



PHARMACOLOGY IN CURRENT USE

PHARMACOLOGY TEACHING GUIDE AND NOTES FOR DIPLOMA IN NURSING SCIENCES (DNS)

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ABOUT THE AUTHOR



MASEREKA ENOS MIREMBE is a nursing teaching staff at Fortportal International Nursing School, he pursued his diploma in nursing science (DNS) from 2005 to 2008 at Kagando school of nursing and midwifery (KSNM), after which he enrolled for a Bachelor in Nursing Science from 2009 to 2012 at Mbarara University of Science and Technology (MUST) and completed his internship from Mulago National referral Hospital to qualify for a practicing license by the Uganda Nurses and Midwives Council (UNMC). In 2013, the author pursued an advanced diploma in Health Leadership and Management (HLM) from Uganda Institute of Allied Health and Management Sciences-Mulago to comprehend his management skills and currently he bears an appointment of a Senior Nursing Officer and an assignment of duty as the focal person for Maternal and Child health (MCH) services in Ntoroko District, Western Uganda.

The author has also served as a nursing clinical instructor in a number of Nursing Institutions, to mention but a few- Kagando School of Nursing and Midwifery (2008-2009), Mayanja Memorial Medical Training Institute-Mbarara (2010-2012) which therefore equipped him with the necessary teaching, and student handling skills. In his teaching experiences, the author has taught subjects like Nursing Foundations, Anatomy and Physiology, First Aide, Paediatric Nursing, Medical nursing aspects, Pharmacology, Nursing Education and clinical methods/assessment. He is also currently a nursing research supervisor and mentor for nursing/midwifery students undertaking diploma in nursing/midwifery sciences. He personally likes the profession and looks forward to further

his career even at master level more especially in teaching, and reproductive health issues (women and children health).

COURSE OUTLINE

- 1. INTRODUCTION**
- 2. DEFINITIONS**
- 3. DRUG CONTROL**
- 4. DRUG ORDERING, STORAGE, & PRESCRIPTION**
- 5. DRUG CLASSIFICATION**
- 6. ROUTES OF ADMINISTRATION**
- 7. PHARMACOKINETICS**
- 8. PHARMACODYNAMICS**
- 9. DRUG METABOLISM**
- 10. DRUG DISCOVERY**
- 11. PRESCRIPTION OF DRUGS**
- 12. ANTIBACTERIAL DRUGS**
- 13. ANTIFUGAL DRUGS**
- 14. ANTIPARASITIC DRUGS**
- 15. ANTIRETROVIRAL DRUGS**
- 16. GASTROINTESTINAL DRUGS**
- 17. DRUGS ACTING ON THE RESPIRATORY SYSTEM**
- 18. CARDIOVASCULAR DRUGS**

19. BLOOD AND BLOOD FORMING DRUGS

20. ENDOCRINE AND METABOLIC DRUGS

21. DERMATOLOGICAL DRUGS

22. DRUGS FOR THE EYE AND EAR

23. DRUGS USED IN ANAESTHESIA

24. OBSTETRICAL AND GYNAECOLOGICAL DRUGS

25. DRUGS ACTING ON THE GENITAL URINARY SYSTEM

26. ANTI CANCER DRUGS

27. VACCINES AND IMMUNOGLOBULINS

28. ANALGESICS

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Pharmacology is a science that deals with drugs, their modes of action on body cells and microorganisms in the counteraction of disease

TERMS USED IN PHARMACOLOGY

1. Drug: this is a substance used for treatment, relief or prophylaxis of disease
2. Pharmacy: is the preparation and dispensing of drugs or it is the premises registered to dispense drugs
3. Pharmacist: is a person who is qualified by examination, registered and authorized to dispense medicines
4. Dose: this is the amount of prescribed drug that is given to a patient at any one time
5. Side effects: these are undesired effects produced by a drug in addition to its desired therapeutic effects
6. Therapeutics: this is the use of a drug in the treatment or alleviation of a disease in light of their pharmacological effects
7. Pharmacokinetics: this refers to the handling of a drug within the body and includes its absorption, distribution, metabolism and excretion
8. Pharmacodynamics: this is the interaction of a drug with cells. It includes factors such as binding of a drug to cells, their uptake and intracellular metabolism.
9. Toxic effects: these are poisonous effects produced by the drug
10. Toxicity: the degree to which the drug is poisonous
11. Toxicology: this is the study of poisonous materials and their effects upon living organisms

SOURCES OF DRUGS

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Drugs are as old as disease and every part of the world has thought of drugs from different sources. Both modern and ancient medicine has extracted drugs from any of the following;

1. Crude vegetables

This is the oldest group of drugs and includes substances from leaves, roots, and seeds, plus barks of plants. The examples of modern drugs that are still extracted from medicinal plants are

Quinine and quinidine obtained from the bark of cinchona trees

Digoxin used in treatment of heart disease is obtained from Austrian fox glove

Atropine used in treatment of many conditions is got from belladonna

2. Animal products

This group enjoyed considerable popularity in the past. Witches used a variety of animal parts for many conditions. Today few drugs are still being obtained from animal products. Examples are;

Insulin used in treatment of DM is got from pigs and cattle

Ant-tetanus serum is prepared from hoarses

3. Mineral origin

There are so many drugs got from minerals, most drugs are extracted from metallic compounds such examples are;

Iron sulphate

Magnesium sulphate

Potassium chloride

Sodium bicarbonate

Calcium gluconate

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Zinc sulphate

4. Synthetic drugs

These are drugs that are prepared by chemicals in chemical laboratories. They include most of the drugs used today e.g.

Pethidine

Adrenaline

Hydrocortisone

Septrine

Morphine

5. Antibiotics

These are antimicrobial substances produced during the growth of certain organisms. Examples of these are the popular penicillins which are obtained from moulds. Penicillins are obtained from moulds and are used in the treatment of many bacterial infections.

DRUG USES

1. Symptomatic treatment
2. Prevention
3. Diagnosis
4. Curative
5. Contraception
6. Health maintenance

DRUG FORMULATIONS

Why formulate drugs?

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1. Most drugs are either weak acids or bases
2. Need for formulation into acceptable forms
3. Formulation optimizes absorption, reduces degradation, enhances or optimizes biological drug activity, preserves the drug, ensures stability in usage, improves patient acceptability, masks taste, and improves elegance.

THE DIFFERENT FORMS IN WHICH DRUGS EXIST INCLUDE

1. Tablets

These are small discs containing one or more drugs and are made by compressing powdered form of drugs e.g. Aspirin, Paracetamol tablets

2. Capsule

This is a soluble case usually made of gelatin in which powder or liquid is enclosed. They are used as means of administering bitter drugs e.g. capsule of tetracycline or chloramphenicol.

3. Mixture

This is an aqueous solution or suspension of drugs dissolved in water

4. Syrups

These are sweetened concentrated solutions of drugs in water and sugar e.g. Ampicillin syrup

5. Infusions

These are aqueous solutions of the active particles of drugs. These are usually in large amounts and are administered usually as intravenous infusions and slowly i.e. quine infusion, metronidazole or ciprofloxacin infusions.

6. Linctus

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This is a sweet syrup preparation of a drug used in the treatment of cough i.e codeine linctus, mist cough linctus e.t.c

7. Elixirs

These are flavoured and sweetened solutions or suspensions of drugs. The preparation usually contains alcohol

8. Tinctures

These are alcoholic solutions e.g. iodine tincture used for skin preparation before surgery

9. Suppositories

These are solid products prepared for rectal use. The drug is incorporated in a fatty or glycogelatin base that melts at body temperature e.g indomethacin, paracetamol, diclofenac suppositories.

10. Pessaries

These are medicated solid products prepared for vaginal use and intend to have local effects i.e. nystatin or clotrimazole pessaries

11. Ointments

These are semi-solid preparations intended for application to mucous membranes i.e. skin, eyes, e.g. tetracycline ointment

12. Emulsions

This is a term used to describe a mixture of oils and water rendered homogenous by addition of other emulsifying agents e.g. liquid paraffin contains methyl cellulose as the emulsifying agent.

13. Pills

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This is a solid round mass which contains one or more drugs and usually coated with sugar e.g. contraceptive pills

14. Liniments

These are thin creams or oily preparation of drugs usually applied to skin e.g. white liniment, methyl salicylate liniment.

15. Paste

This is an ointment that consists of high proportions of insoluble powder that makes it stiff and difficult to spread e.g. zinc oxide and salicyclic acid paste.

16. Creams

These are semi-solid emulsions and differ from ointment in containing a high proportion of water. Examples are cetrinide and chlorhexidine creams.

17. Inhalations

These are products containing aromatic and antiseptic substances of volatile nature e.g salbutamol inhaler.

18. Injections

These are sterile aqueous solutions or suspensions or drugs intended for parenteral administration by I.M. I.V or S/C injection routes or less frequently intradermal or intra-articular.

NURSES RESPONSIBILITIES FOR HANDLING OF DRUGS

1. Ordering drugs from pharmacy
2. Storage of drugs
3. Preparation of drugs e.g. diluting injectables which are in powder form
4. Administration of drugs

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5. Record of administration of drugs
6. Observing patients for side effects of drugs
7. Prescription of drugs in emergencies where there is no doctor.

CARE AND STORAGE OF DRUGS

1. All drugs are potentially dangerous and all must be stored in locked cupboards reserved specifically for drugs
2. Keys to the drug cupboards must be held by an in charge, staff nurse or in charge of the ward at the time.
3. Drugs in current use may be stored in drug trolley provided that these are locked and immobilized between drug rounds
4. Topical preparations such as ointments, lotions and disinfectants are also dangerous if misused and these too must be locked in a cupboard.
5. Storage conditions are important for most drugs and it is the nurse's responsibility to ensure that the labels on containers and instructions are followed i.e. store in a refrigerator, keep drugs in cool and dry places, remember that most drugs if stored in unappropriate conditions will lose their potency
6. All drugs will bear expiry dates desired or assigned by manufacturer and if the drug is nearing its expiry date, it should be used first before it expires. This can be arranged with pharmacist who may allocate it to the other ward that may use it first.
7. Special attention should be paid to emergency drug cupboard where most drugs may be, but less frequently used.
8. The drug cupboard should be dust free and drugs should be arranged in their order i.e injectables, tablets, mixtures, and syrups and those for external use should not be mixed with those intended for internal use

THE LEGAL CONTROL OF DRUGS, PHARMACY AND THE DRUG ACT

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The pharmacy and the drug act 1971 was drawn in Uganda to govern the use of drugs. This law was passed in parliament in 1970 and was put in force in Uganda on 15th June .1971, the act consists of a summary of rules governing the safe custody , supply and use of classified drugs in hospitals , dispensaries ,pharmacies , stores and similar institutions.

The act states that “dangerous drugs act and the pharmacy and poisons acts hereby repealed “All drugs used in medicine are registered drugs which means that they may only be obtained lawfully from the registered pharmacist, a properly trained qualified medical practitioner or member of the hospital staff who is responsible for the supply of drugs”.

Drugs were classified as: –

1. CLASS A- NARCOTICS (Previously DDA)

These are drugs that were formally known as dangerous drugs. They were called so because they are habit forming and lead to addiction, tolerance, and dependence. Narcotics relieve pain and also induce stupor and insensibility.

Addiction – it is an over whelming craving compulsion to get the drug by which ever means resulting from habitual taking of drugs. Examples of class A drugs are pethidine, morphine , methadone , levorphanol, opium , diamorphine , cocaine , perthiorphan etc.

STORAGE OF NARCOTICS

- Class A drugs and their preparations shall except under use be stored in separate cupboard or store apart from all other drugs
- The cupboard should be inside another locked cupboard which should be fixed in one place. The cupboard should be labeled class A cupboard.
- The key for the cupboard should be in the personal position of the ward in charge. At the time in-charge of the cupboard.
- A separate register is kept giving the total quantity of each drug, date ,name of patient , time, ward, doctor who ordered and nurses who gave the drug and witnessed how it was given.

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- Drugs should be arranged well in the cupboard according to their preparations i.e. syrups, tablets, injectables separately kept and those for external use shall be separated from those for internal use.
- These drugs should be checked regularly for expiry dates and damages should be reported and recorded.

ORDERING OF CLASS A DRUG

- A written order written in a special class a narcotics book is issued from the department requesting for the drug from the pharmacy.
- The order must be signed by the ward in-charge or assistant incharge.

N.B in emergency the drug may be obtained without a written order but it must be written within 24hours.

- On receiving the drug both the ward sister and the pharmacist must sign the requisition form with eligible signature and date.
- Still on reaching the ward, the ward sister has to cross check the stock.
- The record form should be kept on ward for at least two years

PRESCRIPTION OF CLASS A DRUGS

The prescription of class a drugs should be made by a medical officer indicating drug, dose, route, duration, and it should be his own hand writing on the patient's form , he/she must sign and put his/her names.

N.B A midwife in private practice may prescribe class A drugs.

Health workers working in palliative care/medicine department may prescribe class A drugs

ADMINISTERING CLASS A DRUG

- ✓ The administration of class A drugs must be by 2 nurses, one of which must be a state registered nurse and the other any other staff nurse.
- ✓ The doctor's prescription sheet is collected and read

- ✓ Two nurses witness the collection of the drug and dose
- ✓ Check and make sure that the patient has not been given the drug before .
- ✓ Find the entry of the drug in the record book and check the quantity of the drug against what is recorded.
- ✓ Put the right dose in a container or syringe and then lock up the un used drugs.
- ✓ Enter the patients' name, dose, date, drug given and bed number in the book.
- ✓ Take the drug and prescription sheet to the patient's beside and cross check the patient's particulars against the prescription.
- ✓ One nurse administers the drug as the other witnesses.
- ✓ Enter the time of administration and then both nurses sign.

CLASS B DRUGS

These are drugs that are referred to as controlled drugs and previously known as part one poisons. They are divided into two groups:

Group one.

This consists of drug that can only be prescribed by a doctor or appropriately qualified personnel and examples are:

- ❖ All anti-biotics e.g Ampicillin, chloramphenicol
- ❖ Antidepressants-amitriptyline, lithium e. t. c
- ❖ Barbiturates-phenobarbitone.
- ❖ Diuretics-furosemide(lasix), chlorothiazide, bendroflumethiazide, sprinolactone
- ❖ Anticoagulants- heparin
- ❖ Steroids-dexamethasone, hydrocortisone
- ❖ Sulphonamides-sulfadimidine, cotrimoxazole
- ❖ Anti-TB drugs-Rifampicin, streptomycin isoniazid, pyrazinamide
- ❖ Anti-diabetic drugs eg insulin
- ❖ All injectables
- ❖ All anesthetics
- ❖ Digitalis

Group two

This comprises a list of items/drugs that can be given out by a licensed pharmacist and he keeps records of all sales and the customer has to sign against what he/she has taken.

They include drugs like

- Insecticides
- Vaccines i.e. BCG, DPT, Polio vaccine
- Anti-histamines e.g. piriton

STORAGE

- ✓ All class B drugs should be stored in a separate cupboard with a lock.
- ✓ The key to the cupboard should be kept by in charge.
- ✓ They should be arranged in order i.e. those intended for external use should be in their own shelf.
- ✓ There should be regular check for expiry date and any damage should be reported and signed for

ORDERING

- ⊕ The ward in-charge orders supply from the pharmacy accompanying it with a prescription.
- ⊕ On receiving the supply, he/she signs and the pharmacist sign on what has been given.
- ⊕ The duplicate forms should remain on the ward for at least a period of 2 years

ADMINISTRATION

In administration of class B drugs, all rules for drug administration should be followed.

- ❖ Read the patient's full names from the prescription sheet and cross check.
- ❖ Read the prescription, checking the validity of the item of last administration.
- ❖ Read the name of the drug from the label when removing the container from the shelf.
- ❖ Check the label of the container for the name, strength and dose of the drug, the route of administration and if possible check for expiry date.

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- ❖ Measure or count the correct dose and when giving mixtures, syrups or liquids, shake bottle before pouring.
- ❖ Re-check the label before returning the containers to the shelf.
- ❖ Two nurses must make sure it is the right patient, right drugs right dose, right route and right time (5R^S).
- ❖ Make sure the patient is fit to receive the drug.
- ❖ Give the drugs and ensure patient has swallowed it.
- ❖ Record the administration and sign.
- ❖ Observe patient for any reaction to the drug.

CLASS C DRUGS (LICENCED DRUGS)

This concerns of drugs that are popular with ordinary people they are divided into two groups

GROUP 1

This consists of drugs that can be sold in ordinary shops or by pharmacists.

A special license is obtained by such shop keeper and is known as a licensed drug seller.

The drugs under this group;

INCLUDE:

- Aspirin
- Chloroquine tablets
- Paracetamol
- Multi-vitamins
- Folic acid
- Ferrous sulphate (FeSO_4)

GROUP II

This consists of strong dangerous laboratory chemicals; they may be sold by a pharmacist and a licensed drug seller with special license.

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The group consists of drugs such as:

- ✓ Rat poison
- ✓ Insecticide
- ✓ Plant chemicals
- ✓ Acids like H₂SO₄ and other many laboratory chemicals

STORAGE:

Regulation for controlling class drugs

- ❖ All class C drugs should be kept in cupboard except when in use.
- ❖ They should be stored in locked cupboards.
- ❖ The key to the cupboards should be in personal position of the person in charge of drugs at that time.

All drugs should be kept in separate place that does not contain food

ORDERING

- The order is written by in charge to pharmacy in a book meant for class C drugs.
- The pharmacist and the person ordering the drug both sign against their order.
- The drug is then across-checked on reaching the ward.

ADMINISTRATION

All the rules and regulations for giving drugs followed as in class B.

ROUTES OF ADMINISTRATION OF DRUGS

For any drug to produce its effects in the body, it must have been absorbed and distributed to the tissues involved. There are so many factors that may interfere with the absorption and

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distribution of drugs and the most important factor is the route of administration. There are a variety of routes.

- 1) Oral
- 2) Parenteral
- 3) Rectal
- 4) Inhalation
- 5) Local application topical.

ORAL:

The oral route is the most common route, safest and easiest. Tablets, capsules, mixtures syrups linctures and pills can all be administered through this route. The drugs are absorbed in the gastro intestinal tract, pass via the portal vein to the liver to be metabolized and later enters the general circulation.

The absorption of these drugs depends on the physical properties of the drug which determine whether they will pass through the walls of the gut or not

The other factor is the rate at which the stomach empties, the presence of food in the stomach and some times the interaction of the drug with others substance. This explains why some drugs like tetracycline should not be taken with milk.

The bioavailability of drugs given orally is reduced due to this factor. Bioavailability is term used to denote that portion of administrated drugs that reaches the circulation.

There other drugs than can readily be absorbed from the mucous lining of the mouth and these are either chewed or given sublingually.

The sublingual administration avoids the destruction effects of gastric juices or inactivation of the drug in the liver before it reaches the general circulation.

Advantages of oral route

- a. Most common and economical route.

- b. Most convenient in terms of time, place and dose.
- c. Allows drug to be taken at home by patient without need for special equipment, procedures, or medical personnel.
- d. Least likely to cause allergic responses (except in very young children).

Disadvantages to the oral route

- a. Requires patient compliance.
- b. May result in erratic and incomplete absorption.
- c. Emphasizes difference in bioavailability among different preparations.
- d. Some drugs are not absorbed from GI tract, e.g. streptomycin and some other antibiotics.
- e. Some drugs are destroyed in the GI tract, e.g. insulin and other protein hormones.
- f. Patient may be unconscious. More rapid responses may be needed in an emergency.
- g. Other routes may provide for more carefully controlled administration.
- i. The form of the drug may preclude oral administration, e.g., general anesthetics must be inhaled.
- j. Results in most rapid drug metabolism.
- k. Provides greatest opportunity for suicide attempts via overdosage.

PARENTERAL (INJECTION)

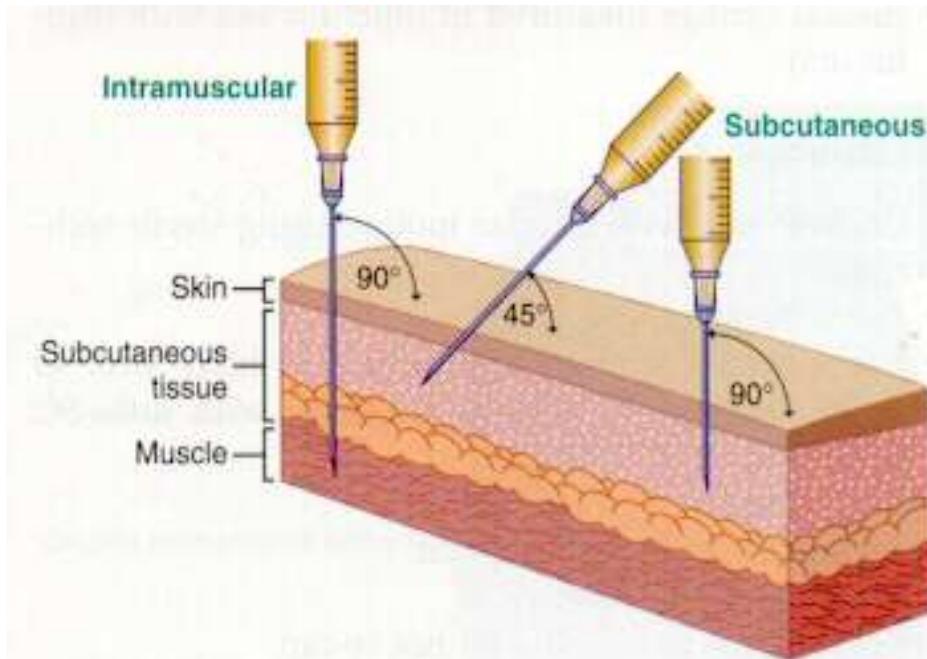
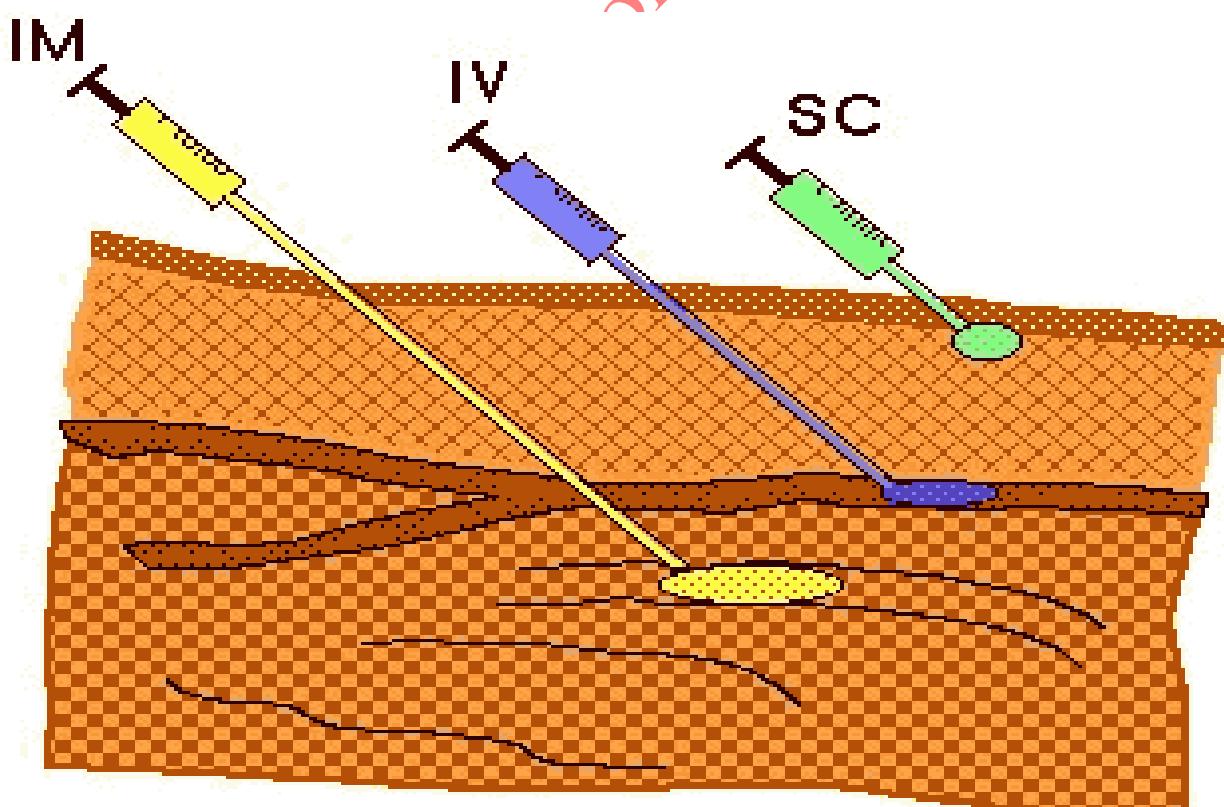


Figure 3–19

Needle–skin angle for intradermal, subcutaneous, and intramuscular injections.



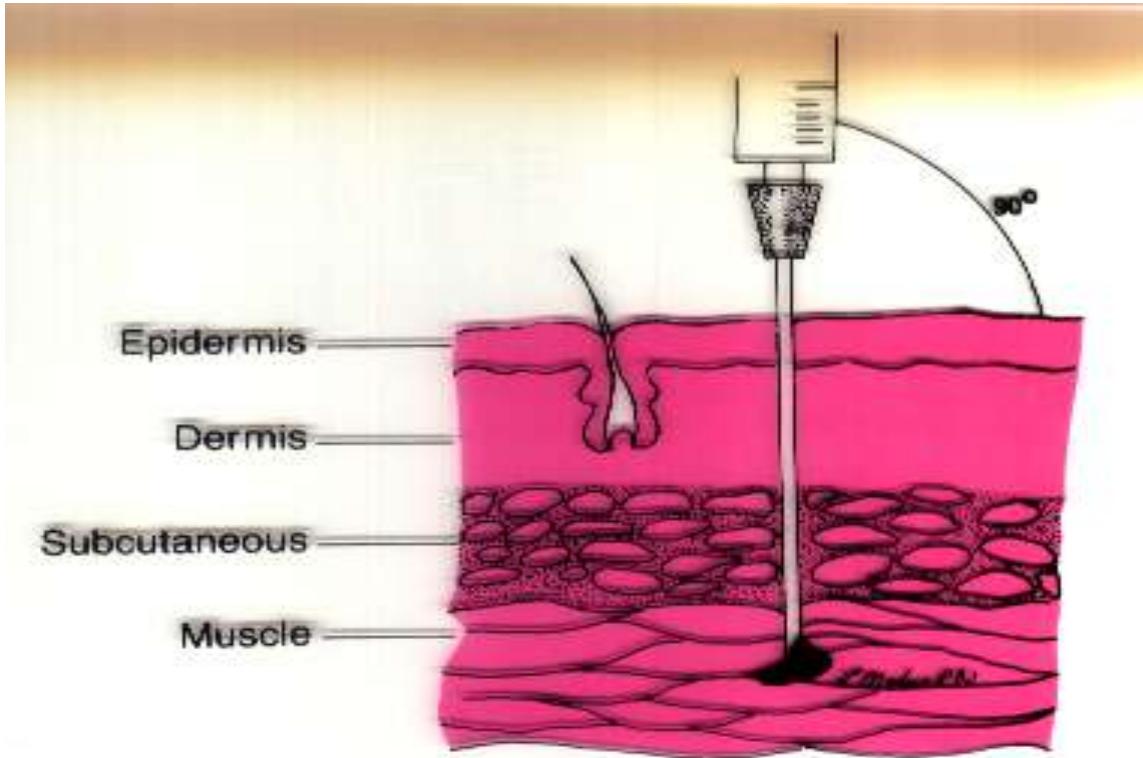
In injections may be given in various routes, that is I.V, I.M, S.C, I.D, intrathecal. They can be also injected in various body cavities such as pleura, peritoneum, spinal theca and in bone modularly canal.

INTRAVENOUS:

This is where the drug is given directly into the vein, it is used where rapid action is required and complete bioavailability is achieved.

This is also the route used for drugs that called irritate the muscles; large volumes of drugs can be administered in form of infusions.

INTRAMUSCULAR



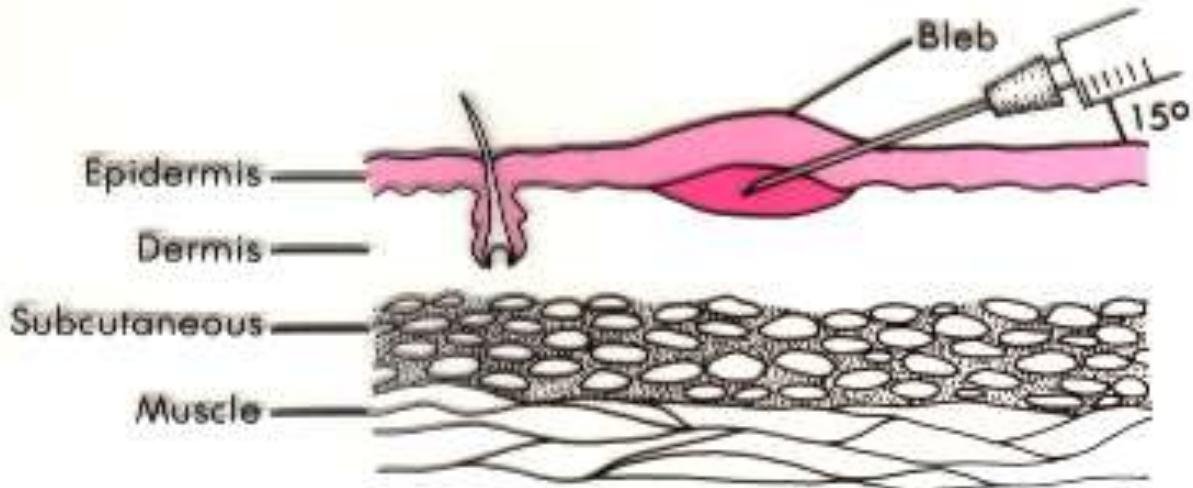
SOI

This is where drugs are injected into the muscles. Absorption from the site of injection is visible. It depends on the muscle blood circulation and is increased by exercises and decreased by shock.

SUBCUTANEOUS ROUTE

1. Used infrequently.
2. Local anesthetics coupled with vasoconstrictors may prolong action of the drugs administered by this route.
3. Rate of absorption controlled by vasculature.
4. Irritating materials may cause local tissue damage.
5. Repository preparations may be implanted subcutaneously.
6. Insoluble suspensions may be given via this route.

7. Volumes must be small.

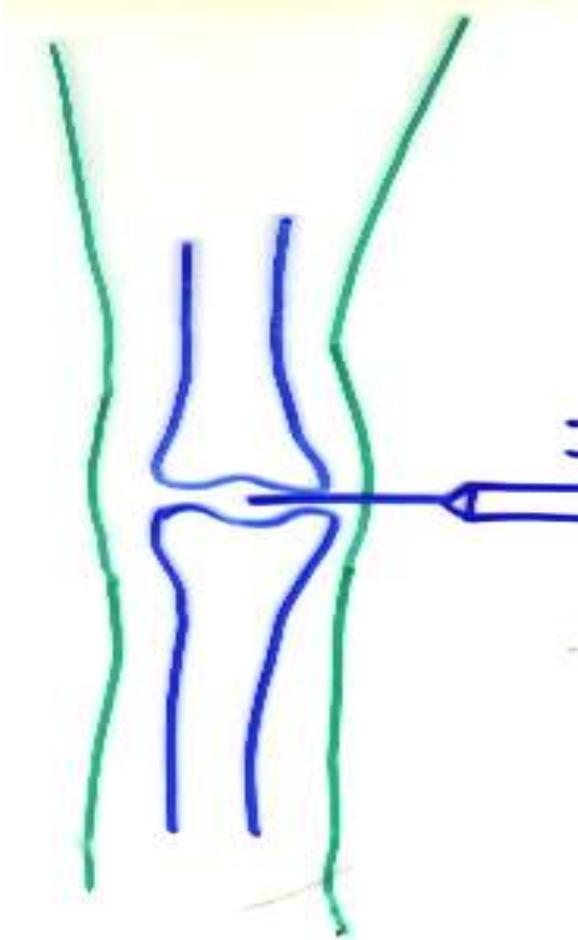


INTRADERMAL

This is where drugs are injected into the skin. It is used for small doses of drugs e.g BCG and rabies vaccines

INTRAARTICULAR INJECTION

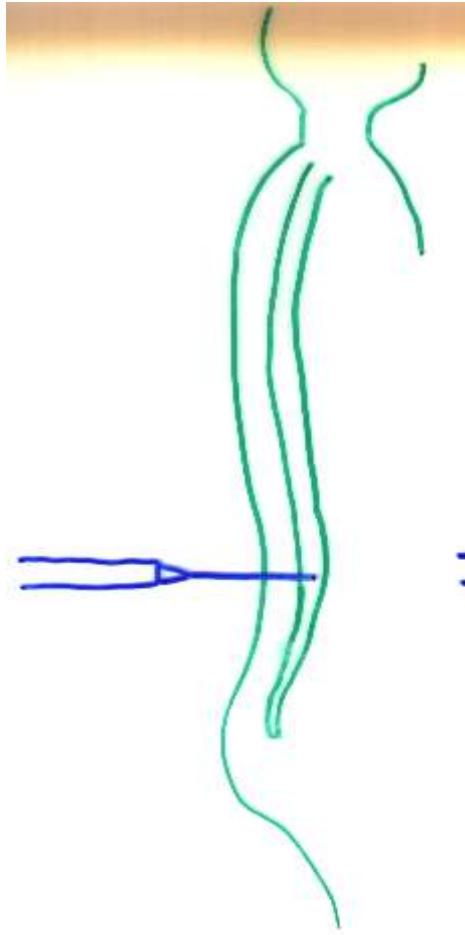
- Injection into Synovial Joint Fluid
- Administered by MD Only
- Produces Local Effect
- Example- Cortisone, Antibiotic in Case of arthritis



INTRATHEACAL

This is where the drugs are injected into the spinal canal. It is used when it is necessary for the drug to reach the nervous and by pass the blood brain barrier (BBB).

Examples of this, is as in spinal anesthesia. This route is not commonly used as severe brain damage may result from wrong doses, wrong drugs, and failure to maintain aseptic technique. It is only used by doctors and anesthetists.



INHALATION

This is where drugs in form of gas/ vapor or aerosols are breathed

The absorption is rapid and takes place in the lungs.

It is the best route for drug administration in emergencies like broncho asthma in acute attacks.

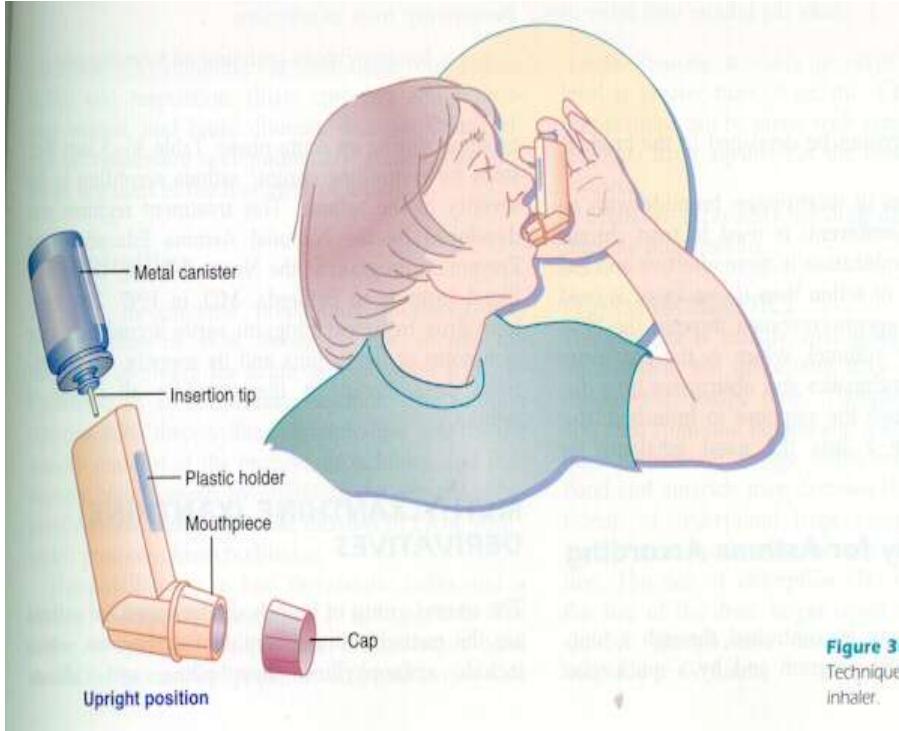


Figure 3i
Technique
inhaler.

RECTALLY

This is where certain drugs are injected into the rectum and are observed by the mucous membranes, this drug administrated can be in form of suppositories or enemata.

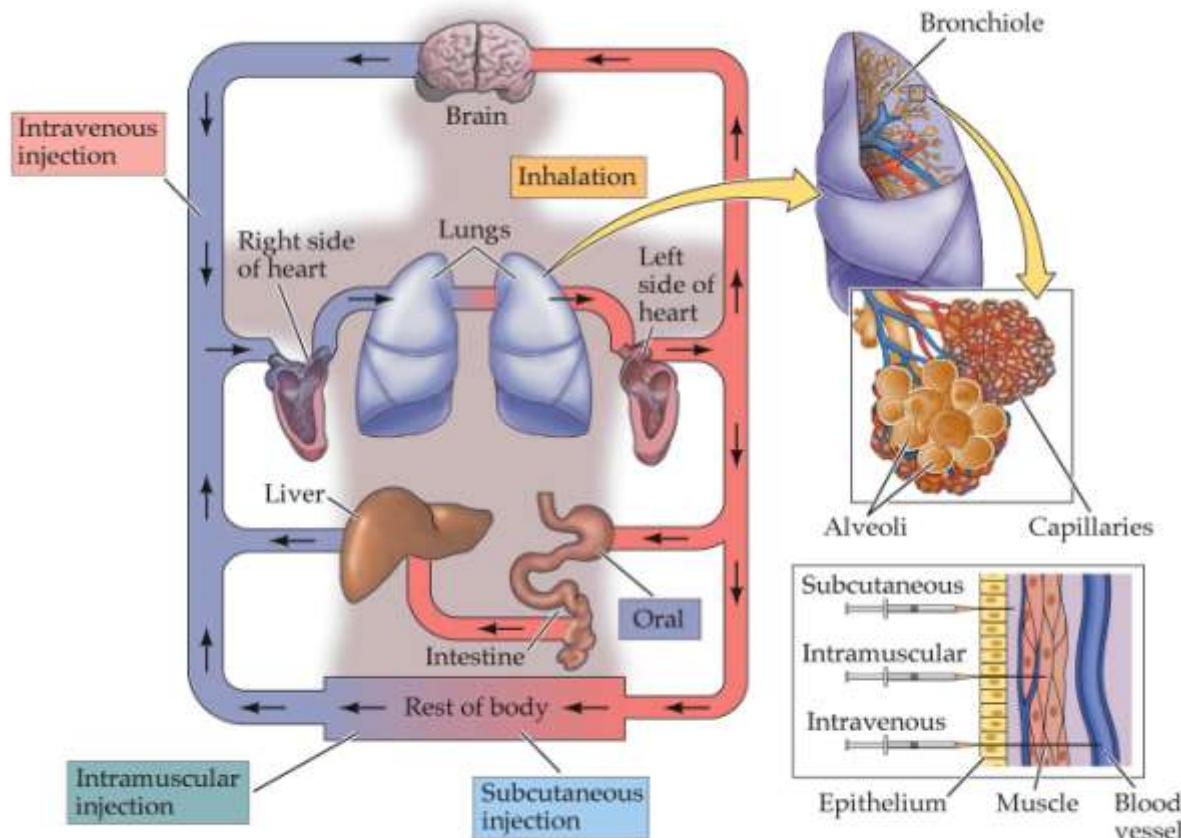
This route is mostly used where nausea and vomiting are present and if the drugs are gastric irritants examples of such drugs are aminophylline suppositories, paracetamol suppositories, diclofenac suppositories e.t.c.

LOCAL APPLICATION:

Drugs can be applied topically as lotions liniments, ointments, and creams.

They are applied to the skin and mucous membranes.

IN SUMMARY



PSYCHOPHARMACOLOGY, Figure 1.2 © 2005 Sinauer Associates, Inc.

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Other Injection types

- **Intraperitoneal = (I.P.) into stomach cavity (between organs).** Faster than P.O.
- **Intrathecal = into subdural spaces of the spinal cord; bypasses blood- brain barrier but invasive**
- **Intracerebroventricular = into the ventricles (where cerebrospinal fluid is produced) in the brain; bypasses blood- brain barrier but extremely invasive**
- **Intracerebral = into the brain itself**



Transdermal = diffusion through the skin

<u>Pros</u>	<u>Cons</u>
<ul style="list-style-type: none">• Easy• Not painful• Slow, sustained release• Bypasses GI tract & first pass• Only have to change every few days / weeks• E.g., estrogen, motion-sickness medications, nicotine, fentanyl, LSD	<ul style="list-style-type: none">• Can fall off• Potential toxicity to children and pets• Very few drugs absorbed sufficiently, low permeability of skin• Local irritation possible• Toxicity if additional drug consumed

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Mucous Membranes

Pros

- Quick absorption
- Easy and discreet
- Little chance of infection or tissue harm (except with vasoconstrictors)

Cons

- Can taste bad or irritate membranes
- Not all drugs absorbed readily
- Ease and speed exacerbate abuse liable drugs' potential for abuse



Various Types of Absorption via Mucous Membranes

- **Sublingual** = through the oral mucosa under the tongue; e.g., nitroglycerin
- **Buccal** = through the oral mucosa between the cheek and gum; e.g., chewing tobacco
- **Intranasal** = snorting it into the nose; e.g., cocaine
- **Rectal** = inserting it into the anus; good for person vomiting or unconscious but absorption iffy; e.g., meds for constipation
- **Vaginal** = inserting it into the vagina; e.g., meds for yeast infection

Inhalation = inhale gas or vapor into lungs

Pros

- Painless and quick
- Easy and discreet
- Very rapid; comparable to I.V. injection or faster
- 5 - 8 sec to brain
- Intense effects
- Smoke Examples:
 - Nicotine, opium, marijuana, free-base cocaine, crystalline methamphetamine
- Vapor examples:
 - Paint thinners, gasoline, glues, anesthetics

Cons

- Potential harm to lungs
 - Short term = pneumonia
 - Long term = cancer
- Exacerbation of abuse liability
- Only viable for volatile forms of drugs or that can be in very tiny particles
- Drug is sometimes destroyed in process

~~FCI PORTAL SITE~~ SELECTION OF THE ROUTE OF ADMINISTRATION:

Given that chemicals may take any of several physical forms, any of several routes of administration may be used to administer a chemical.

THE SELECTION OF THE ROUTE OF ADMINISTRATION IS BASED ON:

- A. Physical form of the chemical, e.g., is it a gas, liquid or solid,
- B. Route relevant to human exposure.
- C. Route expected to produce a specific effect.
- D. In test animals, route most consonant with humane treatment, which provides an acceptable basis for interpreting experimental results.

E. Issues of practicality and economics, consonant with an acceptable basis for interpreting experimental results.

PHARMACOKINETICS & PHARMACODYNAMICS; RATIONAL DOSING & THE TIME COURSE OF DRUG ACTION

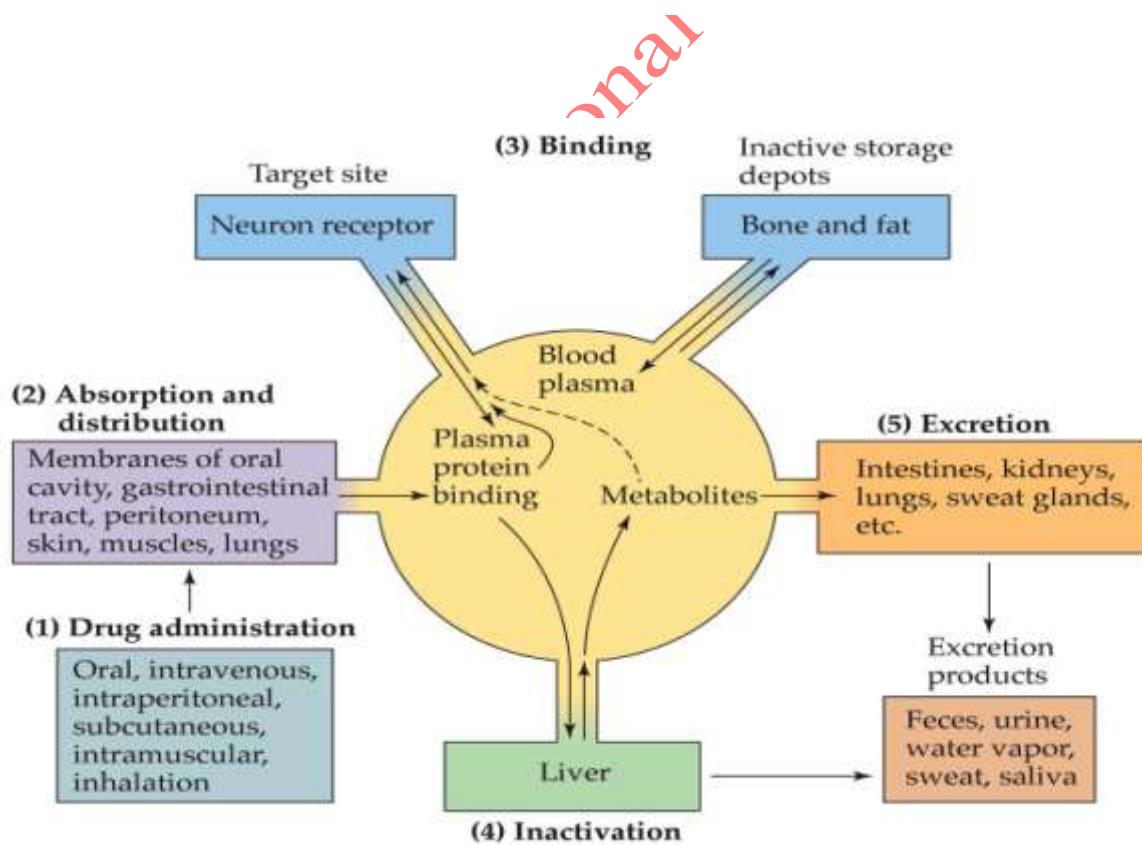
The goal of therapeutics is to achieve a desired beneficial effect with minimal adverse effects. When a medicine has been selected for a patient, the clinician must determine the dose that most closely achieves this goal. A rational approach to this objective combines the principles of pharmacokinetics with pharmacodynamics to clarify the dose-effect relationship.

Pharmacodynamics governs the concentration-effect part of the interaction, whereas pharmacokinetics deals with the dose-concentration part. The pharmacokinetic processes of absorption, distribution, and elimination determine how rapidly and for how long the drug will appear at the target organ. The pharmacodynamic concepts of maximum response and sensitivity determine the magnitude of the effect at a particular concentration.

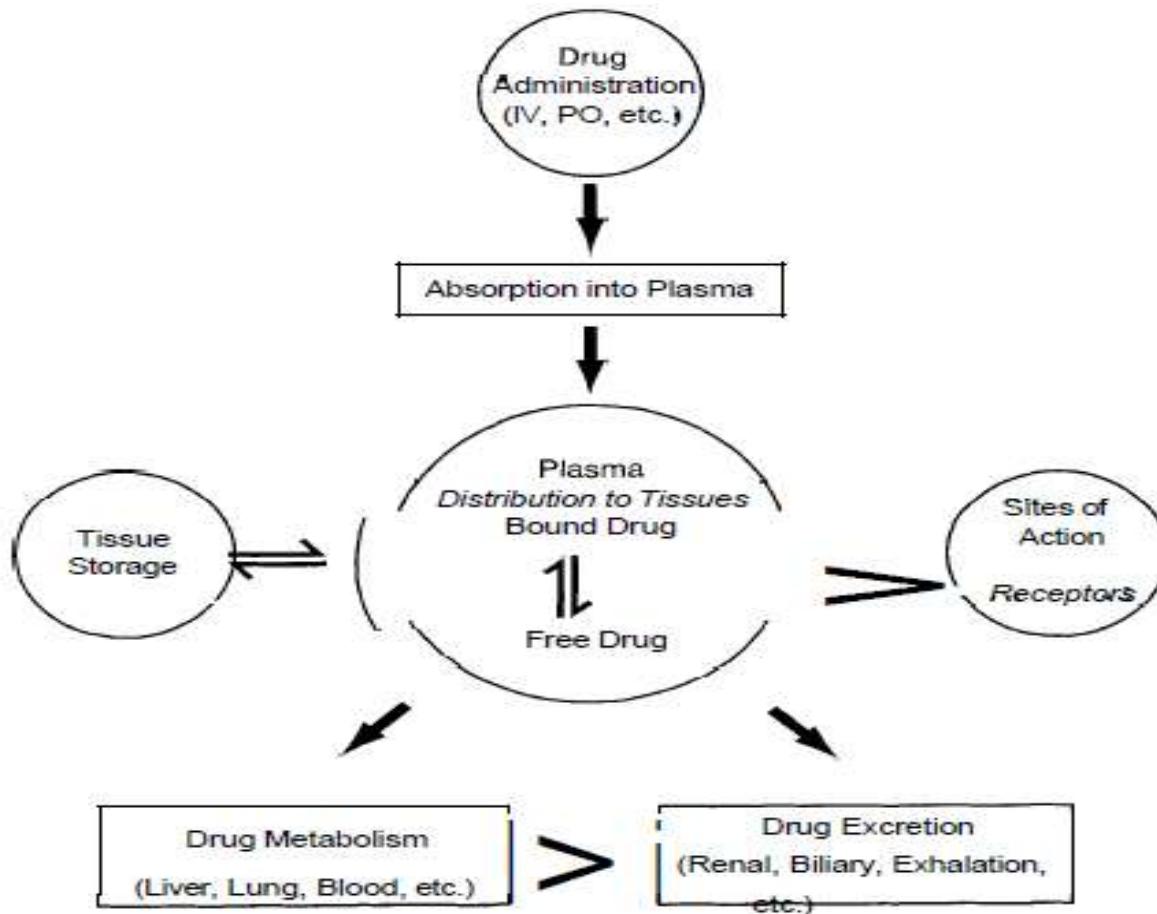
PHARMACOKINETICS

Pharmacokinetics

- Primarily concerned with what the body does to the drug (rather than pharmacodynamics which is concerned with what the drug does to the body)
- Pharmacokinetics refers to the dynamics of the movement of drugs through the biological system, includes
 - Drug absorption
 - Distribution
 - Metabolism
 - Elimination



PSYCHOPHARMACOLOGY, Figure 1.1 © 2005 Sinauer Associates, Inc.



