LECTURE NOTES

For Health Science Students

Pharmacology

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INTRODUCTION

Pharmacology is a medical science that forms a backbone of the medical profession as drugs form the corner stone of therapy in human diseases. Therefore, it is of utmost importance to describe the pharmacological basis of therapeutics in order to maximize the benefits and minimize the risks of drugs to recipients. This lecture note on pharmacology is primarily a note for undergraduate health science students such as health officer, nursing, midwifery and laboratory technology students. However, other health professionals whose career involves drug therapy or related aspects should also find much of the material relevant.

The goal is to empower the practitioner through an understanding of the fundamental scientific principles of pharmacology. The effects of prototypical drugs on physiological and pathophysiological processes are clearly explained to promote understanding. Other related drugs are touched briefly. The selection of the drugs is based on the national drugs list for

Table of Contents

List of Abbrevations

ACE=	angiotensin converting enzyme
ACH=	Acetylcholine
ACTH=	Adrenocorticotropic hormone
AIDS=	Acquired Immuno deficiency syndorme
ANS=	Autonomic nervous system
B.C.G vaccine=	Bacille Calmette-Guerin Vaccine
CAMP=	Cyclic adenosine Monoposphate
CHO=	Carbohydrate
CMS=	Cytomegalovirus
CNS=	Central nervous system
CSF=	Cerebrospinal fluid
CTZ=	Chemoceptor trigger zone
CVS=	Cardiovascular system
DKA =	Diabetic ketoacidosis
DNA=	Deoxyribonucleic acid
EBV=	Epstein-barr virus
FSH=	Follicle Stimulating hormone

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CHAPTER ONE

GENERAL PHARMACOLOGY

Learning Objectives

At the end of this chapter the student will be able to:

1. Define various terminologies used in Pharmacology.
2. Know about nature and sources of drugs.
3. Understand pharmacodynamics like mechanism of drug action, dose relation ship and pharmacokinetics like absorption, distribution, metabolism and excretion (ADME) of drugs.
4. Understand theoritical pharmacokinetics like half-life, order of kinetics, steady state plasma concentration.
5. Understand drug safety and effectiveness like factors affecting drug action and adverse drug reactions.
6. Understand new drug development and evaluation.

I. Introduction to Pharmacology

A. Definitions:

1. **Pharmacology:** Pharmacology is the study of interaction of drugs with living organisms. It also includes history, source, physicochemical properties, dosage forms, methods of administration, absorption, distribution mechanism of action, biotransformation, excretion, clinical uses and adverse effects of drugs.
2. **Clinical Pharmacology:** It evaluate the pharmacological action of drug preferred route of administration and safe dosage range in human by clinical trails.
3. **Drugs**: Drugs are chemicals that alter functions of living organisms. Drugs are generally given for the diagnosis, prevention, control or cure of disease.
4. **Pharmacy**: It is the science of identification, selection, preservation, standardisation, compounding and dispensing of medical substances.

- Receptors are protein molecules present either on the cell surface or with in the cell e.g. adrenergic receptors, cholinoceptors, insulin receptors, etc.
- The endogenous neurotransmitters, hormones, autacoids and most of the drugs produce their effects by binding with their specific receptors.
- Aluminium hydroxide and magnesium trisilicate, which are used in the treatment of peptic ulcer disease act by non-receptor mechanism by neutralizing the gastric acid.

Many drugs are similar to or have similar chemical groups to the naturally occurring chemical and have the ability to bind onto a receptor where one of two things can happen- either the

synthesis and release of another intracellular regulatory molecule termed as second

2. Quantal dose effect: It is all or none response, the sensitive objects give response to small doses of a drug while some will be resistant and need very large doses. The quantal dose-effect curve is often characterized by stating the median effective dose and the median lethal dose.

Median lethal dose or LD_{50}: This is the dose (mg/kg), which would be expected to kill one half of a population of the same species and strain.

Median effective dose or ED_{50}: This is the dose (mg/kg), which produces a desired response in 50 per cent of test population.

Therapeutic index: It is an approximate assessment of the safety of the drug. It is the ratio of the median lethal dose and the median effective dose. Also called as therapeutic window or safety.

