

Pharmacology refers to the branch of science that deals with the study of the action of drugs on biological systems.

BRANCHES OF PHARMACOLOGY

There are 2 major branches namely

- Pharmacokinetics
- Pharmacodynamics

Pharmacokinetics: Deals with action of body on the drug i.e what the body does to the drugs.

It includes the study of absorption, distribution, metabolism and excretion of drugs (ADME).

Pharmacodynamics deals with the action of drugs on the body i.e what the drug does to the body.

Other branches of pharmacology may include

- Pharmacotherapeutics: A branch in which pharmaceutical information together with the knowledge of the disease is applied for prevention and cure of diseases.

- Pharmacognosy: Deals with the study of the properties of drugs in unprepared forms.

- Clinical pharmacology: Use of drugs in the clinical routine with the aim of maximizing the therapeutic effects of drugs and minimizing adverse effects.

- Pharmaco-economics: Study of economic factors regarding the cost of drug therapies.

- Pharmacogenetics / pharmacogenomics: Deals with the study of genetic variations that account for response among different

pandemic : epidemic that affects globally

epidemic : a disease that affects a large popn

endemic : is a common disease in a community

individual :

- Pharmacoepidemiology : Deals with the study of effects of a drug on a large population.

- Neuropharmacology :

Branch of pharmacology that deals with the action of drugs on the nervous system.

- Phisiology : Deals with the study of doses of drugs.

- Toxicology : Deals with the study of adverse effects of drugs.

- Chemotherapy : Use of drugs to cure diseases.

Side effect : Is a minor unwanted effect of a drug.

Adverse effect : Harmful or seriously unpleasant effect of a drug.

Toxicity : Implies direct action of a drug, often at high doses that leads to damaging of cells.

Therapy : Refers to treatment intended to heal or treat a disorder.

Dose : Is the appropriate amount drug needed to induce a certain degree of response in a patient at a particular time.

Dosage : Is the total amount of the drug required to complete therapy.

Therapeutic dose : Is the dose between the minimum effective dose and the maximum dose which provides a desired effect without toxicity.

Therapeutic index : Is the ratio of the dose that produces toxicity (lethal dose) to the dose which produce clinical response (effective dose) i.e.

It is the measure of the drug's safety.

The higher the therapeutic index the safer the drug.

$$TI \text{ (Therapeutic index)} = \frac{LD_{50}}{ED_{50}}$$

Adverse effect : Harmful or seriously unpleasant effect of a drug.

Hypersensitivity : Is an expected immune exaggerated immune response to a drug after administration.

Chemoprophylaxis : Is the use of drugs to prevent occurrence of a disease.

Drug efficacy : It is the ability of a drug to cause maximum

~~g~~ doxycycline
↓
UTI ↓
idegna substance
teratogenicity
[a]rogenic drugs able to cross the placenta

therapeutic effect. ie antiseptic is more efficacious compared to Al.

Potency: Amount of drug required to cause desired therapeutic effect.

The lesser the amount the greater the potency ie morphine is more potent than paracetamol (pain killers)

Agonists: These are drugs or substances that activate receptors of natural transmitters or hormones (they usually resemble the natural transmitter or hormone partial cause a minimum and full agonists cause the same or even greater effect)

Antagonists: These are drugs that block or prevent the natural agonists from exerting its effects by occupying receptors without activating them.

Drug tolerance: This refers to when the drug no longer produces the required effect at normal doses hence necessitating an increase in the dosage.

Sensitivity: Drug sensitivity refers to an increased response to the same drug with repeated exposure.

To agree / follow
Drug compliance: This is the degree to which patients / clients follow the prescribed dose and all other instructions provided by the health care provider / work

Drug adherence ^{"consistently" "specified period of time"} is the degree to which the patient consistently follows the prescribed dose of a drug for a specified period of time.

Drug addiction: This is having or possessing a strong urge / craving to obtain and use a substance or drug irrespective of its harm to the body.

Physical tolerance dependency / physiological dependency

It refers to when a person's body needs a substance or drug to function normally.

Ideosyncrasy: Is an inherent abn. inherent abnormal reaction to the drug.

usually due to genetic abnormalities.

DRUG NOMENCLATURE

There are three ways that can be used to identify drugs -

i) Chemical name: Describes the drug's chemical composition and molecular structure.