The "standard" dose of a drug is based on trials in healthy volunteers and patients with average ability to absorb, distribute, and eliminate the drug

This dose will not be suitable for every patient. Several physiologic processes (eg, maturation of organ function in infants) and pathologic processes (eg, heart failure, renal failure) dictate dosage adjustment in individual patients. These processes modify specific pharmacokinetic parameters. The two basic parameters are **clearance**, the measure of the ability of the body to eliminate the drug; and **volume of distribution**, the measure of the apparent space in the body available to contain the drug

Drug Absorption

Drug absorption is the movement of drug from the site of administration into the fluids of the body that will carry it to its site(s) of action

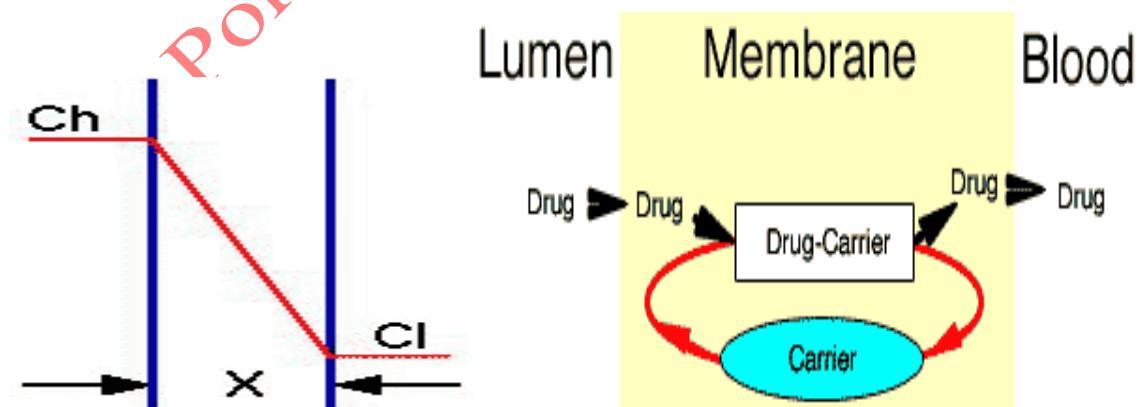
The rate & efficiency of absorption depends on the route of drug administration. For I/V delivery absorption is complete.i.e. the total drug reaches systemic circulation.

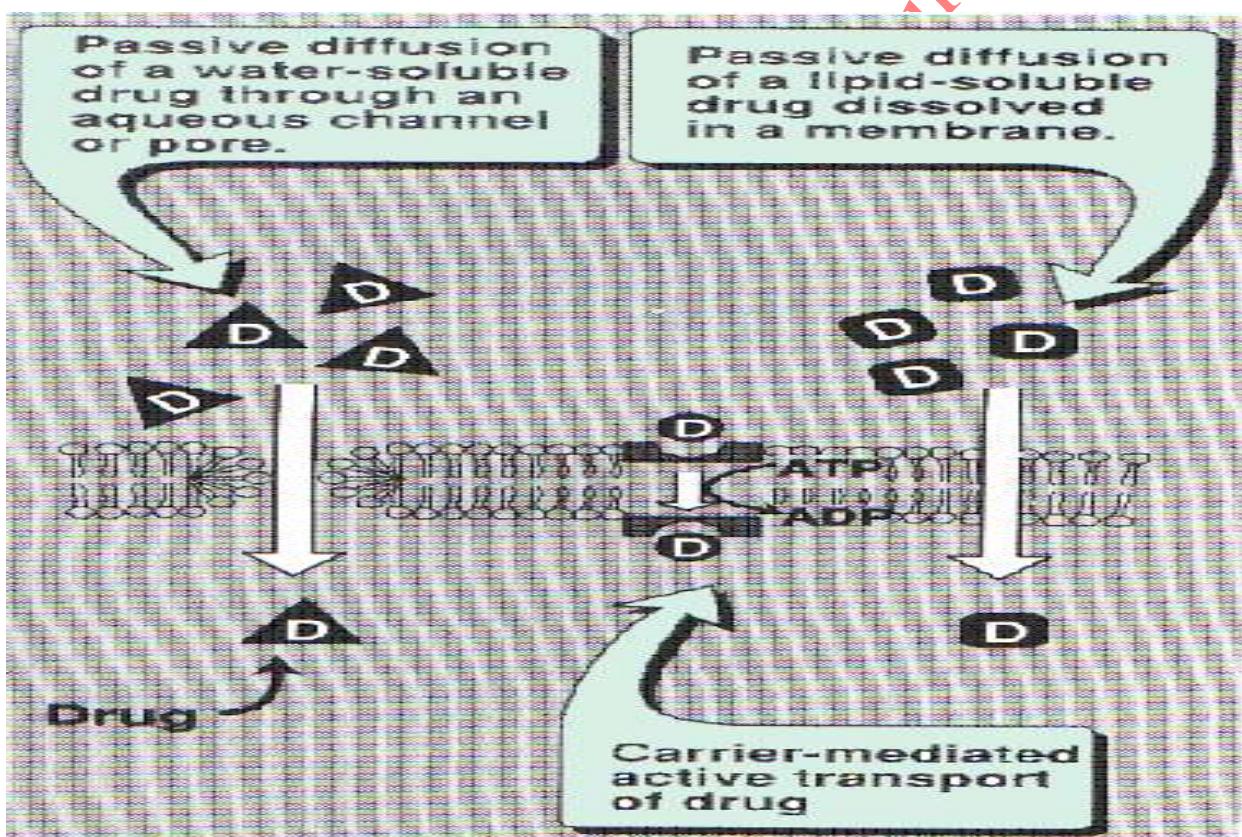
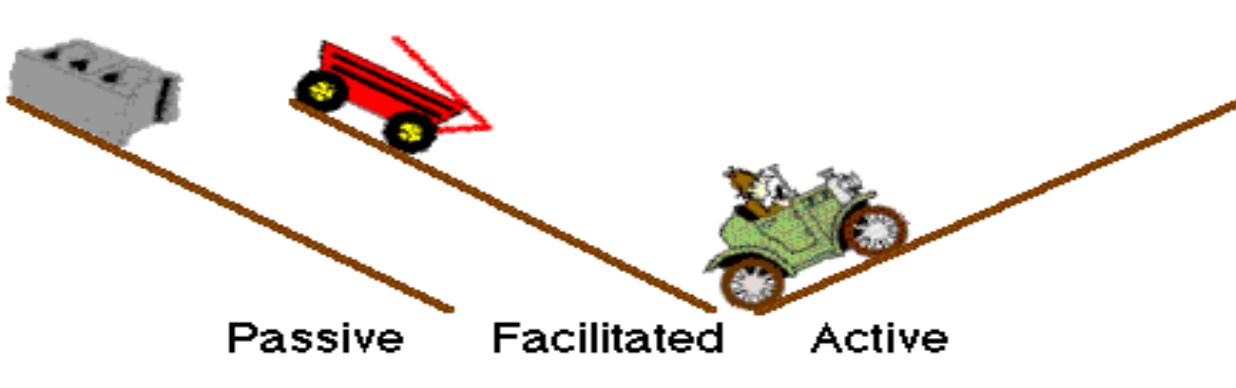
- Drug factors include drug solubility, pH, and molecular size
- Patient factors include the age and health status
- Drug delivery by other routes may result in partial absorption & hence lower bioavailability.
E.g. the oral route requires that a drug dissolves in GI fluids & then penetrate the epithelial cells of intestinal mucosa before reaching the systemic circulation.

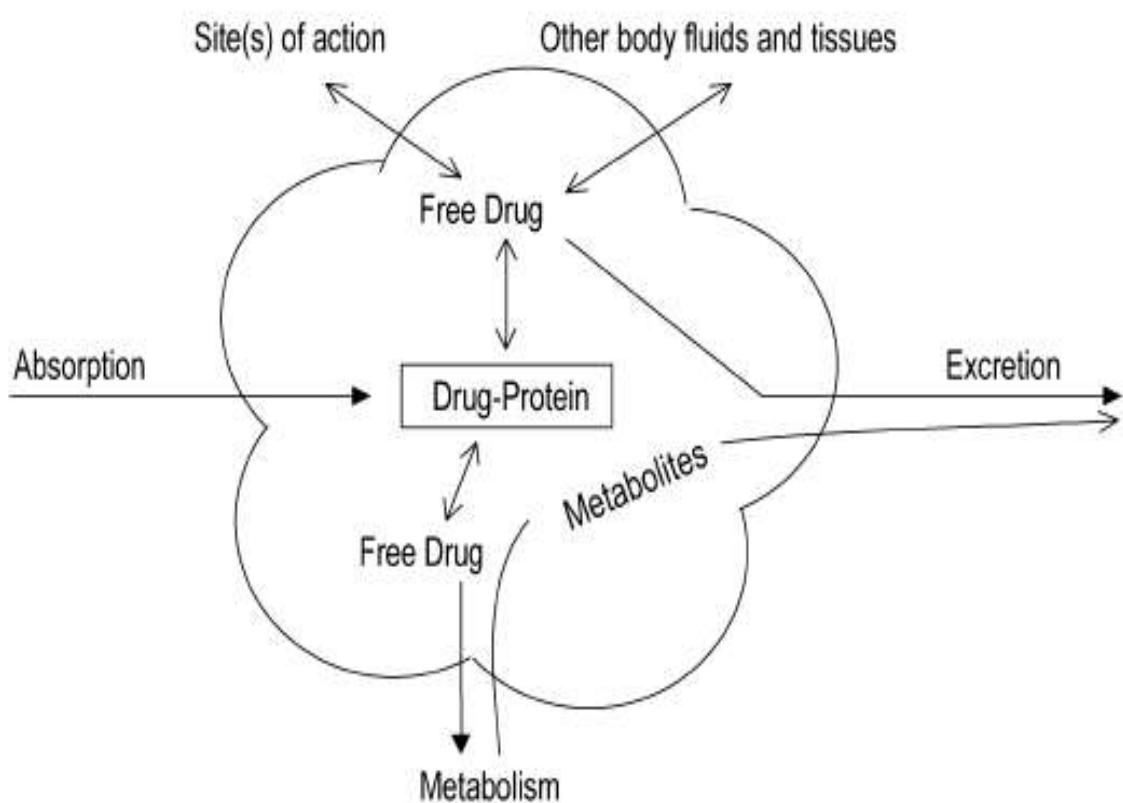
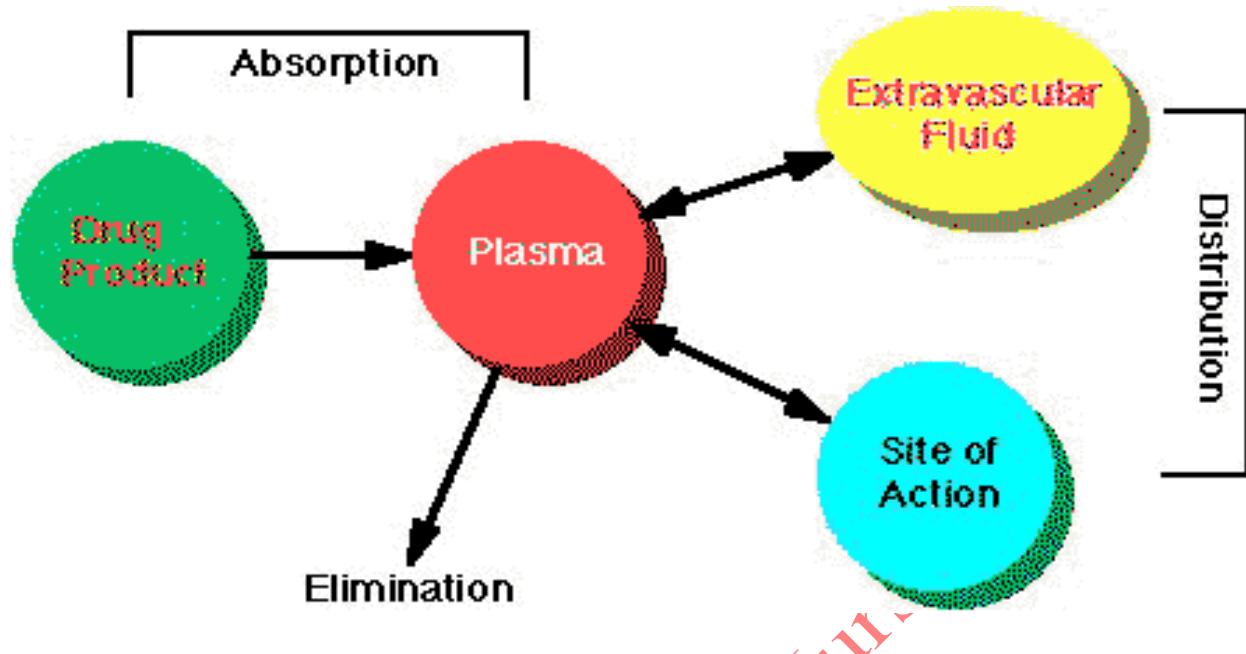
Movement of Drugs across the Cell Membrane

- There are a number of mechanisms of drug absorption.
- Passive diffusion of water & lipid soluble drugs
- Pinocytosis and phagocytosis
- Active transport
- Facilitated diffusion
- Passive filtration
- Adsorption of drugs to cell contents
- Passage via gap-junction

Illustration of Different Transport Mechanisms







Passive diffusion: movement of particles from an area of high concentration to an area of low concentration

Good for small, lipophilic, nonionic particles

Facilitated diffusion: passive diffusion that uses a special carrier molecule
Good for bigger molecules that are not lipid soluble

Active transport: molecules move against the concentration gradient from areas of low concentration of molecules to areas of high concentration of molecules; involves both a carrier molecule and energy

Good for accumulation of drugs within a part of the body

Pinocytosis/phagocytosis: molecules are physically taken in or engulfed. Pinocytosis is engulfing liquid; phagocytosis is engulfing solid particles

Good for bigger molecules or liquids

FACTORS THAT AFFECT ABSORPTION

- The particle size (drug molecular weight) of drug dosage forms. Smaller size is better if lipid solubility is low.
- The relative concentration of the drug molecule on the two sides of the membrane. i.e. more concentrated drugs are absorbed better.
- The pH levels. This affects the degree of ionization. A drug passes through membranes more readily if it is in unchanged form
- Blood flow to absorption site. Blood flow to intestines is much greater than bld flow to stomach thus absorption from stomach is favored over that from stomach.
- Total surface area available absorption. The intestines is rich microvilli, this offers a large surface area for absorption.
- Organ function, lipid & water solubility
- Contact time at the absorption site. If a drug moves through GI very quickly, as in severe diarrhea, it will not well absorbed & anything that delays the transport of drugs from stomach to intestines delays the rate of absorption of the drug.

WHAT DETERMINES RATE OF RELEASE OF DRUG FROM PHARMACEUTICAL PREPARATION?

A: DOSAGE FORM

- Solutions: No Delay, Immediate Release
- Capsules & Tablets: Delay (Dissolution) Followed by Rapid Release
- Creams, Ointments & Suppositories: No Delay, but Slow Release

B: ADDITIVES (EXCIPIENTS)

Decrease Rate of Dissolution

- Binders
- Lubricants
- Coating Agents

Increase Rate of Dissolution

- Disintegrants

Variable Effects on rate of Dissolution

- Diluents
- Coloring Agents
- Flavoring Agents

C: MANUFACTURING PARAMETERS

- Tablet Compression - Hard tablets dissolve more slowly
- Tablet Shape - Round tablets dissolve more slowly
- Tablet Size - Large tablets dissolve more slowly

EXTENT OF ABSORPTION

After oral administration, a drug may be incompletely absorbed, eg, only 70% of a dose of digoxin reaches the systemic circulation. This is mainly due to lack of absorption from the gut. Other drugs are either too hydrophilic (eg, atenolol) or too lipophilic (eg, acyclovir) to be

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absorbed easily, and their low bioavailability is also due to incomplete absorption. If too hydrophilic, the drug cannot cross the lipid cell membrane; if too lipophilic, the drug is not soluble enough to cross the water layer adjacent to the cell. Drugs may not be absorbed because of a reverse transporter associated with P-glycoprotein. This process actively pumps drug out of gut wall cells back into the gut lumen. Inhibition of P-glycoprotein and gut wall metabolism, eg, by grapefruit juice, may be associated with substantially increased drug absorption.

DRUG DISTRIBUTION

Drug distribution is the process by which a drug leaves blood stream & enters the extracellular fluids & tissues.

Once drugs have been absorbed from various sites of extra-vascular admn, they are distributed to (i) plasma compartment (ii) extracellular fluid (iii) total body water(iv) intracellular & interstitial (v) other sites e.g. in pregnancy the fetus may take up some drugs & thus increase the volume of distribution, others may be stored in body fat(eg thiopental)

Dosing must take into consideration all of the factors that tend to reduce or increase free drug concentrations at intended sites of action. These factors include:-

- Binding to plasma proteins, tissues & organs (liver, kidneys).
- Deposition into body fat.
- Metabolism to inactive or less active or more active compounds.
- Elimination active drugs through various pathways.

BARRIERS TO DRUG DISTRIBUTION

- Brain-blood barrier. B'se of the nature of brain blood barrier, ionized or polar drugs distribute poorly into the CNS. Inflammation .eg. Meningitis may increase the ability of ionized drugs, poorly soluble drugs to cross the brain-blood barrier.
- Placental barrier. Lipid soluble drugs cross the placental barrier more easily than polar drugs, drugs with a molecular weight of less than 600 pass the placental barrier than larger molecules.

DRUG DISTRIBUTION PATTERNS

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- 1) The drug may remain largely within the vascular system. Plasma substitutes such as dextran are an example of this type, but drugs which are strongly bound to plasma protein may also approach this pattern.
- 2) Some low molecular weight water soluble compounds such as ethanol and a few sulfonamides become uniformly distributed throughout the body water.
- 3) A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action. Iodine is concentrated by the thyroid gland. The antimalarial drug chloroquine may be present in the liver at concentrations 1000 times those present in plasma. Tetracycline is almost irreversibly bound to bone and developing teeth. Consequently tetracyclines should only be given to young children or infants in extreme conditions as it can cause discoloration and mottling of the developing second set of teeth.
- 4) Most drugs exhibit a non-uniform distribution in the body with variations that are largely determined by the ability to pass through membranes and their lipid/water solubility. The highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of drug being excreted.
- Pattern 4 is the most common being a combination of patterns 1, 2 and 3.

FACTORS AFFECTING DRUG DISTRIBUTION

- Membrane permeability
- Blood perfusion rate.
- Extent of Distribution e.g. Plasma protein binding
- Tissue localization of drugs(drug affinity)
- Weight considerations.

Drug distribution

- Factors that affect absorption also affect storage or accumulation in tissue
- Drugs will accumulate greatly in adipose or fat tissue (18-28% of body is fat)
 - Usually are not active in fat unless person begins using the fat tissue (dieting, starving); will slowly reenter the bloodstream
 - E.g., thiopental, an anesthetic is very lipid soluble
 - Enters brain quickly, has rapid onset
 - Enters muscle tissue quickly too, & follows its concentration gradient out of the brain back into circulation
 - Enters fat tissue and is stored there
 - Therefore, effect is short, but may linger for many hours
- Women have less water (54 vs. 60%) and more fat (28 vs. 18%) than men: drug action differs

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Body Membranes that Affect Drug Distribution

- Cell membranes
 - Stomach/GI tract into bloodstream
 - Fluid around tissue cells into the cell
 - Interior of cells back into fluid around them
 - Kidneys back into the bloodstream
- Cell membranes are permeable to
 - Small molecules
 - Lipid-soluble molecules

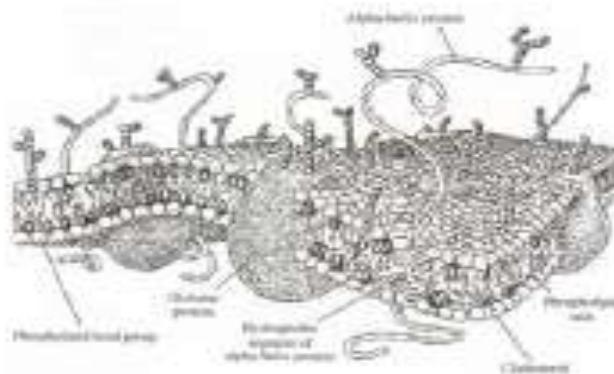


FIGURE 1.7 A diagrammatic representation of the cell membrane, a phospholipid bilayer in which phospholipid and protein molecules are embedded. Both glycolipids and other kinds of proteins separate the bilayer. Cholesterol interdigitates randomly between the tails of the phospholipids, separating them and adding to the rigidity. Below is the hydrophobic cytoskeleton layer, the parts of the cells closest to the core of the membrane consist mostly of proteins. (From M. S. Blitschek, "The Function of the Cell Membrane," *Scanning Microscopy* 13(3) (1989), 1-94.)

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Body Membranes that Affect Drug Distribution

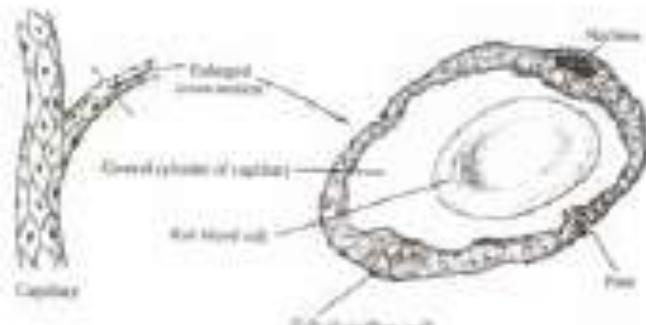


FIGURE 1.8 Cross section of a blood capillary. Within the capillary are the blood vessels, and only of the blood, involving the red blood cells. The capillary itself is made up of cells that completely surround and define the central lumen or channel of the capillary. Photo=Edie Jones, altered from *Basic of Medical Terminology*.

- **Capillaries**
 - Drugs enter all body tissues via the capillaries
 - Rate that drug enters tissue depends on blood flow to that area and ease of passing through capillary membranes
- **Permeability**
 - Drug molecules pass easily through the pores in the membranes (but not red blood cells or proteins)
 - Independent of lipid solubility
 - Drugs that bind to proteins won't pass out of capillaries

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Body Membranes that Affect Drug Distribution: the Blood-Brain Barrier (BBB)

- The BBB is located in the specialized endothelial cells of the capillaries that deliver blood to the brain
- The walls of the capillaries, which are lipid endothelial cells, are the last membrane into the brain
- Liquid diffuses through brain capillaries or via choroid plexus in the ventricular system (which makes CSF) into the fluid surrounding the brain cells or into the astrocyte processes
- Foot processes of the astrocyte cells surround the capillaries and line the ependymal cells of the ventricles, and make contact with neurons
- Astrocytes are glial cells in the brain and do much of the "housekeeping"

VOLUME OF DISTRIBUTION

Volume of distribution relates the amount of drug in the body to the concentration of drug in blood or plasma:

The volume of distribution may be defined with respect to blood, plasma, or water (unbound drug), depending on the concentration used.

Drugs with very high volumes of distribution have much higher concentrations in extravascular tissue than in the vascular compartment; that is, they are *not* homogeneously distributed.

Drugs that are completely retained within the vascular compartment, on the other hand, have a minimum possible volume of distribution equal to the blood component in which they are distributed.

THE DRUG CONCENTRATION IN BLOOD STREAM

It is important to achieve the levels of drugs in the blood stream to overcome certain conditions, since blood is the main transport for all substances to various tissues of the body.

There are factors that govern this and these include;

1) The dose

The term dose refers to the amount of drug to be given at once. It is obvious that the larger the dose the higher the concentration achieved.

2) THE ROUTE OF ADMINISTRATION:

As mentioned earlier, I.V injection produce a rapid rise in blood concentration whereas oral administration gives a lower peak concentration of drug and I.M injection rates between the two.

3) THE DISTRIBUTION OF THE DRUG.

The way in which the drug can be distributed to various tissues and parts of the body determines its blood concentration. Some drugs are only confined to the blood stream whereas others can enter tissue spaces and others enter cells and spread through the total H₂O of the body which is around 36 litres, therefore that the more widely a drug diffuses, the lower will be the blood concentration produced by the given dose.

(4) THE RATE OF ELIMINATION:

The faster the body breaks down or excretes the drug, the more rapidly the drug will follow. Drugs are eliminated in one or two ways;

- They are broken down or combined with some chemicals so that they are no longer pharmacologically active- this occurs in the liver by liver enzymes.
- Drugs and their broken down products may be excreted through the kidneys and if these are damaged by disease, excretion will be damaged and accumulation will occur.

By the age of 80 years, kidney functions are reduced to about half of a young adult. So doses must be reduced in such age.

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Rarely some drugs are eliminated through the lungs. The speed of elimination is very important in deciding the duration of action of the drugs and this referred to as plasma half life ($t^{1/2}$)

THE DRUG DOSE

The therapeutic dose of a drug is based on the amount that will produce a response and the dose that can be tolerated without producing excessive side effects. The dose may vary basing on the following factors;

(1) AGE AND WEIGHT.

Age is most important factor as far as selection of doses is concerned. Elderly patients above 60yrs require less doses because of the state of their liver and kidneys.

A heavy individual will require large dose than a small individual, this is why it is very important to take patients' weight on every visit to hospital.

(2) ROUTE OF ADMINISTRATION.

The route used for administration of drug will determine the amount to be given; this is so because drugs given by mouth will take long to reach the blood stream whereas those given by I.V will achieve a high concentration immediately.

(3) DISEASES:

Doses vary in different diseases and depending on the severity of the condition.

(4) TOLERANCE:

This is a state in which one has got a reduction or loss of normal response to a substance that usually provoke a reaction in the body. Therefore where drug tolerance has occurred the patient will require a high dose than normally it would have been.

(5) INITIAL AND MAINTENANCE DOSES

It is very necessary to give higher doses initially to achieve required blood levels to combat certain conditions but later small doses may be required for maintenance.

the decreased renal and skeletal muscle mass and consequent decreased tissue binding of digoxin to Na^+/K^+ ATPase.

BIOAVAILABILITY

This is the fraction of unchanged drug reaching the systematic circulation following administration by only route. For an I/V dose of a drug bio-availability is equal to unity (one). For a drug administered orally bio-availability may be less for several reasons;

- The drug may be incompletely absorbed
- It may be metabolized in the gut
- The drug may undergo hereto-hepatic cycling
- First pass effect in the liver

Factors that influence bioavailability

- First-pass metabolism. When the drug is absorbed across GI, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolised, the amount of unchanged drug that gains access to the systemic circulation is decreased. e.g. propranolol or lidocaine undergo significant biotransformation during a single passage through the liver.
- Solubility of the drug. Very hydrophilic drugs are poorly absorbed b,se of their inability to cross lipid rich membranes. Drugs that are extremely hydrophobic are also poorly absorbed b,se they are totally insoluble in aqueous body fluids.
- Chemical instability. Some drugs such as penicillin G are unstable in the pH of the gastric contents. Insulin can be destroyed by digestive enzymes.
- d) Nature of the drug formulation.e.g. particle size, salt form, crystal polymorphism & presence of excipients(such as binding & dispensing agents) can influence the ease of dissolution & therefore alter rate of absorption
- *Ionization:* the property of being charged, Hydrophilic = ionized, Lipophilic = nonionized
- Nature of the drug: pH of drug
- Weakly acid drugs = hydrophilic form in alkaline environment
- Weakly alkaline drugs = hydrophilic form in acid environment

- *Ion trapping:* when drugs change body compartments, they may become ionized and trapped in the new environment
- Drug form is important; oral drugs must have different properties than parenteral drugs

FIRST-PASS ELIMINATION

Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into the systemic circulation. A drug can be metabolized in the gut wall (eg, by the CYP3A4 enzyme system) or even in the portal blood, but most commonly it is the liver that is responsible for metabolism before the drug reaches the systemic circulation. In addition, the liver can excrete the drug into the bile. Any of these sites can contribute to this reduction in bioavailability, and the overall process is known as first-pass elimination. The effect of first-pass hepatic elimination on bioavailability is expressed as the extraction ratio (ER):

MAINTENANCE DOSE

In most clinical situations, drugs are administered in such a way as to maintain a steady state of drug in the body, ie, just enough drug is given in each dose to replace the drug eliminated since the preceding dose. Thus, calculation of the appropriate maintenance dose is a primary goal. Clearance is the most important pharmacokinetic term to be considered in defining a rational steady-state drug dosage regimen. At steady state, the dosing rate ("rate in") must equal the rate of elimination ("rate out").

DOSAGE CALCULATION

This is one of the most complicated yet simple tasks that usually is the source of errors in drug administration;

Patients may be prescribed doses of drugs which are not precisely equivalent to a single tablet or vial or capsule.

Formula;

Dose = strength required ÷ strength in stock X diluent

Example

Quinine injection has 600mg in 2mls. The patient is prescribed 80mg. how much would you administer to this patient

$$80\text{mg} \div 600\text{mg} \times 2 = 0.27 \text{ mls}$$

LOADING DOSE

When the time to reach steady state is appreciable, as it is for drugs with long half-lives, it may be desirable to administer a loading dose that promptly raises the concentration of drug in plasma to the target concentration

DRUG METABOLISM/ BIOTRANSFORMATION

Metabolism

- Metabolism = biotransformation
 - any process which results in a chemical change in a drug in the body
 - Catabolism = when complex compounds are broken down into simpler ones
 - Anabolism = when simpler compounds or molecules are combined into more complex ones

Metabolism may go in stages, and generally goes from more lipophilic to increasingly hydrophilic

A drug may have several metabolites (by-products or waste products)

– Metabolites may be inactive or active

Drugs may undergo four general kinds of transformations(chemical reactions).

- ❖ Phase one (oxidation, hydrolysis, reduction).
- ❖ Phase two- Conjugation processes.
- ❖ Many organs are capable of metabolizing drugs. The liver is the major organ of drug biotransformation but the kidneys, lungs, intestines & enzymes in blood are capable of significant drug metabolism.

Phase 1 reactions.

Oxidation . The oxidation of drugs & other compounds involves insertion of an O₂ atom into substrate. This process involves a cascade of reactions collectively referred to as microsomal electron transfer chain. Most of oxidation reactions takes place in sER.

Reduction & hydrolysis take place in the cytosol of the cell or in extracellular fluid

Phase 1 reactions.

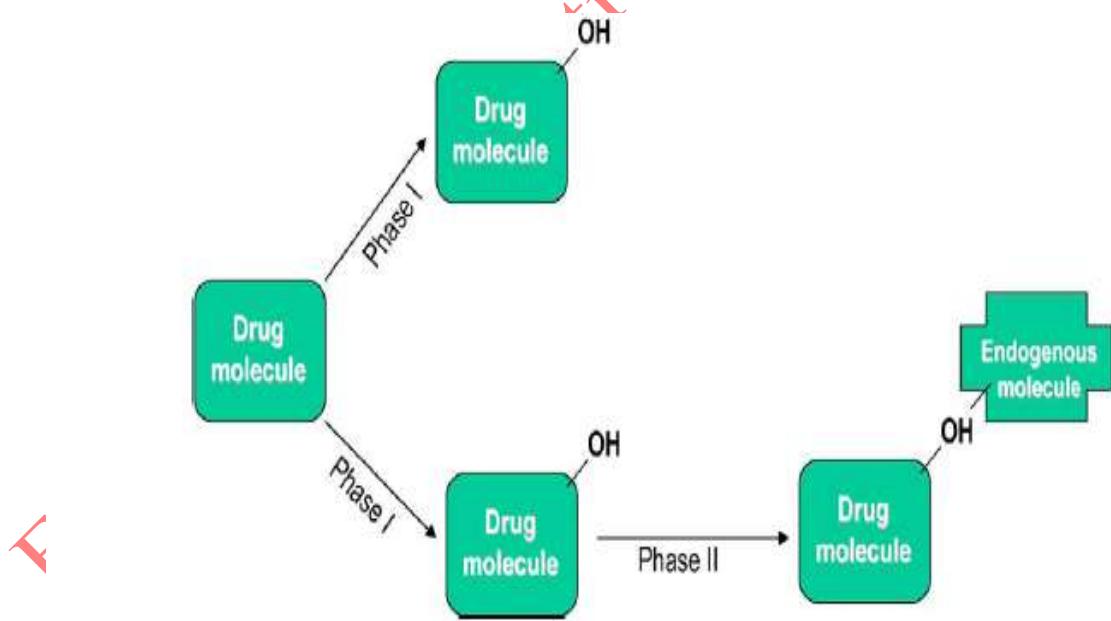
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Reduction & hydrolysis take place in the cytosol of the cell or in extracellular fluid

In the liver, drugs like other substances such as digested food products enter the sinusoids & partition into hepatocytes. In hepatocytes drugs enter smooth endoplasmic reticulum where they are then oxidized by the hepatic monooxygenase system sometimes referred to as mixed function oxidase(MFO) system.

Phase II drug biotransformation(metabolizing) reactions.

Phase II reactions results in conjugation products. Reactive sites(e.g. hydroxyl, thiol, carboxylic acid or amino groups) on the drug molecule can combine with endogenous metabolic products such as glucuronic acid, sulfate, methyl groups or acetate to form conjugated products. Conjugated products are almost always pharmacologically inactive in contrast to phase one products which may remain pharmacologically active & in some cases be as or more active than a parent drug. Glucuronidation is the most common metabolic reaction followed by sulfate conjugation.



- Enzymes catalyzing phase 1 reactions include:-the cytochrome p-450, aldehyde & alcohol dehydrogenase, deaminases, esterases, amidases & epoxide hydratases.

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- Enzymes catalysing phase II reactions include:- glucuronyl transferase (glucuronide conjugation), sulfotransferase(sulfate conjugation, transacyclases(amino acid conjugation), acetylases, ethylases, methylases & glutathione transferase. These enzymes are present in numerous tissues & some in plasma & sub cellular locations.
- Cytochrome p-450**(mixed function oxidase) & primary location of this enzyme is the liver. This enzyme plays a role in drug biotransformation. Large number of families of cytochrome p-450 exists. Abbreviated "CYP" .e.g.CYP1, CYP2 & each family has a number of subfamilies.e.g. CYP2A, CYP2B. With in each subfamily there are other sub families.e.g.CYP3A1, CYP3A2,etc. Genetic polymorphism of several clinically important cytochrome P-450 especially CYP2C & CYP2D is the source of variable metabolism in Humans including differences in race & ethnic groups.

- Inducers of cytochrome P450**

The cytochrome p450-dependant enzymes are an important target for pharmacokinetic drug interactions. One such interaction is the induction of selected CYP isozymes. Drugs like phenobarbital, rifampicin & carbamazepine are capable of increasing the synthesis of one or more CYP isozymes. The increased biotransformation rates can lead to significant decrease in plasma concentrations of drugs measured by AuC, with concurrent loss of pharmacologic effect.

For example, rifampin an antiTB drug significantly decreases the plasma concentrations of HIV protease inhibitors diminishing their ability to suppress HIV virion maturation. Some p450 isozymes.

S/N	Isozyme	Common substrates	Inducers
1	CYP2C9/10	Warfarin, phenytoin, ibuprofen, tolbutamide	Phenobarbital, rifampin
2	CYP2D6	Desipramine, imipramine, haloperidol, propranolol	

3	CYP2A4/5	Carbamazepine, erythromycin, verapamil	cyclosporine, nifedipine,	Carbamazepine, dexamethasone, phenobarbital, rifampin	phenytoin,
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- **Inhibitors of p450.**

The most form of inhibition is through competition for the same isozyme. Some drugs are capable of inhibiting reactions for which they are not substrates(eg. Ketoconazole). Numerous drugs have been shown to inhibit one or more of the CYP dependant biotransformation pathways of warfarin.e.g. omeprazole is a potent inhibitor of three of the CYP isozymes responsible for warfarin metabolism.

If two drugs are taken together, plasma concentrations of warfarin increase, which leads to greater inhibition of coagulation & risk of hemorrhage & serious bleeding reactions.

Note: the most important inhibitors of CYP are erythromycin, ketoconazole & ritonavir because they each inhibit several CYP isozymes.

Metabolic processes can occur in any tissue, but are most likely to occur in liver, kidneys, lungs, & GI tract

- Cleavage = splitting of the molecule into 2 or more simpler molecules
- Oxidation = combining the molecule with oxygen, or increasing the electropositive charge by the loss of hydrogen or of one or more electrons
- Conjugation = the combining of the molecule with glucuronic or sulfuric acid
- Reduction = the molecule gains 1 or more electrons and becomes more negatively charged

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What is first-pass metabolism?

- Drugs metabolism occurs primarily in the liver through its enzymes, particularly the cytochrome P450 family of enzymes
 - Enzymes are catalysts that induce chemical changes in other substances, but not themselves (proteins)
 - These cytochrome P450 enzymes have diversified to accomplish the metabolism (detoxification) of environmental chemicals, food toxins, and drugs that are foreign to our needs
 - There are several cytochrome P450 families, designated CYP (e.g., CYP1 or CYP-3A4)

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Role of the liver in drug metabolism

- Drugs diffuse out of the blood into liver cells (hepatocytes) where they are acted on by the cytochrome P450 enzymes
- Metabolites and the drug will diffuse back into the blood plasma and/or be secreted into the bile
- Metabolites that are sufficiently water-soluble will be excreted via urine, if not water-soluble they will recirculate and may be further metabolized in the liver
- Metabolites in the bile that are water-soluble will be excreted via feces, if not water-soluble they will be re-absorbed, and undergo further metabolism

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- Liver cells (hepatocytes) biotransform some drug molecules into metabolites that are less fat-soluble
- The metabolites are carried to the kidneys via blood, and those that are water-soluble will be excreted via urine
- Metabolites that are still fat-soluble will be reabsorbed into blood and circulate back to the liver again

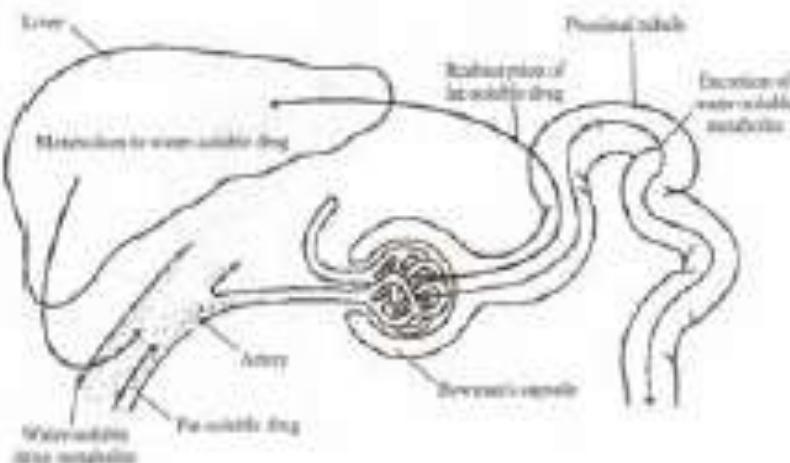


FIGURE 1.13 How the liver and kidneys interact to eliminate drugs from the body. Drugs may be filtered into the kidney, reabsorbed into the bloodstream, and carried to the liver for metabolic transformation to a more water-soluble compound that, having been filtered into the kidney, cannot be reabsorbed and is therefore excreted in urine.

Factors affecting drug metabolism

- **Drug Dose**
 - The higher the plasma concentration of a drug the higher the rate of metabolism (first-order kinetics) for most drugs (but not alcohol)
 - A drug that is easily hepatically metabolized must be given in higher doses
- If a person's liver is altered or damaged, the effectiveness of a drug given orally may be greatly changed
- **Enzyme changes**
 - Many drugs cause induction of liver enzymes (increases due to continued use); this reduces the effectiveness of those drugs and other drugs that are metabolized by those enzymes (one aspect of tolerance)
 - Some drugs inhibit the activity of enzymes, which will increase the effect of all drugs metabolized by that enzyme
- Some drugs have direct effects on rate of metabolism of other drugs
 - E.g., they may compete for the same enzyme
- **Individual differences**
 - Sex, Age, Species, Past experience with drugs

DRUG INTERACTIONS

- ✓ Patients receiving so many drugs face the risk of numerous drug interactions
- ✓ Health care professionals should be aware of the potential for many medications to interact with others.
- ✓ Common medications like opioids, antidepressants, anti-convulsants and benzodiazepines interact with ant-retroviral medicines, rifamycins, antifungal drugs and others.

HOW DO DRUG INTERACTIONS COME ABOUT?

Note: the cytochrome p450 enzyme system.

The liver is the major site of drug metabolism and it is mediated by a group of mixed function enzymes including the cytochrome p450 enzymes most of the serious drug interactions involve hepatic biotransformation through this system.

HEPATIC BIOTRANSFORMATION/METABOLISM OF DRUGS

Orally administered drugs are first metabolized in the liver before being cleared from the body or before release to the general circulation to achieve the intended function.

Metabolized drugs are mainly chemically modified/ bio-transformed to suit the criteria for clearance or excretion from the body.

Therefore the goal of metabolism in general is to detoxify drugs and make them either more water soluble (for excretion in the urine) or more fat soluble (for excretion in bile and then the faeces)

Note: The metabolism of drugs taken orally in the liver before entering the systemic circulation is called first pass metabolism or effect.

Note: we shall look at metabolism in detail and the stages involved i.e, phase one and two.

Note : we have seen that cytochrome p450 system of enzyme participate in the metabolism of most drugs, however there are drugs that inhibit it or induce it or act as its substrates bringing up what we call drug interactions.

CYTOCHROME P450 INHIBITORS

These drugs slow or stop the metabolism of drugs by cyt p450 enzymes and result in accumulation of unmetabolized drugs in the circulation.

These unmetabolized drugs may be inactive or even toxic.

EXAMPLE OF CP450 INHIBITORS

(1) ART

Protease inhibitors

- Ritonavir
- Indinavir
- Nelfinavir
- Saquinavir
- NB. the most potent inhibitor of cyt p450 is Ritonavir

NNRTIS

- Delavirdine
- Efavirenz

(2) ANTIBIOPATICS e.g. MACROLIDES

- Erythromycin
- Clarithromycin

(3) ANTIFUGALS e.g. AZOLEs

- ketoconazole
- itraconazole
- fluconazole

(4) HISTAMINE ANTAGONISTS

- Cimetidine

(5) ANTIDEPRESSANTS

- Fluoxetine
- Paroxetine

- Sertraline

(6) ANTI PSYCHOTICS

- Holoperidol

CYTOCHROME P450 INDUCERS:

These accelerate the metabolism of other drugs by cyt p450 enzymes resulting in;

- ✓ Decreased plasma concentration of such drugs
- ✓ Decreased pharmaceutical effect
- ✓ Increased toxicity if active metabolites are formed

EXAMPLE OF CYT P40 INDUCERS

(1) ART

NNRTIS

- Efavirenz
- Nevirapine

PI's

- Nelfinavir
- Ritonavir

(2) ANTICONVULSANTS

- ❖ Dexamethasone
- ❖ Prednisolone

CYTOCHROME P450 SUBSTRACTES:

These are drug that are metabolized by one or more of the p450 enzymes and so are affected by drugs that either induce or inhibit these enzymes.

EXAMPLES OF CYT P450 SUBSTRACTES

(1) OPIOIDS

- Codeine
- Methadone
- Fentanyl

(2) BENZODIAZEPINES

- Clonazepam

- Diazepam

- Midizolam

(3) ANTIHISTAMINES

- Terfenadine

- Astremizole

(4) ANTIDEPRESSANTS

- Tricyclics

- SSRI'S

(5) ANTIPSYCHOTICS

- Haloperidol

(6) SEDATIVE HYPNOTICS

- Zolpidem

SUMMARY OF DRUG INTERACTIONS

(1) Inhibition of cytochrome p450 enzymes

(2) Induction of cytochrome p450 enzymes

(3) Synergism

(4) Potentiation

DRUG CLEARANCE

Drug clearance principles are similar to the clearance concepts of renal physiology. Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration

Clearance, like volume of distribution, may be defined with respect to blood plasma or unbound in water, depending on the concentration measured.

It is important to note the additive character of clearance. Elimination of drug from the body may involve processes occurring in the kidney, the lung, the liver, and other organs. Dividing the rate

of elimination at each organ by the concentration of drug presented to it yields the respective clearance at that organ. Added together, these separate clearances equal total systemic clearance.

"Other" tissues of elimination could include the lungs and additional sites of metabolism, eg, blood or muscle.

The two major sites of drug elimination are the kidneys and the liver. Clearance of unchanged drug in the urine represents renal clearance. Within the liver, drug elimination occurs via biotransformation of parent drug to one or more metabolites, or excretion of unchanged drug into the bile, or both. The pathways of biotransformation are discussed in Chapter 4. For most drugs, clearance is constant over the concentration range encountered in clinical settings, ie, elimination is not saturable, and the rate of drug elimination is directly proportional to concentration

Elimination: Role of the Kidneys

- Renal (kidney) excretion is the primary removal mechanism for drugs
- Major functions of kidneys
 - Excrete most of the products of body metabolism
 - Closely regulate the levels of most of the substances found in body fluids
- Kidneys filter about 1 liter (1000 cubic cm) of plasma per minute
 - Only 1 cubic cm of urine is formed per minute, so most of the filtered fluid is reabsorbed
 - Lipid-soluble drugs are reabsorbed back into plasma along with the other 99% of filtered fluid

The Nephron is the functional unit of the Kidneys

- Blood flows into the glomerulus
- Pressure causes fluid (water) to flow into the Bowman's capsule
- Fluid flows through tubules and some will go into a duct which collects fluid from several nephrons
- Fluid in ducts will collect in ureters and then flow into the urinary bladder
- Rest of fluid diffuses back into capillaries and recirculates

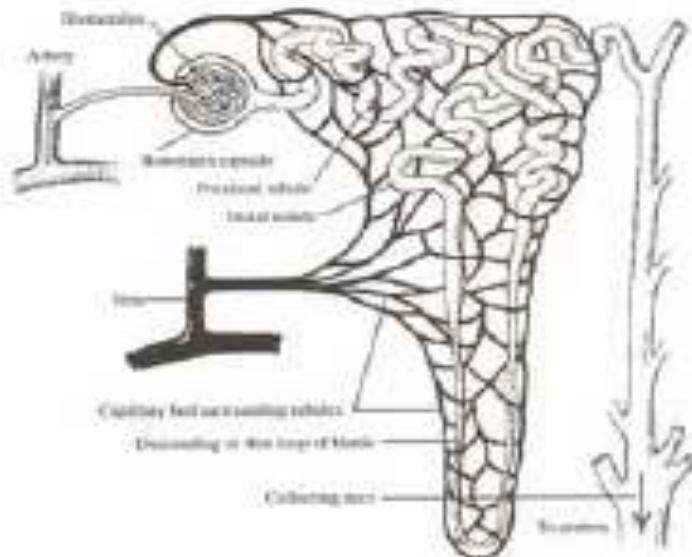


FIGURE 1.12: Nephron within a kidney. Note the compactness of the structure and the intimate relation between the blood supply and the nephron. Each kidney is composed of more than a million such nephrons.

Other forms of drug excretion

- Many drugs and their metabolites may be found in other secretions, but their concentrations are generally low
 - Excretion of drugs via sweat, tears, or salivation is minuscule
 - Small amounts are excreted in breast milk, but small amounts may be too much for babies
 - Excretion occurs from the lungs with some drugs (e.g., alcohol). Lungs can excrete volatile substances (which may not be water-soluble)
 - Bile (feces)

FC

HALF-LIFE

Half-life ($t_{1/2}$) is the time required to change the amount of drug in the body by one-half during elimination (or during a constant infusion). In the simplest case and the most useful in designing drug dosage regimens, the body may be considered as a single compartment of a size equal to the volume of distribution. The time course of drug in the body will depend on both the volume of distribution and the clearance:

Half-life is useful because it indicates the time required to attain 50% of steady state or to decay 50% from steady state conditions after a change in the rate of drug administration.