Herapeutic index (T. I) =

The larger the therapeutic index, the safer is the drug. Penicillin has a very high therapeutic index, while it is much smaller for the digitalis preparation.

D. Structural activity relationship

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Advantages: rate of absorption is uniform, onset of action is faster than oral and it can be given in diarrhoea or vomiting.

Disadvantages: Pain at local site of injection, the volume of injection should not exceed 10 ml.

(iv) **Intravenous**: Drugs directly given into a vein, produce rapid action, no need of absorption as they enter directly into blood, can be given as bolus e.g. furosemide, morphine, dopamine or as continous infusion e.g. fluids during shock or dehydration.

Advantages: It can be given in large volumes, production of desired blood concentration can be obtained with a well designed dose.

Disadvantages: Drug effect cannot be halted if once the drug is injected, expertise is needed to give injection.

(v) **Intrathecal**: Injected into subarachnoid space of spinal cord e.g. spinal anaesthetics.

(vi) **Intraperitonial**: Injections given into the abdominal cavity e.g. infant saline, glucose.

(vii) **Intra-articular**: Injected directly into a joint e.g. hydrocortisone.

c) Transcutaneous route:

i) **Iontophoresis:** Galvanic current is used for bringing about the penetration of drugs into the deeper tissue e.g. salicylates.

ii) **Inunctions:** Absorbed when rubbed in to the skin e.g. nitroglycerin ointment in angina pectoris.

iii) **Jet injection:** With help of high velocity jet produced through a micro fine orifice; No need of needle and therefore painless. e.g. mass inoculation programmes.

iv) Adhesive units

absorbed for systemic effects e.g. salbutamol spray used in bronchial asthma and volatile general anaesthetics.

2. Bioavailability:

It is the rate and amount of drug that is absorbed from a given dosage form and reaches the systemic circulation following non-vascular administration. When the drug is given IV, the bioavailability is 100%. It is important to know the manner in which a drug is absorbed. The route of administration largely determines the latent period between administration and onset of action. Drugs given by mouth may be inactive for the following reasons:

a) Enzymatic degradation of polypeptides within the lumen of the gastrointestinal tract e.g. insulin, ACTH.

b) Poor absorption through gastrointestinal tract e.g. aminoglycoside antibiotic.

c) Inactivation by liver e.g. testosterone during first passage through the liver before it reaches systemic circulation.

3. Factors affecting drug absorption and bioavailability:

a) Physico-chemical properties of drug

b) Nature of the dosage form

c) Physiological factors

d) Pharmacogenetic factors

e) Disease states.

a) Physico-chemical properties of drug:

i) **Physical state**: Liquids are absorbed better than solids and crystalloids absorbed better than colloids.

ii) **Lipid or water solubility**: Drugs in aqueous solution mix more readily than those in oily solution. However at the cell surface, the lipid soluble drugs pevel7ate anteothe lell sore -5.5(c]TJ0 -1.

d) Pharmacogenetic factors:

Individual variations occur due to the genetically mediated reason in drug absorption and response.

e) Disease states:

Absorption and first pass metabolism may be affected in conditions like malabsorption, thyrotoxicosis, achlorhydria and liver cirrhosis.

4. Bioavailability curves

Single dose bioavailability test involves an analysis of plasma or serum concentration of the drug at various time intervals after its oral administration and plotting a serum concentration time curve.

$$\text{Bioavailability (F)} = \frac{\text{AUC after oral dose}}{\text{AUC after I.V. dose}}$$

AUC= Area under curve – which provides information about the amount of drug absorbed.

