some water-soluble substances.
- Filtration is mainly important in drug excretion by glomerular filtration.
- Capillaries (except those in the brain) have large pores and most drugs filter through these.
- Diffusion of drugs through capillaries is dependent on the rate of blood flow through them rather than on lipid solubility or pH.

Filtration…

- Drugs may also pass through aqueous pores in the membrane.
- Majority of cells (including intestinal mucosa) have very small pores and drugs with molecular weight of more than 100 or 200 are not able to penetrate.

Carrier-mediated transport

- This comprises active transport and facilitated diffusion
- In carrier transport, the drug combines with a carrier present in the membrane and the complex then translocates from one face of the membrane to the other.
- The carriers for polar molecules appear to form a hydrophobic coating over the hydrophilic groups and thus facilitate passage through the membrane.
- Carrier transport is specific, saturable and is competitively inhibited by analogues which utilize the same carrier.

Active transport

- This is a specialized process requiring energy and enables some drugs to move into or out of cells against a concentration gradient.
- They often require a carrier substance, and the movement is independent of the physical properties of the membrane.
- It results in selective accumulation of the substance on one side of the membrane.

Facilitated diffusion

- This is carrier mediated transport that does not require energy.
- This proceeds more rapidly than simple diffusion and translocates even non-diffusible substrates, but along their concentration gradient.
- It, therefore, does not require energy.
- Vitamin B12 absorption is an example.

Diffusion

- This is the most important means by which a drug enters the tissues and is distributed through them.
- Simple diffusion requires:
  - A favorable concentration gradient of the drug
  - Sufficient lipid-solubility to pass through the membrane.

Diffusion …

- In the context of an individual cell, the drug moves passively at a rate proportional to the concentration difference across the cell membrane; that is, it shows **first-order kinetics**.
- Cellular energy is not required, which means that the process does not become saturated and is not inhibited by other substances.

Diffusion…

- Drugs exhibit greater or less degrees of lipid solubility according to environmental pH and the structural properties of the molecule.
- Broadly, water solubility favored by the possession of alcoholic (-OH), amide (-CO.NH2) or carboxylic (-COOH) groups, and the formation of glucuronide and sulphate conjugates.
- Presence of a benzene ring, a hydrocarbon chain, a steroid nucleus or halogen (-Br, -Cl, -F) groups favours lipid solubility.

Physicochemical classification of drugs

- Drugs can be classified in a physicochemical sense into:
- Those that are **variably ionized** according to environmental pH (electrolytes). These can either be **lipid soluble** or **water-soluble**, depending on the environmental pH.
- Those that are **incapable of becoming ionized** whatever the environmental pH (unionized, non-polar substances). These are **lipid soluble**.
- Those that are **permanently ionized** whatever the environmental pH (ionized polar substances). These are **water-soluble**.

Drugs that are variably ionized according to the environmental pH

- Many drugs are weak **electrolytes**, i.e. their structural groups ionize to a greater or lesser extent, according to environmental pH.
- Most such elements are present partly in the ionized and partly in the un-ionized state.
- The degree of ionization influences lipid solubility (and hence diffusibility) and so affects absorption, distribution and elimination.

Drugs that are variably ionized…

- Ionizable groups in a drug molecule tend either to lose a hydrogen ion (acidic groups) or to add a hydrogen ion (basic groups)

Drugs that are variably ionized…

- In an acidic environment, i.e. one already containing many hydrogen ions, an acidic group tends not to lose a hydrogen ion and remains un-ionized.
- A relative deficit of hydrogen ions, i.e. a basic environment, favors dissociation of the hydrogen ion from an acidic group which thus becomes ionized.
- The opposite is the case for a base.

Drugs that are variably ionized…

- **In summary:**
  - Acidic groups become less ionized in acidic environment
  - Basic drugs become less ionized in a basic (alkaline) environment and vice versa.
  - This in turn influences diffusibility since:
  - Un-ionized drugs are lipid-soluble and diffusible, and
  - Ionized drugs are lipid-insoluble and non-diffusible.

Drugs that are incapable of becoming ionized

- These include digoxin and chloramphenicol.
- Having no ionizable groups, they are unaffected by the environmental pH, are lipid-soluble and diffuse readily across tissue boundaries.

Drugs that are predominantly ionized

- These drugs **remain ionized** at all values of pH. This is because they carry groups which dissociate so strongly.
- Such compounds are called **polar**, as their groups are either negatively charged (acidic, e.g. heparin) or positively charged (basic, e.g. tubocurarine) and all have very limited capacity to cross cell membranes.
- Advantage: heparin is a useful anticoagulant in pregnancy because it does not cross the placenta.
- Disadvantage: heparin must be given parenterally as the gut does not absorb it.