Disease states can affect both of the physiologically related primary pharmacokinetic parameters: volume of distribution and clearance. A change in half-life will not necessarily reflect a change in drug elimination. For example, patients with chronic renal failure have decreased renal clearance of digoxin but also a decreased volume of distribution; the increase in digoxin half-life is not as great as might be expected based on the change in renal function. The decrease in volume of distribution is due to

Time Course of Drug Distribution and Elimination: Concept of Drug Half-Life

- Dose response function- expresses relationship between the dose administered and the response observed

Plasma or drug half-life

- A huge determinant of a drug's effects is the length of time for a dose to be metabolized, and presence of active metabolites (breakdown products).
- The plasma half-life is the time it takes for half of a dose of a drug to be eliminated from the bloodstream.
- Metabolites have half-lives also. They can be inactive, more active than the parent drug, or somewhere in between.
- Prozac (fluoxetine) has a half life of 1 to 3 days; its primary metabolite (norfluoxetine) is even more active and the metabolite's half-life can be 7 to 15 days!!!

PHARMACODYNAMICS

- (1) Pharmacodynamics –the effects of a drug on biological system and the mechanisms by which a drug acts.
- (2) Drug receptor- specific molecule (site) of a biological system with which drugs interact to produce changes in a biological system
- (3) Drug effectors-a component of a biological system that accomplishes the biological effects after being activated by the receptor
- (4) Receptor site –specific region of a receptor molecule onto which drug binds
- (5) Agonist-a drug that causes a specific positive response of a specific receptor site binding
- (6) Antagonist-Drug that causes a specific receptor site binding
- (7) Efficacy -Measure of how well a drug produces a response. Is the maximum response an agonist can produce at the highest dose.

- (8) Potency- The dose of a drug required to produce 50% of the maximum effect or that which can produce effect in 50% of the population.
- (9) Affinity- Ability of drug to bind to a receptor.
- (10) Full agonists-Are drugs that produce a maximum response and have maximum efficacy.
- (11) Partial agonists-Are drugs that are incapable of eliciting/producing a maximum response
- (12) Potentiation-Means the enhancement of the response of particular drug by another, all given concurrently; the potentiating agent has no such effect if given alone.
- (13) Synergism – The enhancement of the response of two drugs when given concurrently (together). The effect of the interaction is greater than the total effect of either drug.
- (14) Tolerance- Is the gradual decrease of a drug's responsiveness due to chronic use of that drug.
- (15) Resistance- Refers to loss of drug's effect on the invasive organism.
- (16) Hyper sensitivity- Usually refers to allergic or other immunologic responses to a drug.

THE DRUG RECEPTORS

Drug receptors are protein in nature or are macro cell molecules.

The receptors are

- ✓ Extra cellular
- ✓ Intra cellular
- ✓ Transmembranal

NB- binding of an agonist drug to its receptor activates an effect or signaling mechanism.

SIGNALING MECHANISMS

There are five different types of drugs –responsive signaling mechanisms known;

- (1) Intracellular receptor-Involves transmembrane diffusion of the drug to its receptor in the cell which it stimulates to produce signals that in turn stimulate the effectors to produce a response.
- (2) Membrane receptors directly coupled to ion channels- Involves drugs binding to receptors on ion channels on cell membranes. This activates flow of ions through excitable membranes

The excitation of cell membranes produces signals that activates the effectors to produce a response.

(3) Receptors linked via coupling proteins to intracellular effectors.

Many receptor systems are coupled via G-protein to the enzymes (second messenger) intracellularly and to the effector which produces a response.

(4) Receptors that function as transmembrane enzymes: Receptors on which drug binds located within cell membrane and second messengers transport the signal to the effectors.

DRUG DISCOVERY AND DEVELOPMENT

Involves 4 stages;

(1) Stage one –discovery/ identification

(2) Stage two – preclinical's. Preclinical trials are done on animals. The pharmacological preparation is exposed to animals and assessed for

- i) Toxicity
- ii) Carcinogenesis (ability to cause cancer)
- iii) Mutagenesis (ability to cause mutations)
- iv) Effect on reproductive system.

(3) Stage three –clinicals

- i) Phase 1
 - ✓ The drug is exposed to healthy people
 - ✓ A small group of people is used (25-50 volunteers)
 - ✓ Assessments are done for;

Toxicity

Drug response

Dosage range

ii) **Phase ii**

- ❖ The drug is exposed to patients with disease
- ❖ About 100-200 volunteers are needed

- ❖ Assessments are done for;
 - Efficacy
 - Toxicities
- iii) **Phase iii**
 - Drug is exposed to thousands of people
 - This is done to find out any errors
 - Assessments for efficacy are further done.

(4) Stage four- regulatory stage.

- ✓ Done even when the drug is on market
- ✓ Involves monitoring of the drug
- ✓ Done to determination of toxicities as reported by physicians.

PRESCRIPTION WRITING

A prescription is a written order to prepare or dispense a specific treatment usually medication for a specific patient

Rational prescribing

Refers to prescribing a drug with a scientific/medical reason

It is a stepwise process based on the following;

- (1) First making a specific diagnosis
- (2) Understanding the pathophysiological basis of the diagnosis
- (3) Selecting a specific therapeutic objective
- (4) Selecting a drug of choice
- (5) Determining the appropriate dosing regimen
- (6) Devising a plan for monitoring the drug's action and determining an end point for therapy.
- (7) Patient education-especially about dosing, side effects, adherence e.t.c.

NOTE: That a prescription;

- ✓ Is a legal document
- ✓ A specific or standard format is used

- ✓ Has key features

KEY FEATURES

(1) Identification of the prescriber

- Name
- License or classification/number (e.g. professional degree)
- Address
- Office telephone number

(2) Date of the prescription

(3) Patient Identification

- a) Name
- b) Address

4. Body of a prescription

- Name of the medication
- Strength
- Quantity to be dispensed
- The dosage
- Directions for use

EXAMPLE OF A PRESCRIPTION

PETER M. JONES MBChB

PLOT 25, SEKANYOLYA RD,

P O BOX 1232 KAMPALA.

TEL 0777-6677896

Name..... Date.....

Address.....

Rx: Drug name, strength (qty), direction for use e.g. dosing frequency.

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- (1) Caps Amoxyl 500mg t.d.s.x5/7
- (2) Tabs Paracetamol 1g t.d.x3/7
- (3) Tabs Quinine 600mg t.d.sx7/7

Refill: No of times (or until).....

Number of containers.....

Warning.....

Sign

MBchB

License number

CASE STUDY.

Imagine you are a medical practitioner working in Maraca regional referral hospital (as you may very soon) write a prescription for the case described below;

Mrs Jane Kiisho , a 56 year old type 2 diabetic patient, from Bushenyi has presented in the diabetic clinic for review, today.

She is being treated with combination therapy of mixtand insulin S/C 20i.u twice a day, pre breakfast and pre-supper and tablets metformin 1000mg slow release once daily with breakfast.

Her blood sugar has been well controlled of recent, and you counsel her about the signs and symptoms of hypoglycaemia, with the precautions and warnings about her diet and physical activity.

She also suffers from peptic ulcers disease and you prescribe further tablets Esomeprazole 40mg once at bedtime for two weeks.

She will report back after one month.

ABBREVIATIONS USED IN PRESCRIPTION

Abbreviation

- | | |
|--------------------------|-----------------------|
| 1) a — | - Before |
| 2) ac | -Before meals |
| 3) Agit | -Shake, stir |
| 4) Aq | -water |
| 5) Aq dest | -Distilled water |
| 6) bid | -twice daily |
| 7) C — | -with |
| 8) Cap | -capsule |
| 9) D5W, D ₅ W | -dextrose 5% in water |
| 10) Dil | -dissolve/ dilute |
| 11) Disp, dis | -dispense |
| 12) Elix | -Elixir |
| 13) Ext | -Extract |
| 14) g | -gram |
| 15) gr | -grain |
| 16) gtt | -drops |
| 17) h | -hour |
| 18) hs | -at bed time |
| 19) IA | -intra-arterial |
| 20) IM | -intramuscular |
| 21) IV | -intravenous |
| 22) IVPB | -IV piggyback |
| 23) Kg | -kilogram |
| 24) MEq, meq | -milliequivalent |
| 25) Mg | -milligram |
| 26) Mcq,ug | -microgram |

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27) No	- number
28) Non rep	-do not repeat
29) OD	-right eye
30) OS,OL	-left eye
31) OTC	-over the counter
32) Ou	-both eye
33) p	- After
34) PC	-After meals
35) Po	-by mout
36) PR	- Per rectum
37) Prn	-when needed/whenever necessary
38) q	-Every
39) Qam, om	-every morning
40) Qd	- every day (daily)
41) Qh,Q1h	-every hour
42) Q2h,Q3h,e,t,c	-every 2 hour, every 3 hours e.t.c
43) Qhs	- every night at bedtime
44) Qid	-Four times aday
45) Qod	-every other day
46) qs	- sufficient quantity
47) rept, repet	-may be repeated
48) Rx	-take
49) S —	-without
50) SC, SQ	-subcutaneous
51) Sid(veterinary)	-once a day

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- 52) Sig, S -label
53) sos - if needed
54) ss, ss- - one-half
55) stat -at once
56) sup,supp -suppository
57) susp -suspension
58) tab -tablet
59) tbsp, T -tablespoon
60) t.i.d -three times a day
61) Tr, tinct -tincture
62) tsp - tea spoon
63) μ -units
64) vag -vaginal
65) i,ii,iii,iv, e.t.c -one, two, three, four e.t.c

COMMONLY USED ABBREVIATIONS

- ✓ Bid
- ✓ Cap
- ✓ D₅W
- ✓ g
- ✓ I.M
- ✓ I.V
- ✓ kg
- ✓ mg

- ✓ mcq
- ✓ µg
- ✓ Pr
- ✓ prn
- ✓ Qid
- ✓ Rx
- ✓ Sc
- ✓ Stat
- ✓ Tab
- ✓ t.i.d, or, t.d,s

ANALGESICS

These are drugs which relieve pain they mainly work at various sites along the pain path way

- (1) They mainly act on the brain and spinal cord and reduce the appreciation of pain. These are the major sites of action of opioid analgesics
- (2) They may suppress conduction in nerves carrying impulses from painful area. This is where local anesthetics acts.
- (3) They may reduce inflammation and other causes of pain in the painful area; this is the site of action of the non steroidal and some other analgesics.

CLASSIFICATION OF ANALGESICS

- (1) Paracetamol/Acetaminophen
- (2) Non steroidal anti-inflammatory drugs (NSAIDS)
- (3) Opioid analgesics

PARACETAMOL/ ACETAMENOPHEN/PANADOL

This is a widely used minor analgesic legally class c.

ROUTES OF ADMINISTRATION

- Oral

- Rectal

DOSE

- Adult dose 500mg 1g t.d.s
- 1-5 years of age 125mg t.d.s
- 6-9 years of age 250mg t.d.s
- 10-15 years of age 500mg t.d.s

MECHANISM OF ACTION

Paracetamol has only analgesic and antipyretic actions

The mechanism of analgesic action of acetaminophen is unclear.

This drug is only a weak COX-1 and COX-2 inhibitor accounting for its lack of inflammatory effect.

As an antipyretic, it reduces sympathetic out flow from hypothalamic temperature regulating centre.

INDICATIONS

- (1) Relief of mild to moderate pain of various origin e.g musculo-skeletal, headache, toothache, dysmenorrhoeal, common cold etc
- (2) Reduction of elevated body temperature associated with cold and flu and other parasitic, bacterial and viral infections.

PHARMACOKINETICS

Paracetamol is well absorbed from the GIT; the onset of action is 15-30 minutes and duration of action is 3-5 hours, it is metabolized in the liver and ~ 80% is excreted in urine

SIDE EFFECTS

- It is a safe drug

- However very easy drug to over dose
- Occasionally skin rash

TOXIC EFFECTS

- Over dose with a single dose of 7-8g (or more than 150-200mg /kg in children) is considered highly toxic because may cause liver damage
- Renal failure
- Jaundice
- Nausea
- vomiting

NURSING CONSIDERATIONS

- Avoid use of paracetamol in liver disease

NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDS are groups of chemically dissimilar agents that differ in their antipyretic, analgesic and anti-inflammatory activities.

The term “non steroidal” is used to distinguish these drugs from steroids which have similar anti-inflammatory actions.

The most prominent members of this group of drugs are;

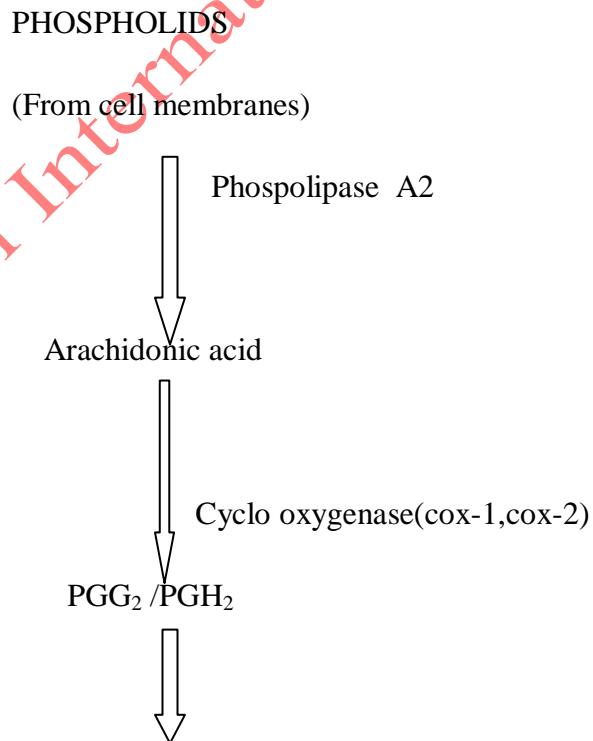
- (1) Aspirin (Acetyl Salicylic Acid-AsA)
- (2) Ibuprofen
- (3) Naproxen
- (4) Indomethacin (indocid)
- (5) Keroprofen.

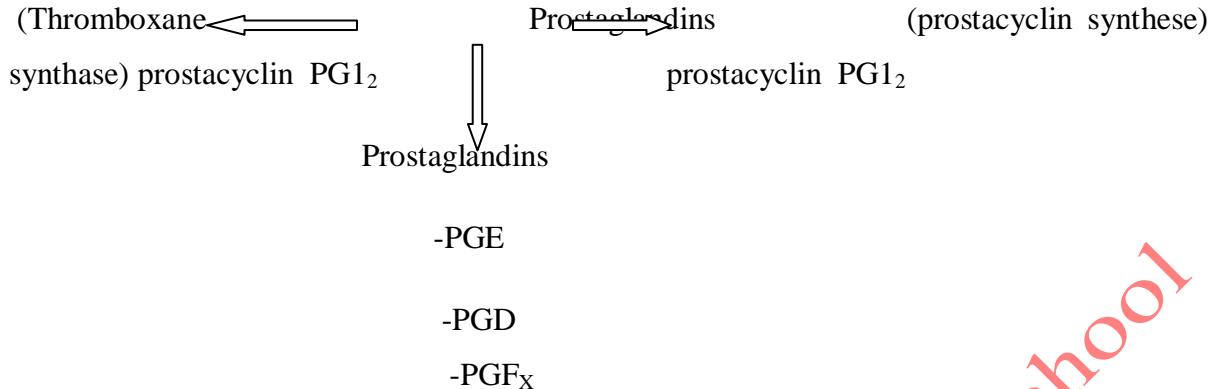
MECHANISM OF ACTION OF NSAIDS

The analgesic, anti-inflammatory and anti-pyretic actions of NSAIDS are thought to be due to inhibition of prostaglandin synthesis.

SUMMARY OF PROSTAGLANDIN (PG) SYNTHESIS

- (1) Phospholids (from cell membranes) under action of phospholipase A₂ are converted to arachidonic acid.
- (2) Arachidonic acid under action of prostaglandin H synthase (also called cyclooxygenase-COX-2) is converted to prostaglandin G₂ and or prostaglandin H₂
- (3) Prostaglandin G₂ (PGG₂) or prostaglandin H₂(PGH₂) under action of different enzymes are converted to
 - Thromboxane
 - Prostaglandins E,D,F_{2α} e.t.c
 - Prostacyclin





NB- prostaglandins and other products of arachidonic acid like leukorienes, epoxides play part in inflammatory processes resulting in pain, therefore their inhibition by use of NSAIDS is of pharmacological importance

- NSAIDS are also classified according to selectivity for cox, some are non selective cox inhibitors, some are cox-2 selective inhibitors and others are cox-1 selective inhibitors

COX-1 INHIBITORS

- Indomethacin
- Sulinac

COX-1 AND COX-2 INHIBITORS ALSO CALLED NON SELECTIVE COX INHIBITORS.

- Ibuprofen
- ketoprofen
- Flurbiprofen
- Fenoprofen
- Aspirin

COX-2 SELECTIVE INHIBITORS (COXIBS)

- Celecoxib
- Etoricoxib
- Meloxicam
- Rofecoxib

- Etc

ACETYL SALICYLIC ACID- ASA (ASPIRIN)

This is a mild analgesic that is largely class C

ROUTE OF ADMIN

- Oral

DOSE

- Adult dose 300-600mg t.d.s

MECHANISM OF ACTION

ASA irreversibly inhibitors cox-1 and cox-2 and hence interfering with prostaglandin synthesis

- (1) Analgesic effect is related to inhibition of prostaglandin production. It also interferes with the transmission of pain impulses at the thalamus in the brain
- (2) As antipyretic- it inhibits production of prostaglandins in the hypothalamus resulting in re-setting (normalization) of thermoregulation and also resulting in vaso-dilation and increased heat loss
- (3) As anti-inflammatory- this is through decreasing capillary permeability and leakage of blood into the surrounding tissues.

It inhibits synthesis of prostaglandin which is an endogenous substance that is thought to mediate inflammation reactions by causing swelling and pain in tissues

- (4) As anticoagulant- being an anticoagulant, aspirin decrease platelet aggregation through inhibition of prothrombin formation (A step where ASA inhibits thromboxane formation)

INDICATIONS

- (1) Relief of mild to moderate pain that are associated with inflammatory states e.g. myalgia
- (2) Headache

- (3) Reduction of fever that is associated malaria, arthritis.
- (4) Prophylaxis for prothromboembolic complications e.g. venous embolism, cerebral ischaemia associated with cardiovascular disorder.

PHARMACOKINETICS

ASA is rapidly and completely absorbed from the stomach and upper intestines. it is excreted in urine

SIDE EFFECTS

- 1. Gastric distress
- 2. Heart burn
- 3. Drowsiness
- 4. Nausea
- 5. Peptic ulcers

TOXIC EFFECTS

- 1. Tinnitus
- 2. Dizziness
- 3. Drowsiness
- 4. Hyperventilation
- 5. Anemia
- 6. Sweating
- 7. Palpitations
- 8. Impaired hearing

CONTRA-INDICATIONS

- 1. In patients with peptic ulcer
- 2. Known hypersensitivity
- 3. In children below 12 years due to reyes syndrome associated with it.
- 4. In asthmatic patients

NURSING CONSIDERATIONS

1. Take it with or after a meal

INDOMETHACIN

It is a non steroidal anti-inflammatory drug

It is legally class C

MECHANISM OF ACTION:

Like ASA, it produces anti-inflammatory, analgesic and antipyretic effects through inhibition of prostaglandin synthesis.

ROUTES OF ADMINISTRATION

- Oral
- Rectal
- Intravenous

DOSE

25 – 50mg t.d.s (Adults)

0.3mg /kg body weight (for infants)

INDICATIONS

1. Moderate to severe Rheumatoid arthritis
2. Ankylosing spondylitis
3. Acute gouty arthritis
4. Osteoarthritis
5. Assists in closure of patent ductus arteriosus in premature infants.

PHARMACOKINETICS

It is absorbed from the GIT.

Onset of action is 1-2hours and half life is $4\frac{1}{2}$ hours

It is metabolized in the liver and kidney and excreted in the urine and faeces.

SIDE EFFECTS

1. Headache
2. Dizziness
3. Nausea
4. Dyspepsia
5. Epigastric pain
6. Heart burn
7. Diarrhea

TOXIC EFFECTS

1. GIT-Anorexia, ulceration, perforation
2. CNS-Depression, anxiety, convulsion
3. CVS-Palpitations, tachycardia and chest pain.

CONTRAINDICATION

1. In people with aspirin allergy
2. Nasal polyp
3. Pregnant mothers
4. Children below 14 years

NURSING CONSIDERATIONS

1. Always administer the drugs with food, milk or anti acids to minimize gastric upset
2. Do not give indocid with aspirin

IBUPROFEN

It is a non steroidal anti-inflammatory drug having pharmacological spectrum of action similar to aspirin with a slight lower incidence of milder gastro intestinal side effect and less of inhibitory effect on platelet aggregation. It is legally class C

ROUTE OF ACTION

Oral

DOSE

Adult - 200mg – 400mg t.d.s

MECHANISM OF ACTION

Produces anti inflammatory, analgesic and anti pyretic effects through inhibition of prostaglandin

INDICATIONS

1. Rheumatoid arthritis
2. Osteoarthritis
3. Fibrositis
4. Dysmenorrhea
5. Strains and sprains

PHARMACOKINETICS

Ibuprofen is rapidly and almost completely absorbed in the stomach. The peak serum level is achieved in 1 – 2 hours. It is excreted in urine

SIDE EFFECTS

1. Gastro – intestinal upsets
2. Dizziness
3. Headache
4. Constipation
5. Tinnitus
6. Nausea
7. vomiting

TOXIC EFFECTS

1. Peptic ulceration
2. Bloating

- 3. Skin rash
- 4. Palpitation
- 5. Tachycardia

CONTRA - INDICATIONS

- 1. Aspirin sensitivity patients
- 2. Active peptic ulcers

DICLOFENAC

OPIOD ANALGESICS

Opiods e.g morphine are drugs that produce analgesia, tolerance, addiction and dependence.

Opiates – are derivatives from opium e.g morphine, heroin

Opium alkaloids are used to make semi synthetic opioids.

Other opioids are prepared synthetically e.g methadone

Opiopeptins (endogenous opioid peptides) are natural substances of the body that have opioid like activity.

Generally opioids interact with opioid receptors in the body to bring about

- 1. Analgesia
- 2. Respiratory depression
- 3. Sedation
- 4. Euphoria
- 5. Dependence
- 6. etc

CLASSIFICATION OF OPIOIDS

1. STRONG OPIOD AGONISTS

- Morphine
- Pethidine
- Hydromorphone
- Oxymorphone
- Levorpanol
- Heroin
- Methadone
- Meperidine
- Fentanyl
- Sulfentanil
- Alfentanil
- Remifentanil

2. WEAK OPIOID AGONISES

- Codeine
- Oxycodone
- Hydrocodone
- Tramadol

3. OPIOID ANTAGONISTS

- Naloxone
- Naltrexone
- Nalmefene

MORPHINE

This is a narcotic analgesic that belongs to a group of naturally occurring alkaloids of opium.

Legally class A “controlled”

ROUTES OF ADMINISTRATION

- Oral

- Intravenous
- Intramuscular
- Intrathecal

DOSE

- Adult 4mg – 15mg
- Children 0.1 – 0.2 mg /kg body weight

MECHANISM OF ACTION

It binds with opiate receptors at many sites of the CNS altering both perception and emotional **response** to pain.

It has both depressing and stimulating effects-These effects are used in the management of certain conditions

DEPRESSING EFFECTS

- It acts as analgesia by depressing appreciation of pain by the brain.
- It is a euphoric and allays anxiety.
- Depresses respiration
- Depresses the cough reflex
- It is a mild hypnotic and may cause sleep and drowsiness

STIMULATING EFFECTS

- Stimulates the chemoreceptor trigger zone (CTZ) in the brain in some patients and therefore causes nausea and vomiting.
- It causes constriction of the pupils (miosis) due to its effects on the nucleus of the 3rd cranial nerve.

OTHERS

- It causes constipation by decreasing peristalsis.

INDICATIONS

- Severe pains of acute forms i.e. acute abdomen.

- Chronic severe pain as in inoperable terminal cancer.
- Acute left heart failure (cardiac asthma).
- To relieve pain and anxiety in severe frightening conditions
- Post operative treatment of severe pain
- For treatment of diarrhea
- Pre operative treatment.

PHARMACOKINETICS

Morphine is slowly absorbed from the GIT, but following parenteral use, it is faster.

It is bound to plasma protein, metabolized in the liver.

Excreted in the urine and faeces.

Morphine crosses the placenta barrier and may cause respiratory depression in neonates.

SIDE EFFECTS

- ✓ Respiratory depression
- ✓ Addiction
- ✓ Dependence- physical dependence(withdraw symptoms) tremors, psychological dependence also called Addiction
- ✓ Nausea
- ✓ Vomiting
- ✓ Constipation
- ✓ Hypotension
- ✓ Drowsiness

TOXIC EFFECTS

- Respiratory depression associated with constricted pupils
- Depression of cough reflex.

NURSING CONSIDERATION

- Monitor circulatory and respiratory observations in all patients receiving morphine
- Follow all regulations governing administration of class A drugs.
- When given intravenously, give slowly over 5 minutes.

TRAMODOL

CODEINE

It is a drug obtained from opium legally class A controlled

ROUTES OF ADMINISTRATION

- ✓ Oral
- ✓ Intramuscular
- ✓ Subcutaneous

DOSE

- ✓ Adult dose 30 – 60mg
- ✓ Children 3mg /kg body weight in divided doses.

MECHANISM OF ACTION:

- It binds with opiate receptors at many sites in the CNS altering both perception and emotional response to pain.
- Also suppresses the cough reflex by a direct action on the medulla.

INDICATIONS:

- Symptomatic relief of productive cough.
- Used in moderate to severe pain particularly dysmenorrhea or orthopaedic conditions.
- It can be used in treatment of diarrhea.

PHARMACOKINETICS

Codeine is well absorbed when taken orally, the onset of action is 10-20 minutes, and duration of action being 3-6 hours and the drug is metabolized by the liver and largely excreted in urine.

SIDE EFFECTS

- Tolerance
- Dependence
- Dizziness
- Nausea

- Constipation
- Sweating

TOXIC EFFECT

- Respiratory depression
- Dry mouth
- Euphoria
- Hypertension
- Bradycardia

NURSING CONSIDERATIONS:

- ✓ Monitor respiratory and cardiovascular status frequently.
- ✓ Warn ambulatory patients to avoid activities which require alertness.
- ✓ Use with extreme caution in patients with head injury, increased intracranial pressure and hepatic diseases.

PETHIDINE/MEPERIDINE

It is a strong analgesic belonging to the group of Narcotics that is synthesized.

It is less potent than morphine, legally class A “controlled”.

ROUTES OF ADMINISTRATION.

- Oral
- Intramuscular
- Intravenous
- Subcutaneous

DOSE

- Adult dose 50 – 100mg
- Children 0.5 – 2mg /kg body weight.

MECHANISM OF ACTION:

It binds with opiate receptors at many sites in the CNS, altering both perception and emotional response to pain.

INDICATIONS:

- As a pre-medication to relieve anxiety and pain.

- Post operative analgesic
- Used as analgesic in obstetric procedures to relief pain
- As anaesthetic in a combination of other drugs.

PHARMACOKINETICS

It is well absorbed after oral or SC administration:

It is metabolized in the liver and eliminated in urine.

SIDE EFFECT

- ✓ Tolerance
- ✓ Addiction
- ✓ Dependence
- ✓ Nausea
- ✓ Vomiting
- ✓ Hypotension
- ✓ Euphoric
- ✓ Blurred vision
- ✓ Dizziness
- ✓ Sweating

TOXIC EFFECTS

- Convulsions
- Respiratory depression
- Tremors

CONTRA INDICATIONS

- ✓ In patients known to be hypersensitive to pethidine.

NURSING CONSIDERATIONS:

- 1) Observe and follow all rules governing administration of class A drugs.
- 2) Monitor respiratory and cardiovascular status, especially do not give if the respiratory rate is below 12 breathes per minute.
- 3) Always have Narcotic antagonist (Naloxone) available when administering pethidine.
- 4) Monitor respiration of new borns exposed to pethidine during labor; always have resuscitation equipment available.

NARCOTIC ANAGONISTS:

These are drugs that are capable of reversing many of the effects of Narcotic analgesics, examples are:-

- Naloxone
- Naltrexone
- Nalmefene

NALOXONE (NARCAN)

It displaces previously administered Narcotic analgesic from its receptors, thus termed as a competitive antagonist.

ROUTES OF ADMINISTRATION

- ✓ Intravenous
- ✓ Umbilical vein for neonates

DOSE

- Adult 0.1 – 0.2mg repeated every after 2 – 3 minutes prn and noting the response.
- Neonates 0.01mg /kg body weight.
- Repeated at intervals of 2 – 3 minutes for 3 doses.

INDICATIONS:

- ✓ Known or suspected Narcotic induced respiratory depression
- ✓ Neonatal Asphyxia secondary to Narcotic use in mother in labour.

PHARMACOKINETICS

It is well absorbed following intravenous use; onset of action is 2 – 5 minutes. Duration of action is variable depending on route but generally is 1 – 4 hours.

It is metabolized in the liver and excreted in urine.

SIDE EFFECTS:

In normal doses, they are rare.

TOXIC EFFECTS:

- ✓ Hypertension
- ✓ Nausea
- ✓ Vomiting

- ✓ Tachycardia
- ✓ Hyper ventilation
- ✓ Tremors

NURSING CONSIDERATIONS

- Always observe the response of the patient to the dose of antagonist.

ANTI-MALARIAL DRUGS

CLASSIFICATION OF ANTIMALARIAL DRUGS

(1) Drugs used as prophylaxis

Mefloquine

(2) DRUGS USED MAJORLY FOR TREATMENT

- Quinidine
- Quinine

(3) DRUGS USED FOR PROPHYLAXIS AND TREATMENT

- Chloroquine
- Primaquine
- Doxycycline

(4) DRUGS AGAINST PARASITES IN ERYTHROCYTIC CYCLE

- Primaquine
- Proguanil
- doxycycline
- Tetracycline

(5) DRUGS AGAINST PARASITES IN ERYTHROCYTIC CYCLE

- Chloroquine
- Quinine
- Mefloquine
- Halofantrine
- Proguanil
- Pyrimethamine

- Artesunate

(6) DRUGS AGAINST PARASITES IN SEXUAL CYCLE.

- Quinine
- Mefloquine
- Chloroquine
- Artesunatemisin
- Primaquine

CLASSIFICATION OF ANTI-MALARIAL DRUGS ACCORDING TO CHEMICAL COMPOSITION

(1) 4- aminoquinolones

- Chloroquine
- Amodiaquine

(2) 8- Aminiquinolones

- Pamaquine
- Primaquine

(3) Arylamino- alcohols

- Quinine
- Mefloquine

(4) Antibiotics

- Tetracycline
- Minicycline
- Doxycycline
- Clindamycin

(5) Sesquiterpenes

- Artesunate
- Artemether

(6) Biquanides

- proguanil
- chloproguanil

(7) Pyrimidines

- pyrimethamine
- Trimethoprim
- Sulfadoxine

CHLOROQUINE

It is an anti-malarial drug that occurs in injectable, syrup and tablet forms the injectable is legally class B, the tablet is legally class C.

The use of chloroquine has been seriously compromised by drug resistance

M/A

- As an anti-malarial drug, it binds to the parasitic DNA, hence altering its properties.
- It is schizontocidal drug against erythrocytic forms of all 4 plasmodial species.
- It also concentrates in the parasite food vacuoles preventing conversion of haem to haemozoin, hence haem accumulates and this is toxic to parasite.

RESISTANCE

Resistance to chloroquine has occurred and is due to decreased accumulation of chloroquine in the food vacuole which occurs in a number of species of plasmodium falciparum.

ROUTE OF ADMINISTRATION

- Oral
- Intramuscular
- Subcutaneous
- Intravenous

DOSE

- Day 1 + day 2- 10 mg /kg body weight per day.
- Day three 5mg / kg body weight.

NB Now used in combination with fansidar on day one.

INDICATIONS

- Treatment of malarial
- Treatment of amoebiasis
- Rheumatoid arthritides (chloroquine has some anti-inflammatory action)
- Prophylaxis against malaria attack.

PHARMACOKINETICS

The drug is completely absorbed from the GIT and extensively distributed through the body tissues. Concentrates in the liver, spleen and the CNS more than in plasma.

It concentrates particularly in parasitized RBCs.

It is metabolized in the liver

Half life is 3-4 days.

It is excreted in urine.

SIDE EFFECTS

- Dizziness
- Nightmares
- Fatigue
- Blurred vision
- Irreversible, sometimes progressive retinal changes leading to atrophy and blindness.
- Deafness
- Vertigo
- Tinnitus

- Anorexia
- Vomiting
- Diarrhea
- Abdominal cramps
- Pruritus (itching).

QUININE

- It is a drug derived from the bark of cinchona tree; it is an anti-malarial drug, legally class B.
- It is first line for complicated malaria by falciparum plasmodium, but second line treatment of uncomplicated malaria.

M/A

- It inhibits malarial parasitic replication by interfering with its DNA.
- It results in accumulation of cytotoxic heme in the food vacuoles of the parasite. Heme is a product of Hb degradation.
- It is blood schizonticidal against the four species of malarial parasites.
- Gametocidal against P. Vivax, P.Ovale.

ROUTES OF ADMINISTRATION

- Oral
- Intramuscular
- Intravenous.

DOSE

- Adult -600mg 8hourly
- Adults and children 10mg 1 kg body weight.

INDICATIONS

- Treatment of cerebral malaria

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- Second line Rx of all forms of malaria.

PHARMACOKINETICS

- It is rapidly absorbed orally.
- Peak serum level occurs 2-3 hours
- It is metabolized in the liver
- It is excreted in urine
- Half life is 4-5 hours.

SIDE EFFECTS

- Tinnitus
- Dizziness
- Blurred vision
- Impaired hearing
- Photophobia
- Nausea
- Anorexia
- Epigastric distress
- Hypotension
- Cardiovascular collapse with over dose or rapid administration.
- Haemolytic anaemia
- Agranulocytosis
- Hypoglycaemia

NURSING CARE

- Administer after meals to minimize gastric upsets.
- Observe for effects of cinchonism (tinnitus, dizziness, visual disturbance and explain to the patient that they will disappear where the drug is stopped).

MEFLOQUINE

Used for chemoprophylaxis of malaria, treatment of uncomplicated malaria.

P/K

- Well absorbed from GIT
- Highly protein bound, extensively distributed to tissues and slowly excreted as mefloquine and its metabolites.
- Terminal half life is 20 days
- The drug may be detected in blood for months after completion of therapy.

M/A

- It is schizontocidal, highly active against blood schizonts.
Has no activity against early hepatic stages and mature gametocytes of P. falciparum or latent tissue forms of P. Vivax.

ADVERSE EFFECTS

- Nausea
- Vomiting
- Dizziness
- Sleep and behavioral disturbance
- Epigastric pain
- Diarrhoea
- Abdominal pain
- Headache
- Rashes
- Seizures
- Leukocytosis
- Thrombocytopenia

DOSE

20-25 mg /kg body weight as single dose or 2 divided doses 6-8 hours apart, given orally.

PRIMAQUINE

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Eradicates dormant liver forms of p.vivax and p. ovole.

M/A

Leads to formation of electron transferring redox compounds that act as cellular oxidants that kill parasitic cells.

P/K

- Well absorbed from GIT
- Widely distributed to tissues
- Half life 3-8 hours
- Rapidly metabolized in the liver
- Excreted in urine.

CLINICAL USES

- Treatment of vivax and ovale malaria
- Prophylaxis of vivax and ovale malaria
- Pneumocystis carinii infection (usually combined with clindamycin)

DOSE

Adult 15-30mg daily for 14 days

Child 0.5mg/ kg o.d x 4days

SIDE EFFECTS

- Nausea
- Vomiting
- Anorexia
- Abdominal pain
- Haemolytic anaemia

INHIBITORS OF FOLATE SYNTHESIS

- Pyrimethamine + sulfadoxine (fansidar)
- Proguanil

PYRIMETHAMINE + SULFADOXINE (FANSIDAR)

This is an anti-malarial drug that has two drugs in one

Pyrimethamine 25mg } 525mg
Sulfadoxine 500 mg }

It is legally class B

Used in combination with C/Q on the first day

M/A

It interferes with folic acid synthesis in the protozoa.

ROUTE OF ADMINISTRATION

Oral

DOSE

- Adults 3 tablets single dose (stat)
- 12-15 yrs – 2 tablets
- 7-11- yrs- 1 ½ tablet
- 4-6 yrs-1 tablet
- 1-3 yrs – ½ tablet
- Up to 1 yr- ½ tablet

INDICATIONS

- Treatment of malaria
- Prophylaxis against malaria

PHARMACOKINETICS

Fansidar is well absorbed orally

The component displays peak concentration within 2-8 hours and are excreted mainly by the kidney.

Average half life is about 170hours for sulfadoxine and 100hours for pyrimethamine.

NB. Sulfadoxine + pyramethamine is abbreviated as SP.

SIDE EFFECTS

- Anorexia
- Vomiting
- Nausea
- Diarrhea
- Steven Johnson's syndrome
- Agranulocytosis
- Bone marrow suppression
- Crystal formation(renal stones)

PRECAUTIONS

- Pregnant mothers in first trimester.
- Renal dysfunction

NURSING CARE

- Take drug with meals to minimize GIT upsets.
- Plenty of fluids
- Stop the drug and notify senior if skin rash occurs.
- Use with caution in patients with renal or hepatic dysfunction.

HALOFANTRINE AND LUME FANTRINE

Lumefantrine is an aryl – amino alcohol similar to quinine, mefloquine and halofantrine in the mechanism of action. Effective against all four species, but not hepatic forms

Adverse effects

- Cardiotoxic
- Diarrhea
- Cough
- Vomiting
- Rash
- pruritus

CLINICAL USES

- Alternative to Quinine and mefloquine in treatment of malaria due to chloroquine resistant P. falciparum.

ARTEMISININ – SESQUITERPENES

- Artisunate
- Artemether
- All are rapidly acting schizonticides against all human malaria parasites
- Have no effect on liver stages.
- The only drugs against quinine resistant strains of malaria parasites

M/A

Artemether acts by releasing free radicals in the food vacuoles of the parasite causing its death.

P/K

- ❖ Half life of artemether is 2hours
- ❖ Arthemether is rapidly absorbed, metabolized in the liver and eliminated through the faecal route and kidneys.
- ❖ Fatty meals improve absorption of this medicine.

ADVERSE EFFECTS

- Nausea

- Vomiting
- Diarrhea

ARTEMISININ BASED COMBINATION THERAPIES (ACTS)

These are new and effective medicines that are recommended by WHO. In Uganda the ministry of health (MOH) has selected coartem as first line medicine for the treatment of uncomplicated malaria.

FIRST LINE TREATMENT OF UNCOMPLICATED MALARIA

ARTEMETHER + LUMEFANTRINE (COARTEM)

- It should be taken with foods or fluids.
- Fatty meals or milk improve absorption of this medicine
- Pregnant women in the first trimester of pregnancy should not take artemether + lumefantrine (coartem).

Artemether + lumefantrine is contraindicated for children below 5kg weight. Such patients should be treated with quinine.

ALTERNATIVE FIRST LINE TREATMENT OF UNCOMPLICATED MALARIA

- (1) Artesunate + Amodiaquine
- (2) Artesunate +Sulfadoxine & Pyrimethamine (SP)
- (3) Artesunate + mefloquine
- (4) Amodiaquine + Sulfadoxine & Pyrimethamine (SP)

SECOND LINE TREATMENT OF UNCOMPLICATED MALARIA

Quinine should be given when the first line medicine has failed or when it is contra-indicated.

TREATMENT OF UNCOMPLICATED MALARIA DURING PREGNANCY

All pregnant women should receive two doses of SP as prevention and treatment.

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- ✓ First dose of SP (2 tablets) is given as directly observed therapy (DOT) during the 4th and 6th months of pregnancy (second trimester).
- ✓ Second dose of SP (3tablets) is given as DOT during the 7th to 9th months (3rd trimester) of pregnancy

DOSE OF COARTEM

The dose ranges from 1 tablet 12 hourly to 4 tablets 12 hourly depending on patients body weight or age and should be given in three days only.

WT(Kg)	AGE	DOSE	COLOUR CODE
5-14	4/12- 3yrs	1 tab 12 hrly x3/7	Yellow
15-24	3-7 years	2 tabs 12 hrly x3/7	Blue
25-34	7-12 years	3tabs 12hrlyx3/7	Brown
>35	12yrs+ above	4tabs 12hrly x3/7	Green

ARTEMETHER + LUMEFANTRINE

COARTEM (LUMARTEM)

Contains

Artemether 20mg

Lumefantrine 120mg

PHARMACODYNAMICS

M/A

- The site of antiparasitic action of both components of coartem i.e artemether and lumenfantrine is the food vacuole of the malaria parasite where they are thought to interfere

with the conversion of haem (a toxic intermediate produced during haemoglobin breakdown) to the non toxic haemozoin.

- Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid and protein synthesis within the malaria parasite.
- The antimalarial activity of the combination of lumefantrine and artemether is greater than that of either substance alone.
- Artemether /lumefantrine is active against blood stages of *P.virax*, but is not active against hypnozoites (dormant resistant forms of malarial parasites in the liver). Therefore subsequent treatment with primaquine should be used to achieve hypnozoite eradication in cases of *P. falciparum*.

PHARMACOKINETICS

- Food enhances the absorption of both artemether and lumefantrine
- High fatty meal doubles the bio-availability of artemether and markedly increases that of lumefantrine.
- Artemether and lumefantrine are both highly bound to human serum proteins (95.4%) and 99.7% respectively)
- The artemisinin metabolite dihydro artemisinin (DHA) is also bound to human serum proteins (47-76%).
- Artemether is rapidly and extensively metabolized in the liver by human liver microsomes mostly through the enzymes CYT3A4/5 with a substantial first pass metabolism. The main active metabolite is DHA.
- Lumefantrine is also metabolized predominantly by the enzyme CYP3A4 in human liver microsomes.
- Artemether and DHA are rapidly cleared from plasma with an elimination half life of 2-3 hours conversely lumefantrine is cleared more slowly, showing a terminal half life of 4-6 days in patients with *P. falciparum* malaria.

INDICATIONS

- Uncomplicated infections due to

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(1) P. falciparum

NB. (1) Artemether lumefantrine is not indicated and has not been evaluated in the treatment of malaria due to

- P.vivax
- P. malarae
- P.ovale

(2) To less extent it is only active against P.vivax but not hypnozoites.

DOSE

Artemether / lumefantrine dosage schedule according to body weight.

Body weight	Day 1	Day 2	Day 3
5>, 15kg	2x1tablet	2x1tablet	2x1tablet
15>25kg	2x2 tablets	2x2 tablets	2x2 tablets
25>35kg	2x3 tablets	2x3 tablets	2x3 tablets
>35kg (adults + children	2x4 tablets	2x4 tablets	2x4 tablets

ROUTES OF ADMINISTRATION

- Oral

Take with high fat food or drinks such as milk.

UNDERSIRABLE EFFECTS/ SIDE EFFECTS OR ADVERSE EVENTS

- Immune system
- Rarely hypersensitivity
- Nervous system (NS)

- Headache
- Dizziness
- Sleep disturbance
- Somnolence
- Involuntary muscle contractions
- Paraesthesia
- Hypoaesthesia
- Abnormal gait
- Ataxia
- CVS
 - Heart palpitations
- Respiratory system (RS)
 - Cough
- GIT
 - Abdominal pain
 - Diarrhea
 - Vomiting
 - Nausea
- Skin
 - Pruritus
 - Rash
- Musculoskeletal
 - Arthralgia
 - Myalgia
- General problems
 - Asthenia
 - Fatigue

CONTRAINDICATIONS

- Patients with hypersensitivity to the drug.

- Patients with severe malaria
- First trimester of pregnancy /drug is category D
- Patients with known disturbances of electrolyte balance e.g hypokalaemia or hypomagnesaemia.
- Lactating mothers (because no data is yet available about its effect)
- Patients taking any drug that is metabolized by CYP2D6 e.g flacainide, metoprolol, imipramine, amitriptyline, clomipramine as lumefantrine significantly inhibits the enzyme cyP2D6.

NAPHTHOQUINE PHOSPHATE

TRADE NAME ARCO

Each tablet contains artemisinin 125mg, Naphthoquine 50mg.

Pharmacodynamics

The compound is composed of naphthoquine and artemisinin.

It is a schizonticide to emithrocytic plasmodium parasite.

This drug combines quick action of artemisinin and long effect of Naphthoquine phosphate.

Produces delayed drug resistance.

Pharmacokinetics

(1) Naphthoquine

- Absorption by oral route is quick
- Mean absorption half time (life) is 1.3hours
- Peak time after oral administration on empty stomach is 2-14hours
- Drug can still be detected in blood till 120 hours.
- Distribution of this drug is quick
- Distribution half life is 2.71 hours
- Elimination of the drug is comparatively slow.
- Elimination half life is 40.39 hours

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- Drug is metabolized in the liver
- Hepato – enteric circulation is involved for the drug to reach the liver
- Plasma protein binding rate is 87-89%
- In 44% of the drug in totality is excreted mainly in urine.

(2) ARTEMISININ

- It is quickly absorbed after oral administration in intestines.
- It is mainly converted to dihydro artemisinin after administration in the body.
- Blood drug concentration reaches peak after 0.5- 1 hour.
- Distribution half life is in 4 hour
- Only trace quantity of the drug can be detected in blood after 72hrs
- Concentration of artemisinin in the RBCs is lower than in plasma.
- Artemisinin is distributed in tissues and organs, higher concentration is found in intestines, liver and kidney.
- Artemisinin is lipophilic, therefore can pass blood brain barrier to enter brain tissues.
- It is quickly metabolized
- Mainly excreted in kidney and intestines, 84% of which is excreted in 24 hours.
- Effective blood drug concentration maintaining time is comparatively shorter due to quick metabolism and excretion.

DOSE

Adults 8 tablets single dose equivalent to – Naphthoquine 400mg and Artemisinin 1000mg

CHILDREN DOSE

Age	Body wt	Total tablet /N/A mg
4-6months	< 7kg	½ tab 25/62.5mg
6-12 months	7-10kg	1 tab 50/125mg
1-3 years	10-15kg	2 tabs 100/250mg
4-6 years	15-25kg	4 tabs 200/250mg

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7-12 years	25-35kg	6tabs 300/750mg
Above 12 years	>35kg	8tabs 400/1000mg
And adults		

N/A - Naphthoquine/ Artemisinin

ROUTE

Oral

ADVERSE EFFECTS

- Nausea
- Stomach discomfort/ cramps
- Elevated ALT or AST (transient) usually reverses to normal after stopping the drug.

CONTRAINDICATIONS

- Patients with known hypersensitivity / allergy to the drug.
- Patients with impairment of liver
- Patients with impairment of kidney
- Early pregnancy – Animal test demonstrated that artemisinin derivates have teratogenic effect on embryo, while have no effect in later pregnancy.

DRUG INTERACTIONS

Quick acting artemisinin and long effecting naphthoquine phosphate have a synergistic effect.

OTHER COMBINATIONS

- (1) Sulfadoxine + pyrimethamine

Trade names:

- Fansidar
- Falcistat
- Malarest
- Malaren
- Kamsidar

(2) Artemether + Lumefantrine

Trade Names:

- Coartem
- Artefan
- Co-artesiane
- Lumartem
- Co-malartem

(3) Artesunate + Mefluquine

Trade Names:

- Artequine

(4) Artesunate + Amodiaquine

Trade Names:

- Amonate
- Coarsucan

(5) Dihydroartmisinin + piperaquine

Trade Names

- Duo-cotexin
- P-Alaxin

(6) Artemisinin + Naphthoquine

Trade Names: Arco

ANTI-HELMINTICS

Helminthes types include,

- Flat worms
- Nematodes (round worms- Ascaris lumbricoides).
- Trematodes (flukes, Schistosomiasis)
- Tape worms(taeniasis)
 - Taenia segnata (beef tape worm)
 - Taenia solium (pork tape work)
- Filarial worms
 - Wucheria bancrofti
 - Onchocerca volvulus
 - Loaloa (loaisis)
- Hook worms
 - Ancylostoma duodenale
 - Nector Americanus
 - Whip worms (trichuris trichuria)
 - Pin worms (Enterobiasis vermicularis)
 - Strongyloides stercoralis (thread worms)
 - Guinea worm.

ANTI HELMINTIC DRUGS are drugs that are used in controlling the parasitic worms or helminths that inhabit the GIT, other tissues and organs of the body.

Anti- helmintic drugs include

- (1) Anti-nematodes – Effective against nematodes
 - Albendazole
 - Mebendazole
 - Pyrantel pamoate
 - Diethylcarbamazine
- (2) Anticestodes - Effective against cestodes

- Niclosamide
- Albendazole
- Mebendazole
- Praziquantel

(3) Anti-trematodes – Effective against trematodes

- Praziquantel
- Metrifonate
- Oxamniquine

CLASSES OF ANTIHELMINTICS

(1) Benzimidazoles

- Albendazole
- Mebendazole
- Thiabendazole

(2) Antimony compounds

- Stibogluconate

(3) Piperazines

- Diethyl carbamazine

(4) Macrocylic Lactones

- Ivermectin

(5) Imidazothiazole derivatives

- Levamisole

(6) Organophosphates

- Metrifonate
- Dichlorophen

(7) Salicylamide derivative

- Niclosamide

(8) Tetrahydroquinoline

- Oxamniquine

(9) Tetrahydroquinoine

- Pyrantel pamoate

MEBENDAZOLE

It is a synthetic drug which has a wide spectrum of anti-helminthic activity and a low incidence of side effects.