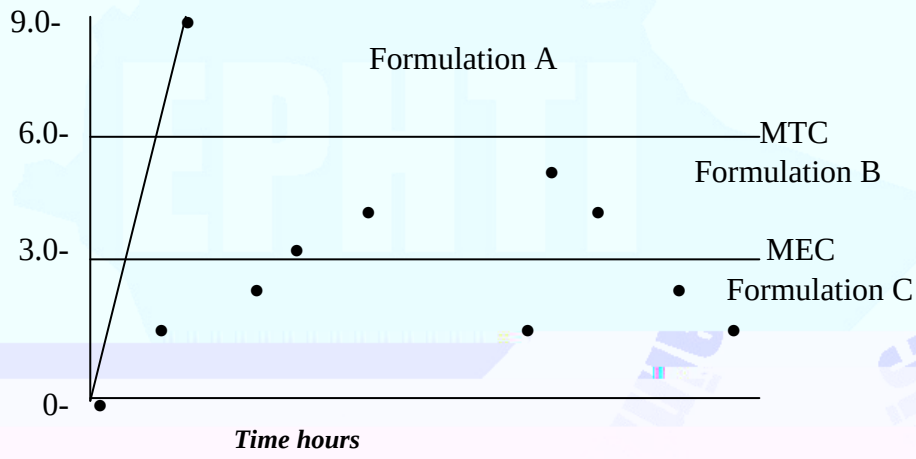


Fig 1.2 : The plasma drug level curves following administration of three formulations (A, B and C) of the same basic drug.

MTC: Minimum toxic concentration

MEC: Minimum effective concentration

Formulation A = would produce quick onset and short duration of action, produce toxic effects.

Formation B = Effect would last much longer and nontoxic

Formulation C = gives inadequate plasma level so therapeutically ineffective.

C) Distribution of drugs

1. **Definition**: Penetration of a drug to the sites of action through the walls of blood vessels from the administered site after absorption is called drug distribution. Drugs distribute through various body fluid compartments such as (a) plasma (b) interstitial fluid compartment (c) trans-cellular compartment.

Apparent Volume of distribution (VD): The volume into which the total amount of a drug in the body would have to be uniformly distributed to provide the concentration of the drug actually measured in the plasma. It is an apparent rather than real volume.

Factors determining the rate of distribution of drugs:

1**. Protein binding of drug:** A variable and other significant portion of absorbed drug may become reversibly bound to plasma proteins. The active concentration of the drug is that part which is not bound, because it is only this fraction which is free to leave the plasma and site of action. (a) Free drug leave plasma to site of action (b) binding of drugs to plasma proteins assists absorption (c) protein binding acts as a temporary store of a drug and tends to prevent large fluctuations in concentration of unbound drug in the body fluids (d) protein binding reduces diffusion of drug into the cell and there by delays its metabolic degradation e.g. high protein bound drug like phenylbutazone is long acting.

   Low protein bound drug like thiopental sodium is short acting.

2**. Plasma concentration of drug (PC):** It represents the drug that is bound to the plasma proteins (albumins and globulins) and the drug in free form. It is the free form of drug that is distributed to the tissues and fluids and takes part in producing pharmacological effects.

The concentration of free drug in plasma does not always remain in the same level e.g.

i) After I.V. administration plasma concentration falls sharply

ii) After oral administration plasma concentration rises and falls gradually.

iii) After sublingual administration plasma concentration rise sharply and falls gradually.

Fig 1.3: Plasma concentration of drug after different routes of administration.

3. **Clearance:**

c) Acetyl conjugation: The enzyme acetyl transferase, which is responsible for acetylation, is present in the kupffer cells of liver. Acetic acid is conjugated to drugs via its activation by CoA to form acetyl CoA. This acetyl group is then transferred to-NH_2 group of drug e.g. dapsone, isoniazid.

d) Glycine conjugation: Glycine conjugation is characteristic for certain aromatic acids

e.g. salicylic acid, isonicotinic acid, p-amino salicylic acid. These drugs are also metabolized by other path ways.

e) Methylation: Adrenaline is methylated to metanephrine by catechol-o-methyl transferase.

Here the source of methyl group is s – adenosyl methionine.