The clinical relevance of drug passage across membranes

Blood-brain barrier:

- The capillaries of the cerebral circulation lack the channels between endothelial cells through which substances in the blood normally gain access to the extracellular fluid.
- There are tight junctions between adjacent capillary endothelial cells, which together with their basement membrane separate the blood from the brain tissue.

Clinical relevance – blood-brain barrier

- This blood-brain barrier places constraints on the passage of substances from blood to the brain and CSF.
- Compounds that are lipid-insoluble do not cross it readily, e.g. atenolol, compared with propranolol (lipid-soluble), and CNS side effects are prominent with the latter.
- Therapy with methotrexate (lipid-insoluble) may have no effect on leukaemic cells in the CNS.

Clinical relevance…

- Lipid-soluble substances enter brain tissue with ease.
  - thus diazepam (lipid-soluble) given intravenously is effective in one minute for status epilepticus;
  - the level of general anaesthesia can be controlled closely by altering the concentration of inhaled anaesthetic gas (lipid-soluble)

The clinical relevance of drug passage across membranes

Placenta:

- Chorionic villi, consisting of a layer of trophoblastic cells that enclose foetal capillaries, are bathed in maternal blood.
- The large surface area and blood flow (500ml/ min.) are essential for gas exchange, uptake of nutrients and elimination of waste products.

The clinical relevance of drug passage across membranes

- The fetal and maternal blood streams are therefore separated by a lipid barrier that readily allows the passage of lipid-soluble substances but excludes water-soluble compounds, especially those with molecular weight exceeding 600.
- This exclusion is of particular importance with short-term use, e.g. tubocurarine (lipid-insoluble) given as a muscle relaxant during Caesarean section, does not affect the infant.

The end

Thank you.

Structure-activity relationship, Dose-response relationship: drug potency, efficacy and therapeutic index

PHARMACODYNAMICS

Learning objectives …

- Show how the knowledge of the chemical structure of a drug is useful
- Explain the terms:
  - Potency
  - Therapeutic efficacy
  - Therapeutic index

3

Structure activity relationship

Pharmacodynamics

Structure activity relationship

- The activity of a drug is intimately related to its chemical structure.
- Knowledge about the chemical structure of a drug is useful for:
  - Synthesis of **new compounds** with more specific actions and fewer adverse reactions
  - Synthesis of **competitive antagonists**
  - Understanding the **mechanism of drug action**

Structure activity relationship …

- **Synthesis of new compounds**, for the following purposes:
  - To **increase** or **decrease** the **duration of action** of the original drug or to get a more potent compound. E.g.
    - **Procaine** –When given intravenously reduces the rate and excitability of the myocardium, but is very rapidly hydrolyzed in plasma hence cardiac action is too transient.
    - **Procainamide,** is structurally similar to procaine but resistant to hydrolysis, and is a valuable antiarrythmic drug.

Structure activity relationship …

- Synthesis of new compounds :
  - To **restrict drug action** to a particular system of the body. E.g.
    - **Chlorpromazine** has antihistaminic, anticholinergic, hypotensive and tranquillizing actions.
    - By structural modification of chlorpromazine molecule, **trifluoperazine** was produced and has more potent tranquillizing effect but negligible antihistaminic and hypotensive properties.

Structure activity relationship …

- Synthesis of new compounds …
  - To **reduce the adverse reactions**, toxicity and other disadvantages associated with the available drugs
    - E.g.
    - New penicillins have been synthesized which are not inactivated by gastric acid, and hence can be taken by mouth.
    - Penicillins that destroy staphylococci resistant to benzyl penicillin have been synthesized – cloxacillin, flucloxacillin.

Structure activity relationship …

- Synthesis of **competitive antagonists**:
  - Para-amino benzoic acid (PABA) is an essential growth factor for several micro-organisms
  - **Sulphonamides** are structural analogues of PABA. They act by competing with PABA for uptake by bacteria in the synthesis of folic acid. This arrests folic acid formation and bacterial multiplication stops.

Structure activity relationship …

- **Understanding the mechanism of drug action**:
  - Understanding the basic chemical groups responsible for drug action gives some idea about their mechanism of action.
  - E.g. C**hlorpromazine** is a tranquillizer. Structurally related **Imipramine**, on the other hand, is an antidepressant due to slight alteration in chemical group in the formula.

Dose-response relationship

Pharmacodynamics

Dose-response relationship

- When a drug is administered systemically, the dose-response relationship has two components:

1. Dose-plasma concentration relationship and
2. Plasma concentration-response relationship.

- Generally, the intensity of response increases with increase in dose.