It is legally class C.

MODE OF ACTION

It selectively and irreversibly inhibits uptake of glucose and other nutrients to susceptible worms.

ROUTE

Oral

DOSE

- 100-200mg b.d x3/7
- 500mg stat.

INDICATIONS

- Hook worms
- Ascaris (round worms)
- Whip worm (trichuris trichuria)
- Pin worm (thread worm)
- Tape worm
- Strongyloidiasis

PHARMACOKINETICS

- It is readily insoluble in H₂O
- Less than 10% oral drug administered is absorbed.
- It is metabolized in the liver
- Peak serum/ plasma level are achieved in 2-4 hours.
- It is excreted in urine

- Higher absorption occurs if the drug is ingested with fatty meals.

SIDE EFFECTS

- Nausea
- Vomiting
- Diarrhea
- Oral passage of ascaris in children below 5 years

THIABENDAZOLE

- It is rapidly absorbed from the gut
- It is rapidly metabolized and excreted in urine in the conjugated form.
- Given b.d daily x3/7 for guinea worm and strongyloides and for up to 5/7 for trichnosis.
- **Adverse effects**
 - Transient GIT disturbances
 - Headache
 - Dizziness
 - Drowsiness
 - Allergic reactions (fever, rashes)
 - Rarely liver damage

M/A

Also inhibits uptake of glucose by the worm.

ALBENDAZOLE

- Most recently introduced
- It is a broad spectrum anti-helminthic
- Rapidly absorbed from the gut
- Metabolized to sulphoxide and sulphone which may be responsible for the anti-helminthic actions
- Plasma concentrations of its active metabolite are 100 times greater than those of mebendazole.

- Also works by inhibiting glucose uptake by the worm.
- Side effects – Rarely GIT disturbances.

NICLOSAMIDE

This is the drug of choice for the treatment of tape worms.

MODE OF ACTION

It inhibits the metabolic process of oxidative phosphorylation in a tape worm resulting in its death. The ova are not affected by the drug.

ROUTE

Oral

DOSE

Adult – 2grams single dose

Children (11-34 kg) - give 1 g single dose

INDICATIONS

- *Taenia saginata* (Beef tape worm)
- *Taenia solium* (pork tape worm)
- *Diphyllobothrium lactum* (fish tape worm)

PHARMACOKINETICS

- It is well absorbed from the GIT
- The unaltered drug has not been found in the blood.

SIDE EFFECTS

- Drowsiness
- Dizziness

- Headache
- Oral irritation
- Nausea
- Vomiting
- Anorexia
- Diarrhea
- Pruritus

NURSING CONSIDERATIONS

- Take a single dose after break fast
- Instruct patient to chew tablets

PRAZIQUANTEL (BICTRICIDE)

This is an anti-helminthic drug that is effective in the treatment of schistosomal infections.

MODE OF ACTION

It acts by increasing membrane permeability to calcium. This causes marked contraction of the musculature of the worm and eventually results in paralysis and death of the worm.

ROUTE

- Oral

DOSE

40mg / kg body weight as single dose

INDICATIONS

- Schistosoma haematobium
- Schistosoma japonicum
- Schistosoma mansoni

PHARMACOKINETICS

It is rapidly absorbed from the GIT following oral intake.

Peak serum levels are reached in 1-2 hours.

Metabolized in the liver

Half life is 1-5 hours

It is excreted in urine

SIDE EFFECTS

- Drowsiness
- Dizziness
- Headache
- Nausea
- Vomiting
- Abdominal discomfort
- Urticaria

NURSING CARE

- Due to drowsiness, it brings about, people who drive or operate machinery should be cautioned
- Take drugs with food.

DIETHYLCARBAMAZINE (HETRAZAN)

It is an antihelminthic synthetic piperazine derivative.

MODE OF ACTION

It immobilizes the microfilaria and increases susceptibility to phagocytosis by the macrophages.

ROUTE

ORAL

DOSE

2 mg /kg body weight 8 hourly

INDICATIONS

- Wucheria bancrofti
- Brugia malayi
- Brugia timori
- Loaloa
- Onchocerca volvulus.

PHARMACOKINETICS

It is well absorbed from the GIT

Peak serum levels occur very quickly

Plasma half life ~2-3 hours

It is metabolized in the liver

It is excreted in the Urine.

SIDE EFFECTS

- Headache
- Malaise
- Nausea
- Allergic reactions due to release of helminthic protein
- Visual disturbances
- Joints pains
- Facial oedema
- Pruritus in patients with onchocerciasis

PIPERAZINE

This can be used to treat infections with the common round worm (*Ascaris lumbricoides*) and thread worms (*enterobius vermicularis*)

M/A

Peperazine inhibits neuromuscular (nervous) conduction / transmission in the worm, the worm gets paralyzed and is usually expelled alive.

P/K

- Partly absorbed from the gut
- The absorbed drug is partly metabolized and the remainder is eliminated unchanged.
- The drug has significantly little pharmacological actions in the host.

ADVERSE EFFECTS

- Un common, but include
 - GIT disturbances
 - Urticaria
 - Bronchospasm
 - Dizziness
 - Paraesthesia
 - Vertigo
 - Un co-ordination

CLINICAL USES

- (1) Round worms – Give single dose
- (2) Thread worms- Give longer course for 7/7 at a lower dose

IVERMECIN

- A semi-synthetic macrocyclic lactone derived from a group of natural substances called ivermectines obtained from the soil actinomyces, streptomyces.

- It is used in the treatment of onchocerciasis
- It is given orally
- It has a half life of 11 hours.
- Doxycycline 200mg daily for 4 weeks greatly enhances the action of ivermectine.

M/A

This drug increases nervous transmission of impulses resulting in motor paralysis of the worm.

DOSE

150 mcg/ kg P.O single dose

Retreatment necessary at intervals of 6-12 months until adult worms die out

INDICATIONS

(1) Onchocerciasis (drug of choice)

ADVERSE EFFECTS

- Itching
- Rashes
- Fever
- Giddiness
- Headaches
- Pains in muscles
- Pain in joints and lymph glands

INTRODUCTION TO ANTIBIOTICS/AN OVERVIEW OF ANTIBIOTICS

ANTI- BIOTICS (ANTIBIOTICS)

Includes anti-bacterial drugs

- (1) Bacterial cell wall synthesis inhibitors (β -lactam antibiotics)
 - (a) Penicillins

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- i) Narrow spectrum penicillins
- Penicillinase susceptible antibiotics e.g pen G have limited spectrum of anti-bacterial activity, are susceptible to beta- lactamases.
- Very narrow spectrum penicillinase resistant drugs e.g
 - Methicillin
 - Cloxacillin
 - Nafcillin
 - Oxacillin
- ii) Wide spectrum antibiotics
- Wide spectrum penicillinase susceptible drugs

e.g

Ampicillin

Amoxicillin

Piperacillin

(b) Cephalosporins- Resistant to β -lactamases.

(i) First generation

e.g

- Cefazolin (Parenteral)

- Cephalexin (oral)

(ii) Second generation E.g

- Cefamandole

- Cefuroxime

- Cefaclor

- Cefetetan

- Cefexitin

(iii) Third generation

- Ceftazidime
- Cefoperazone
- Cefotaxine
- Cefixime
- Ceftriaxone
- Ceftizoxime

iii) Fourth generation

- Cefepime

c) Others

i) Aztreonam (a mono bactam)

Resistant to β -lactams

ii) carbapenems – Resistant to β lactames

- Imipenem
- Meropenem (meronem)
- Ertapenem

iv) Vancomycin

v) β - lactamase inhibitors

- Clavulanic acid
- Sulbactam
- Tazobactam

vi) Fosfomycin

vii) Bactracin

viii) Cycloserine

ix) Daptomycin

(2) Bacterial protein synthesis inhibitors

a) Broad spectrum

- Chloramphenicol

- Tetracyclines e.g
 - o Tetracycline
 - o Minocycline
 - Doxycycline
 - Tigecycline
 - Demeclocycline
- b) Moderate spectrum
- Macrolides e.g
 - Erythromycin
 - Azithromycin
 - Clarithromycin
- Ketolides e.g Telithromycin related to macrolides, but not typically a macrolide.
 - c) Narrow spectrum
- Licosamides

E. g – Lincomycin

- Clindamycin – works similarly to macrolides though not a macrolide.
- Streptogramins e.g Quinupristin – dalfopristin -Clears- MRSA & VRSA
 - Linezolid -Clears MRSA, PRSP & VRE

(3) Aminoglycosides e. g

- Gentamycin
- Streptomycin
- Kanamycin
- Tobramycin
- Amikacin
- Netilmycin
- Neomycin

NB. Spectinomycin is an antibiotic related to aminoglycosides, not typically an aminoglycoside.

(4) Sulfonamides and trimethoprim

- a) Sulfonamides e.g
 - Sulfadiazine
 - Sulfisoxazole (short acting)
 - Sulfamethoxazole (intermediate acting)
 - Sulfadoxine(long acting)
 - b) Trimethoprim
 - c) Sulfonamide + Trimethoprim eg Trimethoprim plus sulfamethoxazole (co- trimoxazole or called septrim)
- (5) Floroquinolones
- (a) First generation e.g
 - norfloxacin,
 - nalidixic acid
 - (b) Second generation e.g
 - Ciprofloxacin
 - Ofloxacin
 - (c) Third generation
 - Levofloxacin
 - Gatifloxacin
 - (c) Fourth generation
 - Genufloxacin
 - Moxifloxacin
- (6) Antimycobacterial drugs
- (a) Drugs used in treatment of tuberculosis (anti-TB drugs)
 - Isoniazid
 - Rifampicin
 - Ethambutol
 - Pyrazinamide
 - Streptomycin
 - Others – Ethionamide, Rifabutin.
 - (b) Anti leprotic (drugs used in treatment of leprosy)

- Sulfones e.g Dapsone, & Acedapsone
- Others

Phenazines – e.g clofazimine

Rifamycins - Rifampicin.

(7) Nitro-imidazoles e.g Metronidazole and tinidazole – Are both antibiotics and anti-protozoan agents.

ANTI-BIOTICS These are drugs that kill or slow the growth of bacteria without effecting host cells (selective toxicity). They can be referred to as being bacteriostatic or bactericidal.

BACTERICIDAL

These are antibiotics that kill (destroy) bacteria often by inhibiting cell wall synthesis. Examples of bactericidal drugs Include;

- (1) Penicillins
- (2) Cephalosporins
- (3) Monobactams
- (4) Carbapenems
- (5) Aminoglycosides
- (6) Quinolones
- (7) Vancomycin

These drugs generally interfere with the cell membrane surrounding the bacteria by altering its permeability allowing escape of cell cytoplasm and ultimately cellular death or it may allow extra cellular fluids to enter the cell hence increasing the pressure within the cell and eventually ruptures and collapses.

BACTERISTATIC

These only inhibit bacterial multiplication or division often by reducing protein synthesis. The immune system therefore eradicates the infection. Examples are.

- (1) Tetracyclines
- (2) Chloromphenicol
- (3) Erythromycin
- (4) Glindamycin and sulfonamides

CLASSIFICATION OF ANTI-BIOTICS ACCORDING TO ACTION

They are divided into two classes basing on the range of organism they can clear and treat.

- (1) Broad spectrum antibiotics- These are antibiotics that can destroy or treat or act on many different micro-organisms i.e chloramphenicol, ampicillin, tetracycline, cephalosporins.
- (2) Narrow spectrum anti-biotics- Act on few types of micro organisms i.e streptomycin.

PENICILLINS

- Benzyl penicillin
- Phenoxymethye penicillin
- Penicillinase resistant Penicillins
 - Methicillin
 - Nafcillin
 - Cloxacillin
- Extended spectrum penicillins
 - Ampicillin
 - Amoxycillin
- Augumentin is a combination of a penicillinase inhibitor and a penicillin like amoxicillin.
- Penicillinase inhibitors
 - Clavulanic acid
 - Sulbactam

Note. Augumentin is a combination of Amoxicillin and clavulanic acid.

Penicillins are the most important group of anti-biotics in use today. They were discovered by sir Alexander Flemin in 1929 and developed by Florey from 1932 and introduced for use in 1940's.

BACTERIAL SPECTRUM

- (1) Gram positive cocci- streptococci, Staphylococci, Pneumococci, Meningococci.
- (2) Grain negative cocci- Gonococci, meningococci.
- (3) Gram positive bacilli clostridia, Corynebacteria diphtheriae.
- (4) Spirochaetes – Treponema pallidum, treponema pertenue and borreiae.
- (5) Actinomyces – Actinomyces israeli.

BENZYL PENICILLIN (PENICILLIN -G)

It is also called crystalline penicillin.

Legal class B

Route of administration- can be given intravenously, intramuscularly and intrathecally.

MECHANISM OF ACTION

It is a bactericidal antibiotic that inhibits cell wall synthesis during active multiplication of the micro organisms.

INDICATIONS

1. Streptococcal infections
2. Pneumonia
3. Tetanus
4. Meningitis
5. Gas gangrene
6. Non Penicillinase producing staphylococci
7. Otitis media
8. Endocarditis
9. Cellulitis

NB. Penicillin G is non Penicillinase resistant

Resistance to pen G is due to lactamase (penicillinase) usually produced by most bacteria.

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DOSE

The average dose is 1-2 m.u given 6 hourly

It may be given in large doses in some conditions like meningitis, endocarditis, Pericarditis.

PHARMA COKINETICS

Crystalline Penicillin is distributed evenly throughout the body. It cannot be given orally for it is destroyed by Hcl.

It has a half life of 30 minutes

It is excreted in urine

If prolonged action is required then it is co-administered with probenecid.

Probenecid Penicillin interferes with excretion of Pen G from renal tubules. Thus increases half life of Pen G.

SIDE EFFECTS

- (1) Hypersensitivity characterized by urticaria (skin rush)
- (2) Anaphylactic shock in some individuals
- (3) High dose given intrathecally can lead to convulsions.
- (4) High doses can result in congestive cardiac failure, however very rare incidence.

MANAGEMENT OF PENICILLIN REACTION

Give adrenaline injection 1/1000 solution I.M immediately, repeat dose in 5-10 minutes.

Dose 0.01 mg /kg.

If no response antihistamines like phenagan injection 25mg I.M are given and if available give hydrocortisone injection 100mg intravenously.

NURSING CARE

Before giving penicillins ask the patient if she/he has ever had any reaction to the drug.

PHENOXYMETHYL PENICILLIN (PEN V)

This is a form of penicillin that is taken orally and legally class B.

MECHANISM OF ACTION

It has a bactericidal effect against microbes by inhibiting cell wall synthesis during active multiplication.

DOSE

- Adult dose 250-500mg 6 hourly
- Children dose 15mg-50mg /kg body weight in divided doses every 6 hours.

PHARMACOKINETICS

It is well absorbed from the GIT and metabolized in the liver.

It reaches the highest peak in 2-5 hours

It is excreted in urine.

INDICATIONS

- (1) Mild to moderate infections caused by streptococci e.g tonsillitis, pharyngitis, laryngitis.
- (2) Given to patient with pneumonia caused by streptococci and staphylococci.
- (3) Given as prophylaxis to patients with rheumatic heart disease
- (4) Given as prophylaxis in dental surgery to prevent bacterial endocarditis.

SIDE EFFECTS

- (1) Allergic reactions e.g skin rash, itching and urticaria.
- (2) Epigastric distress
- (3) Nausea + Vomiting
- (4) Diarrhea
- (5) Leucopenia

CONTRAINDICATIONS

- (1) Patients who are sensitive to penicillins
- (2) Patients who are hypersensitive to cephalosporins

PRECAUTIONS

- (1) It should be used with precaution in patients with asthma and history of allergies of unknown cause.
- (2) In patients with Nausea and vomiting.

NB. Pen V is not penicillinase resistant.

AMPICILLIN

Legal class B

It is a broad spectrum penicillin against a range of both gram negative and gram positive organisms.

DOSE

- Adult dose 250-5000mg orally 6 hourly
- Children dose 25-50mg /kg body weight in divided doses 6 hourly.

ROUTES OF ADMIN

- orally
- Intramuscularly
- Intravenously

INDICATIONS

- (1) Bacterial meningitis
- (2) Respiratory tract infections
- (3) Sinusitis
- (4) Septicaemia

- (5) Otitis media
- (6) Dysentery
- (7) Typhoid fever
- (8) Uncomplicated gonorrhea
- (9) acute and chronic UTI

PHARMA COKINETICS

Oral dose is absorbed from the GIT

It is metabolized in the liver and excreted in urine and some little percentage in breast milk.

Its half life is 1 hour

Duration in blood stream is 6-8 hrs; therefore this drug should be given 6 hourly;

SIDE EFFECTS

- (1) GIT
 - Diarrhea
 - Nausea + vomiting
 - Glossitis + stomatitis
- (2) Hypersensitivity
- (3) Eosinophilia
- (4) Leukopenia

CONTRA- INDICATIONS

- (1) It is used with caution in patients with h/o rxn to cephalosporins

NURSING CARE

- (1) Do not mix ampicillin with Dextrose, for dextrose inactivates this drug.
- (2) If given orally give on empty stomach, but with plenty of fluids.

NB. This drug is not penicillinase resistant.

PROCAINE PENICILLIN FORTIFIELD (PPF)

It is an intermediate active penicillin which may be given once daily.

Legally class B.

Route of administration – Intramuscular.

DOSE

- Adult 0.4- 0.8 M.U daily

INDICATIONS

- Acute gonorrhea
- Syphilis
- Tonsillitis
- Pneumococcal pneumonia

M/A

It is a bactericidal antibiotic against micro organisms. Inhibits cell wall synthesis during active multiplication.

SIDE EFFECTS

- Anaphylactic shock
- Hypersensitivity
- Pain at the site of injection

NB. Always have adrenaline injection on your tray when administering penicillin for quick management of anaphylactic shock.

Benzathine

A drug of choice in treatment of syphilis

AMOXYCILLIN

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Is a broad spectrum antibiotic

It is a penicillin that is legally class B.

M/A

Bactericidal and inhibits cell wall synthesis during active multiplication of micro organisms.

ROUTES OF ADMINISTRATION

- Orally
- Intramuscularly
- Intravenously

DOSE

- Orally 250- 500mg 8 hourly
- Intramuscularly 500mg 8 hourly
- Intravenously 500mg 8 hourly

INDICATIONS

- Urinary tract infections
- Otitis media
- Sinusitis
- Pneumonia
- Salmonellosis
- Meningitis

CONTRA INDICATIONS

- In penicillin hypersensitivity

SIDE EFFECTS

- Nausea
- Vomiting

- Diarrhea
- Rashes

NB. CO- AMOXICLAV a mixture of amoxicillin and clavulanic acid.

PENICILLINASE –RESISTANT PENICILLINS

- Cloxacillin
- Flucloxacillin
- Methicillin
- Nafcillin
- Oxacillin

CLOXACILLIN

Legally class B

DOSE

- Adult dose 250mg-500mg 6 hourly
- Children doses 50-100mg /kg body weight per day in divided (6 hourly)

ROUTES OF ADMINISTRATION.

- Orally
- Intramuscularly
- Intravenously

M/A

- Binds to bacteria cell wall and interferes with its cell wall synthesis leading to the death of the cell.

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- Resists the action of penicillinase (an enzyme that is capable of inactivating penicillins produced by most bacterial strains)

INDICATIONS

- It is of great value in treatment of infections caused by penicillinase producing staphylococci.
- Sinusitis
- Skin infections like cellulitis
- Osteomyelitis
- Septic arthritis

NB, less effective in gram negative infections.

PHARMACOKINETICS

The absorption following oral administration is 37-60%.

Half life is 30 minutes- 1 hour

It is widely distributed in the whole body tissues except has minimal penetration into CSF.

It crosses the placenta barrier and it is metabolized in the liver and is excreted in the urine.

SIDE EFFECTS

- Hypersensitivity characterized by rashes
- Nausea and vomiting
- Epigastric distress
- Diarrhea
- Eosinophilia

CONTRA- INDICATIONS

- It is contra- indicated to patients with known hypersensitivity to penicillins.

CEPHALOSPORINS

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The structure of cephalosporins is similar to that of penicillins to some extent.

The pharmacological properties are also similar to those of penicillins.

They act by inhibiting cell wall synthesis and therefore are bactericidal.

Cephalosporins are less susceptible to penicillinase by staphylococci; however methacillin resistant staphylococcus aureus (MRSA) is also resistant to cephalosporins.

Most cephalospirins are eliminated by active tubular secretion by the urinary system.

Major side effects are.

- Hypersensitivity
- Cross hypersensitivity with penicillins, cephalosporins are divided into.
 - (1) First generation
 - (2) Second generation
 - (3) Fourth generation

FIRST GENERATION CEPHALOSPORINS

- Cephazolin
- Cephalexin
- Are active against gram positive organisms including.
 - (1) Staphylococci
 - (2) Common streptococci
 - (3) E.coli

SECOND GENERATION CEPHALOPORIN

- Cefuroxime
- Cefotetan
- Cefoxitin
- Cefamandole
- Cefaclor
- Are less active against gram positive organisms compared to 1st generation cephalosporins.

- Have extended gram negative activity as in treatment of haemophilus influenza and others.

THIRD GENERATION CEPHALOSPORINS

- Cefazidime
- Cefoperazone
- Cefotaxime
- Ceftriaxone
- Cefixime
- Have increased activity against gram negative organisms
- Have ability to penetrate the blood brain barrier

FOURTH GENERATION CEPHALOSPORINS

- Cefepime
- More resistant to penicillinases or lactamases produced by gram negative organisms like
 - Enterobacter
 - Haemophilus
 - Neisseria

ORALLY ACTIVE CEPHALOSPORINS

- Cefalexin (1st generation)
- Cefradine (1st generation)
- Cefadroxil (1st generation)
- Cefaclor (2nd generation)
- Cefprozil (2nd generation)

NB; Cephalosporins generally have broad spectrum and are active against both gram negative and gram positive organisms

M/A

Similar as for penicillins i.e Bactericidal and inhibits cell wall synthesis during active multiplication of organisms.

PHARMACOKINETICS

- They are administered orally and parenterally
- They are widely distributed in body tissues and fluids including the brain.
- They are excreted by active tubular secretion. This process can also be inhibited by probenecid to increase the half life of cephalosporins.
- Therefore concurrent administration of cephalosporins and probenecid prolongs cephalosporins's duration of action.

SIDE EFFECTS

- Allergic reactions
- There is cross allergy between penicillins and cephalosporins (meaning that if you are allergic to penicillins you are likely to be allergic to cephalosporins)
- Nephrotoxicity which is more pronounced with 1st generation cephalosporins.
- Supra infection, especially to 3rd generation cephalosporins.
- Nausea and vomiting for orally administered cephalosporins.

CLINICAL USES

Cephalosporins are commonly used as 2nd line drugs in the following conditions.

- Bacterial meningitis
- UTI resistant to penicillins
- Otitis media resistant to penicillins
- Respiratory tract infections e.g pneumonia
- Enteric fever / salmonellosis/also called typhoid.
- Septicaemia
- Sinusitis

CEFTRIAKONE

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Ceftriaxone is a third generation cephalosporin antibiotic for intravenous or intramuscular administration.

Legally class B.

It is a broad spectrum anti-microbial agent.

It has a high degree of stability in the presence of beta-lactamases including both penicillinases and cephalosporinases produced by gram negative and gram positive bacteria.

M/A

Like penicillines; ceftriaxone acts by inhibiting cell wall synthesis.

It is bactericidal.

DOSE

- Adult average dose 1-2g o.d or in two divided doses, usual duration of treatment is 4-14 days and in complicated infections, longer therapy may be required.
- Therapy with ceftriaxone, continue for 2/7 after the signs and symptoms have disappeared.
- Children 50-100mg /kg/ day o.d or bid x 7-14/7

ROUTE

Intramuscular

Intravenous

INDICATIONS

- 1- Lower respiratory tract infections including pneumonia caused by susceptible organisms like;
- Streptococcal pneumonia
- Staphylococcus aureus
- Haemophilus influenza
- Haemophilus para-influenza
- Klebsiella spp including klebsiella pneumonia

- E.coli

(2) Urinary tract infections caused by;

- E. coli

- klebsiella

- Others

(3) Uncomplicated Gonorrhea or pelvic inflammatory disease caused by,

- Neisseria gonorrhea

(4) Intra abdominal infections caused by,

- E. Coli

- Klebsiella pneumonia

(5) Bone and joint infections i.e osteomyelitis and arthritis caused by,

- Staphylococcus aureus

- Streptococcus Pneumonia

- Enterococci

- E. Coli

- Klebsiella pneumonia

- Enterobacter spp.

(6) Meningitis caused by;

- Staphylococcus aureus

- Streptococcus pneumonia

- Haemophilus influenza

- Neisseria meningitidis

(7) Bacterial septicaemia caused by;

- Staphylococcus aureus

- Streptococcus pneumonia

- E. Coli

- Haemophilus influenza

- Klebsiella pneumonia

(8) Surgical prophylaxis – A single dose of ceftriaxone pre-operative may reduce chances of post operative infection.

Bacterial spectrum

(A) Gram positive aerobes

- Staphylococcus aureus
- Staphylococcus epidermidis
- Streptococcus pneumonia
- Streptococcus group A
- Streptococcus group B

Note- Methicillin resistant staphylococcus spp are resistant to cephalosporins including ceftriaxone.

- Most strains of enterococci e.g streptococcus faecalis are resistant.

(b) Gram negative aerobes

- Branhamella catarrhalis
- Citrobacter spp
- Enterobacter spp

- Escherichia coli
- Haemophilus influenza, parainfluenza
- Klebsiella spp
- Morganella morganii
- Neisseria Meningitidis
- Proteus mirabilis
- Proteus vulgaris
- Pseudomonas aeruginosa
- Salmonella spp (S. Typhi)
- Shigella spp
- Treponema pallidum

PHARMACOKINETICS

- Ceftriaxone is completely absorbed following I.M administration with mean maximum plasma concentrations occurring within 2-13 hours after dosing.
- Ceftriaxone plasma concentrations maximally achieved following I.V dose within 30 minutes.
- Ceftriaxone is reversibly bound to plasma protein
- Approximately 32-67% is excreted in urine and remaining amount is excreted in bile and finally through faeces.

ADVERSE EFFECTS

- Ceftriaxone is generally well tolerated
- Pain induration, tenderness at the site of injection.
- Phlebitis after I.V doses
- Rash

- Pruritus
- Fever
- Chills
- Diarrhea
- Nausea
- Vomiting
- Headache
- Dizziness
- Monilliasis
- Vaginitis
- Eosinophilia
- Thrombocytosis
- Leukopenia
- Neutropenia
- Lymphopenia
- Thrombocytopenia
- Elevation of liver enzymes SGOT / SGPT / alkaline phosphatase

CONTRAINDICATIONS

- Ceftriaxone is contraindicated in patients with known allergy to cephalosporin class of antibiotics

TETRACYCLINES

- Minocycline
- Tetracycline
- Doxycycline
- Tigecycline

TETRACYCLINE

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This is an antibiotic which has a broad spectrum effect; it is a semi synthetic compound. It was at first derived from cultures of streptomyces.

Legally class B.

DOSE

250- 500mg /kg orally in adults

Children above 8 yrs 25-50mg / kg per body weight

ROUTES OF ADMINISTRATION

- Orally
- Intramuscularly
- Topically

INDICATIONS

- Cholera
- Bacillary dysentery
- Trachoma
- Brucellosis
- Conjunctivitis (topically)
- Syphilis
- Gonorrhea
- Pelvic inflammatory disease
- Non gonococcal urethritis
- Meningitis

M/A

- It is abacteriostatic
- It inhibits protein synthesis in microbial cell by breaking the binding of Transfer RNA (t RNA) to messenger RNA (m RNA) ribosomal complex.
- It may also inhibit replication of DNA on the cell membrane if given in high doses.

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PHARMACOKINETICS

- Oral absorption is generally good but can be impaired by food, milk and other dairy products.
- Tetracycline is well distributed in the CNS. It crosses the placenta barrier and also can appear in breast milk.
- It is excreted via the kidney by glomerular filtrate and bile.

SIDE EFFECTS

- Diarrhea
- Nausea
- Anorexia
- Permanent discoloration of teeth
- Supra infection e.g candidiasis
- Sore throat
- Glossitis

CONTRA-INDICATIONS

- Pregnant mothers
- Nursing /lactating mothers or breast feeding mothers
- Severe renal or liver impairment.

NURSING CARE

- Administer tetracycline 1 hour before food or 2 hours after food.
- Do not give the drug with milk or any diary product.

DOXYCYCLINE

AMINOGLYCOSIDES

- Gentamycin
- Streptomycin
- Amikacin

- Tobramycin
- Neomycin
- Kanamycin
- Spectinomycin (not an amino glycoside, but much related in most of the pharmacological properties)
- Netilmicin.

Aminoglycosides have a bacteriostatic effect on organisms, their effectiveness depends on concentration i.e they have concentration dependent killing of microbes.

Aminoglycosides also have a post antibiotic effect i.e killing action when even drug plasma levels have declined.

Have a greater efficacy when given as single large dose than small multiple dose.

GENTAMYCIN

It is a broad spectrum aminoglycoside

Obtained from an actinomyces organism

It is bactericidal

Legally class B.

M/A

It inhibits protein synthesis in a bacterial cell, and mostly effective against gram negative organisms.

DOSE

-Adult 3-5mg /kg body weight per day in 3 divided doses given I.V or I.M per day in divided doses given 8 hourly.

ROUTES OF ADMIN

- Intramuscularly
- Intravenously
- Intrathecally
- Topically to the eyes and ear.

INDICATIONS

1. Septicaemia
2. Endocarditis
3. Meningitis
4. UTIs
5. Bronchopneumonia.
6. Osteomyelitis
7. Skin infections
8. Otitis media
9. Conjunctivitis
10. Pseudomonas infections
11. Ventriculitis
12. Severe burns
13. Septiceamic shock

PHARMACOLOGICAL PROPERTIES

Absorption following IV and I.M injections is rapid.

Peak blood levels occurs in 1-2 hours

Plasma half life is 2-3 hours with normal kidney function, but may be longer in infants, elderly or patients with renal impairment.

It is widely distributed in the body except the CNS unless meninges are inflamed.

It is not metabolized to significant extent but largely eliminated unchanged by the kidney.

It crosses the placenta barrier.

SIDE EFFECTS

- Headache
- Lethargy
- Tinnitus
- Vertigo
- Hearing loss (ototoxicity)
- Oliguria
- Agranulocytosis
- Anaemia
- Leucopenia
- Renal damage (Nephrotoxicity)
- Neuromuscular blockade
- Skin reactions (allergy)

NURSING CARE

- Monitor renal function i.e output, specific gravity.
- Evaluate patient's hearing before and after giving I.V injections, flush the line with normal saline.

STREPTOMYCIN

MACROLIDES

1. Erythromycin
2. Azithromycin
3. Clarithromycin

ERYTHROMYCIN

This is an antibiotic drug originally isolated from a strain of streptomyces

Legally class B.

M/A

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Generally as for macrolides

It inhibits protein synthesis in the bacteria and are bacteriostatic at normal therapeutic levels, although they may be bactericidal against certain organisms at high concentrations.

DOSE

Adult 250-500mg 6 hourly

Children 30-60 mg / kg body in divided doses 6 hourly.

INDICATIONS

- (1) Whooping cough (partusis)
- (2) Amoebiasis due to entamoeba histolytica
- (3) Diphteria
- (4) Pneumonia
- (5) Pharyngitis
- (6) Pelvic inflammatory disease
- (7) Superficial skin infections
- (8) Acne vulgaris
- (9) Gonococcal ophthalmia
- (10) Treatment of syphilis in patients allergic to penicillins
- (11) Cholera
- (12) Chancroid
- (13) Legiomaire's disease

PHARMACOKINETICS

Oral absorption is good but may be impaired by food.

It diffuses more readily into most body tissues except CNS, unless meninges are inflamed, and passes the placenta barrier although fetal blood levels rather low.

It is concentrated in the liver and excreted in active form primarily in the bile.

SIDE EFFECTS

- (1) Abdominal discomfort
- (2) Vomiting
- (3) Diarrhea
- (4) Eosinophilia
- (5) Allergic reactions like rash, fever, urticaria
- (6) Supra infections by non susceptible organisms.

NURSING CARE

- (1) Administer oral drugs with full glass of H₂ O on an empty stomach unless gastric distress is present.
- (2) Avoid fruit juice or acidic beverages for they may inactivate the drug.

AZITHROMYCIN

CLARITHROMYCIN

CHLORAMPHENICOL

Legally class B

It was originally isolated from cultures of streptomyces; but it is now synthesized commercially for clinical use.

It is a broad spectrum anti-biotic with a bacteriostatic effect against a wide range of gram negative and gram positive bacteria, rickettsia and Chlamydia.

M/A

It inhibits bacterial protein synthesis by interfering with cellular ribosomes

ROUTES OF ADMIN

- Orally

- Intravenously
- Intramuscularly
- Topically

DOSE

50-100mg /kg body weight in divided doses every 6 hours

INDICATIONS

- Meningitis especially that caused by haemophilus influenza plus neiseria fever.
- Typhoid fever
- Lymphogranuloma
- Shigellosis (bacillary dysentery)
- Whooping cough
- Gonorrhea
- Broncho pneumonia
- Local application as in conjunctivitis, otitis media.

PHARMACOKINETICS

- It is rapidly absorbed orally
- Peak serum levels occur in 1-2 hrs
- Distribution is variable, highest concentrations occur in the liver, kidney, while lowest amounts occur in the brain and CSF.
- Half life is 2-3 ½ hrs.
- It is metabolized in the liver
- Excreted in urine.

SIDE EFFECTS

- Aplastic anaemia
- Thrombocytopenia
- Peripheral neuritis

- Hypersensitivity
- Diarrhea
- Vomiting
- Nausea
- Enteritis
- Headache

CONTRA INDICATIONS

Patients known to be with hypersensitivity

PRECAUTIONS

- (1) New born babies and infants
- (2) Severe liver or renal diseases
- (3) Elderly patients
- (4) Pregnancy
- (5) Anemia of any form

Note: toxicities due to chloramphenicol

1. Bone marrow suppression
2. Gray baby syndrome characterized by
 - RBCS
 - Cyanosis
 - CVS collapse

SULPHONAMIDES

- Trimethoprim – A mixture of trimethoprim and sulfamethoxazole
- Sulfadiazine

These were the first group of systemic anti-microbial agents to be effective when used clinically they were discovered in 1930s before the penicillins in 1940s, they have a bacteriostatic broad spectrum effect against both gram positive and gram negative microbes.

They were discovered by Domagic.

COTRIMOXAZOLE/ SEPTRIN

A combination of two drugs i.e Sulfamethoxazole 400mg and Trimethoprim 80mg making a strength of 480mg per tablet, however currently we have tablets with strength of 960mg.

Legally class B

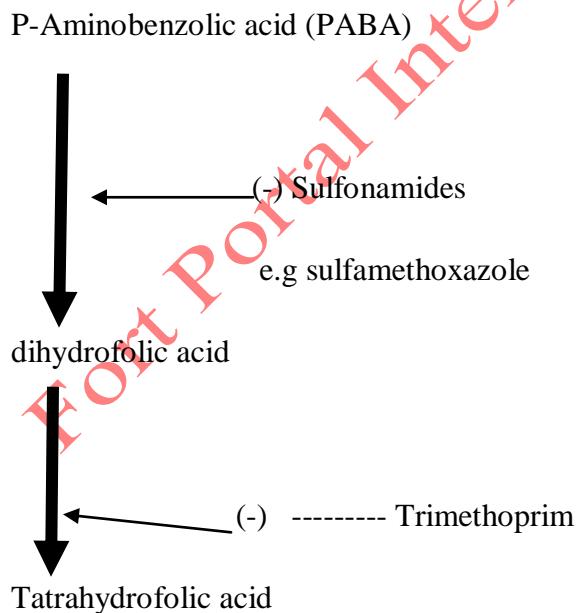
DOSE

Adult 960mg twice a day

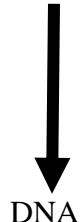
M/A

It inhibits the growth of bacteria by interfering with Folic acid synthesis due to the para amino benzoic acid (PABA) substance it has.

This is explained in the mechanisms of Folic acid synthesis below.



Purines



INDICATIONS

- Typhoid fever
- Bacillary dysentery
- Meningitis
- UTIs
- Pneumocystis carinii pneumonia
- Chronic bronchitis
- Otitis media
- Sinusitis

PHARMACOKINETICS

It is rapidly absorbed from the GIT when taken orally.

Peak serum levels are reached within 2-4 hours.

Half life is 10-15 hours

It reaches high concentration in the lungs and kidney and relatively high concentration in CSF.

It is excreted in urine.

SIDE EFFECTS

- Nausea

- Vomiting
- Diarrhea
- Agranulocytosis
- Aplastic anaemia
- Hypersensitivity especially in HIV/AIDS
- Steven Johnson's syndrome
- Headache
- Jaundice
- Pancreatitis
- Oliguria

CONTRA- INDICATIONS

- Pregnant mothers
- Infants below 2 months
- Nephritis

NURSING CARE

- Tell patient to take plenty of fluids

FLUOROQUINOLONES

Classified according to generations and depending on anti-bacterial spectrum

(1) First generation

- Norfloxacin – Aderavative of Nalidixic acid

(2) Second generation

- Ofloxacin

(3) Third generation

- Levofloxacon
- Gatifloxacin
- Gemifloxacin

- Moxifloxacin

CIPROFLOXACIN

This is a drug that is in a group of Quinolones / fluoroquinolones.

These drugs are active against a variety of gram positive and gram negative bacteria.

They are used in treating infections with organisms that have become resistant to other antibiotics

Legally class B

M/A

It inhibits bacterial growth by interfering with its DNA synthesis

ROUTES OF ADMIN

- Orally
- Intravenously

DOSE

Adult average dose 250-500mg b.d

INDICATIONS

- RTIs
- UTIs
- Gonorrhoea
- Typhoid fever
- Ear, eye, nose and throat infection
- PID (pelvic inflammatory disease)
- Septicaemia
- Skin, bone and foot infections.

PHARMACOKINETICS

Following oral administration ciprofloxacin is well absorbed from the GIT and is widely distributed in body fluids and tissues.

The serum half life is 3-5 hours

Metabolized in the liver

Excreted in urine

SIDE EFFECTS

- Nausea
- Vomiting
- Diarrhea
- Oral candidiasis
- Hallucinations
- Crystalluria
- Dizziness
- Skin rash

CONTRA INDICATIONS

- Pregnancy
- In children below 12 years because

It can lead to arthropathy i.e cartilage problems in developing animals.

URINARY ANTISEPTICS

- Quinolones e.g nalidixic acid
- Nitrofurans e.g Nitrofurantoin
- Methenamines

NALIDIXIC ACID

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This is a urinary anti-infective drug with a bactericidal effect against most gram negative bacteria

Legally class B.

M/A

It inhibits microbial DNA synthesis

ROUTE OF ADMIN

Orally

DOSE

- 1g six hourly for adults
- 55mg /kg body weight in divided doses for children.

INDICATIONS

- UTIs
- Bacillary Dysentery

PHARMACOKINETICS

- It is rapidly absorbed from the GIT
- Peak serum levels occur in 1-2 hours
- Peak urine levels occur in 3-4 hours
- It is highly protein bond in plasma
- It is partially metabolized in the liver
- Rapidly excreted by the kidneys.

SIDE EFFECTS

- Nausea
- Diarrhea
- Abdominal distress
- Streptococcus infections

- Klebsiella infections
- Proteus infections

PHARMACOKINETICS

It is well absorbed orally

Absorption is enhanced by ingestion of food, the therapeutic serum and tissue levels are not attained except in the urinary tract.

Plasma half life is 15-30minutes

SIDE EFFECTS

- Nausea
- Anorexia
- Vomiting
- Dizziness
- Drowsiness
- Hypotension
- Steven- Johnson's syndrome
- Haemolytic anaemia
- Magaloblastic anaemia
- Supra infections in the urinary tract.

CONTRA- INDICATIONS

- Anuria
- Oliguria
- Pregnancy at term
- Children below 3 months-It can lead to haemolytic anaemia

NURSING CARE

- (1) Administer oral nitrofurantion with food to reduce GIT distress and produce / improve absorption

- (2) Instruct the patient to rinse mouth thoroughly after use of oral suspension to prevent staining of the teeth.
- (3) Alert patient that the drug cause urine to be brownish in colour and that it is harmless.

NITRO-IMIDAZOLES

METRONIDAZOLE (FLAGYL) AND TINIDAZOLE

METRONIDAZOLE (FLAGYL)

This is primarily an anti protozoan agent but also active against anaerobic bacteria.

Legally class B

M/A

Disrupts the structure of the DNA in susceptible organisms, causing strand breakage and loss of helical structure, it destroys organisms hence bactericidal action.

ROUTES OF ADMIN

- Orally
- Intravenously

DOSE

200-400mg 8 hourly

INDICATIONS

- Amoebic liver obscess
- Amoebic dysentery
- Trichomoniasis
- Giardiasis
- Pelvic inflammatory disease
- In anaerobic gram positive and gram negative bacterial infections

- Septic abortion
- Dental abscess
- Peritonitis
- Human bite wounds
- Lung abscess

PHARMACOKINETICS

It is well absorbed from the GIT

Peak serum levels occur in 1-2 hours.

Half life is 2 hours

It is metabolized in the liver

Excreted largely in urine.

SIDE EFFECTS

- Abdominal cramping
- Stomatitis
- Anorexia
- Candido- over growth
- Dizziness
- Vertigo
- Ataxia
- Proritus
- Darkened urine
- decreased libido
- Polyuria
- Peripheral neuropathy with I.V use
- Convulsions in I.V use
- Thrombophlebitis following I.V use

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NURSING CARE

- (1) Tell patient to take it with food to minimize gastrointestinal distress.
- (2) Tell patient to avoid alcohol in the course of treatment.

CONTRA INDICATIONS

- (1) In first trimester of pregnancy
- (2) In patients with organic (NS) disease

TINIDAZOLE

ANTIMYCOBACTERIAL DRUGS

1. DRUGS USED IN TREATMENT OF TUBERCULOSIS

- (a) Pyridines
 - Isoniazid
 - Ethonamide
 - Pyrazinamide
- (b) Rifamycins
 - Rifampicin
 - Rifabutin
- (c) Diamines
 - Ethambutol
- (d) Aminoglycosides
 - Streptomycin
 - Amikacin
- (e) Ciprofloxacin
 - Ofloxacin
 - Aminosalicylic acid
 - Capreomycin
 - Cycloserine

ETHAMBUTOL (E)

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Is a synthetic anti-tuberculosis drug, legally class B

M/A

It inhibits protein synthesis by interfering with RNA, it is abacteriostatic drug.

ROUTE

-orally

DOSE

15mg /kg body weight as single dose

INDICATIONS

- It is treatment of pulmonary TB. Usually given in combination with other anti-tuberculosis drugs.

PHARMACOKINETICS

It is readily absorbed from the GIT

Peak serum level occurs in 2-4 hrs

Half life is 3-4 hours

It is metabolized in the liver

Excreted in urine and faeces

SIDE EFFECTS

- Blurred vision
- Dizziness
- Confusion
- Hallucinations
- Gastro-intestinal upset
- Anorexia

- Acute gout
- Vomiting
- Peripheral neuritis i.e numbness, tinkling sensations.

CONTRA- INDICATIONS

- Optic neuritis
- Children below 13 years

NURSING CARE

- (1) Reassure patients that vision disturbance will disappear several weeks after treatment
- (2) Reduce dose in patients with renal impairment.
- (3) Administer with food to minimize gastro- intestinal upset
- (4) Absorption is not altered by the presence of food in the stomach.

RIFAMPICIN (R)

Legally class B

Medically anti-infective, anti- TB agent

M/A

It interferes with proteins synthesis by interfering with bacterial RNA

It has a bactericidal action against a number of gram negative and gram positive organisms.

ROUTE OF ADMIN

Orally

DOSE

10-20mg/ kg body weight orally o.d

INDICATIONS

- (1) Treatment of TB combined with other anti- TB drugs.
- (2) Leprosy
- (3) Elimination of meningococcal infection from the nasopharynx and symptomatic carriers.
- (4) Prophylaxis of haemophilus influenza B.

PHARMACOKINETICS

It is absorbed from the GIT

Peak serum levels reached within 3hrs

It is metabolized in the liver and excreted both in faeces via bile and urine.

SIDE EFFECTS

- Anorexia
- Vomiting
- Diarrhea
- Dizziness
- Ataxia
- Visual disturbance
- Hearing loss
- Pruritus
- Haemolytic anaemia
- Acute renal failure
- Hepatotoxicity
- Red orange coloured body fluids

NURSING CARE

- (1) Advise the patients to avoid alcoholic drinks while taking the drug for it may increase liver damage.
- (2) Alert patient about presencibility of red -orange discolouration of sputum, sweat, tears, saliva and urine during treatment.

PYRAZINAMIDE (Z)

It is medically anti-TB agent and legally class B

M/A

It is bactericidal

Interferes with protein synthesis in the bacterial cell

DOSE

20-25mg / kg body weight o.d

It may be given in 3-4 divided doses.

ROUTE OF ADMIN

Orally

INDICATIONS

- Tuberculosis in combination with other anti-TB drugs.
- Can be given before pulmonary surgery to minimize the spread of infection.

PHARMACOKINETICS

It is readily absorbed from the GIT

Peak serum levels are achieved in 2 hours.

Half life is 9-10 hours.

It is widely distributed in the body tissues and the meninges.

It is metabolized in the liver

Excreted in urine

SIDE EFFECTS

- Anorexia
- Nausea
- Vomiting
- Dysuria
- Hepatotoxicity
- Fever
- Anaemia
- Arthralgia (neurologic pain in joints)

CONTRA- INDICATIONS

Patients with severe liver damage

ISONIAZID (H)

It is a synthetic ant-TB agent that is very effective, cheap and with relatively few side effects.

M/A

It interferes with protein synthesis In the bacterial cell

It is bactericidal

DOSE

Adult dose 5mg /kg body weight o.d

Children dose 1-2mg /kg body weight o.d

ROUTES OF ADMINISTRATION

- Orally
- Intramuscularly

INDICATIONS

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- Treatment of all forms of active TB usually in combination with other ant-TB drugs.
- Prophylaxis in high risk patients such as house hold members or close associates of infected person.

PHARMACOKINETICS

- It is well absorbed from the GIT
- Peak serum levels are achieved in 1-2 hours.
- It is widely distributed throughout the tissues and body fluids.
- An important point is that it penetrates into the caseous TB lesions.
- It is excreted in urine.

SIDE EFFECTS

- Nausea
- Vomiting
- Epigastric upsets
- Hepatotoxicity
- Peripheral neuropathy
- Agranulocytosis
- Haemolytic anaemia

STREPTOMYCIN (S)

It is an aminoglycoside isolated from species of streptomyces, a genus of anaerobic mould like bacteria

It is a bactericidal drug.

Legally class B.

M/A

It inhibits protein synthesis in bacteria by binding directly on the ribosome.

DOSE

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Adult average dose 10-15mg /kg body weight

One vial is usually 1g.

ROUTES OF ADMIN

- Intramuscularly
- Intravenously

INDICATIONS

- Drug of choice for TB in combination with other anti-TB drugs
- Bacteria endocarditis (streptococcal)
- Tularemia (rabbit fever)
- T.B meningitis
- As prophylaxis before surgery on the GIT
- Plaque
- E. coli infection

PHARMACOKINETICS

- It is rapidly absorbed following intramuscular injection
- Half life 2-5 hours with normal kidney function.
- It is well distributed in the body fluids and excreted in urine.
- It crosses the placenta barrier

SIDE EFFECTS

- Dizziness
- Headache
- Tinnitus
- Vertigo
- Hearing loss
- Exfoliative hypersensitivity (rash, fever, urticaria)
- Pain at the site of injection.

- Vomiting
- Ataxia
- Blur vision

NB – First line anti TB drugs include

Isoniazid

Rifampicin

Ethambutol

Pyrazinamide

Streptomycin

Second line anti TB drugs are

Amikacin

Aminosalicylic acid

Capreomycin

Clofazimine

Cycloserine

Ethionamide

Quinolones

Take note of regimens for treatment of the following categories of TB patients

- (1) New cases
- (2) Relapses
- (3) Failures
- (4) Children
- (5) Multi drugs resistant TB (MDRT)

2. DRUGS USED IN TREATMENT OF LEPROSY

(a) Sulfones

- Dapsone
- Acedapsone

(b) Phenazines

- Clofazimine

(c) Rifamycins

- Rifampicin

DAPSONE

Anti-leprotic drug

M/A

Inhibits folate synthesis

PHARMACOKINETICS

- Has good P.O bio-availability
- Enters enterohepatic circulation
- Metabolised in the liver

CLINICAL USES

- Mycobacterium leprae in combination with other anti-leprotic drugs
- PCP (Pneumocystis Carinii Pneumonitis)

DOSE

1-2 mg/kg body weight daily

ADVERSE EFFECTS

- Hypersensitivity

- Agranulocytosis
- Leprae reactions (erythema nodosum)
- Anorexia
- Nausea
- Vomiting
- Tachycardia
- Headache
- Insomnia
- Psychosis
- Hepatitis

CLOFAZIMINE

An anti-leprotic drug

M/A

Inhibit transcription during DNA synthesis.