It is not normally used in prescription as it is difficult to memorize.

ii) The Generic name / Non proprietary name

This is the name approved by a competent drug body eg the Food and Drug Administration (FDA).

It is much simpler than the chemical name and is commonly used in prescription eg paracetamol, chlorophenamine among others.

iii) Brand name / trade name / proprietary name.

It is the copyrighted name that is given by the company manufacturing and selling the drug.

SOURCES OF DRUGS

Plants for example digoxin, quinine and morphine

natural
[Animals eg insulin, adrenaline

- Micro organisms eg ^{fungi} penicillin, ^{horses} streptomycin most of antibiotics.

semi
synthetic
chemicals / chemical substance eg diazepam.

[Minerals eg iron, Zinc, Magnesium.

CLASSIFICATION OF DRUGS.

Drugs may be classified in the following ways:

1. Prescription classification.

2. Classified pharmacological classification

3. Legal classification

NDA National drug bureau ... Bureau

AZT antiviral (zidovudine) stops not responding to the external env
Nifedipine cause it -

a) Prescription drugs classification -

This classification drugs are classified basing on whether they are obtained by prescription (prescription only medicine) or they can't be obtained without a prescription (over the counter drug).

Prescription drugs

These drugs can only be obtained when a patient provider a prescription from a pharmacy or drug outlet. eg Amoxy, doxycycline Nifedipine (for hypertension) etc.

Non prescription drugs (over the counter drugs)

These drugs can be obtained from either a pharmacy or drug shop without prescription eg painkillers, cough syrups,

b) Pharmacological classification:

In this classification, drugs are categorized basing on target body systems eg cardiovascular drugs, respiratory drugs, digestive drugs etc. They can be classified basing on the action or activity of micro-organisms eg antivirals, antifungals, antibiotics etc.

c) Legal classification

In this case drugs are classified as class A, class B and class C drugs.

- Class A drugs (Narcotics): These are drugs that were previously called the "dangerous drugs" because they are habit forming and lead to addiction.

They are usually use to relieve severe or unbearable pain in cancer patients, accident victims, post surgical patients eg pethidine, morphine, cocaine

Storage of narcotics:

These drugs and their preparation should always be stored in a separate cupboard or store away from all other drugs except on under use.

This cupboard should be inside another locked cupboard and is always fixed in one place. Should always be labelled as class A cupboard.

A separate register is kept that contains the total quantity of each drug, date, time, name of the patient, the ward, the doctor that ordered the drug, if administered and witnessed hand of

you are given.

Drugs should be checked regularly for expiry dates and damages should be recorded and reported.

Ordering of class A drugs:

A written order in a special class A narcotics book is issued from the department or ward requesting for the drug from the pharmacy.

The order must be signed by the ward incharge or the Assistant incharge.

N.B: In cases of emergencies, the drug may be obtained without a written order but it ~~must~~ be written up in 24 hours.

On receiving the drug both the ward incharge and the pharmacist must sign the requisition and record the date of issuing.

The ward incharge has to crosscheck w.r.t the stocks before utilizing this class A drug.

A record form should be kept in the ward for at least 2 years.

Always kept under lock and key double lock and key.

Prescription of class A drugs:

Prescription of these drugs should be made by Medical officer indicating the drug, dose, route and duration for treatment.

It should be done in the Doctor's or MO's own handwriting on the patients and must record his/her signature and name.

Administration of class A drugs:

Administration should be carried out by at least two nurses with at least one of them being registered Nurse.

The doctor's prescription is collected and interpreted.

The two nurses witness the collection of the drug, they check and confirm that the patient is due (ready) for the initial or next dose.

They should check the quantity of the drug in reference to what is prescribed.

They should then withdraw the drug and lock the unused medication.

They should enter then the patient's name, dose, date, the drug to be administered, if (in patient) or bed number.

They should take the drug and prescription to the patient's bed side.

and cross check with the patient's particulars against the prescription.

One Nurse administers the drug as the other witnesses

The time of administration is recorded and both nurses sign against / on the treatment sheet or HCN.

Class B drugs : These are referred to as controlled drugs and are divided into two groups i) Group one drugs / class B 1

This consists of drugs which can only be prescribed by a doctor or another trained medical personnel. Examples include all antibiotics, Anticoagulants, steroids, antidepressants etc.

ii) Group two drugs

They include drugs or items we can be given out by a licenced pharmacy and he/she keeps records of all sales.