E. Excretion of drugs

In congestive cardiac failure, the glomerular filtration rate is reduced due to decrease in renal blood flow.

ii) **Active tubular secretion:** The cells of the proximal convoluted tubule actively transport drugs from the plasma into the lumen of the tubule e.g. acetazolamide, benzyl penicillin, dopamine, pethidine, thiazides, histamine.

iii) **Tubular reabsorption:** The reabsorption of drug from the lumen of the distal convoluted tubules into plasma occurs either by simple diffusion or by active transport. When the urine is acidic, the degree of ionization of basic drug increase and their reabsorption decreases. Conversely, when the urine is more alkaline, the degree of ionization of acidic drug increases and the reabsorption decreases.

b) **Hepatobiliary excretion:** the conjugated drugs are excreted by hepatocytes in the bile. Molecular weight more than 300 daltons and polar drugs are excreted in the bile. Excretion of drugs through bile provides a back up pathway when renal function is impaired. After excretion of drug through bile into intestine, certain amount of drug is reabsorbed into portal vein leading to an enterohepatic cycling which can prolong the action of drug e.g. chloramphenicol, oral estrogen are secreted into bile and largely reabsorbed and have long duration of action. Tetracylines which are excreted by biliary tract can be used for treatment of biliary tract infection.

c) **Gastrointestinal excretion:** When a drug is administered orally, a part of the drug is not absorbed and excreted in the faeces. The drugs which do not undergo enterohepatic cycle after excretion into the bile are subsequently passed with stool e.g. aluminium hydroxide changes the stool into white colour, ferrous sulfate changes the stool into black and rifampicin into orange red.

d) **Pulmonary excretion:** Drugs that are readily vaporized, such as many inhalation anaesthetics and alcohols are excreted through lungs. The rate of drug excretion through lung depends on the volume of air exchange, depth of respiration, rate of pulmonary blood flow and the drug concentration gradient.

e) **Sweat**: A number of drugs are excreted into the sweat either by simple diffusion or active secretion e.g. rifampicin, metalloids like arsenic and other heavy metals.

f) **Mammary excretion:** Many drugs mostly weak basic drugs are accumulated into the milk. Therefore lactating mothers should be cautious about the intake of these drugs because they may enter into baby through breast milk and produce harmful effects in the baby e.g.

ampicillin, aspirin, chlordiazepoxide, coffee, diazepam, furosemide, morphine, streptomycin etc.

Clearance of a drug:

It is the volume of plasma cleared of the drug by metabolism (hepatic) and excretion (renal) and other organs.

Total clearance will be calculated by $Ct = C_h + C_r + C$ others

C_t = total clearance

C_h = hepatic clearance

C_r = Renal clearance

IV. Theoretical Pharmacokinetics

Information about the time course of drug absorption, distribution and elimination (pharmacokinetics) can be expressed in mathematical terms and has contributed to our understanding and planning of drug regimens. Pharmacokinetic principles aid in the selection and adjustment of drug-dose schedules.

Half life:

Half life ($t_1/_2$) of a drug is the time taken for the concentration of drug in the blood or plasma to decline to half of original value or the amount of drug in the body to be reduced by 50%. It has two phases i.e half-life of distribution and half-life of elimination.

A half-life value can be readily determined for most drugs by administering a dose of the drug to a subject, taking blood samples at various time intervals and then assaying the samples., For example if a blood level of drug A is 8.6 mg/ml at 10 minutes and 4.3 mg/ml at 60 minutes, so the half – life of that drug is 50 minutes.

In most of the cases the rate of disappearance of a drug from the body is reflected in the rate of lowering of its plasma concentration following a single intravenous dose, the plasma concentration of the drug is focused to fall exponentially. With drugs whose elimination is exponential, the biological half – life is independent of the dose, the route of administration and the plasma concentration. It depends on VD as well as on the metabolism and renal excretion of the drug.

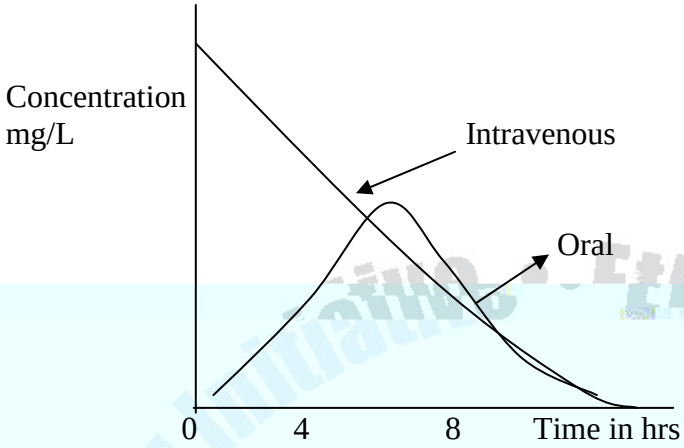


Fig 1.4: Exponential curves of plasma concentration following oral and intravenous drug administration.