PHARMACOKINETICS

- Has good P.O bio-availability
- Highly fat soluble

CLINICAL USES

- Mycobacterium leprae in combination with other anti-leprotic drugs

DOSE

100mg daily

ADVERSE EFFECTS

- Red /black skin discoloration

- GIT upsets- Nausea, Vomiting
- Abdominal pain
- Pruritus.

PHARMACOLOGY OF THE RESPIRATORY SYSTEM

DRUGS ACTING ON RESPIRATORY SYSTEM

There are so many drugs acting on the respiratory tract. These drugs exert different actions.

Examples of these drugs are.

- (1) Expectorants
- (2) Bronchodilators and other drugs used in Asthma.
- (3) Respiratory stimulants
- (4) Mucolytics
- (5) Antitussives (drugs that suppress cough)

DRUGS USED IN TREATMENT OF ASTHMA

ASTHMA – AN ALLERGIC CONDITION

Patients are hypersensitive to allergens

- Chronic obstructive pulmonary disease
- Reversible airway obstructive inflammatory disease
- Obstruction results from;
- Swelling of broncho membranes
- Bronchospasms
- increased mucous production
- Cells that produce the inflammatory cascade are
- Mast cells.
- Neutrophils
- Eosinophils
- Lymphocytes

- When most cells are activated, they produce several mediators.
- These chemical mediators are;
- Histamine
- Bradykinin
- Prostaglandins
- Leukotrienes
- These mediators produce the inflammatory response and broncho-constriction.

CLASSIFICATION OF ANTI-ASTHMATIC DRUGS

(1) Sympathomimetics / beta Agonists, Adrenoceptor agonists

- Epinephrine / adrenaline
- Albuterol/ salbutamol/ ventolin
- Terbutaline
- Isoproterenol
- Ephedrine
- Beclomethasone
- Budesonide
- Flunisolide
- Mometasone
- Triamcinolone
- Ciclesonide

(2) Mast cell stabilizers

- Cromolyn
- Nedocromil

(3) Phosphodiesterase inhibitors/ Methyloxanthines

- Theophylline
- Aminophylline
- Theobromine

NB- Inhibition of phosphodiesterase results in increased concentrations of cAMP, cGMP and cAMP which relaxes smooth bronchial muscles.

(4) Antimuscarinics

- Ipratropium

NB. Muscarinic blockade results in bronchodilation and reduced respiratory secretions.

(5) Leukotriene pathway inhibitors.

- Zarfilukast – antagonizes leukotriene at LD₄ and LTE₄ receptors leading to bronchodilation.
- Zileuton – Inhibits 5-lipoxygenase (a key enzyme in conversion of arachidonic acid to leukotrienes).

AMINOPHYLLINE

Is a broncho-dilator

Legally class B.

M/A

It inhibits the enzyme phosphodiesterase the enzyme that breaks down cyclic AMP; the increased level of c AMP relaxes broncho smooth muscle of the airway and pulmonary blood vessels.

ROUTES

- Oral
- IM
- IV
- Rectally

DOSE

Adult initial dose 500mg then 250-500mg 6 hourly- 8hrly

Children 7.5mg /kg body weight initially then 3-6mg /kg body weight.

INDICATIONS

- Acute and chronic asthma

- Broncho spasm
- Chyne stoke respirations
- Status Asthmaticus

P/K

It is absorbed orally

Rectal absorption is slow

Serum t $\frac{1}{2}$ ranges from 4-9 hours

It is metabolized in the liver

Excreted in urine.

SIDE EFFECTS

- GIT upsets
- Nausea
- Nervousness
- Urinary frequency
- Insomnia
- Tachycardia
- Anorexia
- Palpitations
- Rectal suppositories may cause proctitis.

N/C

- Dilute I.V drug with 5% dextrose to prevent vessel burn.
- GIT upset maybe minimized by taking drug with food.
- I.V injection should be given slowly.

SALBUTAMOL (VENTOLIN)

It is a broncho – dilator

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Legally class B

M/A

It relaxes the broncho smooth muscles causing broncho dilation through interacting with β_2 adrenergic receptors along the broncho tree.

ROUTE

- Oral
- Inhalation

DOSE

- Adult average dose 2-4 m.g t.d.s or Qid
- Inhalation 1-2 puffs t.d.s
- Paediatric dose 0.1 mg / kg body weight.

INDICATIONS

- Prevention and treatment of broncho- spasms in patients with reversible obstructive airway disease as in asthma.
- Prophylaxis against exercise induced Asthma.

P/K

It is well absorbed when taken orally or inhaled

It is metabolized in the liver

Elimination $t_{1/2}$ is 4 hours

It is excreted in urine.

SIDE EFFECTS

- It has minimal side effects at recommended dose like

- Nausea
- Headache
- at high dose
- Palpitations
- Tachycardia
- Hypertension
- Vertigo
- Heart burn
- Vomiting
- Muscle cramps
- Drying and irritation of the nose and throat resulting from the inhaled form.

NURSING CONSIDERATIONS

- Use the drug with caution in patients with cardiovascular disorders
- Teach patients how to administer or use an inhaler
- Store the drug in light resistant containers.

EPHENDRINE

It is a broncho dilator and legally class B

It has some other pharmacological effects other than those produced on the respiratory tract

M/A

It has both direct acting sympathomimetic effect (i.e stimulate β and α adrenergic receptors) and indirect action through release of norepinephrine from pre-synaptic nerve terminals

ROUTES

Oral

IV

IM

S/C

DOSE

Adult average dose 25-50mg 4 hourly children 2-3 mg /kg body weight 4-6 hours in divided doses

INDICATIONS

- Broncho asthma
- Bronchitis
- Relief of nasal mucosal congestion
- Maintenance of BP during spinal anesthesia
- In control of postural hypotension

P/K

- It is readily absorbed orally or parenterally
- Crosses BBB and exerts central stimulating effect.
- Duration of effect is 3hours, but long acting ones may take 8 hours.
- It metabolized in the liver and largely excreted in urine.

SIDE EFFECTS

- Nervousness, and anxiety due to CNS stimulation
- Insomnia
- Sweating
- Palpitations
- Tachycardia
- Hypertension
- Vomiting
- Nausea

NURSING CONSIDERATIONS

- Contra indications in HTN or coronary artery dose.

- Always monitor BP when patient is on the drug
- Give I.V injections slowly
- To avoid insomnia, give the drug at least more than 2hours before bed time.

RESPIRATORY STIMULANTS, ANTITUSSIVES

EXPECTORANTS AND COUGH SUPPRESSANTS

Anti tussives-Drugs that specifically inhibit/ suppress the action of cough

- Opiod
- Non opiod
- Central acting
- Peripheral acting

OPIOIDS

- Hydrocodone
- Codeine
- Pholcodine

NON OPIOIDS

- Dextromethorphan
- Ephedrine
- Noscapine

PERIPHERAL ACTING

- Linctus
- Liquorice

EXPECTORANTS

Drugs which make the cough more productive by loosening and liquefying bronchial secretions

- Ipecacuanha
- Ammonium chloride
- Potassium iodide

MUCOLYTICS

Drugs that break down thick mucus making it thinner and easier to cough

- Acetylcysteine
- Bromhexine
- Carbocisteine
- Methylcysteine

RESPIRATORY STIMULANTS

These are drugs that have the ability to enhance depressed respiratory function, they may also be referred to as analeptics.

These drugs are mainly at the level of respiratory centre in the brain stem to increase the frequency and rate of respiration .They are primarily indicated to overcome respiratory depression due to overdose of various classes of CNS depressants like narcotics, hypnotics or overdose resulting from general anesthesia.

NEKETHAMIDE (CORAMINE)

It is a respiratory stimulant and usually reserved for emergency use and is legally class B.

M/A

It has direct stimulation of the medullary respiratory centre.

ROUTE

- Oral
- IV
- IM

DOSE

- Adult average dose 5-10mls of a 25% solution and may be repeated every 30 minutes- 1 hour depending on the degree of severity.
- Neonatal asphyxia – 1.5 mls into umbilical vein stat.

INDICATIONS

- Treatment of CNS, respiratory and circulatory collapse (depression) due to effects of depressants (drugs)
- Aids to restore respiration following an electro shock therapy.

P/K

It is well absorbed following oral or I.M administration with maximum effect in 20-30 minutes

The onset is rapid with I.V injection and effect persists for 5-10 minutes.

It is excreted in urine.

SIDE EFFECTS

- Burning and itching at the back of the nose.
- Sweating
- Flushing
- Sneezing
- Nausea
- Restlessness
- Vomiting
- Tachycardia
- Increased BP
- Muscle twitching

NURSING CONSIDERATION

- Ensure a clear airway before giving the drug.
- Have a resuscitative equipment like oxygen delivery equipment
- Do not inject intra arterially as arterial spasm and thrombosis may result.

RESPIRATORY EXPECTORANTS

These are drugs that facilitate the removal of viscous mucus from the respiratory tree and provide a smoothing action on the respiratory mucosa by stimulating secretion of a lubricating fluid.

Example – Ammonium chloride

It is an expectorant and class B (tablet), while mixtures are class C

AMMONIUM CHLORIDE

It is an expectorant and legally class B (tablet form)

Legally class C (mixture form)

M/A

Increases the flow of the respiratory fluid by reflex action

ROUTE

- Oral

DOSE

Adult 300mg 4 hourly

Children 75-150mg

P/K

It has slow but complete absorption when taken orally

It is metabolized in the liver to urea and HCl which are excreted in urine

ADVERSE EFFECTS

GIT irritation

Nausea

Skin rash

Drowsiness

Confusion in large doses

NURSING CONSIDERATIONS

- Administer the drug with full glass of H₂O as fluid help to stimulate flow of respiratory secretions.
- Avoid giving the drugs with milk and other alkaline solutions.

ANTI- FUNGAL DRUGS

These are drugs used in treatment of fungal infections. These drugs can be used for treating systemic or topical infections.

CLASSIFICATIONS

(1) Drugs for systemic use

i) Polyenes

➤ Amphotericin B

(ii) Azoles

➤ Ketoconazole

➤ Fluconazole

➤ Itraconazole

(iv) Pyrimidines

➤ Flucytosine

(v) Echonocandins

- Caspofungin
- (2) Drugs for superficial infections
 - Griseofulvin
 - Terbinafine
 - Ketoconazole
 - Fluconazole
 - Itraconazole
- (3) Drugs for topical or local use
 - Nystatin
 - Miconazole
 - Clotrimazole
 - Tolnaftate
- (4) Generally Azoles
 - (i) Imidazoles
 - Ketaconazole
 - Clotrimazole
 - Miconazole
 - (ii) Triazole
 - Fluconazole
 - Itraconazole
 - Viriconazole

NYSTATIN

It is a fungicidal antibiotic obtained from species of streptomyces that is used primarily in treatment of candidal infections of the skin, mucous membranes and intestinal tract.

M/A

It inhibits ergosterol in the membrane of the fungal cell and punches holes in it, hence altering its permeability resulting in cellular death.

ROUTES

- Oral
- Vaginal
- Rectally
- Topically

DOSE

500,000 i.u – 1,000,000 i.u t.d.s

INDICATIONS

- Treatment of oral thrush
- Vaginal candidiasis
- Intestinal candidiasis

P/K

There is no detectable systemic blood levels following oral use.

It is excreted largely unchanged in stool.

SIDE EFFECTS

- (1) Nausea
- (2) Vomiting
- (3) Diarrhea

NURSING CARE

- (1) Be sure that the patient's mouth is free from food debris before administering oral suspension tablets.
- (2) Tell the patients to keep the suspension in the mouth for several minutes before he/she swallows the drugs.

AMPHOTERICIN B

It is an anti-fungal anti-biotic first produced from streptomyces.

It is a fungicidal drug.

MECHANISM OF ACTION

It binds ergostrol, makes pores in it, hence increasing cellular membrane permeability allowing leakage of intracellular components and hence death.

ROUTES

- Intravenous
- Topical
- Intrathecal

DOSE

0.25 -1mg/ kg body weight o.d

Given as injection in 5% dextrose and infused over 2-4 hrs.

INDICATIONS

- (1) Cryptococcal meningitis
 - (2) Histoplasmosis
 - (3) Aspergillosis
 - (4) Disseminated moniliasis
 - (5) Coccidioidal arthritis
- Corneal ulcers caused by fungus

P/K

- It is poorly absorbed from the GIT
- Following I.V infusion, the drug is highly bound to plasma protein and has plasma half life of 24 hours.

- It diffuses well into inflamed pleural, peritoneal cavities and joints but poorly into other body cavities.

SIDE EFFECTS

- Anorexia
- Nausea
- Diarrhea
- Vomiting
- Abdominal cramps
- Tinnitus
- Blurred vision
- Oliguria

NURSING CARE

- Monitor the input and output of fluids in patients with renal impairment, therefore use consciously in such patients.
- Store the drug at 2-8⁰ C and protect from light.

NB. Use flucytosine together with Amphotericin B for they have synergistic effect.

GRISEOFULVIN

It is an oral fungi static antibiotic that is effective against dermatophyte infections of the skin, hair and nails.

It is a substance isolated from penicillin griseofulvin.

M/A

It localizes in the keratin precursor cells in the skin, nails and hair and disrupts the mitotic spindle thus arresting cell division.

New keratin that is subsequently formed strongly binds griseofulvin and becomes resistant to fungal invasions.

ROUTE

- Oral

DOSE

500mg- 1g daily as a single dose or in divided doses.

INDICATIONS

- Tinea pedis
- Tinea capitis
- Tinea corporis

P/K

- It is absorbed from the GIT
- Peak plasma blood levels occurs in about 4 hours
- Detectable in the skin in 4-8 hours
- Plasma half is 24 hours
- It is metabolized in the liver and excreted in urine and stool.

SIDE EFFECTS

- Nausea
- Vomiting
- Flatulence
- Headache
- Skin rash
- Blur vision
- Peripheral neuritis
- Granulocytopenia

KETACONAZOLE

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This is an oral infective anti-fungal agent used for treating a variety of oral and systematic fungal infections.

It is legally class B.

M/A

Inhibits synthesis of ergosterol, therefore increasing cell wall permeability making the fungus more susceptible to osmotic pressure

ROUTE

- Oral

DOSE

- Adult – 200-400mg o.d
- Children between 20kg-40kg weight give 100mg o.d.
- Children less than 20kg body weight give 50mg o.d.

INDICATION

- Oral thrush
- Severe cutaneous dermatophyte infections
- Histoplasmosis

P/K

- It's well absorbed orally
- Peak serum levels occur 1-2 hours
- It is widely distributed but low concentration in the CNS

SIDE EFFECTS

- Nausea
- Vomiting
- Dizziness

- Diarrhea
- Gynaecomastia /Breast enlargement in males due to inhibition of adrenal and gonado-steroid synthesis.

NURSING CARE

- Take the drug with food to prevent gastric upset and increase absorption of drugs. Anti acids and rifampicin impairs its absorption.

NB. FLUCONAZOLE

Has widely replaced ketoconazole in the treatment of;

- Cryptococcal neoformans
- Coccidiodes
- Candida (muco-cutaneous, esophageal, oro-pharyngeal, vaginal)

This drug has fewer side effects, high degree of H₂O solubility with good CSF penetration, V. good P.O bioavailability and desirable P/K profile in comparisons with ketoconazole.

DRUGS ACTING ON CARDIOVASCULAR SYSTEM

ANT-HYPERTENSIVE DRUGS

Drug therapy in hypertension is directed towards reducing elevated arterial pressure, which is believed to be the primary cause of vascular degeneration and other complications since the cause of hypertension is unknown, treatment is essentially palliative directed at lowering elevated systolic and diastolic pressure.

Drug therapy is only one aspect of a complete therapy and should include proper rest, exercise reduced caloric and salt intake.

CLASSES OF DRUGS USED IN TREATMENT OF HYPERTENSION

- (1) Rennin antibodies
 - Analogs of prorenin- Renukrein
 - Analogs of angiotensinogen- Enalkrein

(2) Angiotensin converting Enzyme inhibitors (ACEIs)

- Sulfhydryls – captopril
- Dicarboxyls- Enalapril, Lisinopril, benazepril
- Phosphorous containing drugs – Fosinopril

(3) Angiotensin receptor blockers

- Losartan
- Valsartan
- besartan
- Candasartan
- Eprosartan
- Saralasin

(4) Adrenoceptor blockers

- Propranolol
- Atenolol
- Labetalol
- Metoprolol
- Bisoprolol
- Esmolol

(5) Calcium channel blockers

- Nifedipine
- Verapamil
- Nifedipine
- Diltiazem
- Amlodipine

(6) Central nervous system sympathetic blockers

- Clonidine
- Methyldopa

(7) α - Adrenoceptor blockers

- Doxazosin
- Prazosin
- Terazosin

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NB. Diuretics are commonly used in combination with the above drugs in treatment of HTN, common drugs used include;

- Loop diuretics
- Thiazides
- Furosemide
- Hydrochlorothiazide
- Bendruflomethiazide (Aprinox)
- Metolazone
- Potassium sparing diuretics – spironolactone

METHYLDOPA (ALDOMET)

It is a CNS sympathetic out flow blocker

Legally class B.

M/A

It inhibits the central vasomotor centre (mid brain) thereby increasing sympathetic outflow of vasoconstrictor and cardio accelerator impulses. Thereby producing vasodilatation and bradycardia.

ROUTE

- Oral

I.V

DOSE

250mg t.d.s orally

Can also be given I.V 250-500mg 6 hourly diluted in 5% dextrose and administered over 30 minutes to 1 hour.

Children 10mg /kg body weight in 2-4 divided doses.

INDICATIONS

- Mild hypertension
- Moderate hypertension either alone or with other anti- hypertensive
- I.V use in acute hypertensive crisis

P/K

It is 50% absorbed in the GIT and metabolized in the liver.

Peak plasma half is 2 hours

It is excreted in urine.

SIDE EFFECTS

- Sedation
- Headache
- Dizziness
- Reduced mental activity
- Bradycardia
- Dry mouth
- Impotence
- Gynaecomastia
- Weight gain
- Otostatic hypotension
- Nausea
- Vomiting
- Black tongue
- Haemolytic anaemia

PROPRANOLOL (INDERAL)

This is a beta adrenergic blocking agent

Legally Class B.

M/A

It reduces heart rate and force of contraction by ^sing out flow of sympathetic vasoconstrictor and cardioaccelerator fibres from the brain.

It blocks the effects of adrenaline on β_1 , and β_2 adrenoceptors bringing about decrease of heart rate and vasodilatation.

ROUTE

Oral

DOSE

40-120 mg b.d

INDICATIONS

- Hypertension
- Angina pectoris
- Myocardial infarction
- Migrane headache

P/K

It is well absorbed from the GIT

Onset of action is 30 minutes

Peak effects reached in 1-1 $\frac{1}{2}$ hours

Duration of action 4 hours

It is highly bound to plasma protein

It readily enters the CNS

It is excreted in urine.

SIDE EFFECTS

- Bradycardia
- Palpitations
- Hypotension
- Nausea
- Vomiting
- Diarrhea
- Lethargy
- Sore throat
- Hallucinations
- Agitation (urge to fight)
- Memory loss
- Hypoglycaemia

CONTRA- INDICATIONS

- Diabetes
- Asthma
- CCF

NURSING CARE/ CONSIDERATIONS

- Always check patient's pulse rate before giving the drug.
- Glucagon can be given to reverse propranolol overdose.
- Give the drug with food as it increases absorption.

CAPTOPRIL

Angiotensin converting enzyme inhibitors

It is an anti- hypertensive drug legally class B

M/A

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It inhibits angiotensin converting enzyme, prevents primary conversion angiotensin 1 to angiotensin 2, thereby causing vasodilation.

ROUTE

- Oral

DOSE

25mg- 50mg b.d or t.d.s depending on the severity of the illness

INDICATIONS

- Moderate to severe hypertension
- CCF

P/K

It is rapidly absorbed orally but absorption is impaired by food.

Peak serum levels occur within 1 hour

25-30% is bound to plasma protein

$t_{\frac{1}{2}}$ is 2-3 hours.

It is metabolized in the liver

Excreted in urine

SIDE EFFECTS

- Tachycardia
- Hypotension
- Angina pectoris
- Nausea
- Diarrhea
- Gastric irritation

- Dizziness
- Insomnia
- Loss of taste
- Anorexia
- Rash
- Agranulocytosis

NURSING CARE/ CONSIDERATIONS

- Monitor BP and pulse regularly
- Take the drug 1 hour before meal since absorption is reduced by food.

NIFEDIPINE

It is a calcium channel blocker

Legally class B

M/A

It inhibits calcium influx across cardiac and smooth muscle cells, hence decreasing myocardial contractility and oxygen demand. Dilates coronary arteries and arterioles.

ROUTE

Oral

DOSE

10-20mg b.d to t.d.s

INDICATIONS

- Hypertension
- Angina pectoris

P/K

- It is absorbed when orally given
- Metabolized in the liver
- Excreted in urine.

SIDE EFFECTS

- Headache
- Flushing
- Ankle oedema due to vasodilation
- Hypotension
- Nasal congestion
- Heart burn
- Nausea

NURSING CONSIDERATIONS

- Monitor BP regularly especially patients who are taking β - blockers as severe hypertension may occur.
- Monitor potassium levels
- Note that cemitidine and ranitidine increase the metabolism of nifedipine.

HYDRALAZINE

Legally class B

M/A

It directly relaxes arterial smooth muscles leading to increased peripheral resistance

Diastolic pressure is usually lowered more than systolic

ROUTE

- Oral
- I.V
- I.M

DOSE

Oral 10mg Qid gradually ^sed to 50mg

I.M 1.7- 3.5 mg / kg body weight in 4 divided doses

I.V 1.7 – 3.5 mg / kg body weight in 4 divided doses.

INDICATIONS

- Moderate form of hypertension sometimes alone or with other anti-hypertensives
- Short term treatment of essential hypertension, use as I.V or I.M.

P/K

It is well absorbed

Levels are reached in 3-4 hours

Onset following I.M injection is 10-15 minutes

Duration of action 3-4 hours

IV administration results in immediate onset with maximal response in 1 hr

It is metabolised in the liver

Excretion largely is in faces.

SIDE EFFECTS

- Headache
- Dizziness
- Nausea
- Vomiting
- Sweating
- Tachycardia

- Orthostatic hypotension
- Wt gain
- Palpitations
- Peripheral neuritis (numbness, tinkling sensations)

CONTRA- INDICATIONS

- Rheumatic heart disease

NURSING CONSIDERATION

- (1) Monitor patient's pulse and BP regularly
- (2) Advice patient to avoid sudden position changes as this may bring about orthostatic hypotension.
- (3) Advise patients to take drug with food, for injection of food enhances absorption

DRUGS USED IN TREATMENT OF HEART FAILURE

CLASSIFICATION

- (1) Stimulate myocardial contraction

- a) Cardiac glycosides

- Digoxin

- Digitoxin

- b) Phosphodiesterase inhibitors

- c) β_1 -stimulants

- Reduce preload

- Diuretics

- Nitrates

- 3) Reduce after load

- Hydralazine

- Nitroprosside

4) Drugs that reduce the preload and after load

- ACE inhibitors.

DIGOXIN

This is a drug that belongs to digitalis and is derived from leaves of fox glove plant. Legally class B.

M/A

It strengthens myocardial contractions, this is achieved by the drug promoting the movement of calcium from extracellular to intracellular cytoplasm and inhibiting sodium, potassium activated adenosine.

ROUTES

- Oral
- IV

DOSE

The dose may vary depending on the condition, but the average adult dose ranges from 0.125mg – 0.5mg

INDICATIONS

- 1) CCF
- 2) Arterio fibrillation
- 3) Arterio flutter

P/K

It is well absorbed from the GIT

It is not extensively metabolized

It is widely distributed in all body tissues

It is excreted unchanged in the kidney

SIDE EFFECTS

- Anorexia
- Nausea
- Headache
- Fatigue
- Dizziness
- Hallucinations
- Blur vision
- Bradycardia

CONTRA- INDICATIONS

- Severe myocarditis

NURSING CONSIDERATIONS

- Take pulse rate regularly, slow pulse rate below 60b/m may be a sign of drug toxicity.
- Give I.V dose slowly at least 5 minutes
- Always obtain baseline blood pressure pulse before starting patients on the drug.

ADRENALINE

(EPINEPHRINE)

It is a drug used in vascular shock, but also has some other pharmacological effects on other systems.

Legally class B.

M/A

It stimulates alpha and beta adrenergic receptors within sympathetic nervous system.

ROUTE

- I.V
- I.M
- S.C

DOSE

0.1 mg – 0.5mg for adults or 0.01mg /kg body weight.

INDICATIONS

- cardiac arrest
- hypersensitivity
- anaphylactic shock
- acute Asthmatic attack
- Potentiating and prolongation of the action of local anaesthetics.
- Management of simple open angle glaucoma (decrease production, and ^se out flow of aqueous humour)
- Topical treatment of haemostasis (control of superficial bleeding)
- Nasal decongestion

P/K

- It is readily absorbed by mucus membranes, but rapidly destroyed by digestive enzymes. Thus it is useless when given orally.
- Effects occur quickly following sc, I.M, intraocular or inhalation routes
- It is metabolized in the liver
- Excreted in urine.

SIDE EFFECTS

- Dizziness
- Anxiety

- Nausea
- Palpitations
- Hypertension
- Headache
- Tachycardia
- Hyperglycaemia
- Agitation

CONTRA- INDICATIONS

- Narrow angle glaucoma
- Organic brain damage

N/C

- Massage site after injection to counteract possible vessel constriction
- Repeated local injection can cause necrosis at the site from vasoconstriction.
- Epinephrine solution deteriorates after 25 hours.
- Do not use drug on organs with end arteries i.e finger, penis.

ANTI-DIABETIC DRUGS

Diabetes Mellitus- A chromic- metabolic disorder characterized by hyperglycaemia due to absent or decreased insulin secretion or impaired insulin action

Insulin is a hormone secreted by the β -cell of the pancreatic islets of langerhans

AETIOLOGY

- Genetic-factors
- Environmental factors

ASSOCIATED COMPLICATIONS IF NOT WELL CONTROLLED

- Microvascular diseases especially of the;
Heart

Kidney

Brain

Eyes

- Neuropathy
- Increased susceptibility to infection
- Complications in pregnancy-big baby

TYPES

(1) IDDM (Insulin Dependent Diabetes Mellitus)

- Type 1
- Juvenile onset
- Ketosis prone

(2) NIDDM (Non Insulin Dependent Diabetes Mellitus)

(3)

- Type 2
- Maturity onset
- Characterized by resistance to insulin with relative insulin increase

(4) SECONDARY DM

- Has identifiable cause e.g. pancreatic tumor, drugs, chemical toxicity

(5) GESTATIONAL DM

- Onset is in pregnancy

INSULIN THERAPY

Insulin is the corner stone treatment for DM type 1, also used in other types

Forms of insulin

- Animal derived or animal insulin (from beef and pork)
- Human insulin
- Biosynthetic human insulin

INSULIN PREPARATIONS

(1) RAPID ACTING

- Lispro (humalog)
- Aspart

This is recombinant human insulin

Onset of action 5-15 minutes (lispro), 10-20 minutes (Aspart)

Duration of action 3-5 hours

(2) SHORT ACTING

- Regular humulin (soluble)
- Constituents-crystalline zinc insulin (CZI)
- The only type suitable for I.V
- onset of action 0.5-1 hours
- Duration of action 5-8 hours

(3) INTERMDIATE ACTING

- Lente
- Constituents- protamine zinc, phosphate buffer, amorphous acetate buffer
- onset of action 2.5 hours

Duration of action 10-14 hours

(4) LONG ACTING

- Ultra lente
- Glargine (soluble)
- Onset of action 8-14 hours (ultralente), 1-5 hours glargine)
- Duration of action 18-24 hours (ultralente), 11-24 hours (glargine)

(5) PREMIXED

- Mixtard

Onset of action 1-2 hours

Duration of action 4-14 hours

M/A OF INSULIN

- (1) It facilitates the transport of glucose across selected cell membranes thereby accelerating the entry of glucose into cell in muscles, adipose tissue e.t.c

- (2) Promotes the conversion of glucose to its storage form- glycogen
- (3) Insulin stimulates formation of triglycerides (lipolysis) accelerating fatty acid and glycerol phosphate synthesis and enhances cellular permeability to fatty acid leading to increased deposition of it in fatty tissues.

SUMMARY OF EFFECTS OF INSULIN

- (i) Increase glucose uptake
- (ii) Increase glycogen synthesis and formation
- (iii) decreased plasma glucose
- (iv) Alter lipid and protein metabolism (increases protein synthesis and inhibits protein catabolism)

ROUTES OF ADMINISTRATION

- I.M
- I.V
- S.C

INDICATIONS OF INSULIN

- D.M
- Diabetic ketoacidosis
- To promote intracellular shift of K^+ in treatment of hyperkalaemia

DOSE

- Adjusted according to blood sugar levels
- Sliding scale

P/K

- Insulin is rapidly absorbed from I.M, I.V and S.C routes
- Plasma peak achieved averagely between 2-3hours
- Onset of action 30 minutes-1hour
- Duration of action solely depends on the type of insulin

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- It is well distributed throughout extracellular fluids
- Metabolism is primarily in the liver and
- Eliminated in urine

SIDE EFFECTS

- Hypoglycaemia
- Hypersensitivity leading to anaphylaxis
- Lipo-atrophy in some body parts
- Itching
- Redness
- Tissue fibrosis at injection site
- Orthostatic hypotension

NURSING CONSIDERATIONS

- ✓ Store insulin in cool area
- ✓ Don't use insulin that has changed color
- ✓ Press but do not rub site after injection and rotate injection sites.
- ✓ Advise patient not to smoke within 30 minutes after injection for cigarette smoking decreases the amount of insulin absorbed.
- ✓ Advise and health educate patient on how to recognize insulin and diabetic coma signs
- ✓ Always inject insulin in the presence of food.
- ✓ Advise patient to always carry an ampoule of insulin and syringe on trips, and always carry some sugar for any emergency

ORAL HYPOGLYCAEMICS

CATEGORIES

(1) Insulin secretagogues

- Sulfonylureas
- Meglitinides
- D-phenylamines-d-phenylalamines

These decrease release of insulin from the pancreas

(2) Biguanides

- ❖ Phenformin
- ❖ Metformin

These;

Decrease hepatic gluconeogenesis

Increase glycolysis

Decrease glucose absorption from the gut

Decrease plasma glucagon

(3) Thiazolidinediodes

- ✓ Troglitazone
- ✓ Pioglitazone
- ✓ Rosiglitazone

Target tissue sensitivity to insulin

- Increase sensitivity of cells to insulin
- Allows entry of glucose to cell for metabolism

(4) α -glucosidase inhibitors

- Acarbose
- Miglitol

These are carbohydrate analogs

Act within the intestines to inhibit α -glucosidase-an enzyme necessary for conversion of complex sugars to monosaccharides (a form that is readily absorbed)

SULFONYLUREAS

M/A-close K⁺ channels in the pancreatic β -cell membrane causing depolarization and hence increasing of insulin release

CLASSIFICATION

(1) 1st generation

- Chlorpromide
- Tolbutamide
- (2) Second generation
- Glyburide
- Glipizide
- Glimepride
- Glibenclamide

MEGLITINIDES example is Repaglinide

D-PHENYLALAMINES example is Nateglinide

TOLBUTAMIDE

It is an anti-diabetic drug legally class B controlled

it is a sulphonamide classified under sulphonylureas

M/A

Stimulates insulin release from pancreatic β -cells and reduces glucose output from the liver

ROUTES

Oral

I.V

DOSE

1g-2g daily in DDD b.d or t.d.s

INDICATIONS

- (i) Treatment of stable non-ketotic or acidotic maturity onset diabetes Mellitus
- (ii) Used in combination with insulin in IDDM (insulin dependent maturity diabetes) to reduce on insulin dosage

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- (iii) In diagnosis of pancreatic insulinoma (insulin producing tumour of the pancreatic islets of langerhans)

P/K

- It is well absorbed from the GIT
- Peak serum level is achieved in 3-5 hours
- It is well distributed into extracellular fluids
- It is metabolized in the liver
- Half life is 7 hours
- Excreted in urine and faeces.

SIDE EFFECTS

- (1) Mild hypoglycaemia
- Fatigue
- Weakness
- Drowsiness
- Hunger
- (2) GIT distress
- Nausea
- Heart burn
- Anorexia
- (3) Rash
- (4) Facial flushing
- (5) Hypersensitivity reactions

NURSING CONSIDERATIONS

- (1) Give dose before meals
- (2) If the drug is to be used in pregnancy, it should be discontinued two weeks before EDD to prevent prolonged severe hypoglycaemia
- (3) Counsel patients on how to realize early signs of hypoglycaemia
- (4) Administer the drug in the morning to minimize nocturnal hypoglycemia

(5) Caution patients against alcohol absorption (consumption while taking the drug)

CHLOPROMIDE

It is an oral anti-diabetic agent legally class B-controlled

M/A

- ✓ It stimulates insulin release from the pancreatic β-cells and reduces glucose output by the liver.
- ✓ It also exerts anti-diuretic effect in patients with pituitary deficient diabetes insipidus.

ROUTE

- ✓ Oral

DOSE

- ❖ The initial dose is 250mg daily with food
- ❖ It may be a single dose or given in DDD
- ❖ Maintenance doses ranges from 250-500mg per day depending on the condition

P/K

- Well absorbed when taken orally
- Long acting
- Duration of action may go as far as 72 hours
- Metabolized in the liver
- Excreted in urine

SIDE EFFECTS

- ✓ Nausea
- ✓ Heat burn
- ✓ Vomiting
- ✓ Hypoglycaemia
- ✓ Hypersensitivity

- ✓ Rash
- ✓ Pruritis

NURSING CONSIDERATIONS

- ❖ Advise patient on avoidance of alcohol while on the drug
- ❖ Observe patients urinary output to guard against renal insufficiency
- ❖ Elderly patients may be more sensitive to the drug

GLIBENCLAMIDE

- Long acting sulphonylureas
- Indicated in type II DM
- Legally class B

Dose

The initial dose is 250mg daily with food, adjusted according to severity of condition; can be increased to 500mg daily

Mode of action

It increase insulin secretion and pancreatic activity

It is effective when residual pancreatic β -cell activity is present

During long term administration, it leads to extra pancreatic action

Side effects

Hypoglycaemia (uncommon)

METFORMIN

- Long acting biguanide

DOSE-initially 500mg t.d.s, can be increased to 2g-3g DDD

M/A

It exerts its effects mainly by decreasing gluconeogenesis and increasing peripheral utilization of glucose since it acts only in presence of endogenous insulin

It is effective only if there are some residual functions of pancreatic islets

Side effects

- Anorexia

- Nausea
- Vomiting
- Diarrhoea
- Abdominal pain
- Metallic taste
- Erythema
- Increased vitamin B₁₂ absorption

CENTRAL NERVOUS SYSTEM PHARMACOLOGY

The major CNS neurotransmitters are;

1. Acetylcholine
2. Amino acids
 - a) Aspartate
 - b) Gramma-aminobutyric acid (GABA)
 - c) Glutamate
 - d) Glycine
3. Biogenic amines
 - a) Dopamine
 - b) Histamine
 - c) Norepinephrine
 - d) Serotonin
4. Peptides

Opioid peptides (enkephalins)

Tachykinins (neurokinin and substance p)

Classes of drugs to be covered under this chapter include;

(1) Sedative-hypnotic and anxiolytic drugs

(i) Sedative-hypnotic drugs

a) Benzodiazepines

- Alprazolam

- Chlordiazepoxide

- Diazepam

- Flurazepam

- Lorazepam

- Midazolam

- Oxazepam

- Temazepam

- Triazolam

b) Barbiturate

- Phenobarbital

- Pentobarbital

- Thiopental

c) Antihistamines

- Diphenhydramine

- Hydroxyzine

d) Others

- Chloral hydrate

- Melatonin
 - Zolpidem
- (ii) Non sedating anxiolytic drugs
- Buspirone
 - Propranolol
- (2) Antiepileptic drugs

Also called anticonvulsant or anti-seizures drugs

- (i) Drugs for partial seizures and generalized tonic-clonic seizures
- Carbamazepine
 - Phenobarbital
 - Phenytoin
 - Valproate
- (ii) Adjunct drugs for partial seizures
- Gabapentin
 - Lamotrigine
 - Topiramate
- (iii) Drugs for generalized absence, myoclonic or atonic seizures
- Clonazepam
 - Ethosuximide
 - Lamotrigine
 - Valproate
- (iv) Drugs for status epilepticus
- Diazepam
 - Lorazepam
 - Phenobarbital
 - Phenytoin
- (3) Antidepressants

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Note the monoamine hypothesis of depression that major depressive disorders result from functional deficiencies of norepinephrine (NE) or serotonin (5HT)

These neurotransmitters help in the pathways that function in the expression of mood.

(i) Tricyclic antidepressants (TCAs)

- Imipramine
- Amitriptyline
- Clomipramine
- Doxepin

(ii) Selective serotonin reuptake inhibitors (SSRIs)

- Fluoxetine
- Paroxetine
- Sertraline

(iii) Atypical (heterocyclic 2nd and 3rd generation)

2nd generation

- Amoxapine
- Maprotiline
- Bupropion

3rd generation

- Venlafaxine
- Mirtazapine
- Nefazodone

(iv) Monoamine oxidase inhibitors (MAOIs)

- Tranylcypromine
- Phenelzine
- Isocarboxazid

(4) Antimanic drugs

- Lithium

- Carbamazepine
 - Valproate
 - Lamotrigine
 - Atypical antipsychotic
 - Resperidone
 - Olanzapine
 - Clonzapine
- (5) Antipsychotic drugs
- (i) Conventional antipsychotic drugs
- High potency drugs
 - Piperazine phenothiazines e-g fluphenazine, haloperidol, and chlorpromazine (CPZ)

NB- These drugs are more likely to produce extra pyramidal reactions

- Low potency drugs
- Aliphatic phenothiazines e-g trifluromazine
- Piperidine phenothiazines e-g thioridazine

NB: These drugs are less likely to produce acute extra pyramidal reactions and are more likely to produce sedation and postural hypotension

- Atypical antipsychotic drugs
- Risperidone
- Olanzapine
- Clozapine

SEDATIVE-HYPNOTIC AND ANXIOLYTIC DRUGS

Definitions

- (1) A sedative is a drug that reduces a persons response to external stimuli and causes drowsiness
- (2) A hypnotic is a drug that induces sleep
- (3) An anxiolytic is a drug that reduces anxiety
- (4) Anxiety is an adaptive response that prepares a person to react to a threatening event.

Anxiety disorders

- ✓ Acute anxiety disorder
- ✓ Panic disorder-characterized by feeling of an impending sense of doom, accompanied by sweating tachycardia, tremors and other symptoms
- ✓ Phobic disorders- an individual becomes over fearful about a particular condition
- ✓ Obsessive compulsive disorder- an anxiety disorder in which people have unwanted repeated thoughts, feelings, ideas, sensations or behaviors
- ✓ Generalized anxiety disorder-a persistent state of fear and apprehension concerning future events

Apprehension – anticipation of adversity or misfortune, suspicion or fear of future trouble or evil

DIAZEPAM (VALIUM)

This is a sedative-hypnotic drug with anxiolytic effects classified under benzodiazepines

It is a drug that acts on the nervous system and also has anti-convulsant effects

It is legally class B “controlled”

M/A

Generally benzodiazepines including diazepam bind to receptors on the GABA-chloride ionophore. Benzodiazepine receptors are called omega (ω)- activation of these receptors increases the affinity of GABA receptor for GABA and increases the frequency with which the chloride channel opens. GABA is an inhibitory neurotransmitter; therefore its activation reduces the rate of transmission of impulses.

Hence as an anticonvulsant, this is how diazepam and other benzodiazepines are going to suppress the spread of seizure activity produced by epileptogenic foci in the brain

ROUTES OF ADMINISTRATION

- ❖ Oral
- ❖ Intravenous
- ❖ Intramuscular
- ❖ Rectal

DOSE

Adult average dose 2-10mg t.d.s

Children dose 0.3mg /kg body weight

INDICATIONS

- Anxiety
- Insomnia
- Convulsions/seizure disorder
- Titanic muscle spasms
- Status epilepticus
- Acute alcohol withdraw
- Spasticity-here the drug works as a muscle relaxant

P/K

- ✓ It is well absorbed from the GIT
- ✓ Onset of action is 30-60 minutes for oral, 30-60 minutes following I.M , immediate following I.V administration
- ✓ Excreted in urine

SIDE EFFECTS

- i) Drowsiness
- ii) Lethargy
- iii) Drug hunger over
- iv) Bradycardia
- v) Cardiovascular collapse

- vi) Ataxia
- vii) Fainting
- viii) Slurred speech
- ix) Blue vision
- x) Nystagmus
- xi) Respiratory depression
- xii) Mild dependence
- xiii) Withdraw symptoms like;
 - Rebound anxiety
 - Insomnia
 - Headache
 - Irritability
 - Muscle twitches

NB treatment of adverse effects

Anti-dote is flumezanil

Antidote- a substance which can counteract a form of poisoning

CONTRAINDICATIONS

- (1) In shock
- (2) Coma
- (3) Acute alcohol detoxification

NURSING CONSIDERATION

- (i) Monitor respiration
- (ii) Do not mix or dilute the drug with other drugs
- (iii) Do not inject the drug in small veins to avoid extravasations.
- (iv) Alert the patient to avoid activities that require alertness and good psychomotor coordination during administration of the drug

CHLORDIAZEPOXIDE

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It is a sedative-hypnotic drug with anxiolytic properties, legally class B and medically classified under benzodiazepines.

M/A

It binds to receptors on the GABA chloride ionophore increasing the affinity of GABA receptors for GABA and increases the frequency with which the chloride channel opens producing the inhibitory effects of GABA on the nervous system.

ROUTES

- Oral
- I.M
- I.V

DOSE

Average adult dose 20-25mg t.d.s or qid

children dose (> 6yrs) 5mg t.d.s or qid

INDICATIONS

- (1) All forms of anxiety
- (2) Pre-operative apprehension(fear)
- (3) Alcohol withdraw.

P/K

- Well absorbed from the GIT
- Onset of action ranges from 30-60 minutes following oral route
- It is metabolized in the liver
- Excreted in urine

SIDE EFFECTS

- Drowsiness

- Drug hang over
- Nausea
- Fatigue
- Ataxia
- Changes in libido
- Hypersensitivity
- Jaundice
- Abdominal distress

NURSING CONSIDERATIONS

- (1) Do not withdraw the drug abruptly
- (2) The dose should be reduced in elderly
- (3) Warm patients to avoid activities that require alertness and good psychomotor co-ordination while on the drug

PHENOBARBITAL (PHENOBARBITON)

It is a sedative-hypnotic drug, medically under the class of barbiturates and legally class B “controlled”.

It is effective in controlling of fits at non sedating doses.

M/A

Generally, barbiturates including Phenobarbital binds to a site on the GABA ionophore to increase the affinity of the receptor for GABA and the duration of time that the chloride channel remains open hence enhancing the inhibitory action of GABA on the nervous system. This reduces the excitability of nerve cells and the firing of impulses.

ROUTES

- Oral
- I.V
- I.M

INDICATIONS

- Treatment of insomnia
- Seizure disorders -all forms of epilepsy including status epilepticus
- Infantile spasms
- As a sedative
- Treatment of convulsions

DOSE

- (1) Adult average dose 30-60mg t.d.s
- (2) Children dose 4-6mg/kg body weight in DDD

P/K

- Well absorbed following oral administration
- Onset of action following oral administration ranges from 20 minutes to 2 hours, whereas following I.V injection is 10 minutes to 15 minutes
- Duration of action is 6-10 hours
- It is partly metabolized in the liver and excreted both as metabolites and unchanged drug in urine

SIDE EFFECTS

- Lathery
- Dizziness
- Irritability
- Drowsiness
- Nausea

- Vomiting
- Drug hung over
- Steven Johnson syndrome
- Paradoxical excitement in elderly
- Ataxia
- Megaloblastic aneamia
- Withdraw symptoms if the drug is withdrawn abruptly.

ANTI-EPILEPTIC DRUGS

- ✓ Also called anti seizure drugs
- ✓ Seizures are episodes of abnormal electrical activity in the brain (mainly in the cerebral cortex) that causes involuntary movements, sensations or thoughts
- ✓ Seizures that are recurrent and can not be attributed to any proximal cause constitute “epilepsy”
- ✓ Two main categories of the seizure are;
 - Partial seizures (focal)
 - Generalized seizures
- ✓ Status epilepticus is a condition in which a patient experiences recurrent episodes of tonic-clonic seizures without regaining consciousness.

CLASSIFICATION OF PARTIAL SEIZURES

Partial seizures arise from one cerebral hemisphere

- (1) Simple partial seizure- no alteration of consciousness, involve a single part of the body.
- (2) Complex partial seizure-there's alteration of consciousness, automatisms, and behavioral changes
- (3) Secondarily generalized seizure-focal seizure becomes generalized accompanied by loss of consciousness

CLASSIFICATION OF GENERALISED SEIZURES

(A rise from both cerebral hemispheres)

- (1) Tonic- clonic (grand mal) seizures
- (2) Tonic seizure- characterized by increase of muscle tone
- (3) Clonic seizures- characterized by jerking of body limbs
- (4) Myoclonic seizures- involves muscles and jerking
- (5) Atonic seizure- characterized by loss of muscle tone
- (6) Absence (petit mal) seizure- a brief loss of consciousness with minor muscle twitches and eye blinking.

PHENYTOIN

It is a drug that is an anticonvulsant, legally class B and used in treatment of both partial and generalized tonic-clonic seizures

M/A

It binds voltage sensitive Na^+ channels and inhibits the repetitive firing of impulses in a seizure activity

Or

It limits seizure activity by interrupting efflux and influx of Na^+ ions across cell membranes in the motor cortex during generation of nerve impulses

ROUTES

- o Oral
- o I.M
- o I.V

DOSE

Adult- 100-200mg t.d.s

Children- 4-7mg /kg body in 3 divided doses

INDICATIONS

- (1) Treatment of partial seizures
- (2) Treatment of generalized seizures (grand mal epilepsy)
- (3) Status epilepticus
- (4) Alcohol withdrawal syndrome
- (5) Trigeminal neuralgia
- (6) Cardiac arrhythmias especially ventricular arrhythmia due to digitalis intoxication

P/K

- ✓ It is slowly absorbed orally
- ✓ Peak phenytoin serum levels occurs in 48 hours after oral dose
- ✓ It is metabolized in the liver and excreted largely as conjugated metabolites in urine
- ✓ Elimination $t^{1/2}$ range 6-8 hours

Side effects

- ❖ Sluggishness
- ❖ Ataxia
- ❖ Nystagmus
- ❖ Confusion
- ❖ Slurred speech
- ❖ Dizziness
- ❖ Fatigue
- ❖ Insomnia
- ❖ Steven Johnson's syndrome
- ❖ Interferes with folate metabolism and causes megaloblastic anaemia
- ❖ May contribute to birth defects such as those seen in hydantoin syndrome(cardiac defects, malformation of ears, lips, palate, mouth, nasal bridge, mental retardation, microcephaly, ptosis)
- ❖ Impairs cerebellar function resulting in ataxia, diplopia, nystagmus and slurred speech
- ❖ May interfere with vitamin D metabolism
- ❖ Decreases Ca^{2+} absorption from the gut resulting in osteomalacia
- ❖ May affect collagen metabolism

- ❖ May cause gingival hyperplasia

NURSING CONSIDERATIONS

- Discontinue the drug If skin rash appears
- When giving I.V , administer it slowly to avoid hypotension and bradycardia
- Stress oral hygiene, regular gum massage and frequent brushing to minimize gingival hyperplasia
- Warn patients to avoid activities that require alertness like driving and operating machinery
- Do not mix the drug with 5% dextrose because it will precipitate.

CARBAMAZEPINE

It is an anti convulsant used in the treatment of both partial and generalized tonic- clonic seizures,

Legally class B.

M/A

It blocks voltage sensitive Na^+ channels and inhibits the spread of abnormal electrical discharges or impulses.

Or

It limits seizure activity by either interrupting efflux or influx of Na^+ ions across the cell membrane in the motor cortex during generation of a nerve impulse.

ROUTE

Oral

DOSE

The dose is gradually stepped up but initially 200mg b.d and increased daily by 200mg maximum of 200mg/day

1 st day 200mg b.d	400mg
2 nd day 300mg b.d	600mg
3 rd day 400mg b.d	800mg
4 th day 500mg b.d	1000mg
5 th day 600mg b.d	1200mg

INDICATIONS

- (i) Partial seizures
- (ii) Generalized seizure (tonic- clonic)
- (iii) Mixed seizure patterns
- (iv) Trigeminal neuralgia

P/K

- Oral absorption is slow but complete
- Plasma levels achieved in 2-6 hours
- Widely distributed
- Metabolized in the liver
- Excreted in urine

Side effects

- Drowsiness
- Dizziness
- Ataxia
- Nausea
- Blur vision
- Diarrhoea
- Vomiting
- Jaundice
- A plastic aneamia

NURSING CONSIDERATION

- (i) advise patients to avoid hazardous task while on the drug
- (ii) advise patients to attend ophthalmic- examination
- (iii) tell patients to notify or immediately inform doctor if fever, sore throat, mouth ulceration or bruising occurs

Contraindications

- severe HTN
- patients with history of bone marrow depression

MAGNESIUM SULPHATE

This is an effective anti convulsant used in treatment of seizures associated with toxæmia in pregnancy and other condition caused by abnormally low plasma levels of magnesium.