The client or customer has to sign e.g. vaccines

Storage of class B drugs :

All class B drugs should be stored in a separate cupboard with the lock and the key should be kept by the ward incharge or head of department. They should be arranged in order ie drugs for external use and those for internal use should be in separate shelves.

There should be regular check for expiry dates and damage must be recorded and reported.

Ordering of class B drugs

The ward incharge orders for supply from the pharmacy accompanying each with a prescription

On receiving the drug supply, both the pharmacists and the incharge sign on the drug

The duplicate form should remain on the ward for at least 2 years.

Class C drugs : These are drugs which are popular amongst ordinary people.

They are divided into two groups

i) Group 1 : This consists of drugs which can be sold by ordinary shops or pharmacists.

A special licence is required by such shop keepers and is known as

a licensed drug seller.

These drugs include Folic Acid, Aspirin, multi-vitamins, paracetamol.

ii) Group 2 : This consists of strong dangerous laboratory chemicals.

They may be sold by pharmacists and licensed drug sellers.

These include insecticides, rat poisons, acids and other laboratory chemicals.

N_{1B}

All drugs should be stored in a separate place that does not contain food.

PREScription.

A prescription is a written instruction from the prescriber (Doctor, clinical officer, Midwife or nurse) on medicines to be administered to a patient.

The prescriber should be eligible to do so and must be registered by a professional body A HPC, the Uganda Medical and Dentist council, Nurses and Midwifery council among others.

QUALITIES OF A GOOD PRESCRIPTION.

available
Prescriber's name & drug
Signed, dated
Date
Address & name
Instructions & route
Diagnosis

- ✓ It should be written legibly in ink (clear) readable)
- ✓ It should be dated and indelible (permanent cannot easily be erased)
- ✓ State the patient's biodata i.e the full name, Address, Age, weight, occupation, marital status, level of education among others) for easy identification
- ✓ Should state the patient's diagnosis
- ✓ It should state the name, of drugs written in full name, the form, the dose or dosage and the strength of the prescribed drug and frequency of administration
- ✓ Should state the quantity of the drug to be supplied and duration of treatment.
- ✓ Should have clear instructions for the patient.
- ✓ Should be signed in ink by the prescriber
- ✓ Have the address and telephone no. of the prescriber
- ✓ Should contain the name and address of the health facility.

QUALITIES OF A GOOD PRESCRIBER

- Prescribes medication when necessary
- He/she chooses a treatment regimen (plan) that is appropriate to the disease and the patient.
- Continues therapy / treatment for an appropriate time and alters therapy when necessary.
- Gives a clear explanation to the patient about his/her condition, the effect of the drugs prescribed, possible and adverse effects and the remedies.
- Monitors the patient's prognosis and advises the patient when to return for review.

IRRATIONAL PRESCRIPTION

(Outline any ten errors of irrational prescription.)

Rational prescription requires the medical practitioner to make an accurate diagnosis, select the most suitable drug from those available and prescribe the medicine in adequate doses, thewright period of time according to standard guidelines of treatment.

REASONS FOR IRRATIONAL PRESCRIPTION.

- ✓ Inadequate training in clinical pharmacology and therapeutics - study of management of diseases.
- ✓ Lack of continuous professional development and supervision.
- ✓ Inappropriate desire for prestige.
- ✓ Promotional activities of drug companies.
- ✓ Lack of time due to heavy patient load.
- ✓ Unnecessary pressure of patients and.
- ✓

CONTENTS / COMPONENTS OF PRESCRIPTION

- a) **Supscription** (demographic information) Rx and w/nd meaning take medicine dose, name of the drug as Tab. P.C.M. 1g & h.rly x 3/4
- b) **Inscription** instructions for use M to the dispenser and S to the patient.
- c) **Subscription** signature below the subscription on the left side.
- d) **Transcription**

They are four main parts as shown above

1. Subscription: It contains the biodata and demographic information about the patient

It also consists of Rx which means to "take"

2. Inscription: Is the main part of the prescription and contains the following

- The generic name and strength of drugs
- Dosage form of the drug
- The amount of drugs ordered

3. Subscription: It entitles dispensing directions to the dispenser eg dispense or supply 30 tabs.

Usually it begins with the word Misce (M)

4. Transcription (sig, signature, sign): It entitles direction to the patient

These should be simple and directed towards the doses, time of taking the medicine, how to take and where to store the medicine

It is preceded by the word signa or its abbreviation sig or S

It ends with the prescribers signature on the left hand side

COMMON ABBREVIATIONS USED IN PRESCRIPTION.