DOSE-RESPONSE CURVE

- The measured dose (usually in milligrams, micrograms) is generally plotted on the X axis and the response is plotted on the Y axis.
- The curve produced is the dose-response curve.

Drug potency and efficacy

Potency

- Drug potency refers to the amount of drug needed to produce a certain response.
- A dose-response curve positioned rightward indicates lower potency
- If 10mg of morphine = 100mg of pethidine, morphine is 10 times more potent than pethidine.

Potency …

- If weight for weight, drug A has a greater effect than drug B, then drug A is more potent than drug B, but the maximum therapeutic effect obtainable may be similar with both drugs.
- The diuretic effect of Bumetanide 1mg is equivalent to Frusemide 50mg, thus bumetanide is more potent than Frusemide but both drugs achieve about the same maximum effect.

Efficacy

- Drug efficacy refers to the maximal response that can be elicited by the drug
- If drug A can produce a therapeutic effect that cannot be obtained by drug B however much of drug B is given, then drug A has the higher therapeutic efficacy. e.g. morphine produces a degree of analgesia not obtainable by any dose of aspirin. So morphine is more efficacious than aspirin.

Efficacy …

- Efficacy is a more decisive factor in the choice of a drug.
- The slope of the DRC is important in that, a steep slope indicates that a moderate increase in dose will markedly increase the response, while a flat one implies that little increase in response will occur over a wide dose range (standard dose can be given to most patients)

Therapeutic index

- The **therapeutic index (TI)** (also referred to as **therapeutic window** or **safety window** or sometimes as **therapeutic ratio**) is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity

TI

- The concept of therapeutic index refers to the relationship between toxic and therapeutic dose.
- This pharmacodynamic parameter is relevant to clinical practice because it determines how safe (or toxic) a drug is.

Therapeutic Index

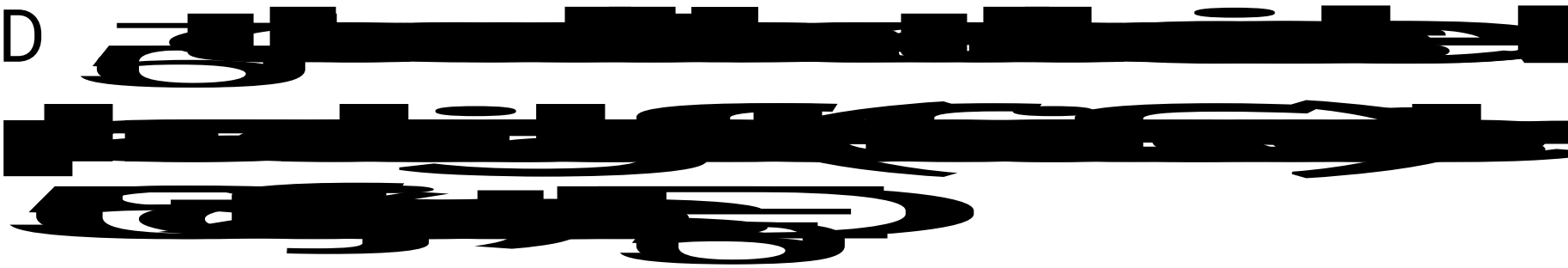
- TI is therefore an approximate assessment of the safety of the drug.
- It is the gap between the therapeutic effect DRC and the adverse effect DRC.
- In experimental animals, it is expressed as the ratio of the median lethal dose to the median effective dose.

Therapeutic Index …

- For animal studies, ‘the median lethal dose’ or LD_{50} is the dose (mg/kg) that results in death of 50% of the study population.
- ‘the median effective dose’ or ED_{50} is the dose (mg/kg) which produces a desirable response in 50% of the test population.
- Therapeutic index (TI) = $\frac{LD_{50}}{ED_{50}}$

TI in human trials

- Classically, in an established clinical indication setting of an approved drug, Therapeutic Index refers to the ratio of the dose of drug that causes **adverse effects (toxic dose)** at a severity not compatible with the targeted indication, in 50% of subjects, TD