M/A

It decreases the release of acetylcholine from the motor nerve terminals, thereby reducing the neuromuscular transmitters and transmission of impulses across synapses

ROUTES

- I.M
- I.V

DOSE

Loading dose 4g

Normal range 1-2g of 25-50% solution

- Note that dose may be altered with different conditions

INDICATIONS

- (1) Prevention or control of fits in pre-eclampsia
- (2) Fits secondary to hypomagnesaemia
- (3) Epilepsy
- (4) Fits in eclampsia

P/K

- Immediate onset with injection
- Effects are persistable for 30minutes following I.M injection
- Duration of action is 3-4hours
- Elimination is by the kidneys

SIDE EFFECTS

- ✓ Flushing
- ✓ Sweating
- ✓ Drowsiness
- ✓ Circulatory collapse
- ✓ Hypokalaemia
- ✓ Confusion
- ✓ Respiratory depression

CONTRADICTIONS

- ❖ Severe renal disease
- ❖ Heart block

NURSING CONSIDERATIONS

- Monitor BP, and pulse during I.V therapy.

ANTI-DEPRESSANTS

-drugs used in treatment of depression

Depression is a mental disorder characterized by;

- ✓ Persistent low mood (without moments of happiness)
- ✓ Reduced capacity to feel pleasure
- ✓ Excessive self blame and feeling of worthlessness

- ✓ Suicidal thoughts

Cause

Remember the monoamine hypothesis of depression that major depressive disorders result from functional deficiencies of norepinephrine or serotonin

AMITRIPTYLINE

- It is an anti depressant drug
- Found under the medical class of tricyclic antidepressants (TCAs)
- Legally class B

M/A

It increases the amount of norepinephrine and serotonin along the CNS by blocking their re-uptake by transporters into pre-junctional nerve endings. This action allows the neurotransmitters to accumulate.

ROUTES

- Oral
- I.M
- I.V

DOSE

- Adult dose 50-100mg p.o at bed time increased gradually to 200mg
- Injection dose 20-30mg I.M 6hourly

INDICATION

- Depression
- Well absorbed from GIT
- Peak serum concentration attained within 3-4 hours

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- Widely distributed in the body and highly bound to plasma protein
- Metabolized in the liver
- Excreted in urine

SIDE EFFECTS

CNS

- ✓ Sedation, drowsiness
- ✓ Confusion
- ✓ Memory dysfunction
- ✓ Mania
- ✓ Agitation
- ✓ Tremor
- ✓ Insomnia

CVS

- ❖ Postural hypotension
- ❖ Tachycardia
- ❖ Arrhythmias

AUTONOMIC EFFECTS

- Dry mouth
- Blurred vision
- Urinary retention
- Constipation

OTHERS

- Dizziness
- Nausea
- Headache
- Fatigue
- Weight gain

- Sexual dysfunction
- Haemolytic anaemia
- Obstructive jaundice
- Allergic reactions

NURSING CONSIDERATIONS

- Reduce dose in elderly or debilitated patients
- Don't withdraw drug abruptly

IMPRAMINE

It is an antidepressant under a class of tricyclic antidepressants (TCAs) and legally class B

M/A

Potentiates the actions of norepinephrine (NE) serotonin (5-HT) or both by blocking their re-uptake by transporters into prejunctional nerve endings

ROUTES

- Oral
- I.M

DOSE

- Average adult dose 75-100mg p.o I.M in DDD (b.d or t.d.s)
- Children 25-75mg daily

INDICATIONS

- Major depression

P/K

- Well absorbed from GIT
- Well distributed in the body
- Highly bound to plasma proteins
- Plasma $t^{1/2}$ is 10-25 hours

- Metabolized in the liver
- Excreted in urine

Side effects

As for amitryptyline

- ❖ Drowsiness
- ❖ Dizziness
- ❖ Dry mouth
- ❖ Blurred vision
- ❖ Tachycardia
- ❖ Constipation
- ❖ Headache
- ❖ Orthostatic hypotension
- ❖ Weight gain
- ❖ Insomnia
- ❖ Lethargy
- ❖ Altered libido
- ❖ Delayed ejaculation
- ❖ Gynaecomastia
- ❖ Impotence

NURSING CONSIDERATIONS

- (1) Carefully observe severely depressed patients during initial improvement phase, suicide tendency may increase as depression and psychomotor retardation lessens
- (2) Instruct patient to change position gradually since orthostatic hypotension can easily result
- (3) Do not withdraw drug abruptly
- (4) Chart mood changes
- (5) Avoid combining the drug with alcohol or other depressants.

ANTI MANIC DRUGS

- These are drugs used in treatment of mania
- Mania is a mental state characterized by excessive cheerfulness, activity and elation of mood
- The mood is euphoric and changes rapidly to irritability
- Thought and speech are rapid
- Behavior is overactive, extravagant and sometimes violent
- Judgment often impaired and there may also be grandiose delusions

DRUGS

- ✓ Lithium
- ✓ Carbamazepine
- ✓ Valproate
- ✓ Lamotrigine
- ✓ Atypical antipsychotics- olanzapine, risperidone and Clozapine

LITHIUM CARBONATE

Note that mania is due to excess NE, and 5-HT

It is an antipsychotic drug used in treatment of mania

Legally class **B**

M/A

Promotes the re-uptake of norepinephrine and serotonin thereby causing more rapid inactivation of their effects hence regulating the mood

It may also reduce NE release, this calms down the elated mood.

ROUTE

Oral

DOSE- 300-600mg t.d.s

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INDICATION

Control of acute mania and its symptoms like
Talkativeness
Restlessness
Grandiose delusions
Aggressiveness
Prophylaxis of recurrent manic-depressive episode -bipolar affective disorder (BAD)

P/K

Rapidly absorbed orally
Peak serum levels occurs 1-4 hours
Widely distributed in the body
Crosses BBB
Excreted in urine

Side effects

Fine hand tremors

Nausea
Vomiting
Diarrhoea
Polydipsia (thirst)
Oedema
Weight gain
Drawsness
Polyuria
Mild muscle weakness
Dizziness
Impaired vision
Slurred speech

CONTRAINDICATIONS

Severe renal or cardiovascular diseases

Organic brain syndrome

Early pregnancy

Children below 12years

Dehydration and Na⁺ depletion

N/C

Determination of patient's lithium blood level is critical for the safe use of the drug and should range between 1-1.5 m/l

Patient should carry identification instruction card while on the drug

Weigh patient daily

NB

Lithium normalizes the mood in 70% of patients. The onset of therapeutic effect takes 2-3 weeks

Antipsychotic agents like CPZ, haloperidol can be used in the initial stages of the disease to control acute agitation.

PSYCHO-THERAPEUTIC DRUGS

These are drugs commonly used in the treatment of psychosis

They are at times referred to as antipsychotic drugs for they are capable of improving the mood and calming the disturbed behavior of psychotic patient without causing marked sedation and habituation

Although the term tranquilizer is often used to describe these drugs, they are not CNS depressants.

Examples are

Conventional antipsychotic drugs

Fluphenazine

Chlorpromazine

Haloperidol

Atypical antipsychotic drugs

Risperidon

Olanzapine

Clozapine

CHLORPROMAZINE-CPZ (LARGACTIL)

It is an antipsychotic drug or tranquilizer , legally class B

M/A

Has antagonistic activity at post junction D- receptors

As anti psychotic, it blocks the post synaptic dopamine receptor in the brain causing reduced agitation, decreased paranoid ideation, lessening hallucinations and disturbed thought processes

As an anti-emetic it decreases the activity of chemoreceptor trigger zone (CTZ) of the brain stem

ROUTES

Oral

I.V

I.M

Rectal

DOSE

It varies in different conditions i.e. psychosis

Adult 100-150mg 8 hourly p.o

Children 0.25mg/kg body weight 4-6 hourly/day

INDICATIONS

Schizophrenia

Intended to produce antipsychotic effects like decreased

Thought disorders

Psychosis

Paranoid features

Delusions

Hostility

Hallucinations

Others

Acute mania and BAD

Depression with psychotic manifestations

Nausea and vomiting

Post operative sedative

Intractable hiccups

Control of spasms in tetanus

Mild alcohol withdraw syndrome

P/K

Adequately absorbed p.o

Well absorbed parenterally

Widely distributed to most body tissues

Found in high concentration in the brain

Duration of action 3-6hours depending on dose and route of administration

Metabolized in the liver

Excreted in urine and feces

SIDE EFFECTS

Extra pyramidal effects

Those related to dopamine receptor blockade which result in imbalance between dopamine and acetylcholine and these are the major causes of non compliance to the drug-they are;

Acute dystonia- characterized by spastic retrocollis or torticollis Respiration usually compromised treatment is basically drug withdraw and anti-muscarinics like benztropine as the antidote

Akathisia-is the irresistible compulsion to be in motion. Treatment is basically withdraw of the drug or reduction on dose and anti muscarinics

Parkinsonian syndrome characterized by tremors, bradykinesia, rigidity. Treatment is basically benzotropine

Tardive dyskinesia- characterized by disfiguring orofaciolingual movements or tics, also occasionally dystonic movements of the trunk. Treatment is discontinuation of the drug.

Neuroleptic malignant syndrome characterized by muscle rigidity, diaphoresis and hyperthermia.

Treatment is bromcriptine, discontinue drug

Sedation

Confusional state with memory impairment

Seizures

Those related to ANS blockade

Alpha-adrenoceptor blockade common with low potency drugs

Orthostatic hypotension

Syncope

Reflex tachycardia

Impotence

Inhibition of ejaculation

Muscarinic blockade

Dry mouth

Blur vision

Constipation

Tachycardia

Difficulty urination

Paralytic ileus

Endocrine and metabolic disturbances

Hyperprolactinemia due to D2 -R blockade

Glactorrhoea

Delayed ovulation

Loss of libido

Gynaecomastia

Impotence

Weight gain

Other effects

Withdraw like effects

Nausea

Vomiting

Insomnia

Headache

Cardiac arrhythmias

Contra-indications

Coma

CCF

Bone marrow depression

Cerebral vascular disorders

N/C

Do not withdraw drug abruptly unless required by severe side effects

Notify senior in case of severe extra pyramidal effects

HALOPERIDOL (HALDOL)

It is an antipsychotic agent legally class B controlled

M/A

It block post synaptic dopamine receptors in the brain

ROUTES

Oral

I.M

DOSE

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p.o dose 0.5-5mg 2-3times

I. M dose 2-5mg 4-8hourly

INDICATIONS

Schizophrenia

Manic phase of BAD

Treatment of severe anxiety

P/K

Adequately absorbed p.o

Well absorbed parenterally

Metabolized in the liver

Excreted in urine

S/E

Extrapyramidal effects

Blur visio

Dry mouth

Urinary retention

Menstrual irregularities

Gynaecomastia

N/C

Dry mouth may be relieved by sugarless gum, sour hard caddy substance and rinsing the mouth

Don't use in children below 12years

Don't withdraw the drug abruptly

OBSTETRICAL DRUGS

DRUGS THAT MODULATE UTERINE FUNCTION

These drugs are classified into;

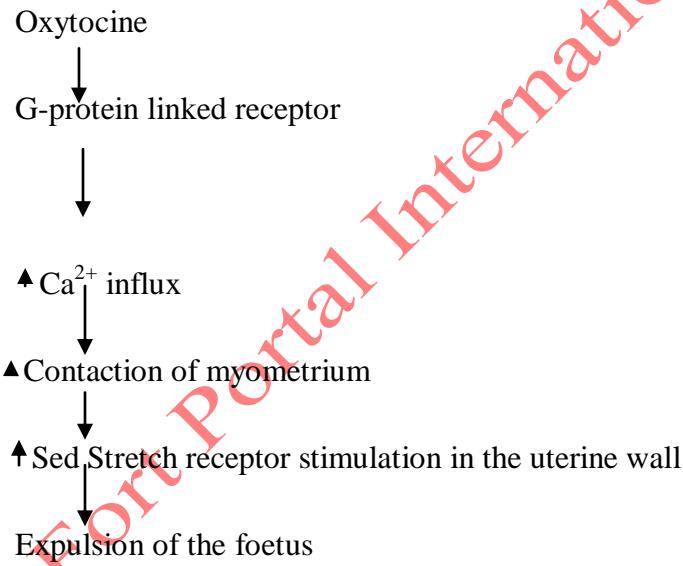
- (a). Those that increase contractility. Also called uterine stimulants (oxytocics)
- (b). Those that decrease uterine contractility. Also called uterine relaxants or tocolytics

UTERINE STIMULANTS

- (1). Oxytocines and its analogs- Pitocin and Syntocinon
- (2). Ergot alkaloids- Ergometrine, Ergonovine and Meleateergotrate
- (3). Prostaglandins
 - PGF 2 α - Dnoprost, PGE₂-Dinoprostone and Mesoprostol

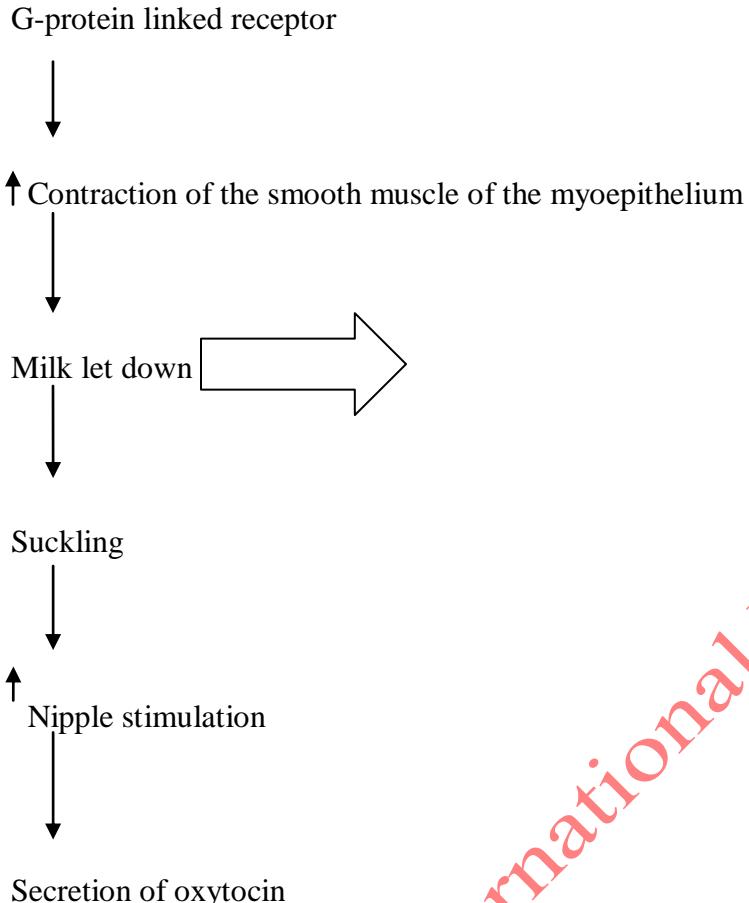
OXYTOCIN

M/A ON UTERINE WALL



M/A OF OXYTOCIN ON BREAST TISSUE

Oxytocin



THERAPEUTIC APPLICATION OF OXYTOCIN

- oxytocine produces dose related increase of uterine contractions, thus used for
 - (i) Induction of labour
 - (ii) Control of PPH
- In the breast, Oxytocin assist in milk let down assisted by suckling that stimulates increased secretion of oxytocin

ADVERSE EFFECTS OF OXYTOCIN

- (1) Maternal

- Uterine hyperactivity and rapture and rapture.
- Hypotension, tachycardia
- ECG changes

(2). Fetal

- Acidosis
- Hypoxia
- Hyperbilirubinemia

CONTRAINDICATIONS OF OXYTOCIN

1. Induction of labour in
 - (i) Cephalopelvic disproportion (CPD)
 - (ii) Placenta previa
 - (iii) Fetal distress
 - (iv) Malpresentation

ERGONOXINE

- Acts via α - adrenoceptors
- Increases Ca^{2+} entry into the cells
- Causes sustained rather than intermittent contractions
- Contraindicated for the induction of labour

Adverse effects

- Hypertension
- Severe headache
- Nausea
- Vomiting
- Angina
- Fetal malformations

PROSTA GLANDINS

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- The endometrium and myometrium generate prostaglandins especially in the second proliferative phase of the menstrual cycle
- PGF_{2α} and PGE₂ (prostacyclin).
- Play a role in dysmenorrhea and menorrhagia.
- NSAIDS are used to treat dysmenorrhea
- Exogenous prostaglandins like --dinoprostone(PGE₂)-Dinoprost (PG_{2α}) and -mesoprostol are used in termination of pregnancy (Abortifacients).

UTERINE RELAXANTS

β_2 -Adrenergic agonists.

- Ritodrine.
- Terbutaline.
- Ioxsuprene .
- Albuterol (sulbutamol).

M/A

Causes uterine muscle relaxation by increasing cAMP in the uterine smooth muscles

USES

Delay or prevent premature labour.

MAGNESIUM SULPHATE (MgSO₄)

M/A

Blocks myometrial Ca₂ channels

Decrease myometrial contractility.

USES

- Prevent premature labour .
- Also used in Rx and prevention of seizures in pre-eclampsia.

ETHANOL

M/A

Stablises the myometrial cells and reduces oxytocin release

USES

- Prevention of premature labour

OXYTOCIN (SYNTOCINON or PITOCIN)

This is a synthetic peptide possessing the pharmacological effects of the endogenous hormone

M/A

It causes potent and selective stimulation of uterine and mammary glands smooth muscles

The contractive activity of uterine smooth muscle is caused by increased permeability of cell membrane of myofibrils to Ca^{2+} mean while the contraction of the myo-epithelial cells surrounding the ducts and alveoli is facilitated by the same M/A.

Large doses of oxytocin may cause inhibition of anti diuretic activity

ROUTS OF ADMINISTRATION

I.M

IV as infusion

DOSE

Average 5 i.u-10 i.u as infusion

INDICATIONS

Initiation of uterine contractions induction of labour

Augmentation of labour

Control of PPH

Facilitation of uterine involution

Management of Inevitable incomplete or missed abortion

May be given to aid milk let down

P/K

The onset of effect is within one minute when given as an infusion, 3-7minutes when given as I.M, and 5minutes when given as nasal spray and 30minutes when given under the buccal cavity
It has short plasma t $\frac{1}{2}$

It is rapidly cleared from the plasma by the liver, kidney and mammary glands.

It is primarily excreted as metabolites by the kidney with small amounts as active drugs.

SIDE EFFECTS TO THE MOTHER

Nausea

Vomiting

Arrythmias

Uterine hypertonicity

Water intoxication due to inhibition of ADH

Convulsions

Anaphylacticreaction

Increased uterine motility

SIDE EFFECTS TO THE FOETUS

Brady cardia

Anythmias

Hypoxia

Asphyxia

CONTRAINDICATIONS

Foetal distress

Hypertonic uterine pattern

Un-dilated cervix

Where vaginal delivery is contraindicated as in cord prolapse, previous uterine scar, placenta previa, and CPD

DRUG INTERACTIONS

Severe hypertension can occur if oxytocin is given in presence of vaso-pressure drugs like enfedrine, adrenaline and mentholamine

NURSING CONSIDERATIONS

- (i) Ensure that oxytocin used for induction of labour is only given by infusion
- (ii) Carefully regulate the rate of infusion to obtain optimum contractions
- (iii) Stop infusion if contractions are frequent i.e <2minutes interval as this may result in foetal hypoxia
- (iv) During prolonged infusion be alert of signs of water intoxication due to anti-diuretic hormone effect of oxytocin

Signs of this are:

Headache

Confusion

Drowsiness

- (v) Monitor input and output

- (vi) Never administer undiluted I.V oxytocin

METHYLERGOMETRIN

This is a synthetic ergot alkaloid.

M/A

It increases motor activity of uterus by direct stimulation hence causing contraction

Increases Ca^{2+} entry into uterine muscle cells resulting in sustained rather than intermittent contractions

ROUTES

- (i). I.V
- (ii). I.M
- (iii). Oral

DOSE

Oral 0.2mg t.d.s

IM/IV 0.2mg after delivery

INDICATIONS

- (i). Management of PPH or sub-involution of uterus following delivery of the placenta
- (ii). Prevention and Rx of post abortion bleeding

P/K

It is well absorbed orally or parenterally

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Onset of action is 5-10minutes following oral Administration, and 1minute following I.M/I.V administration

SIDE EFFECTS

Nausea

Vomiting

Dizziness

Hypertension

Tinnitus

CONTRAINDICATIONS

Hypertension

Toxemia of pregnancy i.e pre-eclampsia and eclampsia

NURSING CONSIDERATIONS

Do not routinely use Ergometrine intravenously as this bares a risk of HTN and CVA

Use with caution in patients with sepsis, hepatic or renal dysfunction

Store the drug in a cool and dry place.

Protect the drug from light

SYNTUMETRINE

A combination of oxytocin 5i.u and ergometrine 0.5 mg

Medical class- B controlled

Use- treatment of PPH

Has rapid and sustained action

Dose-1ampule (5 i.u oxytocin + 0.5mg ergometrine)

At delivery of Anterior shoulder of the baby or if possible as soon as possible after the delivery of the baby

Route- I.M

Side effects

Nausea

Vomiting

CORTICOSTEROIDS

Gluconeogenesis

Lipolysis

Increase water + Na absorption

Anti-inflammatory

Suppression of immune system

Delayed wound healing

Adrenal cortex

-Corticosteroids

-Mineralocorticoids

Adrenal medulla

-Adrenaline

-Noradrenaline

-Androgens

PHARMACOLOGY OF CORTICOSTEROIDS

Are steroid hormones produced by the adrenal cortex.

Are grouped into two physiological and pharmacological groups

1. Glucocorticoids-which affect mainly

- Metabolism
- Immune response
- Inflammation

2. Mineralocorticoids- which regulate renal Na^+ and K^+ re-absorption

GLUCOCORTICOIDS

1. Natural

E.g cortisol [stress hormone]-Hydrocortisone

- Synthesized in the adrenal cortex
- Release is regulated by ACTH in circadian rhythm
- Transported in plasma bound to globulin
- Involved in normal physiological function.

2. Synthetic

PHYSIOLOGICAL EFFECTS OF CORTISOL

- General adaptation syndrome i.e preparing body for physical or stressful activity [in fight or flight situations]. This includes the following;
- Increase epinephrine release
- Increase sensitivity of tissues to catecholamines
- Increase gluconeogenesis
- Increase lipolysis
- Increase CNS arousal
- Increase BP
- Suppression of inflammation

SYNTHETIC GLUCOCORTICOIDS

- Prednisone
- Dexamethasone
- Hydrocortisone
- Triamcinolone

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NB –the following are some commonly used natural and synthetic corticosteroids for general use

-Cortisone

-Prednisone

-Prednisolone

-Methyl prednisolone

-Meperednisone

-Triamcinolone

-Paramethasone

-Fluprednisolone

-Betamethasone

-dexamethasone

-fludrocortisone

HYDROCORTISONE

It is a glucocorticoid that naturally occurs in adrenal cortex and can be synthesized

M/A

It has an anti- inflammatory action by

- Inhibiting capillary dilation and permeability
- Interfering with biosynthesis, storage or release of allergic substances like histamines
- Suppressing leukocyte migration and phagocytosis
- Stabilizing leukocytes, and lysosomal membranes
- Reduction of anti-body formation by lymphocytes and plasma cells

ROUTE

- Oral
- I.V
- I.M
- Rectal

DOSE

100-250mg b.d or t.d.s

INDICATIONS

- Rheumatoid arthritis
- Asthmatic attack/status asthmaticus
- Ulcerative colitis
- Drug sensitivity
- Proctitis
- Ophthalmic use as in conjunctivitis
- Nephrotic syndrome
- Synovitis
- Replacement therapy in primary or secondary adrenocorticoid insufficiency
- Rheumatoid fever
- Rheumatoid carditis

P/K

- It is well absorbed from GIT and circulates well in blood
- Partially bound to plasma proteins
- $t_{1/2} \sim 1 \frac{1}{2}$ hours
- It is metabolized in the liver
- Excreted in urine

SIDE EFFECTS

- Low resistance to affection
- Alteration of electrolyte balance leading to retention of salt and water resulting in oedema and weight gain
- Hypokalaemia
- Peptic ulcers
- Cataracts
- Hypertension
- Delayed wound healing
- Lack of sleep
- Acne
- Muscle weakness
- Mental disturbances
- Withdraw symptoms i.e fatigue, dizziness

CONTRAINDICATIONS

- TB
- CCF
- Cushing's syndrome
- Peptic ulcers
- Hypertension
- Diabetes mellitus

NURSING CONSIDERATION

Monitor patient's weight and BP

- Gradually reduce drug dosage after long term therapy
- Instruct patient to carry steroid cards
- Do not immunize patients undergoing high dose of hydrocortisone because of impaired antibody response
- Give potassium rich foods

PREDNISOLONE

It is a synthetic glucocorticoid and a derivative of hydrocortisone.

Legally class B.

M/A

As an anti –inflammatory;

- It stabilizes leukocytes, lysosomal membranes and also suppresses immune response
- It also influences protein ,carbohydrates and fat metabolism

ROUTES

- Oral
- I.M
- I.V
- Topical

DOSE

Adult – 5-60mg per day in divided doses

Children 1-2mg /kg body weight in 3-4 divided doses

INDICATIONS

- Rheumatic arthritis
- Ophthalmic use in conjunctivitis
- Keratitis
- Acute optic neuritis
- Allergic rhinitis
- Status asthmaticus
- Ulcerative colitis
- Iridocytis [infammation of iris]
- Steven – Johnson’s syndrome

P/K

- It is rapidly absorbed from GIT
- Metabolized in the liver
- Excreted in urine

SIDE EFFECTS

- Peptic ulcers
- Gastro- intestinal irritation
- Increased appetite
- Hyperglycemia
- Hyperkalaemia
- Hypertension
- Delayed wound healing
- Cataract
- Glaucoma
- Insomnia
- Susceptibility to infection

CONTRAINDICATIONS

- Systemic fungal infection
- Peptic ulcers

NURSING CONSIDERATIONS

- Weigh patient and take BP regularly
- Teach patients signs of early adrenal insufficiency i.e fatigue, muscular weakness, joint pain, and fever.
- Give oral dose with food where possible to minimize gastric upsets.
- Do not reduce dose abruptly to prevent withdraw symptoms
- Monitor patient's serum electrolytes regularly
- Patients with DM may need increased insulin and monitor blood glucose levels

DEXAMETHASONE

It is a synthetic adrenocorticosteroid that is class B controlled

It can be obtained from animal adrenal gland e.g cattle

M/A

It decreases inflammation mainly by stabilizing leukocytes lysosomal membranes

Also it suppresses the immune response and influences protein, fat and carbohydrate metabolism

INDICATIONS

- Cerebral oedema
- Allergic reactions
- Conjunctivitis
- Rheumatoid arthritis
- Dermatitis
- Congenital adrenal hyperplasia
- Shock

DOSE

0.25-4mg b.d and increased gradually

ROUTE

- Oral
- I.M
- I.V
- Topical

P/K

- well absorbed from GIT
- Circulates in blood, partially bound to plasma protein
- Metabolized in liver
- Largely excreted in urine
- Has slightly long acting period

SIDE EFFECTS

As for other corticosteroids

ANTI-ANAEMIC DRUGS

These are drugs used as replacement therapy in treatment of anaemia

Anaemia is a decrease in the number of RBCs or decrease in the amount of haemoglobin

Anaemia varies in type depending on the cause

1. Iron deficiency anaemia
2. Anaemia in chronic renal failure
3. Pernicious anaemia (due to lack of intrinsic factor)
4. Folic acid deficiency anaemia
5. Hemolytic anaemia
6. Vitamin deficiency can also lead to anaemia

IRON PREPARATIONS

FERROUS SULPHATE

This is an oral anti-anaemic (haematinic) agent used in the treatment of anaemia.

Legally class C

M/A

Provides elemental iron, an essential component in the formation of HB

ROUTE

- oral

DOSE

Adult 200mg b.d or .td.s

Children 5mg/kg body weight daily increased to 10mg/kg body weight tds

INDICATIONS

1. Iron deficiency anaemia
2. Prophylactic therapy during periods of increased iron requirements like in pregnancy
3. In Haemorrhagic conditions
4. In pre-mature and under nourished children

P/K

- Absorption occurs at most levels of GIT although it is very poor
- Only 5-10% of iron is absorbed in normal person and up to 20% in iron deficient patients.
- It is distributed to storage site in bone marrow, liver, spleen and haemoglobin
- It crosses the placenta barrier and is also present in breast milk
- It is excreted in faeces but small amounts in bile, urine and sweat

SIDE EFFECTS

- Nausea
- Vomiting
- GIT irritation
- Black stools
- Drug's elixir preparation may stain the teeth.

CONTRA INDICATIONS

-Haemolytic anaemia –e.g SCD

NURSING CONSIDERATIONS

1. Alert patient that oral iron turns stools black and that it is harmless

2. To minimize GIT upset, give doses between meals
3. Monitor Hb and RBC count during therapy
4. To avoid teeth staining elixir may be taken with straw
5. Use the drug with caution in ulcerative colitis and peptic ulcers
6. Anti-acids decrease ferrous absorption while vitamin C promotes

IRON DEXTRON

It is an anti-anaemic drug and legally class B

It occurs in injectable form

M/A

It provides elemental iron; an essential component in the formation of Hb

1ml iron dextron provides 50mg elemental iron

ROUTES

I.M

I.V

DOSE

Administer dose after a test dose of 0.5mls

Bellow 5kg 0.5mls

Bellow 9kg 1ml

Bellow 50kg 2ml

Over 50kg 5ml

INDICATION

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Iron deficiency anaemia where oral route has not produced satisfactory response

P/K

It is slowly absorbed from I.M injection

60 % is absorbed within 2-3 days and 90% within 1-2 weeks

It is distributed through reticuloendothelial system [liver, and spleen] and excreted in urine, bile and faeces

SIDE EFFECTS

-Hypersensitivity reaction – rash, itching e.t.c

-Inflammation

- Hypotension

-Dizziness

-Nausea

- Paresthesia

- Brown discoloration

-Sterile injection abscess at I.M site

NURSING CONSIDERATIONS

Always give test dose to minimize hyper-sensitivity

Use large needle of 19-20 gauge and use a z tract technique to avoid leakage into and staining of overlying epithelial substance

Do not inject more than 5mls at one I.M site

Keep patient recumbent 30 minutes to 1 hour following I.V injection to prevent orthostatic HTN.

Do not mix the drug with other drugs.

FOLIC ACID

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It is an anti- anaemic drug belonging to group of vitamins necessary for the development of RBCs. It is legally class C

M/A

It is necessary for normal RBCs development by synthesizing of nucleo-protein and leads to normal erythrocyte production.

ROUTES

-Oral

-I.V

DOSE

[5mg o.d daily]

INDICATIONS

-Megaloblastic anaemia

-Macrocytic- anaemia

-SCD anaemia

P/K

It is well absorbed from GIT

Maximum effect is reached in 30-60 minutes

It is highly bound to plasma protein

Metabolized in the liver and largely excreted by the kidneys

SIDE EFFECTS

Side effects are rare but at many occasions

Allergic reactions

-rash

-itching

-Broncho spasms

Irritability

GIT upsets

NURSING CONSIDERATIONS

Use oral route except where there is known GIT mal-absorption

I.M/SC and I.V routes may be employed in severe diseases of GIT mal-absorption

Increase dose in alcoholic and patient with haemolytic anaemia

VITAMIN B₁₂(CYANOCOBALAMIN)

It is also a vitamin necessary for normal growth of blood cells.

It occurs naturally in food but can't be synthesized

Its legally class C in tablet form but class B in injectable form

M/A

It provides needed vitamin B₁₂ to reverse deficiency state resulting from inadequate GIT absorption of vitamin B₁₂

It allows megaloblastic cells to mature into normal erythrocytes

ROUTES

Oral

I.M

S/C

DOSE

Adult dose 200-500mg orally

INDICATIONS

Pernicious anaemia

Vitamin B₁₂ deficiency caused by inadequate dietary intake, sub-total gastroctomy

P/K

The GIT absorption depends on the presence of intrinsic factor which binds vitamin B₁₂ to protect it from intestinal micro organisms

Small dose less than 50mg is retained in the body but 50-90% is rapidly excreted within 8hours by the kidneys

SIDE EFFECTS

Itching

Flushing

Transient diarrhea

Pain and burning sensation at site of injection

Peripheral vascular thrombosis

GIT- PHARMACOLOGY

OUTLINE

1. DRUGS FOR TREATMENT OF PUD
2. EMETICS -DRUGS THAT CAUSE VOMITING
3. ANTI EMETICS –DRUGS THAT TREAT VOMITING
4. PROKINETICS (DRUGS FOR TREATMENT OF CONSTIPATION)
5. ANTI-DIARRHOEAL DRUGS

INTRODUCTION

Gastric secretion is stimulated by.

1. Gastrin hormone –produced by cells in the duodenum, stimulated by presence of food in the stomach , gastrin stimulates ECL cells to produce histamine which inturn stimulates the parietal cells (proton pump) to release H⁺ into gastric pits.
2. Ach Binds M₁,M₃ leading to release of histamine from ECL cells subsequently resulting in H⁺ release from H⁺/K⁺ ATPase (The proton Pump)

PEPTIC ULCER DISEASE (PUD)

PUD: is a mucosal defect in the stomach or duodenum associated with excessive gastric acid secretion:

Gastric acid secretion depends mainly on:-

1. Gastrin (food stimulated).Gastrin binds to gastric – CCK-B receptors on the parietal cell stimulating H⁺ release from the H⁺/K⁺ ATPase (proton pump).
2. Acetyl chlorine (Ach) – binds to M₁ On ECL cell to stimulate histamine release that in turn stimulates the parietal cell.

Also stimulates /binds M₃ receptors on parietal cell to cause release of H⁺ from the H⁺/K⁺ ATPase (Proton pump)

3. Histamine (from ECL cell by action of Ach and gastrin) – binds to H₂ receptors on the parietal cell to stimulate H⁺ release.

Imbalance between defensive and aggressive factors can precipitate to PUD

1. Defensive factors in the stomach
 - Prevent the stomach and duodenum from self digestion.
 - Mucous produced by goblets
 - Bicarbonate – secreted from endothelial cells
 - Blood flow –Good blood flow maintains mucus integrity.
 - Prostaglandins – stimulate production of bicarbonate and mucus, promote blood flow and suppress secretion of gastric acid.

2. Aggressive factors in the stomach.
- Helicobacter pylori – causes inflammatory response and mucosal toxicity
 - Gastric acid – activates pepsin and injures mucosa
 - Decreased blood flow – causes decrease in mucus production and HCO_3^-
 - NSAIDS – inhibit production of prostaglandins
 - Smoking – nicotine stimulates gastric acid production ,decreased duodenal HCO_3^-
 - Alcohol/ ethanol – causes erosive gastritis
 - Caffeine – increases gastric acid production
 - Severe stress , burns ,surgery, CNS trauma

DRUGS USED IN TREATMENT OF PUD

DRUG CLASSES

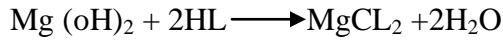
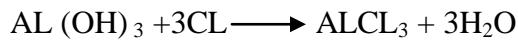
- Antacids
- H_2 receptor blockers
- Muscarinic antagonists
- Proton- pump inhibitors
- Mucosal protectants
- Antibiotics

ANTACIDS

These neutralize gastric acids

- Aluminum hydroxide(Amphogel)
- Magnesium hydroxide(milk of magnesia)
- Sodium bicarbonate(Alkaseletzer)

M/A





Clinical Uses

- PUD
- GERD
- Mendelson syndrome e.g in anaesthesia, coma, and endoscopy

H₂ RECEPTOR BLOCKERS

Selectively block H₂ Receptors on parietal cells reducing acid secretion

- Cimetidine
- Ranitidine
- Nizatidine
- Famotidine

Clinical Uses

- PUD
- GERD
- Zollinger Ellison syndrome (increase acid due to gastrin secreting tumor)
- Systemic mastocytosis
- Mendelson syndrome (Aspiration of acid and chemical pneumonitis as in anaesthesia, coma)
- Stress related gastritis

PROTON-PUMP INHIBITORS (PPIs)

Irreversibly inhibit the H⁺/K⁺ ATPase in gastric parietal cells

- Omeprazole
- Lansoprazole
- Esomeprazole
- Rabeprazole

Clinical Uses

- PUD
- GERD
- Zollinger Ellison syndrome
- Prevention of NSAIDS induced ulcers

MUCOSAL PROTECTIVE AGENTS

I. Misoprostol (PGE₁ analog)

Stimulate mucus and HCO₃⁻ production used to prevent/treat NSAID induced ulcers

II. Sucralfate

Complex of AL (OH)₃ and sulfated sucrose stabilizes mucus

Decrease diffusion of H⁺

III. Colloidal bismuth

- Bismuth combines with mucus glyco-proteins to form a barrier that protects the ulcer from further damage by acid and pepsin
- Increases mucosal HCO₃
- Increases PGE₂
- Inhibits growth of H. pylori

Clinical Uses

- PUD
- GERD
- Traveler's diarrhea (acts by binding enterotoxins)

MUSCARINIC ANTAGONISTS

(Anticholinergics/Antispasmodics)

- Block M₁ receptors on histamine containing ECL cells
- Block M₃ receptors on parietal cells
- a. Pirenzepine

- b. Propantheline
- c. Dicyclomine

Clinical Uses

- PUD (as adjunct therapy)
- Irritable bowel syndrome

ANTIBIOTICS

Eradicate H. pylori

- Clarithromycin
- Metronidazole
- Amoxicillin
- Tetracycline
- Tinidazole may replace metronidazole

TOTAL H. PYLORI TREATMENT

Two forms of therapy are involved:

- Triple therapy
- Quadruple therapy

Either of the above may be PP1 based or bismuth based.

Bismuth based =bismuth+2Antibiotics X $\frac{2}{52}$

PP1 based = PP1 + 2 Antibiotics X $\frac{2}{52}$

TRIPLE THERAPY REGIMENS

Clarithromycin + Metronidazole + PP1 e.g omeprazole

Amoxicillin +Clarithromycin + PP1

Amoxicillin + Metronidazole + PP1

QUADRUPLE THERAPY

Tetracycline + Metronidazole + PP1 +Bismuth

Tetracycline + Metronidazole + H₂ blocker + Bismuth

N.B in bismuth based regimens, PP1 or H₂- blockers may be added to optimize ulcer healing

CIMETIDINE

Is H₂ receptor antagonist

M/A

It reduces gastric acid secretion by blocking the action of histamine at the H₂ –receptors on the parietal cells of the stomach

INDICATIONS

- Peptic ulcers
- Stress ulcers
- Reflux oesopagitis
- Zollinger- Ellison syndrome
- Dyspepsia

DOSE

Dose differ according to route, and condition

400mg b.d for 4 – 6/52 p.o

Routes

- Oral
- IV

- IM

Pharmacokinetics

- Cimetidine is readily absorbed from the GIT when given orally
- Food delays the rate and may slightly decrease the extent of absorption
- It is widely distributed and partly metabolized in the liver
- It crosses the placenta barrier and it is distributed into breast milk
- It is excreted mostly in unchanged form in urine

SIDE EFFECTS

- Dizziness
- Nausea
- Reversible impotence
- Mild gynaecomastia
- Tiredness
- Headache
- Vomiting
- Loss of libido
- Diarrhoea

DRUG INTERACTIONS

Cimetidine decreases the metabolism of phenytoin, metronidazole, oral contraceptives, warfarin and isoniazid

Metoclopramide may reduce the bioavailability of cimetidine due to reduction of GIT transit time

The effects of ferrous sulphate, indomethacin, ketoconazole, fluconazole and tetracyclines may be decreased by cimetidine due to decreased absorption

Antacids may decrease the absorption of cimetidine

NURSING CONSIDERATIONS

Administer cimetidine with food but not with anti-acids

The preferred method of administration of parenteral cimetidine is by continuous infusion or else I.M

Advise Patient to avoid excessive amount of coffee or aspirin

Cimetidine has a weak anti-androgenic effect hence gynaecomastia, impotence, and loss of libido may occur.

RANITIDINE

It is H2-receptor antagonist

M/A

It reduces gastric acid secretion by blocking the action of histamine at the H2-receptor on parietal cells of the stomach

INDICATIONS

- Peptic ulcers
- Prophylaxis of NSAID induced duodenal or gastric ulcers
- Stress ulcer prophylaxis
- GORD
- Zollinger- Ellison syndrome
- Dyspepsia

DOSE

Varies according to age, condition and route of administration

Children and adults (over 12years)

150mg b.d P.oral x 4- 8/52

Routes

- Oral
- IV

Pharmacokinetics

- Ranitidine is readily absorbed from the GIT
- Widely distributed
- Metabolized in the liver
- Excreted in urine

SIDE EFFECTS

- Skin rash
- Visual disturbance
- Gynaecomastia
- Headache
- Diarrhea
- Malaise
- Tachycardia
- Constipation
- Hypersensitivity
- Myalgia

DRUG INTERACTIONS

- Antacids may decrease the absorption of ranitidine
- Ranitidine may decrease the absorption of ketoconazole, cefuroxime,
- Ranitidine may increase the hypoglycaemic effects of glipizide
- Ranitidine may interfere with warfarin clearance

OMEPRAZOLE

Is a proton pump inhibitor (PPI)

M/A

Act by irreversibly binding to and inhibiting the enzyme H⁺/K⁺ ATPase (proton pump) of the gastric parietal cells resulting in long lasting but reversible acid suppression

N.B PPI inhibit gastric acid secretion more than the H₂-receptor antagonists

INDICATIONS

- Peptic ulcers
- Zollinger –Ellison syndrome
- NSAID associated duodenal or gastric ulcer
- Gastric acid reduction during anaesthesia
- Gastro – oesophageal reflux disease (GORD)
- Acid associated dyspepsia

Dose

Varies according to patients condition/disease

20mg o.d X 4/52

Routes

Oral

Pharmacokinetics

- Omeprazole is rapidly but variably absorbed after oral administration
- Absorption is not affected by food
- It is almost completely metabolized in the liver
- 80% of the metabolites are excreted mainly in urine and the rest in faeces

Side effects

- Skin rash
- Vomiting
- Gynaecomastia
- Headache
- Diarrhoea
- Nausea
- Impotence
- Constipation
- Abdominal pain
- Dry Mouth

Contra indications

- Allergy to omeprazole
- Pregnancy
- Lactation

Drug interactions

- Omeprazole increases the plasma concentration of diazepam, carbamezapine, digoxin, phenytoin
- Omeprazole decreases the plasma concentration of the Itraconazole , ketaconazole, Cefuroxime, cyanocobalamin
- Omeprazole may increase the absorption and the potential for hypoglycaemia of glipizide, tolbutamide

Nursing conditions

- Administer before food and the capsules should be swallowed whole without chewing
- Capsules should be used within one month of opening the package
- Possibly malignancy must be exchanged prior to starting starting to avoid delay in treatment

- Reduce dosage in hepatic disease

RABEPRAZOLE

It is a PPI

M/A

Acts by irreversibly binding to and inhibiting the enzyme H⁺/K⁺ ATPase (proton pump) of the gastric parietal cells resulting in long lasting but reversible acid suppression

N.B: PPI inhibit gastric acid secretion more than the H₂-receptor antagonists

INDICATIONS

- Peptic ulcers
- Zollinger –Ellison syndrome
- Gastro – oesophageal reflux disease (GORD)
- Helicobacter pylori eradication in combination with antibiotic

Dose

May Vary according to condition

20mg o.d X 6- 12/52

Routes

- Oral
- I.V
- I.M

Pharmacokinetics

- Rabeprazole is rapidly but variably absorbed from GIT and is 90% protein bound
- It is extensively metabolized in the liver
- Excreted principally in urine

- Crosses the placenta and may appear in breast milk

Side effects

- Skin rash
- Fatulence
- Pharyngitis
- Headache
- Diarrhoea
- Nausea
- Impotence
- Influenza like syndrome
- Constipation
- Abdominal pain
- Dry Mouth
- Cough
- Rhinitis
- Anorexia

Drug interactions

- Co administration with ketoconazole, decreases ketoconazole plasma level
- May increase serum levels and toxicity of benzodiazepines when together

EMETICS, ANTIEMETICS, PROKINETICS AND ANTI DIARRHOEAL DRUGS

EMETICS

Drugs that induce vomiting

STIMULI AND RECEPTORS FOR EMETIC REFLEX

1. CTZ(chemoreceptor trigger zone), receptor – D₂, 5 - HT₃, M₃
2. Labyrinth of inner ear via cerebellum receptors H₁, M₁(motion simulates these receptors and result in vomiting)

3. Cerebral cortex
 - Stimulating factors for vomiting are;
- Memory
- Fear
- Dread
- Anticipation
4. GIT (stomach, ileum)

Receptors 5- HT₃ [serotonin] receptors

5. Solitary tract nucleus

Receptors 5- HT₃, D2, H₁

6. Pharynx [gagging]

7. Sensory input

- Pain
- Smell
- sight

EXAMPLES OF EMETICS

1. IPecac syrup

Acts directly on CTZ

SIDE EFFECTS

Cardio- toxic if absorbed

2. Apomorphine

- Acts on CTZ
- Side effects

Respiratory depression

Circulatory collapse

- Antidote - naloxone

Clinical uses

- Induction of vomiting e. g in treatment of poisoning

ANTI - EMETICS

Drugs used for symptomatic treatment or control of vomiting

Clinical uses -vomiting associated with

- ✓ Motion sickness
- ✓ Chemotherapy
- ✓ Pregnancy
- ✓ Migraine
- ✓ Nervousness
- ✓ Infections
- ✓ Food poisonings

MOTION SICKNESS

(1) Scopolamine

M/A- anticholinergic

Routes

Oral

S/Q

Trans-dermal

S/effects

Vertigo

Dry mouth

Drowsiness

Blurs vision

(2) Dimenhydrinate

M/A-

Antihistamine

Routes:

Oral

PARENTERAL

Rectal

(3) Diphenhydramine

M/A-antihistamine

Routes: oral, parenteral

(4) Meclizine

M/A- antihistamine

Route: oral

(5) Promethazine/ phenergan

M/A – antihistamine

- Blocks central action of dopamine
- Decreases CTZ response

(B) CHEMOTHERAPY (ANTI-CANCER INDUCED VOMITING)

- as a result of D₂, 5-HT₃ receptor activation
- also damage to GIT mucosal enterochromaffin cell results in 5-HT release stimulating 5-HT₃ and increased vagal discharge hence vomiting.

(1) Metoclopramide / Plasil

M/A D₂ and 5-HT₃ antagonist

S/Effects: sedation , diarrhea, extrapyramidal symptoms

(2) - ondansetron

- granisetron
- dolasetron

M/A 5-HT₃ antagonists

S/effect: headache

(3)- Dexamethasone

- methylprednisolone

M/A – block prostaglandins production

- are corticosteroids

(4) - dronabinol

- nabilone

M/A – are delta -9-tetrahydrocannabinol analogues

- activate cannabinoid CB1/CB2 receptor

(5) Haloperidol

M/A- block D₂ receptor, antipsychotic.

PROKINETIC AGENTS

Drugs that increase GIT motility and cause diarrhoea

Receptor of innervation

- (1) 5-HT₄ receptor (agonists)
- (2) D₂ receptor(antagonists)
- (3) 5-HT3 receptor (antagonists)

Effect- increase of ach release leading to increased GIT motility (peristalsis)

EXAMPLES

- D₂ and 5-HT₃ receptor antagonist
 - 5-HT₄ agonist
- (1) Cisapride
- 5- HT₄ agonist on cholinergic motor neurones resulting in increased ach release hence increased peristalsis

ERYTHROMYCIN

- Activates motilin receptors on neurons and smooth muscles

NB- motilin is a GIT hormone that helps initiate gastric emptying and GIT contraction.

ANTIDIARRHOEAL DRUG

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Drugs for symptomatic Treatment of diarrhea

Increase frequency, increase volume decrease consistency of stools

Classes

1. Anti-motility agents

Opiod agonist/opiates

2. Adsorbents

Opiates

- Loperamide
- Diphenoxylate + atropine
- Codeine

M/A

- Active pre-synaptic opioid receptors in enteric nervous system resulting in decrease Ach release leading to
 - Decreased GIT motility
 - Decreased intestinal secretions
 - Increased bowel capacity
 - Increased tone of external anal sphincter.