Tab - Tablet

qd - every day

disc - discontinue

Cap - capsule

qid - every 6 hours

EBM - Expressed breast milk

Susp - Suspension

^{stat} stat - at once

per oral - By mouth

bid - twice a day

PR - Per rectum

tids - Thrice

SL - Sublingual

noc - night

SC - Subcutaneous

Am - morning

IM - Intramuscular

Pm - Evening

IV - Intravenous

hlhr - hour

AC - After meals

Supp - suppository

Pc - Before meals

Pess - Pessary

PRN - when needed

crm - Cream

q - Prey

TPN - Total Parental Nutrition.

PREScription FORM

HOPE MEDICAL CENTRE

Nakirebe, Wakiso district

070388809

Name

Mercy Akiiki

Age

Occupation

Sex

Marital status

Address

Weight

Diagnosis

Rx:

(1)

(2)

(3)

M:

S:

0706277982

THE DISPENSING PROCESS

A dispenser is any registered medical practitioner that gives out or dispenses medicines as per the patient's prescription and this may be a pharmacist, clinical officer, nurse etc.

ROLES OF A DISPENSER

- ✓ To dispense or give out drugs to patients in reference to their prescription.
- ✓ Gives drug information to the patient or client.
- ✓ Records and keeps drug records.
- ✓ Ensures proper storage of drugs.
- ✓ Advises the prescriber about drugs.
- ✓ Occasionally procures drugs.

Note: A dispenser should therefore possess knowledge regarding one

- Combination of drugs, doses and dosages, indications and contraindications,

metro - don't take alcohol
u may stay drunk for long because metro
and

Precautions, side effects and adverse effects of the drug, packaging and labelling procedures, legal requirements regarding supply, storage, records and labelling of controlled drugs (Anesthetics), Have knowledge about drug administration and they should also have knowledge of on disease process.

STEPS FOR DISPENSING.

- ✓ Reception of the patient's prescription.
- ✓ Cross checking and interpretation of the prescription
- ✓ Retrieving ^{collecting} of medicines or drugs as per prescription
- ✓ Proper explanation to the patient about prescribed drugs. The dispenser should ensure that the patient has understood and will comply to the treatment.
- ✓ Proper packaging and labelling of drugs / medicines
- ✓ Recording of the dispensed drugs in the appropriate record book (Dispensing Log).
- ✓ Supplying or dispensing to the drugs / medicines.

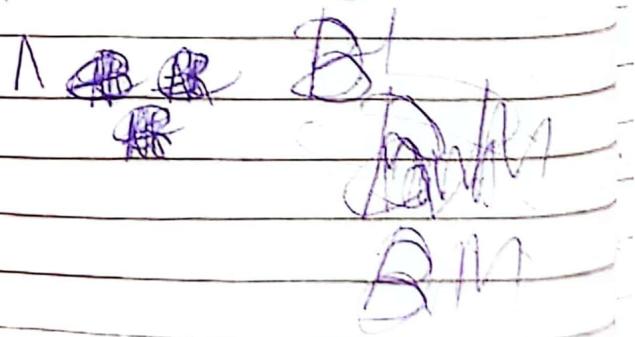
SLECTION OF MEDICINE

It a process that involves reviewing prevalent health problems, identifying treatment of choice, choosing medicines and dosage forms and deciding which medicines to be available at which level of care.

It is done nationally for the public sector (by the ministry of Health) to start determine which items should be available at each level of care.

The private sector is sometimes left out of the national process and selection is left to each facility or organisation.

Selection aims at providing a limited list of medicines and dosage forms that are appropriate to the healthy problems in a country or community.



Exaggerated prescriptions
Implications of irrational drug use.
Factors that contribute to poor drug compliance
and adherence.

ESSENTIAL MEDICINES CONCEPT (EMC)

It is a public health principle that promotes efficient use of resources by establishing and utilizing a limited list of carefully selected medicines.

Essential medicines:

Are those that satisfy the health care needs of the majority of the population at a cost that patients and the community can afford.

These medicines should be available at all times in adequate amounts and in appropriate dosage forms in the presence of a functioning health care system.