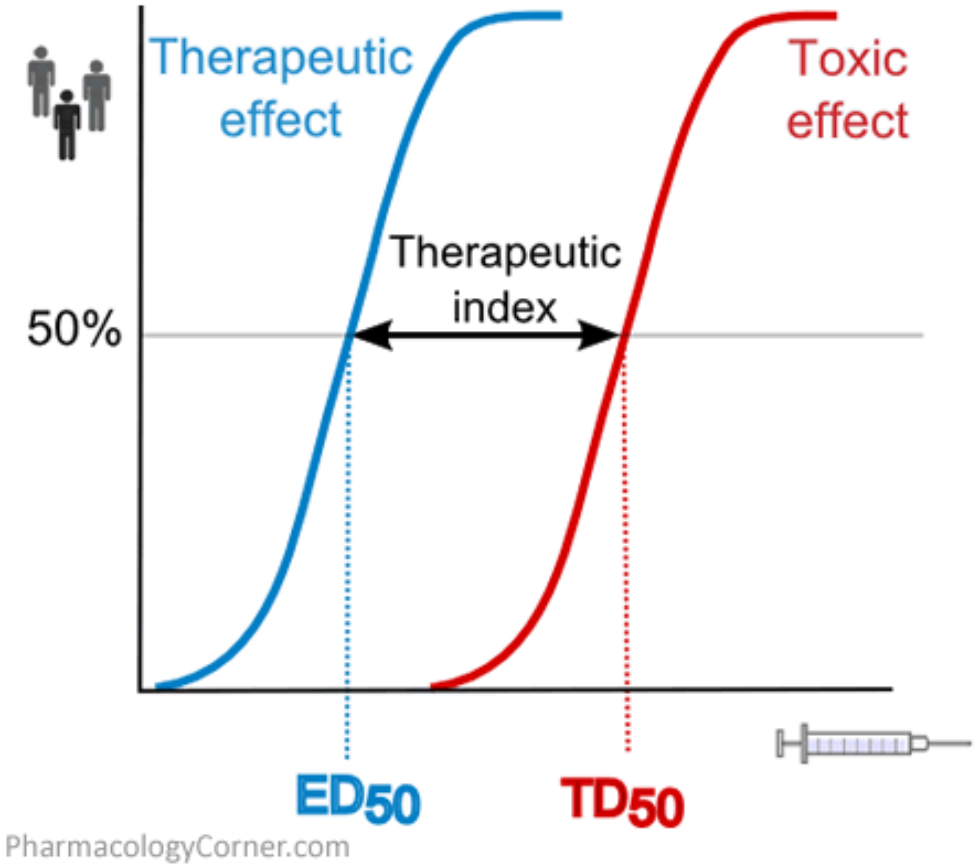
TI

- The dose required to cause a therapeutic effect (positive response) in 50% of a population is the ED 
- The dose required to produce a toxic effect in 50% of the studied population is the TD 

TI

$$\text{Therapeutic index} = \frac{TD_{50}}{ED_{50}}$$

THERAPEUTIC INDEX



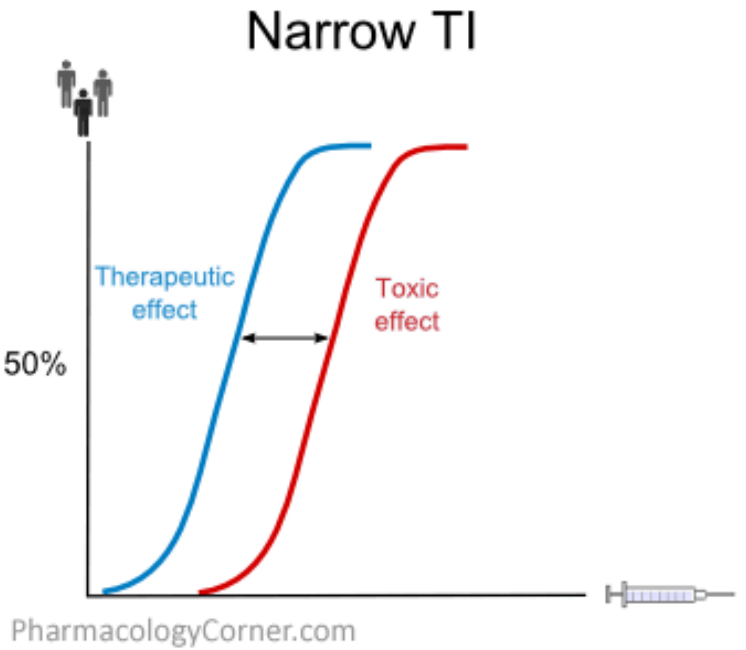
Therapeutic Index

- The larger the TI the safer is the drug
- For safe therapeutic application of a compound, its TI must be more than one.
- Penicillin and sulphonamides have high Therapeutic indices.
- Digitalis preparations have much smaller Therapeutic indices.

Narrow therapeutic index drugs

The list below shows some examples of narrow therapeutic index drugs:

- Warfarin
- Lithium
- Digoxin
- Phenytoin
- Gentamycin
- Amphotericin B
- 5-fluorouracil



The end.

Thanks.