Order of kinetics

Drugs are used for the treatment of diseases but the modes of administration of drugs are different. For example atenolol is administered once daily where as paracetamol needs 3-4 times administration daily. Morphine is more effective in intramuscular route, and insulin is in subcutaneous route. The mode of administration is designed on the basis of absorption, distribution, metabolism and excretion (ADME) of drugs. Drugs usually follow two processes for their phamacokinetic behaviour in the body. These are first order and zero order process.

First order:

This is the most common process for many drugs. The rate at which absorption, distribution, metabolism and excretion occur are proportional to the concentration of drugs i.e. constant fraction of this drug in the body disappears in each equal interval of time.

Zero order kinetic:

It is independent of the amount of drug present at the particular sites of drug absorption or elimination. Few drugs follow this process e.g. ethanol, phenytoin. Here constant amount of the drug is eliminated in each equal interval of time. On repeated administration of drug after certain stage it goes on accumulating in the body and leads to toxic reactions.

Steady state plasma concentration:

When a drug dose is given repeatedly over a given period, a steady state is eventually reached, at which point the amount of drug absorbed is in equilibrium with that eliminated from the body.

The paediatric doses are expressed in terms of body weight (mg/kg per dose or day) or in terms of body surface area (mg/m^2per day). The body surface area can be calculated from the height and weight of the child.

Like children, old people also present problems in dosage adjustment and this may vary widely with different people. The metabolism of drugs may diminish in the elderly and the renal function declines with age. Elderly are sensitive to the drugs like hypnotics, tranquilizers, phenylbutazone, diazepam, pethidine, etc.

i) Dose adjustment on the basis of age (young's formula)

$$\frac{\text{Age in years}}{\text{Age in years} + 12} \times \text{adult dose}$$

ii) Dose adjustment on the basis of body weight (Clark s formula) (1 Kg=2.2 pounds)

$$\frac{\text{Weight of child in pound}}{150} \times \text{Adult dose}$$

e.g. A 3 year old child having body weight of 30 pound requires to administer drug X. The adult dose is 100mg. So

a) Using age of the child the dose will be

$$\frac{3}{3+12} \times 10 = \frac{3}{15} \times 100 = 20\text{mg}$$

b) Using body weight of the child it will be

$$\frac{30}{150} \times 100 = \frac{1}{5} \times 100 = 20\text{mg}$$

5. **Disease state:** Some antimicrobial agents penetrate the cerebrospinal fluid well across the normal meninges while other antimicrobials penetrate well only when the meninges are inflammed (meningitis) e.g. sulphonamides, metronidazole, chloramphenicol, isoniazid and rifampicin penetrate well through the normal meninges and other antimicrobial agents like benzylhrough the liklal men T*.00*41 The metbeobial agents like

Similarly renal and pulmonary diseases may modify the biotransformation of drugs like insulin or isoprenaline. Excretion of drug is impaired in chronic renal disease.

6. **Pharmacogenetics:** The science pharmacogenetics is concerned with the genetically-mediated variations in drug responses. Some examples of genetically mediated variations are:

Acetylation and hydroxylation of drugs: The rate of acetylation of INH, dapsone, hydralazine procainamide and some sulfonamides is controlled by an autosomal recessive gene and the dosage of these drugs depends up on the acetylator status of individuals.

7) Drug interactions:

It is usual for patients to receive a number of drugs at the same time.

It is a phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another drug(s). A drug interaction may result in beneficial or harmful effects and may be classified into:

a) Pharmaceutical drug interactions:

Serious loss of potency can occur from incompatibility between an infusion fluid and a drug that is added to it.