Majority of the health problems for most individuals can be treated with a small carefully selected number of medicines

IMPORTANCES OF SELECTION OF MEDICINE (EMC).

- ✓ Procurement and Management of medicine is very more efficient for few drugs.
- ✓ Higher quality of care because availability of medicines is ensured and quality of prescription improves.
- ✓ Reduction in wastage of resources.
- ✓ Easier training of health workers and prescribers about these medicines.
- ✓ Patient care is improved as better delivery of information to clients is more effective.
- ✓ Promotes rational use of medicines.
- ✓ Improved compliance and adherence to treatment.
- ✓ Wastages are controlled.

QUALITIES OF ESSENTIAL MEDICINES

Efficacy - effective, readily available and accessible
Affordability - affordable, handle and store
Administrability - safety

- ✓ Efficacy: Should be able to produce a minimum required therapeutic effect.
- ✓ Safety: It should have minimum side effects and adverse effects at therapeutic doses.

Should be easy to handle and store.

Should be affordable & should be relatively cheap to cater to needs of the majority of the patients.

Should be readily available and accessible for patients.

Should be ...

(Archille's tendon).

severe shock and low heart rate give Adrenaline

THE CRITERIA FOR SELECTION OF ESSENTIAL MEDICINES

The choice of medicines should be based on the following factors

1) The pattern / prevalence of common diseases in the country or community

- Training and experience of the available personnel or health workers.

Financial resources of the country

Treatment facilities available in Health center II, III, IV hospitals,

Regional hospitals and referrals -

- Genetic, demographic and environmental factors

- Known efficacy and safety of the drug

- Cost effectiveness / affordability of the drug.

METHODS

CLASSIFICATIONS OF ESSENTIAL MEDICINES

The following methods can be utilized to ensure the prioritization of medicines in carried out in a rational manner.

1. The ABC analysis.

2. The VEN analysis

THE VEN CLASSIFICATION / CONCEPT.

This method can be used to prioritize selection / purchase or use of medicines according to potential health impacts.

Selection and purchase of medicines can be carried out at the national level, health facility / hospital level (The health unit medicine's list).

V - Vital drugs - life saving

These drugs have first priority because they are life saving or critical for achieving targeted health outcomes.

Absence of these items of drugs will lead to death in the patient or irreversible strong injury or disability.

These include Adrenaline, hydrocortisone, most antibiotics, antimalarials,

in case of severe inflammations to show it down

Antihypertensives etc.

E - Essential drugs - pain and great discomfort

These have second priority and if not available, the patient will suffer pain or great discomfort eg analgesics (painkillers), topical antifungals

antihelminthic drugs (dewormers) eg Albendazole, mebendazole

N - Necessary drugs minor self limiting illnesses

They are third priority drugs and are usually used for minor self limiting illnesses

These drugs usually have a higher cost compared to their benefits eg cetirizine, anticold drugs

IMPORTANT SELECTION TOOLS

The essential Medicines list : A list of drugs selected drugs that meet the health care needs of the majority of the population in the country.
It is also called the National formulary

The hospital / health unit formulary : It is a list of drugs approved for use in a specific health care setting.

The formulary manual (eg the practice dispensing guideline PDG) .
This is a summary of information on a selected number of drugs usually based on the essential medicines list. (eg specific drugs, doses, indications and side effects).

The standard treatment guideline : It consists of recommendations and treatment of choice for specific diseases.

Bioavailability
fraction reaching <
systemic circulation

PHARMACOKINETICS

It refers to the action of the body on the drug and involves its absorption, distribution, metabolism and excretion. (ADME)

1. DRUG ABSORPTION

This is the movement of the drug from its site of administration into systemic circulation.

If a drug remains at its site of administration, it does not access its target tissue and thereby does not exert its intended pharmacological effect.

Both the fraction / amount of the administered dose that gets absorbed and the rate of absorption are essential.

Accept when the drug is given intravenously, it has to cross biological membranes

FACTORS AFFECTING DRUG ABSORPTION.

- Acqueous solubility of the drug: Drugs given in solid form must dissolve in the aqueous medium or biophase before they are absorbed.

A drug given as a water-soluble salt is absorbed faster than when the same is given in solid form or oily solution.

- Liquid solubility of the drug: The lipid-water partition coefficient of the drug is the ratio of dissolution of the drug in lipid as compared to water.