S/ effects

- 1) Constipation
- 2) Anorexia
- 3) Nausea

4) Dry mouth

2 ADSORBENTS

- Bismuth sub-salicylate binds intestinal toxins and coats the mucosa
antibacterial salicylate decrease P.G synthesis
- Kaoolin (hydrated aluminium silicate + pectin)
- Decrease free water in the intestinal lumen
- Aluminium is constipating
- Activated charcoal [amorphous carbon]-The most effective adsorbent for poisons

LAXATIVES

Drugs for RX of constipation

Classification

- Bulk forming
- Stool surfactants
- Osmotic laxatives
- Stimulant laxatives

BULK FORMING LAXATIVES

1. Natural products

- Psyllium

- Methylcellulose
- Metamucil

Found in bran whole grain, vegetables and fruits

2. Synthetic fibres
 - Polycarbophil

M/A

- Indigestible
 - Absorbs water to form a bulky emollient that triggers stretch receptors in the intestinal wall resulting in increased peristalsis
3. Carbohydrate based laxatives
 - Vegetable fibres e.g psyllium
 - Bran [husks]

STOOL SURFACTANTS / SOFTENERS

1. Docusates [oral , enema]
2. Glycerin [suppository]
3. Mineral oil [liquid paraffin]

Not palatable may be mixed with juice

M/A- soften stool by permitting entry of water and lipids

STIMULANTS LAXATIVE (CATHARTICS)

- (1) Anthraquinones are natural plants
 - Aloe

- Senna
 - Cascara
- (2) Diphenylmenthanes
- Bisacodyl
 - Phenolphthalein
- (3) Castor oil

M/A- directly stimulate the enteric nervous system

OSMOTIC LAXATIVES

- (1) Sodium phosphate
- (2) Magnesium citrate
- (3) Magnesium sulphate
- (4) Milk of magnesia (mg oxide)

These increase duodenal secretion of cck and are cathartics

- (5) Lactulose
- Semi synthetic disaccharide (fructose and galactose)
 - M/A – soluble but non absorbable compound that increase stool fluidity by osmosis

NON DRUG TREATMENT OF CONSTIPATION

- Fibre rich diet
- Physical activity
- Adequate fluid intake

- Emotional improvement.

DRUGS FOR TREATMENT OF DIARRHOEA

(1) LOPERAMIDE

- Is an opiate like codeine used in treatment of diarrhoea

M/A

Activates pre-synaptic opioid receptors in enteric nervous system resulting in release of Ach, leading to

- Decreased GIT motility
- Decreased intestinal secretions
- Increased bowel capacity
- Increased tone of external anal sphincter

INDICATIONS

- Symptomatic treatment of acute diarrhoea
- Chronic diarrhoea in adults only.

DOSE

Initially 4mg, then 2mg after each loose stool for 5 days

Side effects

- Abdominal cramps
- Dizziness
- Drowsiness

- Skin reactions
- Urticaria
- Bloating.

ANTI EMETICS

PROMETHAZINE

- ✓ Also called phenergan
- ✓ It is an antihistamine with anti emetic effects

M/A

As an antiemetic it blocks central actions of dopamine and decrease CTZ response

INDICATIONS

- ❖ Nausea and vomiting
- ❖ Urticaria and angioedema
- ❖ Vertigo
- ❖ Post operative emesis
- ❖ Motion sickness
- ❖ Allergic rhinitis
- ❖ Pruritus in eczema

Dose - adults

25mg 4-6hourly p.o

12.5mg – 25mg 6hourly 1.m

ROUTES

- Oral
- I.M

Pharmacokinetics

- Well absorbed after oral or I.M administration
- Widely distributed.
- Metabolized in liver
- Excreted in urine and bile

SIDE EFFECTS

- Drowsiness
- Dry mouth
- Sedation
- Urinary retention
- Skin rashes
- Headache
- Epigastric pain
- Anorexia
- Constipation
- Disorientation
- Hypotension
- Dizziness
- Fatigue

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DRUG INTERACTIONS

- ✓ Alcohol and other CNS depressants may increase CNS depressant effects of promethazine
- ✓ Promethazine may block the anti-parkinsonian action of levodopa
- ✓ Additive anti-cholinergic effects with anti-cholinergic drugs

Nursing consideration

- ❖ Inform the patient that promethazine may cause drowsiness and impair ability to perform activities requiring mental alertness
- ❖ Advise the patient to avoid prolonged exposure to sun light since promethazine may cause photosensitivity
- ❖ Maintain fluid intake
- ❖ Avoid alcohol in take

METOCLOPRAMIDE/PLASIL

Is an anti-emetic

M/A

Blocks D₂ and 5-HT₃ receptors resulting in cessation of vomiting

INDICATIONS

- Disorders of decreased GIT motility
 - Dyspepsia
 - GORD
 - Diabetic gastroparesis

- Stimulation of lactation
- Nausea and vomiting due to
 - ✓ Migraine
 - ✓ Gastric surgery
 - ✓ Cancer therapy/ chemotherapy
 - ✓ Radiotherapy

Dose

- Adults 10mg t.d.s
- Children
- 9-18yrs 5mg t.d.s
- 5-9 yrs 2-5mg t.d.s
- 3-5yrs 2mg t.d.s
- 1-3yrs 1mg t.d.s
- Neonates 100mcg /kg 6-8 hourly

Routes

- Oral

Pharmacokinetics

- Rapidly and almost completely absorbed from GIT following oral admin
- Undergoes hepatic first- pass metabolism
- Widely distributed in the body
- Excreted in faeces via bile

Side effects

- ✓ Hyperprolactinaemia
- ✓ Tardive dyskinesia
- ✓ Oedema
- ✓ Hypotension
- ✓ Dizziness
- ✓ Headache
- ✓ Parkinsonism
- ✓ Drowsiness
- ✓ Diarrhoea
- ✓ Skin rash
- ✓ Depression
- ✓ Pruritus
- ✓ Restlessness

DRUG INTERACTIONS

- ❖ Reduces absorption of oral digoxin
- ❖ increases Absorption of ASA, paracetamol and diazepam

NURSING CONSIDERATIONS

- May cause drowsiness therefore warn the patient not to drive or operate machinery that require mental alertness
- Advise the patient to take the drug 30 minutes before meals and at bed time.

DRUGS FOR TREATMENT OF CONSTIPATION (LAXATIVES)

LACTULOSE

Is an osmotic laxative

Mode of action

The drug is poorly absorbed therefore the unabsorbed solutes in the intestine draw water from the body into the bowel by increasing osmosis causing bowel distention which in turn increases peristalsis

INDICATIONS

- Constipation
- Hepatic encephalopathy

DOSE

- ✓ Adults 15 ml b.d
- ✓ Children
- ✓ 6-12 years 10ml
- ✓ 1-5years 5ml b.d
- ✓ < 1year 2.5 ml b.d

ROUTES

- Oral

SIDE EFFECTS

- Flatulence
- Abdominal cramps/discomfort

- Diarrhoea
- Nausea
- Vomiting in excess dose

NURSING CONSIDERATIONS

- ✓ Administer the drugs with juice, milk or water to increase palatability
- ✓ Do not take other laxative while on lactulose therapy

BISACODYL

Is a stimulant laxative

Mode of action

It increases peristalsis by directly stimulating nerve endings in the colonic mucosa, thereby increasing intestinal motility

INDICATIONS

- Constipation
- Bowel evacuation before investigational procedures or surgery

DOSE

- Adult 5-10mg o.d p.o nocte
- Children 4-10years 5mg nocte

ROUTES

- Oral (tablet)
- Rectal (suppository)

Pharmacokinetics

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- Absorption after oral administration is minimal
- Absorbed drug is metabolized in the liver
- Excreted in urine faeces and breast milk.

SIDE EFFECTS

- ✓ Nausea
- ✓ Diarrhoea
- ✓ Mild abdominal cramps/discomfort
- ✓ Faintness
- ✓ Suppositories may cause irritation and proctitis

DRUGS INTERACTIONS

- Antacids cemetidine, famotidine , ranitidine milk and other drugs that increase gastric PH level may cause premature dissolution of the enteric coating of bisacodyl resulting in abdominal cramping

NURSING CONSIDERATIONS

- Patients should swallow tablets whole with a glass of water
- Do not administer bisacodyl within 1hour of ingesting antacids milk or dairy products
- Bisacodyl is habit forming, therefore long term use may result in laxative dependency and loss of normal bowel function
- Onset of action is 6-12 hours for tablets 15-60minutes for suppository. Warn the patient that prolonged use of bisacodyl suppositories may cause proctitis

ANTIDIARRHOEAL DRUGS

LOPERAMIDE

An opiate

M/A

Activates pre-synaptic opioid receptors in enteric nervous system resulting in decreased release of Ach, leading to decreased GIT motility

INDICATIONS

- ✓ Acute diarrhea
- ✓ Chronic diarrhea
- ✓ Traveler diarrhea

DOSE

Adult: 4mg start; then 2mg every after each loose stool until when diarrhea is relieved

Children: 9 – 12 years 2mg 6hourly X 5/7

4 – 8 years 1mg 6hourly X 3/7

ROUTES

Oral

PHARMACOKINETICS

- About 40% absorbed from the GIT or undergoes first pass metabolism in the liver
- Excreted in the faeces and as unchanged drug and small amounts in urine

SIDE EFFECTS

- ✓ Flatulence

- ✓ Blur vision
- ✓ Drowsiness
- ✓ Fatigue
- ✓ Constipation
- ✓ Dry mouth
- ✓ Hypersensitivity
- ✓ Dizziness
- ✓ Vomiting
- ✓ Bloating
- ✓ Nausea
- ✓ Urticaria
- ✓ Abdominal Pain
- ✓ Toxic Megacolon
- ✓ Paralytic Ulcers

DRUGS INTERACTIONS

Concomitant use of loperamide with opioid analgesic may cause severe constipation

NURSING CONSIDERATIONS

- Advise patient to drink plenty of fluids to prevent dehydration
- Do not exceed maximum daily dosage
- It may impact ability to perform activities requiring mental alertness
- Advise the patient to avoid alcohol during treatment

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- Loperamide should not be used alone in patients with dysentery

CODEINE

An opioid

M/A

Activates pre-synaptic opioid receptors in enteric nervous system resulting in decreased release of Ach, leading to decreased GIT motility

INDICATIONS

- ✓ Diarrhoea
- ✓ Pain
- ✓ Cough

DOSE

Adult: 30 – 60mg t.d.s

Children: not recommended

ROUTES

Oral

PHARMACOKINETICS

- Absorbed from the GIT
- Metabolism in the liver
- Excreted in urine

SIDE EFFECTS

- ✓ Headache
- ✓ Constipation
- ✓ Anorexia
- ✓ Abdominal Pain
- ✓ Dry mouth
- ✓ Hypotension
- ✓ Dizziness
- ✓ Vomiting
- ✓ sedation
- ✓ Nausea
- ✓ Respiratory depression
- ✓ somnolence
- ✓ Decreased urination

DRUGS INTERACTIONS

Alcohol, narcotic analgesics, hypnotic and tricyclic antidepressants may increase CNS or respiratory depression

NURSING CONSIDERATIONS

- Administer with water or fluids to decrease nausea and GIT upset
- Avoid long term use because of addictive potential

ANTI-VIRAL DRUGS

These are drugs that act against viruses. The susceptible viruses to these drugs are:

6. HIV
7. INFLUENZA
8. HEPATITIS B VIRUS
9. HERPES
10. CYTOMEGALOVIRUS(CMV)
11. VERICELLA ZOSTER VIRUS(VZV)

CHARACTERISTICS OF VIRUSES

1. Very few respond to chemotherapy
2. Do not have own metabolic processes
3. Reproduction depends on host cell machinery
4. They lack cell membranes and walls
5. They are obligate intracellular parasites

SITES OF ACTION

4. Are dependants on cellular replication therefore drugs target viral replication which occurs in host cells
5. Drugs target entry into host cells i.e viral absorption and penetration into host cells
6. Others target nucleic acid synthesis, protein synthesis, viral assembly and release

ANTI-HERPES DRUGS

3. Acyclovir (herpes)
4. Famciclovir (herpes zoster)
5. Valaciclovir (generally treat herpes)
6. Ganaciclovir (cytomegalo virus)
7. Foisanet(cytomegalo virus, herpes simplex virus)
8. Idoxuridine (herpes simplex)
9. Amantadine (treats influenza type A virus)

10. Rimantidine (treats influenza type A virus)
11. Ribavirin (respiratory syncytial virus, influenza ,ebola)
12. Interferon (hepatitis B, C, kaposi sarcoma)

ACICLOVIR

M/A

It inhibits viral DNA synthesis

Indicators

- Herpes simplex
- Varicella zoster

Dose

Adults - 200mg – 400mg 5times a day for 5/7

Routes

- Oral
- Intravenous
- Topical

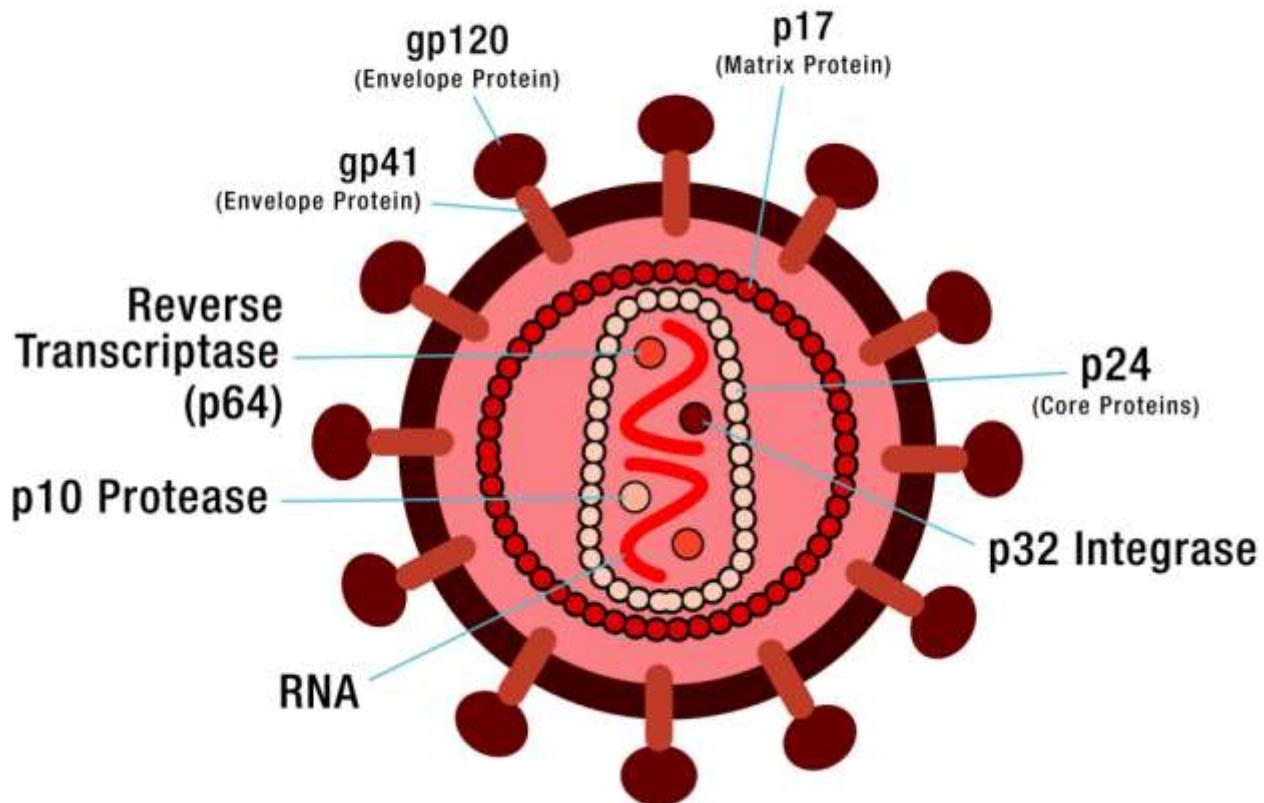
Side effects

- Nausea
- Vomiting
- Abdominal pain
- Headache
- Fatigue
- Rash
- urticaria
- photosensitivity
- when given I.V, causes tremors, seizures, hypertension, nephrotoxicity, delirium
- Rarely hepatitis, jaundice, dyspnoea, angioedema

ANTI-RETROVIRAL THERAPY (ART)

ANTI-HIV DRUGS

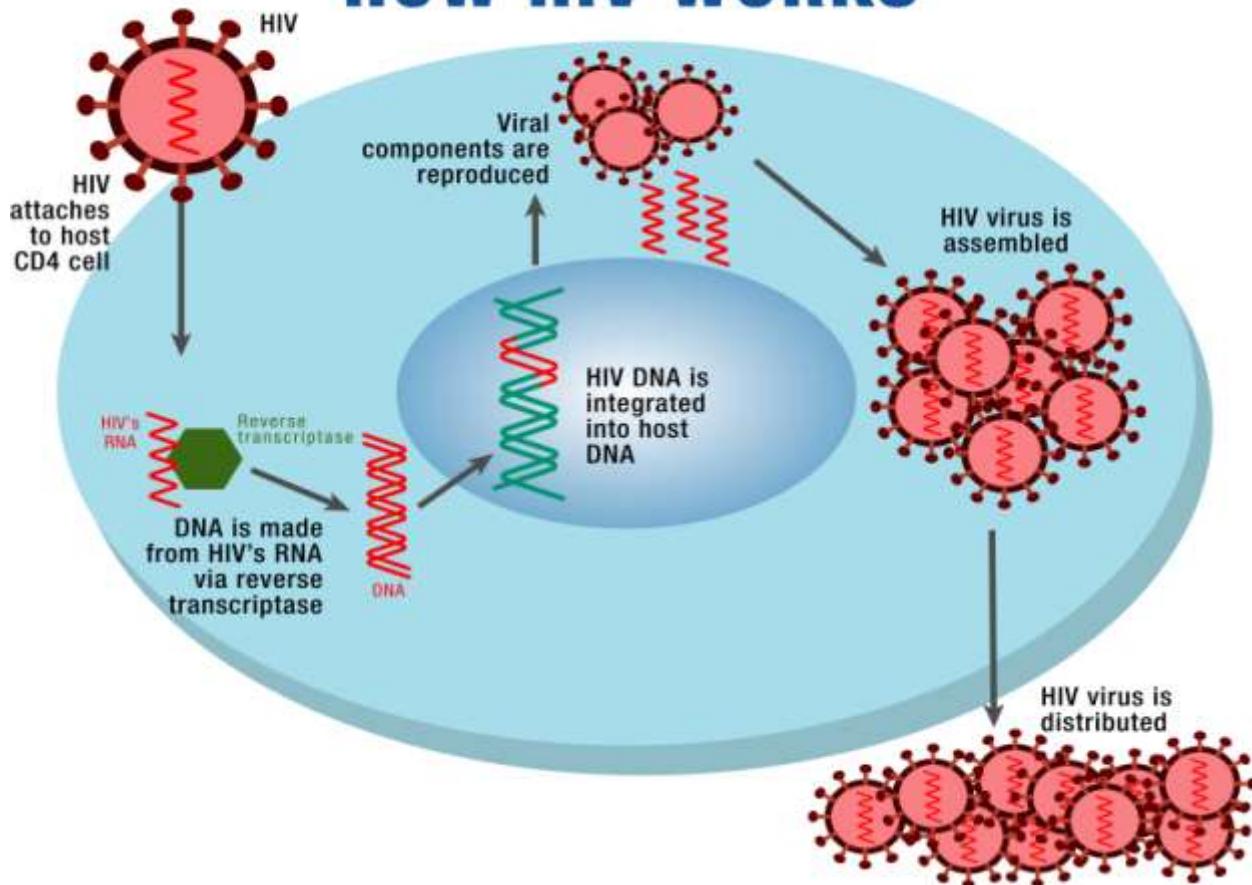
STRUCTURE OF HIV CELL



The diagram showing viral entry and multiplication into human cells

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HOW HIV WORKS



- Steps in HIV replication are illustrated in the diagram.
1. Binding of gp120 to CD4 and co-receptor on the cell surface
 2. Fusion of the viral envelope with the cell membrane
 3. Release and disassembly of the viral core in the cytoplasm
 4. Reverse transcription (Reverse transcriptase enzyme translates HIV's single stranded RNA into a provirus made of double stranded DNA)
 5. Viral DNA moves into cell nucleus
 6. Viral DNA is integrated (by Integrase enzyme) into host genome to form HIV provirus
 7. HIV provirus DNA is transcribed back to both viral genomic RNA and viral mRNA , the latter which is translated to HIV polyproteins.
 8. The RNA virus and polyproteins are assembled beneath the cell membrane
 9. The assembled package becomes enveloped in the host cell membrane as it buds off to form an HIV virion.

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Further assembly and maturation occurs outside the cell by the protease enzyme, rendering the HIV virion infectious.

GOALS OF ART

1. Suppression of HIV replication to as low as possible and for as long as possible
2. The preservation or enhancement of immune function (CD4 restoration) thereby delaying clinical progression of HIV disease
3. Improvement of quality of life
4. Reduction in HIV related mortality and morbidity
5. In children, promotion of growth and neurological development

DEFINITION

HAART – Highly active antiretroviral therapy. This is a therapy which is potent enough to suppress HIV to undetectable level ie <50 copies /ML as measured by the most sensitive assay available

HEART includes 3 or more drugs from two or more classes of anti-HIV drugs

PRINCIPLES OF ART

1. You do not want to start ART too soon (when CD4 is still normal i.e >350) or too late when immune system is irreversibly damaged
2. Efficacy(drug response) of the chosen drug regimen should be high
3. Freedom of patient from serious adverse effects
4. Ease of administration including no food restrictions
5. Affordability and availability of drugs and drug combinations
6. Ongoing support of the patient to maintain adherence

CLASSES OF ART

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1. Nucleoside reverse transcriptase inhibitors (NRTI); these inhibit enzyme reverse transcriptase. Examples are:

- Abacavir(ABC)
- Didanosine(ddi)
- Zidovudine(ZDV/AZT)
- Lamivudine(3TC)
- Stavudine(d4T)
- Zalcitabine
- Emtricitabine

2. Non Nucleoside reverse transcriptase inhibitors (NNRTIs); Examples are:

- Nevirapine(NVP)
- Efavirez(EFZ)
- Delavidine

3. Nucleotide reverse transcriptase inhibitors

- Tenofovir

4. Protease inhibitors (PIs)

- Lopinavir
- Ritonavir
- Sanquinavir
- Indinavir
- Amprenavir

- Atazanavir
- Fosamprenavir
- Nelfinavir

5. Fusion inhibitors

- Enfuvirtide

ZIDOVUDINE (ZDV/AZT)

Used in

1. HAART REGIMENS for HIV- 1and HIV-2
2. Prophylaxis like PEP ,PMTCT/eMTCT

Toxicities

- Bone marrow suspension; dose 300mg b.d
Anaemia,
Thrombocytopenia
Neutropenia
- Hyper pigmentation of nails
- Headache
- Insomnia
- Agitation
- Gynaecomastia
- Dizziness
- Drowsiness

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- Convulsions

DIDANOSINE (ddI)

Clinically used;

In HIV infection in combination with other antiretroviral drugs

DOSE < 60kg 250mg o.d

>60kg 400mg o.d

Toxicities

- Pancreatitis (worse in alcoholics)
- Peripheral neuropathy
- Diarrhoea,
- Hyperuricaemia,
- Hepatic dysfunction

LAMIVUDINE (3TC)

Has a high oral bioavailability equivalent to 80% absorbed in the gut commonly used in HAART regimens and is one of the first line drugs. Also used in treatment of hepatitis B

DOSE

300mg o.d or 150mg b.d

Toxicity

- Well tolerated
- GIT distress
- Mild Headache

- Insomnia
- Fatigue
- Peripheral neuropathy
- Alopecia

STAVUDINE (d4T)

Also indicated in HIV infection in combination with other antiretroviral drugs

Dose: 30mg b.d

Toxicity

- Peripheral neuropathy
- Tremors
- Alopecia
- Visual disturbances

ABACAVIR (ABC)

Most Potent Drug

Also indicated in HIV infection in combination with other antiretroviral drugs

Dose: 200mg o.d

Toxicity

Hypersensitivity reactions

EMTRICITABINE (FTC)

Indicated in HIV infection in combination with other antiretroviral drugs

Toxicity

- Abnormal dreams
- Pruritus
- Hyperpigmentation
- Hypertriglyceridaemia
- Hyperglycaemia

NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS).

They are direct inhibitors of reverse transcriptase

NEVIRAPINE (NVP)

- Has greater than 90% oral bioavailability
- Commonly used in first line HAART regimens and eMTCT
- It is metabolized in the liver
- It is given to mothers at the onset of labor and neonates within 3/7 after delivery

Toxicity

- Mild severe hypersensitivity reaction e.g skin rash, Steven- Johnson's syndrome
- Hepatitis
- Headache
- Abdominal pain
- fatigue
- vomiting
- Fever

- Myalgia
- Diarrhoea

EFAVIREZ (EFZ)

- Commonly used in first line HAART regimens because it has a very long half life of 40 – 55 hours which allows once dosing
- It is metabolized in the liver
- Bioavailability is increased with high fat meal (avoid fat meal while on drug because of risk of toxicity)

Dose 600mg o.d

Toxicity

1. CNS dysfunction

- confusion
- Dizziness
- Seizures
- Delusions
- Night meres

2. Skin rash

N.B – avoid in pregnancy because of risk of teratogenicity (fetal congenital abnormalities)

DELARVIDINE

- It is the least potent among the non nucleoside reverse transcriptase inhibitors
- It is metabolized in the liver

- It causes 20% Skin rash and it is also teratogenic

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

TENOFOVIR (TDF)

It is nucleotide reverse transcriptase inhibitors

Taken with high fat meal

Elimination is by renal excretion

Dose 300mg o.d

Toxicity

- Headache
- Rarely hepatic steatosis (fatty liver)
- Lactic acidosis

PROTEASE INHIBITORS (PIs)

Examples are:

- Lopinavir(LPV)

Dose 400mg b.d

- Ritonovir

- Sanquinavir

- Indinavir(IDV)

- Amprenavir

- Atazanovir(ATV)

- Dose 300mg o.d

- Fozamprenavir
- Neifinavir(NFV)
- Dose 1250mg b.d

INDINAVIR (IDV)

It is a component of PI based HAART

Dose 800mg b.d

Toxicity

- Nausea
- Vomiting
- Diarrhoea
- Thrombocytopenia
- Hyperbilirubinemia

RITONOVIR(RTV)

Indicated for progressive or advanced HIV infection in combination with the NRIIs

Dose 100mg b.d

Toxicity

- GIT irritation
- Bitter rash

N.B – generally PIs

1. Tend to cause GIT adverse effects
2. Associated with metabolic dysfunction like insulin resistance that may lead to hyperglycemia, lipodystrophy syndrome

3. Mostly used as second line

SANQUINAVIR (SQV)

- Has erratic oral bioavailability
- Combination with ritonavir has improves efficiency
- Undergoes extensive first pass metabolism

SIDE EFFECTS

- Nausea
- Diarrhoea
- Dyspepsia
- Rhinitis

Dose: 100mg b.d

FUSION INHIBITORS

ENFUVIRTIDE

- Administer S/C
- It is an adjunct therapy with other drugs in patients with persistent HIV loads

Toxicity

- Injection site reaction
- Hypersensitivity

CRITERIA FOR GIVING CERTAIN COMBINATIONS

1. 2NRTIs + 1NNRTI (first line)
2. 2NRTIs + 1PI

3. 2NRTIs + 2PI
4. 3NRTIs

Examples:

1. 2NRTIs + 1NNRTI (first line)
 - AZT + 3TC + EFV
 - d4T + 3TC + EFV
 - AZT + 3TC + NVP
 - d4T + 3TC + NVP

RECOMMENDED REGIMENS FOR ADULTS

FIRST LINE

1. ZDV/ 3TC +NVP or EFZ

Alternatives

1. TDF +3TC or FTC + NVP or EFZ
2. d4T/3TC + NVP or EFZ

SECOND LINE

1. ABC/ddi +LPV/R or

TDF + 3TC or FTC + LPV/R

ALTERNATIVES

1. ZDV + ddi + LPV/R or

ABC + dd1 + LPV/R

ZDV + 3TC + LPV/R

2. ABC + dd1 + LPV/R

Or TDF + 3TC or FTC + LPV/R

FIXED DOSE COMBINATIONS AND THEIR NAMES

ABC +3TC (Epzicom)

ABC + AZT + 3TC (Trizivir)

d4T + 3TC (zidolam, stavex,virolis)

TDF + FTC (truvada) 300mg/ 200mg o.d

AZT + 3TC (combivir, duovir) 300mg/150mg o.d

d4T + 3TC + NVP (triamondine, virolens) 30mg/150mg/200mg b.d

AZT + 3TC +NVP (Combidipack, Duovir-N) 300mg/150mg/200mg

TDF + FTC + EFZ (Atripla) 300mg/200mg /600mg o.d

DRUGS ACTING ON URINARY SYSTEM

DIURETICS

These are drugs that are capable of increasing the volume of urine produced and promoting a net loss.

The effectiveness of these diuretics is primarily related to their ability to increase the excretion of sodium which is accomplished in most cases by interfering with the re-absorption of sodium ions in the tubules of the kidney.

CLASSIFICATION

1. Carbonic anhydrase inhibitors

- Acetazolamide

2. Loop diuretics

- Furosemide

- Ethacrynic acid
- 3. Thiazides
 - Its Hydrochlorothiazide
 - Bendroflumethiazide
- 4. Potassium sparing diuretics'
 - Spironolactone
 - Amiloride
 - Eplerenone
- 5. Osmotic diuretics
 - Mannitol

BENDROFLUMETHIAZIDE

BENDROFLUAZIDE (APRINOX)

Legally class B

It is a diuretic with antihypertensive effects

M/A

It increases urinary excretion of sodium ions and water by inhibiting re-absorption of sodium, thereby reducing circulatory volume

ROUTES

Oral

DOSE

5-20mg o.d or b.d in 2 divided doses

INDICATIONS

1. Hypertension
2. Oedema associated with CCF,

Liver cirrhosis, steroid therapy

P/K

It is well absorbed orally

Peak effects occur 4-6 hours

It is highly bound to plasma proteins

It is metabolized in the liver

It is excreted in urine.

SIDE EFFECTS

- I. Anorexia
- II. Nausea
- III. Dehydration
- IV. Hypokalaemia
- V. Hypoglycaemia
- VI. Photosensitivity rash
- VII. Agranulocytosis
- VIII. Hepatitis.

CHLOROTHIAZIDE

This is a diuretic of the thiazide group

It is used in combination with other drugs in the treatment of cardiac disorders

Legally class B

M/A

It increases urinary excretion of sodium and water by inhibiting sodium ion re-absorption along the nephron

ROUTE

- Oral
- IV

Dose

Adult 500mg – 2g daily as a single dose or in two divided doses

Children over 6/12 20mg /kg body weight

INDICATORS

- Hypertension
- Oedema associated with CCF, liver cirrhosis, and steroid therapy

P/K

- It is well absorbed following oral route
- Onset of action or diuresis is 1- 2 hours
- It is metabolized in the liver
- It is highly bound to plasma protein
- It is excreted in urine

SIDE EFFECTS

- I. Anorexia
- II. Nausea
- III. Light headache
- IV. Hypokalaemia
- V. Hypersensitivity reactions
- VI. Dehydration

CONTRA-INDICATORS

- Patients known to have hypersensitivity
- Anorexia
- Renal decompensation

NURSING CONSIDERATIONS

- Monitor patient inputs and outputs
- Weigh the patient
- Watch for signs of Hypokalaemia
- Monitor potassium levels
- Administer drug in the morning to avoid nocturia

FUROSEMIDE (LASIX)

It is a loop diuretic that is legally class B

M/A

It inhibits active re-absorption of Na^+ and Cl^- at the proximal portion of the ascending loop hence resulting in excretion of Na^+ , Cl^- , K^+ , H^+ and large amounts of water

ROUTES

- Oral
- I.V
- I.M

Dose

40- 80mg o.d

INDICATIONNS

- Treatment of severe oedema associated with CCF, liver cirrhosis, renal disease
- Relief of pulmonary oedema
- Used in treatment of hypertension
- Short term treatment in children with congenital heart disease
- Used in treatment of nephrotic syndrome
- Renal failure
- Before blood transfusion in patients with chronic anaemia

P/K

It is well absorbed orally

On set of diuresis of oral dose is 30 – 60minutes

Duration of action is 6 – 8 hours

I.V injection produces a diuretic response with 5 – 10 minutes, which peaks within 15 – 45 minutes and persists for 2 hours.

It is bound to plasma proteins

Metabolized in liver

Excreted in urine

SIDE EFFECTS

- I. Hypokalaemia
- II. Hyponatraemia
- III. Thrombophlebitis
- IV. Constipation
- V. Vomiting
- VI. Diarrhoea
- VII. Nausea
- VIII. Active pancreatitis
- IX. Hypochloraemic alkalosis
- X. Dehydration
- XI. Orthostatic hypotension

CONTRA-INDICATIONS

- I. Hepatic coma
- II. Dehydration
- III. Anuria

NURSING CONSIDERATIONS

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- Administer drug in the morning and early evening to avoid nocturia and interruption of sleep
- Determine baseline weight and Weigh patients regularly
- Administer drugs with food if necessary to avoid GIT upsets
- Give potassium supplements to patients receiving lasix

SPIRONOLACTONE (ALDOCTONE)

It is diuretic legally class B

It is a K^+ sparing diuretic

M/A

It antagonizes aldosterone in the distal tubule, a hormone that is involved in the exchange of sodium and potassium ions.

This antagonism of aldosterone results into excretion of sodium and retention of K^+ resulting in diuresis

ROUTES

Oral

DOSE

Adults 25 – 200mg p.o in divided doses

Children 3.3mg /kg body weight, in divided doses

INDICATIONS

1. Treatment of oedema associated with CCF , cirrhosis of the liver, nephrotic syndrome and primary hyperaldosteronism
2. Treatment of essential hypertension in combination with other antihypertensives

3. Treatment of diuretic induced hypokalaemia
4. Detection of primary hyperaldosteronism

P/K

1. well absorbed following oral administration
2. Peak plasma levels occur in 3 – 4 hours
3. Normal diuretic action is seen in 2 – 3/7 hours
4. Metabolized in liver
5. Excreted in urine

Side effects

- Anorexia
- Nausea
- Vomiting
- Menstrual disturbance
- Impotence
- Gynaecomastia
- Hypokalaemia
- Hyponatraemia
- Dehydration

CONTRA- INDICATIONS

- Hypokalaemia
- Active renal insufficiency
- Anuria

NURSING CONSIDERATIONS

1. Monitor intake and output
2. Monitor BP and body weight
3. Administer with meals to enhance absorption
4. Warn patients to avoid excessive K⁺ rich foods

MANNITOL

It is an osmotic diuretic that is readily filtered by the kidney, but poorly absorbed in the renal tubules

Legally class B

M/A

It increases osmotic pressure of the glomerular filtrate, inhibiting tubular re-absorption of water and electrolytes

It also elevates blood plasma osmolarity resulting into enhanced flow of water into extracellular fluids

ROUTES

I.V as infusion

DOSE

Varies in different conditions i.e in acute renal failure

50 – 100mg I.V of a concentrated 5 – 25% solution

Average adult dose ranges between 50 – 200mg in 24 hours

INDICATIONS

1. Prevention and treatment of oliguric phase of acute renal failure before irreversible renal failure occurs
2. Treatment of cerebral oedema and elevated ICP (intracranial pressure) as in head injury
3. Reduction in elevated intra ocular pressure in acute congestive glaucoma
4. Promote diuresis in drug intoxication

P/K

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1. It is confined to extra cellular space, only slightly metabolized and rapidly excreted by the kidney following I.V injection
2. Diuresis occurs in 1 – 2 hours and elevated cranial and ocular pressures are reduced within 30 minutes

SIDE EFFECTS

- Dry mouth
- Blur vision
- Nausea
- Vomiting
- Hypertension
- Electrolytes imbalance
- Rhinitis

CONTRA – INDICATIONS

- Anuria
- Severe pulmonary
- Severe dehydration

NURSING CONSIDERATIONS

- If solution crystallizes as when exposed to low temperature, warm it with hot water bath
- Monitor urinary output and fluid intake

ANTICANCER AGENTS

Cancer is uncontrolled multiplication and spread of abnormal forms of the body's own cells. It is one of the major causes of death in the developed nations.

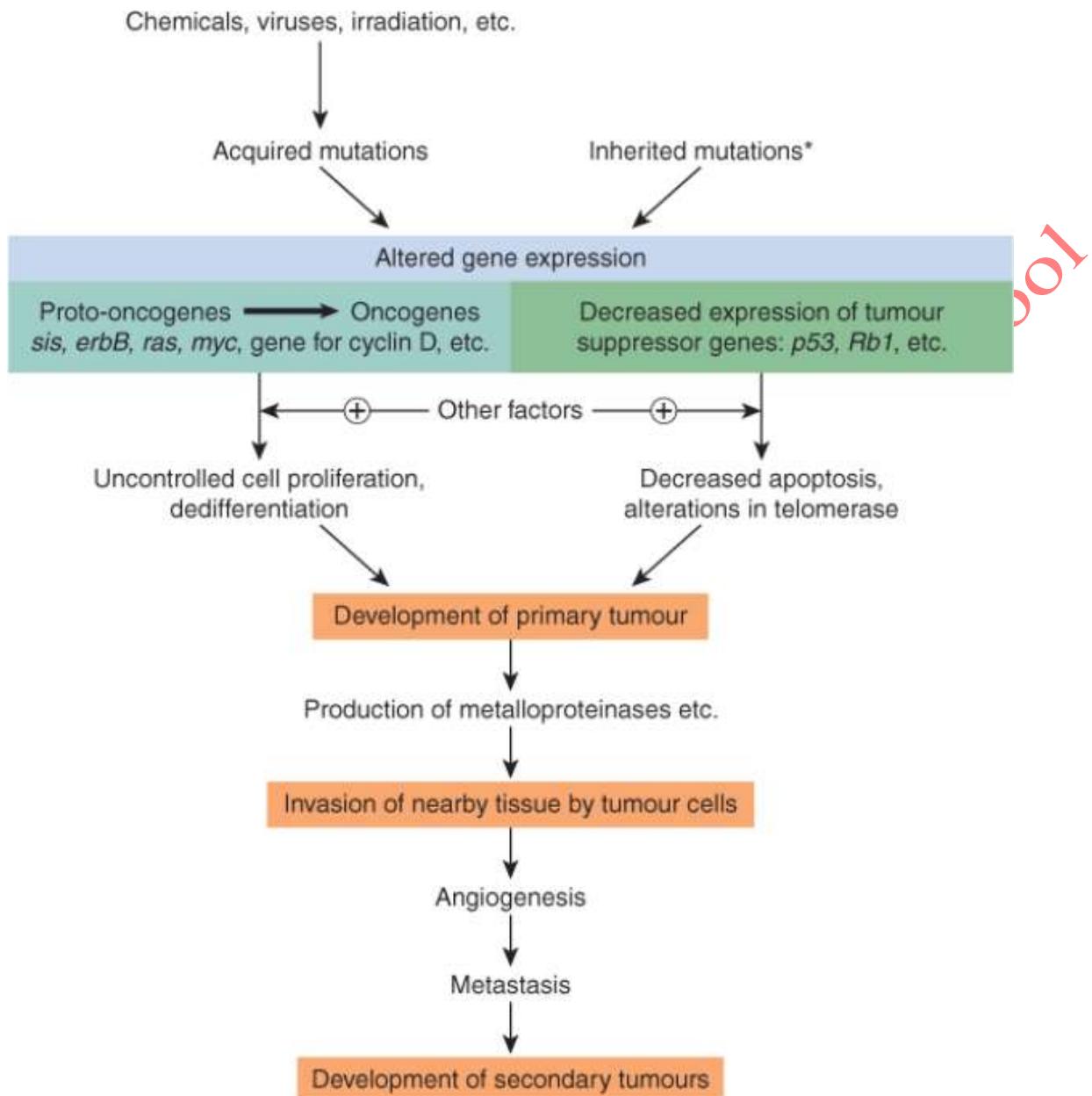
THE PATHOGENESIS OF CANCER

Cancer cells have four characteristics that distinguish them from normal cells.

1. . **Uncontrolled proliferation**
2. **Dedifferentiation and loss of function**
3. **Invasiveness**
4. **Metastasis.**

A normal cell turns into a cancer cell because of one or more mutations in its DNA. A good example is breast cancer; women who inherit a single defective copy of either of the tumour suppressor genes *BRCA1* and *BRCA2* (see below) have a significantly increased risk of developing breast cancer.

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Simplified outline of the genesis of cancer

The genesis of cancer is usually multifactorial, involving more than one genetic change (deregulation). 'Other factors', as specified above, may involve the actions of promoters,

cocarcinogens, hormones, etc. which, while not themselves carcinogenic, increase the likelihood that genetic mutation(s) will result in cancer

Cancer cells become deregulated in many different ways.

One way: Mutations in one or more mitotic checkpoints allow the cell to move from one phase of mitosis to another unchecked.

Another way: Mutations in cellular machinery itself so that mitotic errors are not properly detected/repaired, and the cell is allowed to move through mitosis unchecked.

Stages of Mitosis

Interphase: Technically not part of mitosis, but rather encompasses stages G1, S, and G2 of the cell cycle which prepare the cell for mitosis.

Prophase: Chromatin in nucleus condense; nucleolus disappears. Centrioles begin moving to opposite ends of the cell and fibers extend from the centromeres.

Metaphase: Spindle fibers align the chromosomes along the middle of the cell nucleus. This line is referred to as the ‘metaphase plate.’

Anaphase: The paired chromosomes separate at the kinetochores and move to opposite sides of the cell. Motion results from the physical interaction of polar microtubules.

Telophase: Chromatids arrive at opposite poles of cell, and new membranes form around the daughter nuclei. The chromosomes disperse.

Cytokinesis: Results when a fiber ring composed of a protein called actin around the center of the cell contracts, pinching the cell into two daughter cells, each with one nucleus.

Mitosis

Summary

Mitosis is the process by which a cell duplicates the chromosomes in its cell nucleus in order to generate two, identical, daughter nuclei.

It is followed immediately by cytokinesis, which divides the nuclei, cytoplasm, organelles and cell membrane into two daughter cells containing roughly equal shares of these cellular components.

Mitosis and cytokinesis together define the mitotic (M) phase of the cell cycle.

Mitosis is a normal cellular process necessary to sustain life, but its deregulation in one form or another is found in all cancer cells.

Mitosis can often become abnormal by the change in, or absence of, the normal mitotic checkpoints.

Mitotic Checkpoints

Mitotic checkpoints are points in the cell cycle which act to ensure correct transmission of genetic information during cell division. These checkpoints look for abnormalities within the cycle, specifically chromosomal aberrancy.

Checkpoints take place towards the end of each phase of mitosis and must be passed before the cell can get clearance to enter into the next stage of mitosis.

If errors are found during checkpoints, the cell acts quickly to correct them, arresting cell growth and not proceeding with mitosis until the error has been fixed.

If these errors cannot be fixed, the cell normally undergoes apoptosis, or programmed cell death.

How ‘Cancer’ Arises

The cell is allowed to move through the cell cycle and grow unchecked, and more mutations are accumulated over time that extend past the cell cycle to the cellular machinery itself.

These mutations, in combination with the genetic mutations accrued through abnormal mitotic progression, eventually cause the cell to be completely deregulated in its growth and proliferation.

It becomes unstoppable and even immortal.

Treatment of cancer

There are three main approaches to treating established cancer:

- **Surgery**
- **Radiation therapy**
- **Chemotherapy**

Chemotherapy of cancer, as compared with that of bacterial disease, presents a difficult problem. In biochemical terms, cancer cells and normal cells are so similar in most respects that it is more difficult to find general, exploitable, biochemical differences between them.

General principles of action of cytotoxic anticancer drugs

In experiments with rapidly growing transplantable leukemia in mice, it has been found that a given therapeutic dose of a cytotoxic drug¹ destroys a constant fraction of the malignant cells. Thus a dose that kills 99.99% of cells, if used to treat a tumour with 10^{11} cells, will still leave 10 million (10^7) viable malignant cells.

As the same principle holds for fast-growing tumours in humans, schedules for chemotherapy are aimed at producing as near a total cell kill as possible

History of cancer chemotherapy

Sulfur mustard: During World I and II, sulfur mustard was used as a toxic gas. Later it was found that sulfur mustard was active against animal tumors, but was too toxic to be used for humans. Following this discovery, many nitrogen mustard compounds were synthesized and tested.

The beginnings of the modern era of cancer chemotherapy can be traced directly to the discovery of nitrogen mustard.

During world war II, two pharmacologists, **Louis S. Goodman and Alfred Gilman at Yale School of Medicine** were recruited by the United States Department of Defense to investigate potential therapeutic applications of chemical warfare agents. They found that nitrogen mustard produced abnormally low levels of white blood cells in those exposed to it.

In 1942, in collaboration with a thoracic surgeon, Gustaf Lindskog, they injected mustine into a patient with non-Hodgkin's lymphoma and observed a dramatic reduction in the patient's tumour masses. Although this effect lasted only a few weeks, this was the first step to the realization that cancer could be treated by pharmacological agents (Goodman *et al* 1946).

Types of cancer chemotherapy drugs

Cytotoxic drugs, which include:

Aalkylating agents and related compounds, acting by forming covalent bonds with DNA and thus impeding replication;

1. Antimetabolites, blocking or subvert one or more of the metabolic pathways involved in DNA synthesis
2. Cytotoxic antibiotics, i.e. substances of microbial origin that prevent mammalian cell division
3. Plant derivatives (vinca alkaloids, taxanes, camptothecins) -most of these specifically affect microtubule function and hence the formation of the mitotic spindle.
4. Hormones, of which the most important are steroids, namely glucocorticoids, oestrogens and androgens, as well as drugs that suppress hormone secretion or antagonise hormone action.
5. Miscellaneous agents that do not fit into the above categories. This group includes a number of recently developed drugs designed to affect specific tumour-related targets.

Alkylating agents

Nitrogen mustards: (Chlorambucil, Chlormethine, Cyclophosphamide, Ifosfamide, Melphalan).

Nitrosoureas:(Carmustine, Fotemustine, Lomustine, Streptozocin). *Platinum:* (Carboplatin, Cisplatin, Oxaliplatin, BBR3464). Busulfan, Dacarbazine, Mechlorethamine, Procarbazine, Temozolomide, ThioTEPA, Uramustine

Antimetabolites

Folic acid: (Aminopterin, Methotrexate, Pemetrexed, Raltitrexed). *Purine:*(Cladribine, Clofarabine, Fludarabine, Mercaptopurine, Pentostatin, Thioguanine). *Pyrimidine:*(Capecitabine, Cytarabine, Fluorouracil, Floxuridine, Gemcitabine)

Spindle Poison plants

Taxane (Docetaxel, Paclitaxel. *Vinca:* (Vinblastine, Vincristine, Vindesine, Vinorelbine).

Anticancer Antibiotics

Anthracycline family: (Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone, Valrubicin). Bleomycin, Hydroxyurea, Mitomycin, Actinomycin

Topoisomerase inhibitors

Camptotheca: (Camptothecin, Topotecan, Irinotecan), *Podophyllum*: (Etoposide, Teniposide).

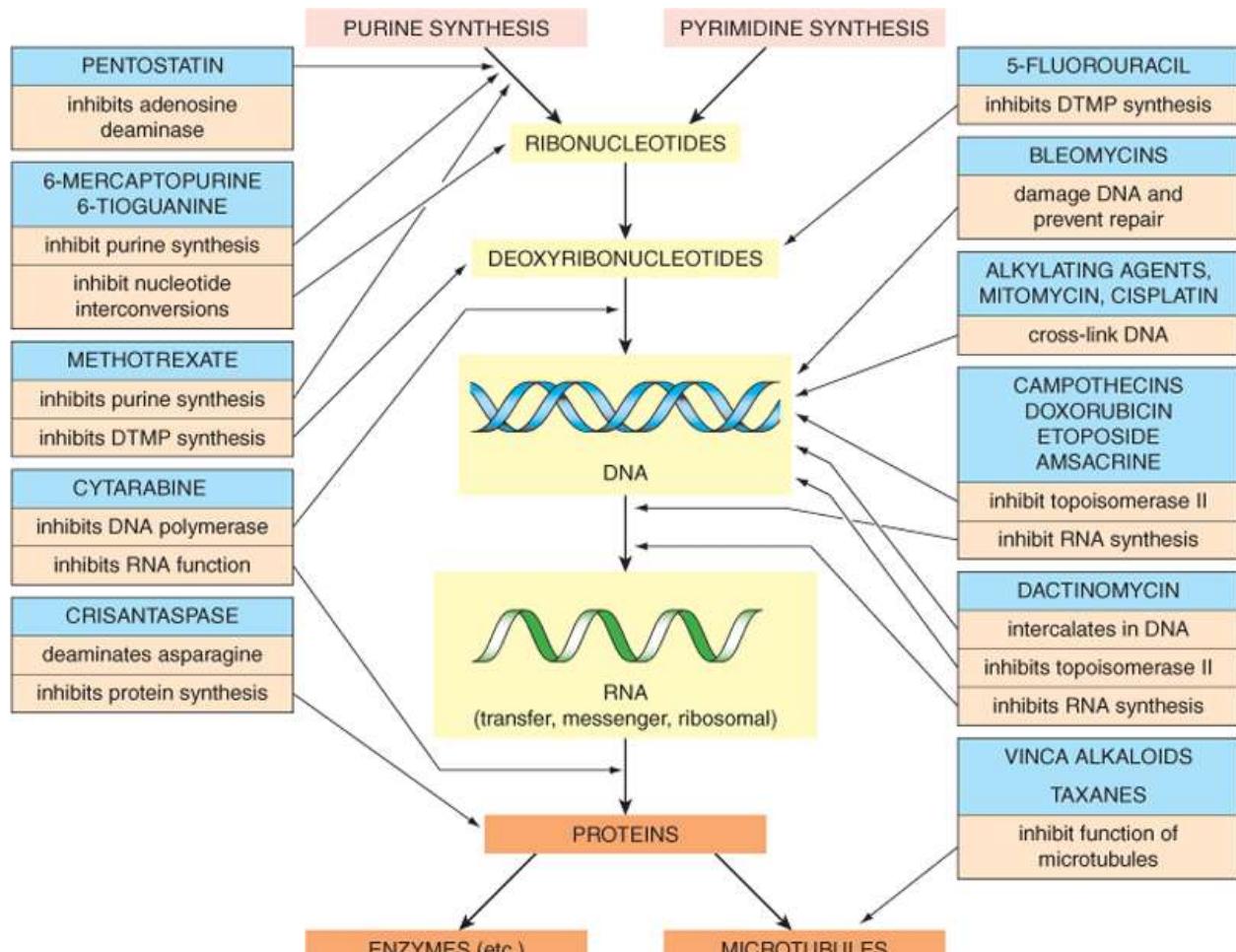
Monoclonal antibodies

Alemtuzumab, Bevacizumab, Cetuximab, Gemtuzumab, Panitumumab, Rituximab, Tositumomab, Trastuzumab

Kinase inhibitors

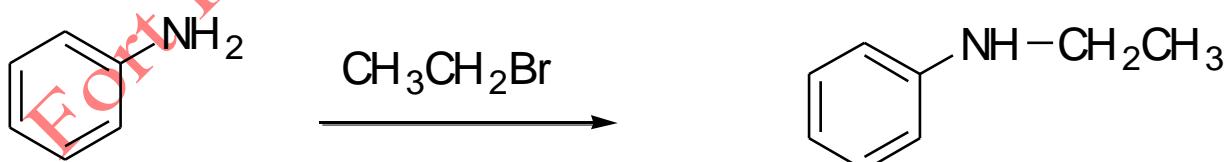
Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Nilotinib, Sorafenib, Sunitinib, Vandetanib (ZD6474)

Summary of the main sites of action of cytotoxic agents. For some groups of drugs, only one or two examples are given.