The greater the co-efficient the more lipid soluble the drug is and the greater the rate of absorption and the reverse is true.

It is bcoz lipid soluble drugs diffuse by dissolving in the lipid matrix or bilayer of the membrane and those more lipid soluble drug attains higher concentration in the membrane and diffuses faster.

pH at the site of absorption: Most drugs are weak electrolytes so their ionization is pH dependent (either acidic or alkaline pH media)

Weakly acidic drugs e.g. aspirin are largely un-ionized at acidic gastric pH and are absorbed by the stomach wall bases like atropine (first and most is chemical).

are largely ionized at acidic pH and are only absorbed at acidic medium until they reach small intestines.

$\text{NaCl} + \text{OH}^-$

trans



- Particle size of the drug; Large size particles take a longer time to disintegrate than smaller particles becoz they take longer to disintegrate for easy dissolution and thus drugs of smaller particles are absorbed faster than larger large ones.

- Concentration of the drug at the absorption site; Passive diffusion depends on concentration gradient and therel drugs given as concentrated solution are absorbed faster than those administered as dilute solution.

- The route of administration; Absorption of drug given by IM route is faster than those given by oral route. presence of food in GIT enzymes, pglycoprotein trans membrane protein present in kidneys

- Surface area of the absorbing surface; The larger the surface area the faster the rate of absorption becoz there are more absorptive cells exposed to the drug. Most drugs are absorbed faster from the small intestine becoz it has a large surface area.

- Vascularity / blood flow to the absorptive site; Blood carries away absorbed drug thereby maintaining a step drug concentration gradient across the absorptive membrane. Therel, the greater the blood supply the faster the absorption.

Poor vascularised tissues have poor absorption of drugs

- Contact time at the absorptive surface: for orally administered drugs, Gastro intestinal motility should be optimal for proper absorption. If GI motility is raised eg in severe diarrhoea it decreases the contact time between the drug molecules and the absorptive cells and thereby poor absorption.

If motility is reduced some drugs will take longer to reach their appropriate absorptive surfaces.

- Presence of other substances at the absorption site: For orally administered drugs, food or other drugs may interact with the drug and alter its rate of absorption. action of pglycoprotein influenced by drugs

- Functional integrity of the absorptive surface: the absorptive surface should be healthy and intact for continuing absorption. Defects in the mucosal barrier affect absorption

and ~~so~~ the presence of erosion along the mucosa decreases the absorption.

- Formulation of the drug: Syrups, suspensions may be absorbed faster compared to capsules and tablets given by the same route.

This is because tablets and capsules need to first disintegrate by the action of the drug is released to dissolve in the aqueous Biophase before it is absorbed.

BIOAVAILABILITY.

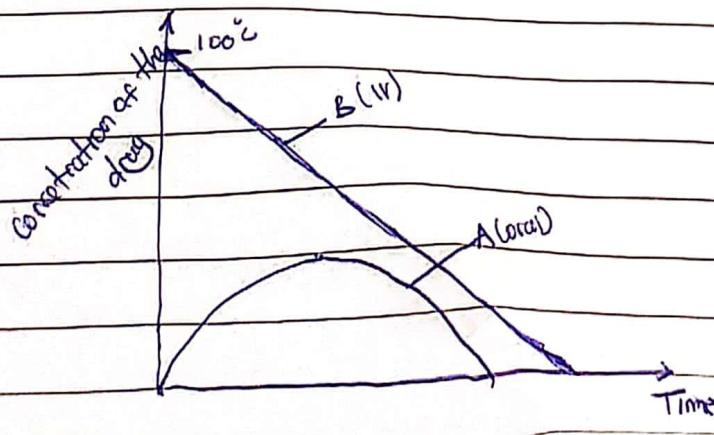
Bioavailability refers to the fraction / amount of the administered dose of the drug by any route that reaches the systemic circulation in unchanged form. Drugs administered via the intravenous route have 100% bioavailability whereas those administered by the oral route have a low bioavailability less than 100% because orally administered drug

- v The fraction of the administered dose is inactivated within the gut lumen by gastric acid, digestive enzymes, bacteria etc. altering its composition
- v First pass pre-systemic metabolism by the liver of the intestinal wall and excretion through bile.
- v Poor absorption of the drug in the GIT

Bioavailability of a drug formulation can be measured experimentally by determining the concentration of the drug in blood at different time and plotting a drug concentration time curve after administration of a specified dose of a drug via the intended route of administration (e.g. the Oral), and during the same for the same dose of the drug given intravenously.

$$\text{Bioavailability} = \frac{\text{AUC}_{\text{oral}}}{\text{AUC}_{\text{IV}}} \times 100$$

AUC: Area under the curve.
= the oral drug



All factors that affect rate of absorption.

FACTORS THAT AFFECT BIOAVAILABILITY

Any thing that affects disintegration and dissolution of the drug ^{preparation} equivalently affects the bioavailability of that drug

- ✓ The degree of first pass metabolism
- ✓ Solubility of the drug.
- ✓ Nature of the drug formulation
- ✓ Chemical instability ^{at different pH}
- ✓ Force used in compressing powder to tablets - disintegration

BIOEQUIVALENCE.

This is a biochemical similarity of two or more drugs that share the same active ingredients and same outcome effect to the patient.

Oral formulations of the drug from different manufacturers or different batches from the same manufacturer may have the same amount of the drug (chemically equivalent) but may not yield the same blood levels (biologically inequivalent).

Two preparations of a drug are considered bioequivalent when rate and extent of bioavailability of the drugs is not significantly different under suitable test conditions.

Two related drugs w/ a significant difference in bioavailability are said to be bioinequivalent.

Note: Two related drugs that are bioequivalent may not have therapeutic equivalence.

Drugs are therapeutically equivalent if they have comparable efficacy and safety.

2. DISTRIBUTION.

This is the process by wch a drug reversibly leaves the blood stream and enters interstitial, extracellular fluid and the body cells of tissues.

Once a drug has gained access to the blood stream, it is distributed to other tissues that initially had no drug, the conc gradient being in the direction of plasma to tissues.

APPARE

The drug can either enter paracellular or transcellular route to cross the blood-brain barrier.
hydrophilic - dissolve in water
lipophilic - dissolve in lipid

APPARENT VOLUME OF DISTRIBUTION

↳ the hypothetical volume through which the ^{drug} blood is dispersed assuming its concentration in all body water compartments is the same as that of the plasma.

Once a drug enters the body from any route of administration has the potential to distribute it to any of the functionally different compartments of body fluid.

- The plasma / intravascular compartment

It has a volume of about 4 litres in an adult $\approx 70\text{kg}$

If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move through the endothelial slit junctions in the capillaries and thereby is effectively confined \approx in the plasma / vascular compartment and will have a low vol. of distribution.

- The interstitial compartment

It consists of interstitial volume that has a vol. of about 10L in an adult $\approx 70\text{kg}$

If a drug has a low molecular weight, but is ^{paracellular route} hydrophilic can move through the endothelial slit junctions in the capillaries into the interstitial fluid.

However, hydrophilic drugs slowly cross the lipid membrane cells to enter water phase inside the cell (cytoplasm) and thereby these drugs distribute into a volume that is the sum of plasma water and interstitial fluid which together constitute the extracellular fluid.

- The intracellular compartment

It consists of the fluid inside all body cells and has a volume of about 28L in an adult $\approx 70\text{kg}$

If a drug has a low molecular weight and is hydrophobic / lipophilic, it not only can it move into the interstitium thru the slit junction but can also move through the cell membrane into the intracellular fluid.

The drug then diff. distributes throughout the total body water of about 42L hence has a high volume of distribution.

haemodialysis to patient
create an external kidney where blood is first filtered
Digoxin (for heart failure) has a long half life utilize muscles as a store

$$\text{Apparent volume of distribution} = \frac{\text{dose} \times \text{exministered drug (mg)}}{\text{concentration in plasma (mg/L)}}$$

FACTORS THAT AFFECT THE VOL. O DISTRIBUTION.

1. Lipid-water partition coefficient of the drug.
2. Chemical stability of the drug CPT^+
3. Degree of plasma protein binding
4. Affinity for different body tissues / localization / Tissue binding
 localization / Tissue binding
 circrosis - scarring
5. Diseases like hemophilia, Heart failure, liver cirro

THE EFFECT OF VOL. O DISTRIBUTION TO HALF LIFE OF DRUGS.

A large volume of distribution has an important influence on the half life of the drug becoz drug elimination depends on the amount of drug delivered in kidney.
Delivery of drug to organs depends not only to blood flow but also on the fraction of the unbound drug in plasma.