ALKYLATING AGENTS

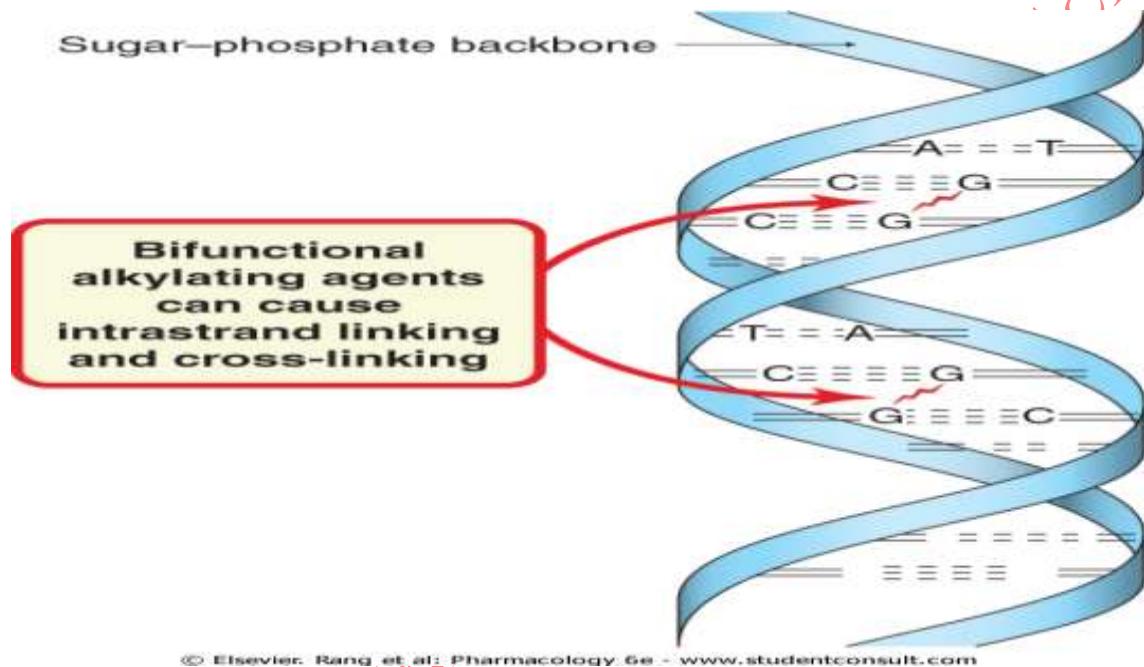
Alkylation is defined as the replacement of hydrogen on an atom by an alkyl group



Alkylation

The effects of bifunctional alkylating agents on DNA

Note the cross-linking of two guanines. A, adenine; C, cytosine; G, guanine; T, thymine



METHCHLORETHAMINE

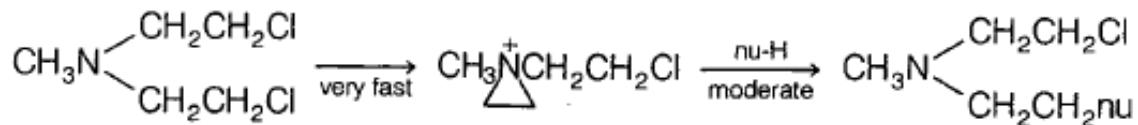
(N-Methyl-N-(2-chloroethyl) 2-chloroethylaminehydrochloride)

Water solution is not stable, especially when pH > 7.

Drug solution is kept at pH 3.0~5.0

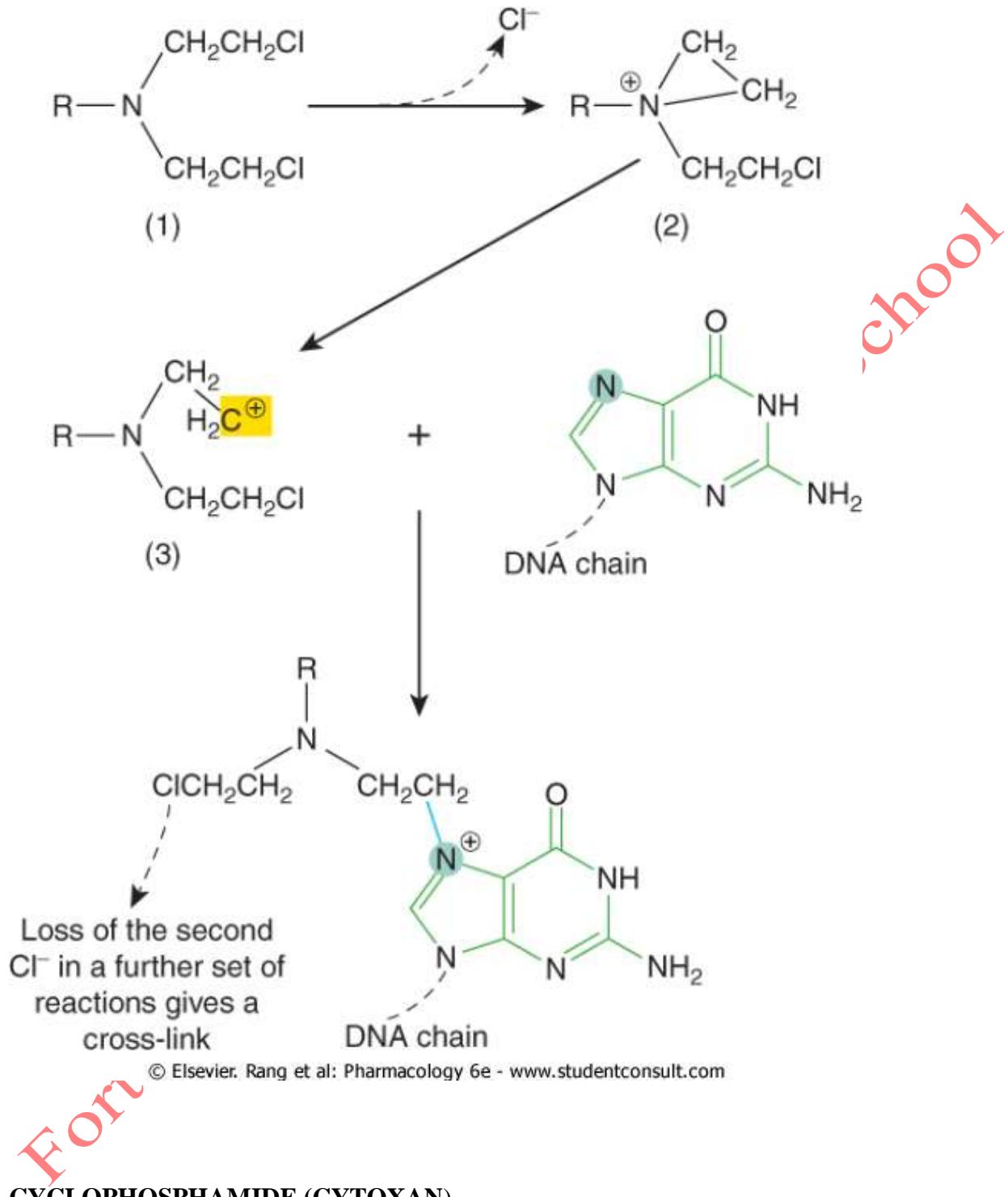
Methchlorethamine is used to treat lymphoma. It is ineffective against other tumors such as lung, liver or stomach cancers. Severe toxic effects.

Mechanism of action: alkylation of DNA



An example of alkylation and cross-linking of DNA by a nitrogen mustard.

A bis(chloroethyl)amine (1) undergoes intramolecular cyclisation, forming an unstable ethylene immonium cation (2) and releasing Cl^- , the tertiary amine being transformed to a quaternary ammonium compound. The strained ring of the ethylene immonium intermediate opens to form a reactive carbonium ion (in yellow box) (3), which reacts immediately with N7 of guanine (in green circle) to give 7-alkylguanine (bond shown in blue), the N7 being converted to a quaternary ammonium nitrogen. These reactions can then be repeated with the other $-\text{CH}_2\text{CH}_2\text{Cl}$ to give a cross-link.

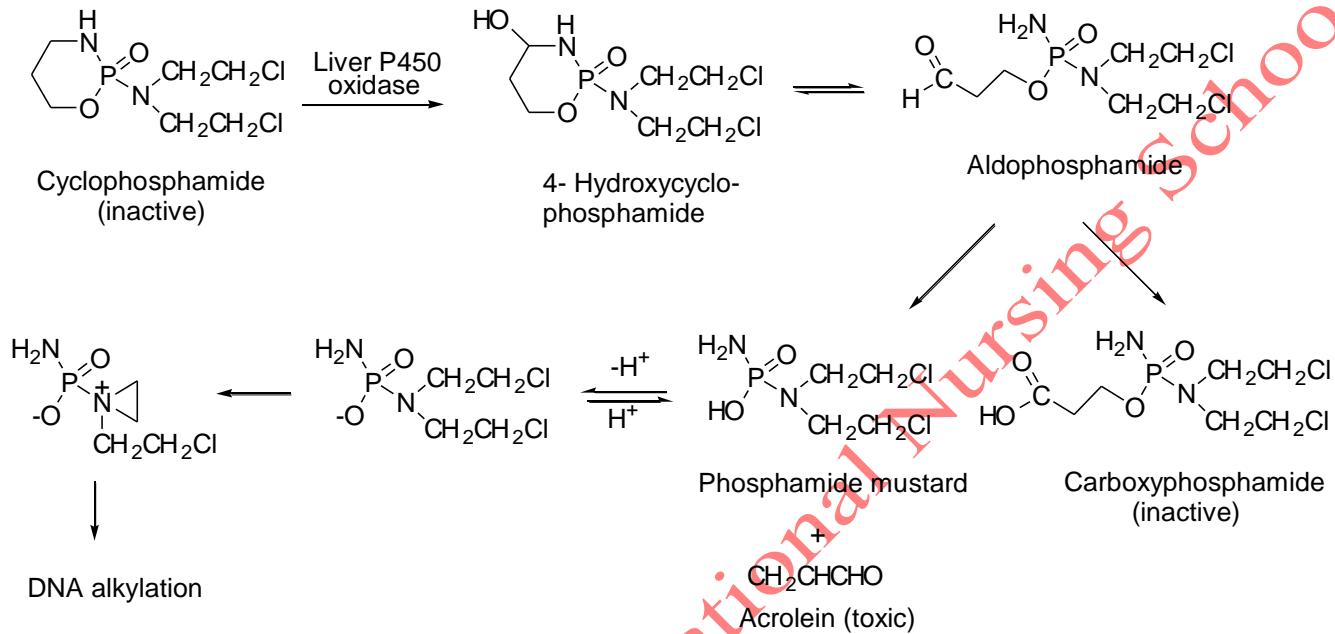


CYCLOPHOSPHAMIDE (CYTOXAN)

N, N-bis(β -chloroethyl)-N', O-propylenephosphoric acid ester diamide hydrate)

Cytoxan itself is not active. It is converted to its active form in the liver

Activation of Cyclophosphamide



Cyclophosphamide is inactive until metabolised in the liver by P450 mixed function oxidases to 4-hydroxycyclophosphamide. Aldophosphamide is conveyed to other tissues, where it is converted to phosphoramide mustard, the actual cytotoxic molecule, and acrolein, which is responsible for unwanted effects.

Cyclophosphamide is used to treat: Lymphoma, leukemia, bone cancer, lung cancer, breast cancer, ovarian cancer etc.

CISPLATIN

cis-Dichlorodiamineplatinum (II), (Z)-

Discovery of *cis*-platinum

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It all started by accident over 40 years ago in the laboratory of physicist-turned-biophysicist Barnett Rosenberg at Michigan State University, East Lansing, United States. Rosenberg was interested in applying electromagnetic radiation to bacterial and mammalian cells to investigate whether electric or magnetic dipole fields might be involved in cell division.

Inadvertently, in the early experiments using *Escherichia coli*, a set of platinum electrodes (considered to be inert) was included in the growth chamber. When the field was turned on, the bacteria appeared as very long filaments (300 times the usual length) rather than as the normal short rods. This effect was shown not to be due to the electric field but, rather, to electrolysis products arising from the platinum electrodes (TIMELINE). Detailed chemical analysis identified two active complexes — the neutral *cis*-isomer [PtII (NH₃)₂Cl₂], which went on to be cisplatin, and a platinum(IV) analogue, *cis*-diamminetetrachloroplatinum(IV).

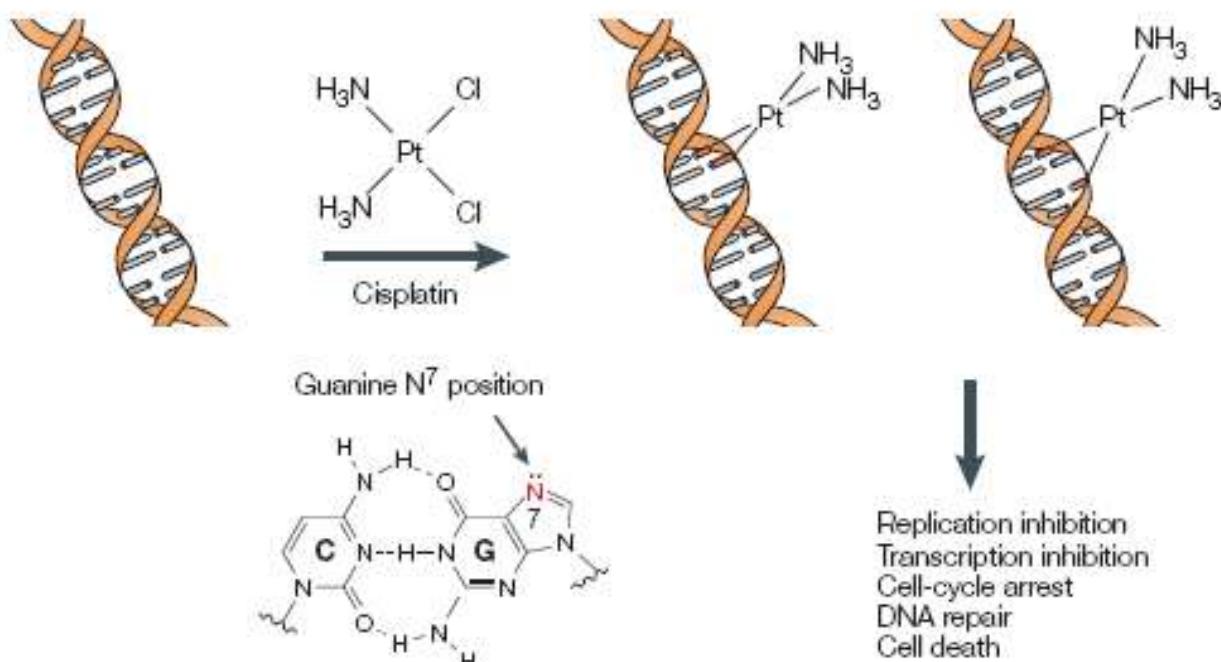
As it turned out, the group had rediscovered a known platinum coordination complex that was originally synthesized and described in 1845, known as Peyrone's chloride.

In 1968, they administered the drug to mice with cancer. In 1971, cisplatin was given to the first cancer patient in the US, and was approved by the US FDA as a cancer drug in 1978.

Cis-platinum is stable at room temperature; It slowly discomposes in water solution.

Use: it is used for the treatment of bladder and ovarian cancers and others.

Mechanism of action: Alkylation of DNA



Formation and effects of cisplatin adducts. The platinum atom of cisplatin binds covalently to the N7 position of purines to form 1,2- or 1,3-intrastrand crosslinks, and interstrand crosslinks. Cisplatin–DNA adducts cause various cellular responses, such as replication arrest, transcription inhibition, cell-cycle arrest, DNA repair and apoptosis.

FDA-approved platinum drugs and the main platinum drugs in development

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Indication	Approval year or approval/ development status	Dose-limiting toxicities
Cisplatin (IV injection)		
Metastatic testicular cancer	1978	Nephrotoxicity
Metastatic ovarian cancer	1978	Neurotoxicity, ototoxicity
Transitional bladder cancer	1993	Nausea and vomiting
Carboplatin (IV injection)		
Ovarian cancer (palliative after previous chemotherapy)	1989	Myelosuppression (thrombocytopenia and neutropenia)
Ovarian cancer, first line	1991	Nausea and vomiting (but less than with cisplatin)
Oxaliplatin (IV injection)		
Accelerated approval, metastatic colorectal cancer (second line with 5FU with LV)	2002	Neurotoxicity (sensory peripheral neuropathy)
Colorectal cancer (previously untreated or adjuvant treatment with 5FU with LV)	2004	Nausea and vomiting
Satraplatin		
Hormone-refractory prostate cancer	Under consideration for approval by the FDA	Myelosuppression (thrombocytopenia and neutropenia)
Picoplatin		
Small-cell lung cancer	Phase III trial about to begin	Myelosuppression (thrombocytopenia and neutropenia)

ANTI-CANCER THERAPY: ANTIMITOTIC AGENTS

Antimitotic Agents: One Possible Treatment

Antimitotic agents: Anti-tumor agents that inhibit the function of **microtubules** through the binding of their subunits or through direct cessation of their growth.

What are microtubules (MTs)?

Protein polymers formed by α-Tubulin and β-Tubulin heterodimers that play an important role in critical cell functions such as movement, phagocytosis and axonal transport. They also play a key role in the formation of the mitotic spindle apparatus and cytokinesis at the end of mitosis.

In normal cells, microtubules are formed when a cell starts dividing during mitosis. Once the cell stops dividing, microtubules are broken down or destroyed.

The crucial involvement of MTs in mitosis makes them a prime target for anti-cancer agents.

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Antimitotic Agents

Three distinct classes of antimitotic agents have been identified thus far.

- 1.) **Taxanes**; include: paclitaxel and docetaxel.
- 2.) **Vinca alkaloids**; include: vincristine, vinblastine, vindesine, and vinorelbine.
- 3.) **Colchicine**.

All must be administrated via intravenous infusion.

Taxanes (First Antimitotic Group)

Prevent the growth of cancer cells by affecting microtubules.

Overall, they encourage microtubule formation, then they stop the microtubules from being broken down so that the cells become so clogged with microtubules that they cannot continue to grow and divide. This results in the cell's arrest in mitosis. Eventually, cell DEATH by apoptosis.

Taxanes: History

Isolated from the bark of the Western yew tree in 1971, this compound became useful in the treatment of cancer when it was discovered that it possessed the unique ability to promote the formation of microtubules by binding to their B-tubulin subunit and antagonizing their disassembly.

However, the amount of paclitaxel in yew bark was small, and extracting it was a complicated and expensive process. In addition, bark collection was restricted because the Western yew is a limited resource located in forests that are home to the endangered spotted owl.

As demand for paclitaxel grew, government agencies and the pharmaceutical company Bristol-Myers Squibb, worked to increase availability and find other sources of paclitaxel besides the bark of the Western yew tree.

This work led to the production of a semi-synthetic form of paclitaxel (docetaxel) derived from the needles and twigs of the Himalayan yew tree *Taxus bacatta*, which is a renewable resource. The FDA approved docetaxel in the spring of 1995.

Taxanes: Paclitaxel

Paclitaxel [Taxol] was the first compound of the series to be discovered and used in cancer treatment.

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Used in the treatment of: ovarian cancer, breast cancer, AIDS-related Kaposi's sarcoma and lung cancer.

Side effects include: bone marrow loss, hypersensitivity, muscle aches, peripheral neuropathy, bradycardia and tachycardia.

Taxanes: Docetaxel

Docetaxel [Taxotere] is partially-synthetic derivative of Taxol and results from the modification of paclitaxel's side chain.

While it is paclitaxel's structural analog, it is much more potent in terms of potential patient toxicity.

It acts to kill cancer cells in the same way as paclitaxel.

Useful in the treatment of: mainly prostate cancer, but also breast, ovarian and lung cancer.

Must be co-administered with dexamethasone to prevent progressive, often disabling, fluid retention in the peripheries, lungs and abdomen.

Side effects are more severe but more short-lived than Taxol and include: leukopenia, peripheral edema, neutropenia.

Taxanes: Complicating Factors

Resistance to taxanes is a complicating factor to successful treatment and is often associated with increased expression of the *mdr-1* gene and its product, the P-glycoprotein.

Other resistant cells have B-tubulin mutations which inhibit the binding of taxanes to the correct place on the microtubules; this renders the drug ineffective. In addition, some resistant cells also display increased aurora kinase, an enzyme that promotes completion of mitosis. Some cells display a heightened amount of survivin, an anti-apoptotic factor.

Side effects can be debilitating.

These drugs are very expensive and must be administered in large amounts at once due to the fact that much of the drug is excreted in the urine or allocated to the plasma. This large administration volume cannot be tolerated in many patients.

Vinca	Alkaloids	(Second	Antimitotic	Group)
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The Vincas work through their ability to bind to the B-tubulin subunit of microtubules, blocking their ability to polymerize with the a-tubulin subunit to form complete microtubules. This causes the cell cycle to arrest in metaphase because, in absence of an intact mitotic spindle, duplicated

chromosomes cannot align along the division plate. The ultimate fate of such cells is to undergo apoptosis.

The Vinca alkaloids are all derived from the Madagascan periwinkle plant, *Vinca rosea*. The plant was reputed to be useful in the treatment of diabetes. Attempts to verify the antidiabetic properties of the plant's extracts in the 1950's led instead to the discovery and isolation of vinblastine.

Scientists first observed its anticancer properties in a lab in 1962 with the observation of regression of lymphocytic leukemia in rats.

Several years later, the successful purification of the plant's alkaloids yielded three other active dimers: vincristine, vinorelbine, vinrosidine.

Vinca Alkaloids: Vinblastine

Vinblastine [Velban] was the first of the Vincas to be used in the treatment of cancer.

Useful in the treatment of: bladder and testicular cancers, Kaposi's sarcoma, neuroblastoma and Hodgkin's disease.

Side effects include: leukopenia, GI disturbances, cellulitis, phlebitis.

Vinca Alkaloids: Vincristine

Vincristine [Oncovin]

Useful in the treatment of: pediatric leukemias and lymphomas, non-Hodgkin's lymphoma, neuroblastoma and rhabdomyosarcoma.

Better tolerated by children than adults.

Side effects: myelosuppression, hyponatremia, numbness/tingling of extremities, loss of deep tendon reflexes, and loss of motor function.

Intrathecal administration results in **fatal** central neurotoxicity.

Vinca Alkaloids: Vinorelbine

Vinorelbine [Navelbine]

Used in the treatment of: lung carcinoma, breast cancer.

Side effects include: granulocytopenia, thrombocytopenia, myelosuppression, and **less** neurotoxicity than all of the other Vincas.

Vinca Alkaloids: Vindesine

Vindesine [Eldisine]

Useful in the treatment of: breast and lung cancer, leukemia.

Side effects: immunodeficiency, anemia, myalgia, fatigue, mouth ulcers, GI upset.

Vinca Alkaloids: Complicating Factors

Resistance to the Vinca alkaloids comes in the form of cross-resistance due to the structural similarity of the four compounds, and their antitumor effects are blocked by multidrug resistance in which tumor cells become cross-resistant to a wide variety of agents after exposure to a single drug. Resistant cells can also display chromosomal abnormalities consistent with gene amplification, and these cells contain increased levels of the P-glycoprotein. Other forms of resistance stem from mutations in B-tubulin that prevent the binding of the inhibitors to their target.

Also, because of the heavy concentration of microtubules in the brain and the drug's disruption of this, patients treated with Vinca alkaloids can experience severe neurotoxicity.

Colchicine (Third Antimitotic Group)

Colchicine was originally extracted from plants of the genus *Colchicum* and used to treat rheumatic complaints, specifically gout.

The colchicine alkaloid was initially isolated in 1820 and was found to bind tubulin, the protein subunit of MTs.

It is a relatively small molecule and inhibits its target in a mechanism similar to the taxanes: by binding to the colchicine binding site of microtubules and promoting their polymerization, thus causing cell clogging and eventually apoptosis.

While it has been shown to kill cancer cells, the drug's usefulness in the treatment of cancer is hindered by its cytotoxicity; in addition, it is a known emetic and teratogen.

Colchicine has proven to have a fairly narrow range of effectiveness as a chemotherapy agent, so it is only FDA-approved to treat gout.

Currently, investigation of colchicine as an antimitotic agent is underway.

Drug Resistance is a **REAL Problem for Cancer Patients**

Multidrug resistance is a major drawback of cancer chemotherapy and can result in patients becoming immune to the effects of many different drugs at once.

A major mechanism of multidrug resistance occurs via an over-expression of ATP transmembrane efflux pumps which pump the drug outside of the cell after its entrance.

Resistance can often result in patient death as a result of lack of effective treatment available.

This remains a problem with all anti-cancer therapies.

More Problems With Antimitotic Agents

Side effects with antimitotic agents, as with many chemotherapies, can be debilitating and even fatal. Chemotherapy targets rapidly-dividing cells, which includes cancer cells but also hair and gut cells. This results in hair loss and nausea in patients. Much research remains to be done in this area of cancer treatment to minimize toxicity.

There are many drug interactions with antimitotic agents, so patients can often only take these drugs alone.

New taxanes and Vinca alkaloids with oral bioavailability are currently undergoing clinical testing.

Inhibitors of mitotic kinesin motors, such as KSP-1A and monastrol, are currently being tested and could soon become the newest members of the antimitotic drug family.

A less toxic form of colchicine is currently being investigated.

Drugs specifically targeting the Aurora kinase are in various stages of clinical development. One is MK-0457 in Phase II clinical trials at Merck.

Drugs formulated specifically to target CNEP-E, a mitotic kinase that is responsible for the segregation of chromosomes during mitosis, are currently in the making; one is GSK-923296 at GlaxoSmithKline.

ANAESTHESIA

Stages of Anesthesia general anaesthesia

Stage I: Analgesia

Stage II: Disinhibition

Stage III: Surgical anesthesia

Stage IV: Medullary depression

General anaesthesia is characterized by;

Sleep induction

Loss of pain responses

Amnesia

Skeletal muscle relaxation

Loss of reflexes

Phases of General Anesthesia

Stage I: Disorientation, altered consciousness

Stage II: Excitatory stage, delirium, uncontrolled movement, irregular breathing. Goal is to move through this stage as rapidly as possible.

Stage III: Surgical anesthesia; return of regular respiration.

Plane 1: “light” anesthesia, reflexes, swallowing reflexes.

Plane 2: Loss of blink reflex, regular respiration (diaphragmatic and chest). Surgical procedures can be performed at this stage.

Plane 3: Deep anesthesia. Shallow breathing, assisted ventilation needed. Level of anesthesia for painful surgeries (e.g.; abdominal exploratory procedures).

Plane 4: Diaphragmatic respiration only, assisted ventilation is required. Cardiovascular impairment.

Stage IV: Too deep; essentially an overdose and represents anesthetic crisis. This is the stage between respiratory arrest and death due to circulatory collapse.

Types of anesthetics

I. Inhalation anesthetics

II. Intravenous anesthetics

III. Local anesthetics

INHALATION ANESTHETICS

Are given in airoform

Mechanisms of Action

Activate K^+ channels

Block Na^+ channels

In general, all general anesthetics increase the cellular threshold for firing, thus decreasing neuronal activity.

Examples

- **Ether** – Slow onset, recovery, explosive
- **Chloroform** – Slow onset, very toxic
- **Cyclopropane** – Fast onset, but very explosive

- **Halothane (Fluothane)** – first halogenated ether (non-flammable)
- 50% metabolism by P450, induction of hepatic microsomal enzymes; TFA, chloride, bromide released
- Myocardial depressant (SA node), sensitization of myocardium to catecholamines
- Hepatotoxic
- **Methoxyflurane (Penthrane)** -
- 50 to 70% metabolized
- Diffuses into fatty tissue
- Releases fluoride, oxalic acid
- Renotoxic
- **Enflurane (Ethrane)**
- Rapid, smooth induction and maintenance
- 2-10% metabolized in liver
- Introduced as replacement for halothane, “canabilized” to make way for isoflurane
- **Isoflurane (Forane)** smooth and rapid induction and emergence
- Very little metabolism (0.2%)
- Control of Cerebral blood flow and Intracranial pressure
- Potentiates muscle relaxants, Uterine relaxation
- CO maintained, arrhythmias uncommon, epinephrine can be used with isoflurane; Preferential vasodilation of small coronary vessels can lead to “coronary steal”
- No reports of hepatotoxicity or renotoxicity
- Most widely employed
- **Desflurane (Suprane)** – Very fast onset and offset (minute-to minute control) because of its low solubility in blood
- Differs from isoflurane by replacing one Cl with F
- Minimal metabolism
- Very pungent - breath holding, coughing, and laryngeal spasm; not used for induction
- No change in cardiac output; tachycardia with rapid increase in concentration, No coronary steal
- Degrades to form CO in dessicated soda-lime (Ba_2OH / NaOH /KOH; not Ca_2OH)

- Fast recovery – responsive within 5-10 minutes
- **Sevoflurane (Ultane)** – Low solubility and low pungency = excellent induction agent
- Significant metabolism (5%; 10x > isoflurane); forms inorganic fluoride and hexafluoroisopropranolol
- No tachycardia, Prolong Q-T interval, reduce CO, little tachycardia
- Soda-lime (not Ca₂OH) degrades sevoflurane into “Compound A”
 - Nephrotoxic in rats
 - Occurs with dessicated CO₂ absorbant
 - Increased at higher temp, high conc, time
 - No evidence of clinical toxicity
- Metallic/environmental impurities can form HF
- Nitrous Oxide is still widely used
- Potent analgesic (NMDA antagonist)
- MAC ~ 120%
- Used ad adjunct to supplement other inhalationals
- Xenon
- Also a potent analgesia (NMDA antagonist)
- MAC is around 80%
- Just an atom – what about mechanism of action?

Ether (diethyl ether)

- Spontaneously explosive
- Irritant to respiratory tract
- High incidence of nausea and vomiting during induction and post-surgical emergence

Nitrous Oxide

- Rapid onset
- Good analgesia
- Used for short procedures and in combination with other anesthetics

- Supplied in blue cylinders

Halothane (Fluothane)

- Volatile liquid
- Narrow margin of safety
- Less analgesia and muscle relaxation
- Hepatotoxic
- Reduced cardiac output leads to decrease in mean arterial pressure
- Increased sensitization of myocardium to catecholamines

Enflurane (Ethrane)

- Similar to Halothane
- Less toxicities

Isoflurane (Forane)

- Volatile liquid
- Decrease mean arterial pressure resulting from a decrease in systemic vascular resistance

Inhalation anesthetics: Pharmacokinetics

- The concentration of a gas in a mixture of gases is proportional to the partial pressure
- Inverse relationship between blood:gas solubility and rate of induction
- Increase in inspired anesthetic concentration will increase rate of induction
- Direct relationship between ventilation rate and induction rate
- Inverse relationship between blood flow to lungs and rate of onset
- MAC=minimum concentration in alveoli needed to eliminate pain response in 50% of patients

Inhalation anesthetics: Elimination

- Redistribution from brain to blood to air
- Anesthetics that are relatively insoluble in blood and brain are eliminated faster

Inhalation anesthetics: Side Effects

- Reduce metabolic rate of the brain
- Decrease cerebral vascular resistance thus increasing cerebral blood flow = increase in intracranial pressure
- Malignant Hyperthermia

Rare, genetically susceptible

Tachycardia, hypertension, hyperkalemia, muscle rigidity, and hyperthermia

Due to massive release of Ca^{++}

With dantrolene (Dantrium), lower elevated temperature, and restore electrolyte imbalance

INTRAVENOUS ANAESTHETICS

- Most decrease cerebral metabolism and intracranial pressure. Often used in the treatment of patients at risk for cerebral ischemia or intracranial hypertension.
- Most cause respiratory depression
- May cause apnea after induction of anesthesia
- Barbiturates, benzodiazepines and propofol cause cardiovascular depression.
- Those drugs which do not typically depress the cardiovascular system can do so in a patient who is compromised but compensating using increased sympathetic nervous system activity.
- Ideal: Rapid Onset, short-acting
- Thiopental (pentothal)- previously almost universally used
- For over 60 years was the standard against which other injectable induction agents/anesthetics were compared
- Others: Surital (thiamylal); Brevital (methohexitol)
- Act at GABA receptors (inhibitory), potentiate endogenous GABA activity at the receptor, direct effect on Cl channel at higher concentrations.
- Effect terminated not by metabolism but by redistribution
- repeated administration or prolonged infusion approached equilibrium at redistribution sites. Redistribution not effective in terminating action, led to many deaths.

- Build-up in adipose tissue = very long emergence from
- anesthesia (e.g.; one case took 4 days to emerge)

Ketamine (Ketaject, Ketalar)

Blocks glutamate receptors

It is a dissociative anesthesia

Causes Catatonia, analgesia, and amnesia without loss of consciousness

Causes disorientation, sensory and perceptual illusions, vivid dreams

Etomidate (Amidate)

Is a Non-barbiturate

Has Rapid onset

Produces Minimal cardiovascular and respiratory toxicities

Has High incidence of nausea and vomiting

- **Most commonly used for induction of anesthesia in patients with cardiovascular compromise; or where cardiovascular stability is most important**
- **Metabolized to carboxylic acid, 85% excreted in urine, 15% in bile**

Propofol (Diprivan)

Has Mechanism similar to ethanol

Produces Rapid onset and recovery

Produces Mild hypotension

Has Antiemetic activity

Short-acting barbiturates

Thiopental (Pentothal)

Benzodiazepines

Midazolam (Versed)

Benzodiazepines

- Diazepam (Valium, requires non-aqueous vehicle, pain on injection); Replaced by Midazolam (Versed) which is water-soluble.

- Rapidly redistributed, but slowly metabolized
- Useful for sedation, amnesia
- Not analgesic, can be sole anesthetic for non-painful procedures (endoscopies, cardiac catheterization)
- Does not produce surgical anesthesia alone
- Commonly used for preoperative sedation and anxiolysis
- Can be used for induction of anesthesia
- Safe – minimal respiratory and cardiovascular depression when used alone, but they can potentiate effects of other anesthetics (e.g.; opioids)
- Rapid administration can cause transient apnea
- **Opioids**
- i.v. fentanyl, sufentanil, alfentanil, remifentanil or morphine
- Usually in combination with inhalant or benzodiazepine
- Respiratory depression, delayed recovery, nausea and vomiting *post-op*
- Little cardiovascular depression; Provide more stable hemodynamics
- Smooth emergence (except for N & V)
- Excellent Analgesic: intra-operative analgesia and decrease early postoperative pain
- Remifentanil: has ester linkage, metabolized rapidly by nonspecific esterases ($t_{1/2} = 4$ minutes; fentanyl $t_{1/2} = 3.5$ hours)
- Rapid onset and recovery
- Recovery is independent of dose and duration – offers the high degree of “minute to minute” control

LOCAL ANESTHETICS

- Topical anesthesia (cream, ointments, EMLA)
- Peripheral nerve blockade
- Intravenous regional anesthesia
- Spinal and epidural anesthesia
- Systemic uses (antiarrhythmics, treatment of pain syndromes)

Cause Blockade of sensory transmission to brain from a localized area

Causes Blockade of voltage-sensitive Na^+ channels

Use-dependent block

Administer to site of action

Decrease spread and metabolism by co-administering with adrenergic receptor agonist (except cocaine)

MOA

- Block sodium channels
- Bind to specific sites on channel protein
- Prevent formation of open channel
- Inhibit influx of sodium ions into the neuron
- Reduce depolarization of membrane in response to action potential
- Prevent propagation of action potential

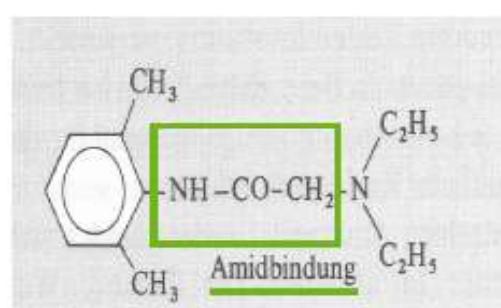
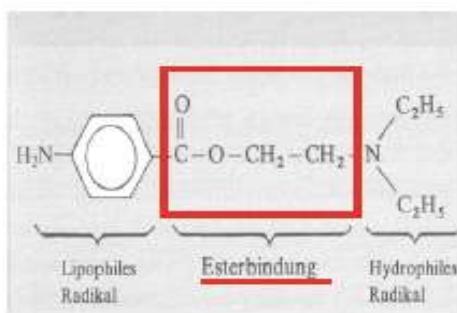
Local anesthetics: Structure-Activity Relationships

➤ Aminoesters:

- Cocaine
- Procaine
- Chloroprocaine
- Tetracaine

➤ Aminoamids:

- Lidocaine
- Prilocaine
- Mepivacaine
- Etidocaine
- Bupivacaine
- Ropivacaine
- Levobupivacaine



Benzoic acid derivatives (Esters)

Aniline derivatives (Amides)

Techniques of administration

Topical: benzocaine, lidocaine, tetracaine

Infiltration: lidocaine, procaine, bupivacaine

Nerve block: lidocaine, mepivacaine

Spinal: bupivacaine, tetracaine

Epidural: bupivacaine

Caudal: lidocaine, bupivacaine

Local anesthetics: Toxicities:

CNS-sedation, restlessness, nystagmus, convulsions

Cardiovascular- cardiac block, arrhythmias, vasodilation (except cocaine)

Allergic reactions-more common with esters

NEUROMUSCULAR BLOCKING DRUGS

- Acetylcholine is released from motor neurons in discrete quanta
- Causes “all-or-none” rapid opening of Na^+/K^+ channels (duration 1 msec)
- Development of miniature end-plate potentials (mEPP)
- Summate to form EPP and muscle action potential – results in muscle contraction
- ACh is rapidly hydrolyzed by acetylcholinesterase; no rebinding to receptor occurs unless AChE inhibitor is present

Non-depolarizing Neuromuscular blocking drugs

- Competitive antagonist of the nicotinic 2 receptor
- Blocks ACh from acting at motor end-plate
- Reduction to 70% of initial EPP needed to prevent muscle action potential
- Muscle is insensitive to added Ach, but reactive to K^+ or electrical current
- AChE inhibitors increase presence of ACh, shifting equilibrium to favor displacing the antagonist from motor end-plate

Nondepolarizing drugs: Metabolism

- Important in patients with impaired organ clearance or plasmacholinesterase deficiency
- Hepatic metabolism and renal excretion (most common)
- Atracurium, cis-atracurium: nonenzymatic (Hoffman elimination)

- Mivacurium: plasma cholinesterase

Depolarizing Neuromuscular blocking drugs

- Succinylcholine, decamethonium
- Bind to motor end-plate and cause *immediate and persistent* depolarization
- Initial contraction, fasciculations
- Muscle is then in a depolarized, refractory state
- Desensitization of Ach receptors
- Insensitive to K⁺, electrical stimulation
- Paralyzes skeletal more than respiratory muscles

Succinylcholine: Pharmacokinetics

- Fast onset (1 min)
- Short duration of action (2 to 3 min)
- Rapidly hydrolyzed by plasma cholinesterase

Succinylcholine: Clinical uses

- Tracheal intubation
- Indicated when rapid onset is desired (patient with a full stomach)
- Indicated when a short duration is desired (potentially difficult airway)



Other Adverse Effects of Depolarizing Blockade (succinylcholine)

- **HYPERKALEMIA**
- **Patients with burns, nerve damage or neuromuscular disease, closed head injury, and other trauma**
- **Release potassium into the blood.**
- **INCREASED INTRAOCULAR PRESSURE**
- **Succinylcholine may increase IOP.**
- **Tonic contraction of myofibrils or transient dilation of ocular choroidal blood vessels.**
- **INCREASED INTRAGASTRIC PRESSURE**
- **Increase in intragastric pressure (5 to 40 cmH₂O)**
- **Increase the risk for regurgitation and aspiration of gastric contents.**
- **MUSCLE PAIN**
- **Myalgias are a common postoperative complaint**

Succinylcholine: Side effects

- Prolonged neuromuscular blockade

- In patients lacking pseudocholinesterase
- Treat by maintaining ventilation until it wears off hours later

Succinylcholine: Phase II block

- Prolonged exposure to succinylcholine
- Features of nondepolarizing blockade
- May take several hours to resolve
- May occur in patients unable to metabolize succinylcholine (cholinesterase defects, inhibitors)
- Harmless if recognized

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors have muscarinic effects

- Bronchospasm
- Urination
- Intestinal cramping
- Bradycardia

Prevented by muscarinic blocking agent

EPI VACCINES

Objectives

1. Describe each vaccine used by MoH/UNEPI to prevent targeted childhood immunisable diseases
2. Discuss the storage of each vaccine
3. State the schedule and dosage
4. Describe site and route of administration
5. Explain side effects and possible contraindications of each vaccine
6. Discuss management of side effects

The unit describes the vaccines used by MoH UNEPI to prevent targeted childhood immunisable diseases. These vaccines are;

Bacillus Calmette Gu  rin (BCG)

Diphtheria-pertussis-tetanus-hepatitis B + haemophilus influenza type b (DPT-HepB+Hib)

Oral polio vaccine (OPV)

Measles

Tetanus Toxoid (TT)

Pneumococcal conjugate vaccine (PCV)

Planned vaccines for introduction

Rotavirus

Human Papilloma Virus (HPV)

BCG VACCINE

Protects the body against tuberculosis

Comes in powder form packed in ampoules or vials. Therefore it must be reconstituted with the accompanying diluents from the same manufacturer before use.

Storage

Should be stored at temperature +2°C and +8°C before and after reconstitution

Dry BCG vaccine (not reconstituted) can be stored at freezing temperatures up to -20°C and is not damaged by freezing

The diluent for BCG is not affected by heat and can be stored at room temperature. However must be pre-cooled a day before reconstitution

Any re-constituted vaccine must be discarded after 6 hours or at the end of the immunisation session.

When is BCG given?

At birth or as soon as possible after birth, preferably before the first birth day

Should not be given to children with clinical AIDS

Dosage

0.05 ml for children less than 12 months old

0.1 ml for children above 12 months

Site of administration

Upper right arm

Route

Intradermal

Side effects

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1. Normal reactions
 - A small raised lump appears at the injection site which usually disappears within 30 minutes
 - After approximately two weeks, a red sore develops which is 10mm in diameter
 - The sore remains for another two weeks and heals
 - A small scar about 5mm across, resulting from the sore remains for life which is a sign that the child has been effectively immunized.
2. Abnormal reactions
 - Swelling of glands or formation of abscesses

DPT-HEPB + HIB vaccine

Protects the body against diphtheria, pertussis, tetanus, hepatitis B, and haemophilus influenza type b

The vaccine is packed in two-dose vials

One vial contains DPT-HepB in liquid form, the other vial contains Hib in freeze dried/pellet form

The vaccine must be reconstituted with freeze dried hib vaccine to make DPT-HepB + Hib vaccine

Storage

DPT-HepB + Hib vaccine should be stored at a temperature between +2°C and +8°C

The vials of DPT-HepB and Hib vaccine should be put next to each other in the refrigerator

Reconstituted DPT-HepB + hib must be discarded after 6 hours or at the end of the immunisation session

DPT-HepB vaccine is damaged by freezing, therefore do not freeze and if you suspect the vaccine has frozen, perform a shake test.

When is DPT-HEPB + HIB vaccine given?

1st dose: 6 weeks (or first contact)

2nd dose: 10 weeks (or 4 weeks after the 1st dose)

3rd dose: 14 weeks (or 4 weeks after the 2nd dose)

The interval between doses must be at least 4 weeks

Dose: 0.5ml

Site: mid outer part of the left thigh

Route: intramuscular

Side effects

Usually mild

Normal reactions are fever and soreness at the site of injection

The fever should disappear within one day

Abnormal reactions Fever that begins more than 24 hours after the injection and Abscesses

Tetanus Toxoid (TT) Vaccine

Is an inactivated tetanus toxin that protects against tetanus

It is provided as a liquid in vials of 10 or 20 doses.

Storage

Should be stored at temperature between +2°C and +8°C

It should never be frozen

When is TT vaccine given?

To reduce the risk of maternal and neonatal tetanus, it is recommended that tetanus toxoid should be given to all women of childbearing age (15-44 years)

Emphasis should be given to pregnant women especially in the antenatal clinics and school health programs

TT dose	When to give	Expected duration of protection
1	At first contact with woman of child bearing age, or as early as possible in pregnancy	No protection
2	At least 4 weeks after TT1	1-3 years
3	At least 6 months after TT2 or during subsequent pregnancy	At least 5 years
4	At least 1 year after TT3 or during subsequent pregnancy	At least 10 years
5	At least 1 year after TT4 or during subsequent pregnancy	

Dose: 0.5ml

Site: left upper arm

Route: Intramuscular

Side effects

At injection site;

1. Mild pain
2. Redness
3. Warmth
4. Swelling for 1-3 days

ORAL POLIO VACCINE (OPV)

Is a live attenuated vaccine that gives protection against the three types of viruses that cause polio.

It is a liquid that usually comes in two types of vials

1. Small plastic vials that have fixed droppers
2. Glass vials with droppers supplied in a separate package

Storage

Should be stored at a temperature between +2°C and +8°C

Where there is sufficient storage capacity and regular power supply, it is stored at -15°C to -20°C

It is easily damaged by heat.

When is OPV given?

OPV0: At birth or within the first 2 weeks of life

OPV1: At 6 weeks (or at first contact)

OPV2: At 10 weeks (or 4 weeks after 1st dose)

OPV3: At 14 weeks (or 4 weeks after the 2nd dose)

The interval between doses must be atleast 4 weeks

Dose: 2 drops

If child has diarrhea, give an extra dose i.e. 5th dose after 4th dose (4 weeks)

Route: Mouth

Side effects: No major side effects

MEASLES VACCINE

It is a live attenuated vaccine that protects the child from measles

It is packaged in powder form together with diluents in a separate vial.

It must be reconstituted before use

It is essential that only the diluents supplied with the vaccine from the same manufacturer be used

Storage

Measles vaccine and diluents should be stored at a temperature between +2°C and +8°C

Measles vaccine can be stored at freezing temperatures and is not damaged by freezing

The diluent is not affected by heat and can be stored at room temperature. However the diluent must be pre cooled a day before reconstitution

Any remaining reconstituted vaccine must be discarded after six hours or at the end of the immunisation session.

When is measles vaccine given?

At 9 months of age or at first contact after this age

Dose: 0.5mls

Site: Upper left arm

Route: Subcutaneous

Side effects

Soreness: pain and tenderness at the site of injection within 24 hours after injection and should resolve within 2-3 days without any medical attention

Mild fever and rash lasting 1-3 days occurs a week after immunisation, usually disappears after 2 days:

PNEUMOCOCCAL CONJUGATE VACCINE (PCV10)

PCV10 is packaged in a 2 dose vial and comes in liquid form

It consists of sugars (polysaccharides) from the capsule of the bacterium streptococcus pneumonia which are conjugated to a carrier protein.

The vaccine contains serotypes 1,4,5,6B,7F,9V,14,18C,19F and 23F

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It protects children younger than 2 years of age against severe forms of pneumococcal disease such as meningitis, pneumonia and bactraemia.

Storage

Store at +2oC to +8oC

Should not be frozen

Partially used vials should be discarded after 6 hours.

When to give PCV?

PCV1: at 6 weeks

PCV2: at 10 weeks

PCV3: at 14 weeks

Dose: 0.5mls

Site: right upper outer thigh

Routé: Intramuscular

1. Common

- Pain, redness and swelling at the injection site
- Fever
- Drowsiness
- Irritability
- Loss of appetite
- Hardness at the injection site

2. Uncommon

- Blood clot, bleeding and small lump at the injection site
- Diarrhea
- Unusual crying
- Apnoea

3. Rare

- Allergic reactions
- Fits without fever

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