If the vol. o distribution of the drug is large most of the drug is in the extracellular space (outside the plasma) and is unavailable to the excretory organs.

Thereby any factor that increases the volume of distribution can lead to an increase in the half life and extend duration of the action of the drug.

Note: Half life of the drug is the time taken for the drug to be broken / disintegrate to half of its original concentration.

REDISTRIBUTION OF DRUGS

Highly lipid soluble drugs get initially distributed to organs with high blood flow that is the brain, heart, liver, kidneys and later plasma concentration of the drug falls and the drug is withdrawn from these sites.

Then less vascular but more bulky tissues eg muscles and fats take up the drug.

If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of drug.

The greater the lipid solubility of the drug the faster its redistribution.

Xenobiotics are foreign chemical substances in the body.

FACTORS THAT AFFECT DRUG DISTRIBUTION

- ✓ **Blood flow:** The rate of blood flow to tissues varies widely as a result un-equal distribution of cardiac output to various organs.

The concentration of the drug is usually higher in greatly vascularised tissues as compared to those with a lower blood supply.

- ✓ **Capillary permeability:** This is determined by the structure of the capillary and by the chemical nature of the drug.

Capillary structure varies widely in terms of the friction of the basement membrane that is exposed by slit junctions between endothelial cells.

In the brain the capillary is continuous, there are no slit junctions well as, the liver, spleen, the large part of the basement membrane is exposed due to large discontinuous capillaries through which substances pass.

Chemical nature of the drug strongly influences its ability to cross cell membranes. Hydrophobic drugs that have uniform distribution of electrons over a low molecular weight readily move across most biological membranes.

- ✓ **Plasma protein binding of drugs**

Fixable binding to plasma proteins maintains drugs in a non-diffusible form and slows their transfer out of the vascular transport.

Plasma albumin a major binding protein and they act as a drug reservoir if the concentration of the free drug decreases due to elimination by metabolism or excretion.

They bind drug plasma dissociates from its binding protein (Albumin).

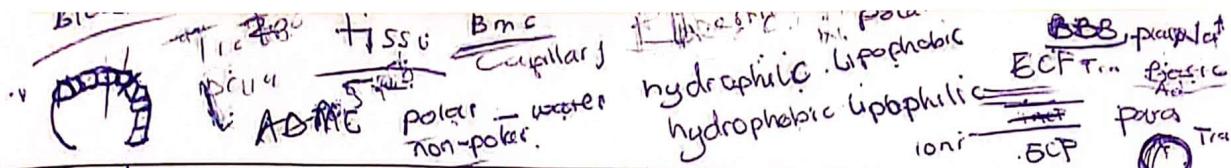
This maintains the free drug concentration as a constant fraction of the total drug in plasma.

IMPLICATIONS OF PROTEIN BINDING

Highly plasma protein bound drugs are largely restricted to the vascular compartment and thus tend to have smaller volume of distribution.

Plasma protein binding of drugs provide temporary storage of the drug by maintaining a steep concentration gradient between bound and free drug in plasma.

Protein binding increases the length (time) of action of the drug because



The bound fraction is not available for metabolism or excretion.

✓ **Tissue storage:** Drugs may accumulate in specific organ or tissues by active transport or by binding to specific tissue constituents / receptors and thereby tend to have large volumes of distribution and long duration of action.

Some of these drugs may exert local toxicity due to high concentration in those tissues eg tetracycline on bones and teeth, digoxine on skeletal muscle.

3. DRUG METABOLISM / Biotransformation.

Biotransformation is the alteration of the structure of the drug in the body.

It is needed to render non polar / lipid soluble compounds / lipophilic substances lipid soluble such that they are not re-absorbed in the renal tubules and excreted.

Most hydrophilic drugs are less biotransformed and are largely excreted unchanged.

Major organs of biotransformation include

- Liver

- GIT Mucosa

- The lungs

- Skin

- Skeletal muscles

- Brain

- Blood etc kidneys

IMPLICATIONS OF DRUG METABOLISM.

✓ Activation of the prodrugs (An inactive drug that requires conversion in the body into one or more active metabolites). Prodrugs offer advantages over the active form to be more stable, having better bioavailability and other desirable pharmacokinetic properties.

✓ Release of active metabolites from an active drug.

Some drugs are metabolized into active metabolites such that the overall