For example diazepam if added to infusion fluid there will be a precipitate formation $\rightarrow$ loss of therapeutic effect.

b) Pharmacokinetic drug interactions:

1) **Interaction during absorption:** Drugs may interact in the gastrointestinal tract resulting in either decreased or increased absorption.
   e.g. Tetracycline + Calcium $\rightarrow$ Decreased absorption of tetracycline.

2) **Interaction during distribution:** A drug which is extensively bound to plasma protein can be displaced from its binding sites by another drug or displacement from other tissue binding sites.
   e.g. (i) Sulfonamide can be displaced by salicylates from plasma proteins and it leads to sulfonamide toxicity.
   (ii) Quinidine displaces digoxin from binding sites in tissues and plasma and leads to digoxin toxicity.

(iii) **Drug Antagonism:** The phenomenon of opposing actions of two drugs on the same physiological system is called drug antagonism.

a) **Chemical antagonism:** In this the biological activity of a drug can be reduced or abolished by a chemical reaction with another agent.

e.g. Antagonism between acids and alkalis.

b) **Competitive or reversible antagonism:** In this the agonist and antagonist compete for the same receptors and the extent to which the antagonist opposes the pharmacological action of the agonist. Competitive antagonism can be overcome by increasing the concentration of the agonist at the receptor site.

e.g. Acetylcholine and atropine antagonism at muscarinic receptors.

c) **Non competitive antagonism:** In this type of the antagonism an antagonist inactivates the receptor (R) so that the effective complex with the agonist cannot be formed, irrespective of the agonist concentration.

2) **Untoward effects:** Untoward effects develop with therapeutic dose of a drug. They are undesirable and if very severe, may necessitate the cessation of treatment.

e.g: Diarrhoea with ampicillin and potassium loss with diuretics.

3) **Allergic reactions**

b) Pharmacological study includes further chronic toxicological study in animal, initially animal metabolic and pharmacokinetic study. When studies in animals predict that a NCE may be useful medicine i.e. effective and safe in relation to its benefits, then the time has come to put it to the test in man i.e. clinical trial.

c) Studies on human or Clinical Trial:

Clinical trial is a means by which the efficacy of drug is tested on human being. It may also give some idea about the risk involved. It is divided into 4 phases. With each phase, the safety and efficacy of the compound are tested progressively.

Phase - I: This is the first exposure of the new drug on man which is usually conducted in healthy volunteers and which is designed to test the tolerable dose, duration of action. This phase is usually carried out in only one centre on 20 to 50 subjects.

Phase - II: This phase comprises small scale trials on patients used to determine dose level and establish that the treatment offers some benefit. It usually involves 100-500 patients and is usually conducted in several centres.

Phase - III: Full scale evaluation of treatment comparing it with standard treatment is done in this phase. It involves randomised control trials on 250 to 2000 patients and is done in multiple centres. Information from all studies are received by the “Committee of safety of medicines” (CSM). If the drug is satisfied by the CSM, the product license is issued then the drug is marketed.

Phase - IV: It is also called as phase of post marketing surveillance. Reports about efficacy and toxicity are received from the medical practitioners and reviewed by the committee of review of medicines. Renewal or cancellation of the product license depends on the comment of the review committee.

Exercise

1) What are different routes of drug administration and write about advantages and disadvantages of parenteral route of administration.

2) Define bio-availability and describe the factors affecting drug absorption.

3) Define the following:

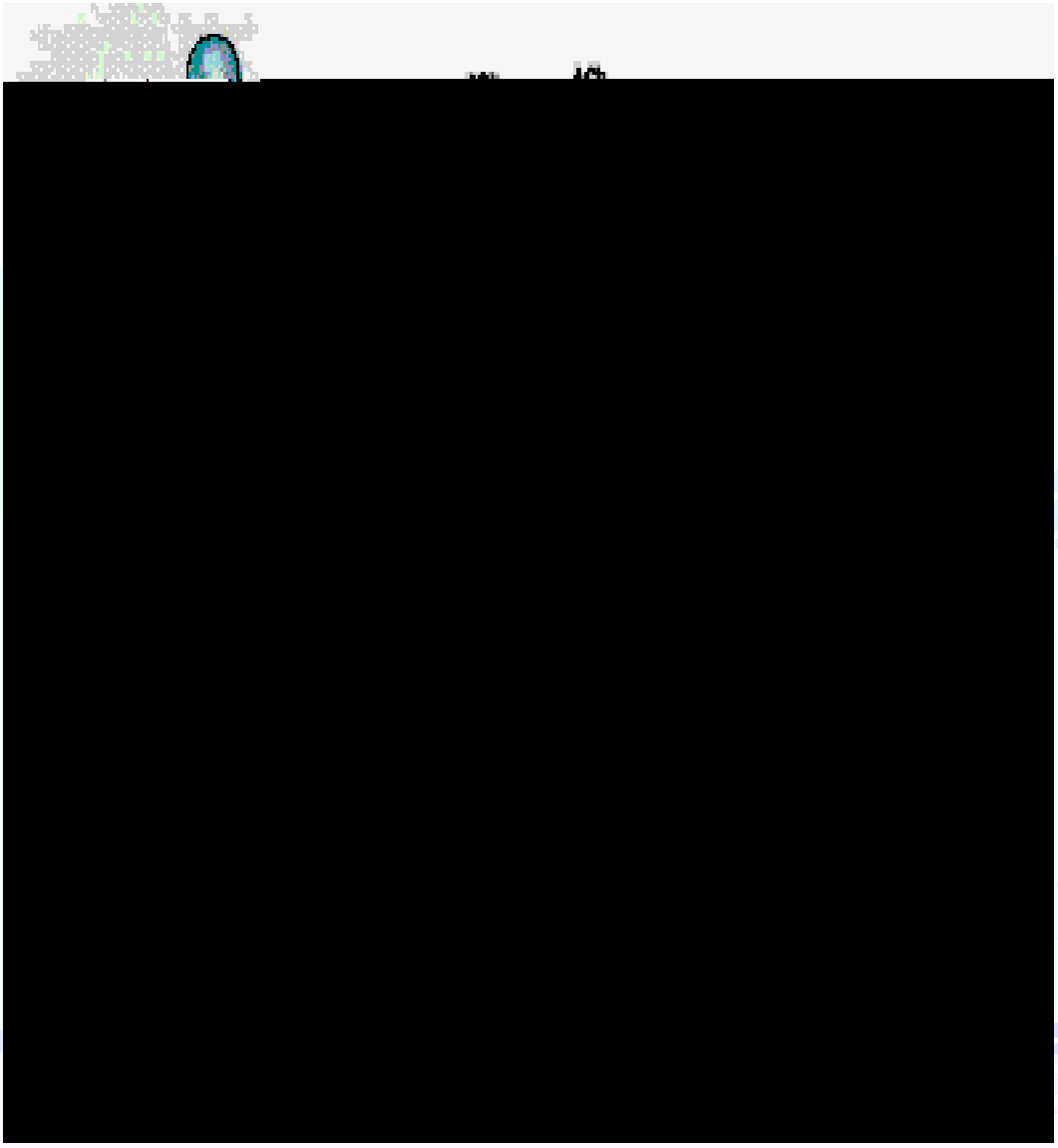
   a) Half-life of a drug

   b) Steady state plasma concentration

   c) Adverse drug reactions

4) Write about the factors modifying drug action.

5) Write about different types of drug interactions.



In terms of function, the parasympathetic nervous system is concerned primarily with conservation and restoration of function.

In contrast, the sympathetic nervous system is concerned with the expenditure of energy, i.e., it has almost opposite functions with parasympathetic nerve stimulation and it is usually associated with arousal or in emergency situations, i.e., prepares the body for fight-or-flight responses.

To understand autonomic nervous system pharmacology, it is very important to know how the system works and clearly identify the mechanisms behind the functions, i.e., nerve transmission.

activity', except in the case of sweat glands and blood vessels to skeletal muscles where acetylcholine is released as a neurotransmitter.

Adrenergic neuron terminals synthesize noradrenaline, store it in vesicles and release it to effector cells upon stimulation of the nerve. The transmitter is synthesized from precursor tyrosine (amino acid) through several processes which are potential sites of drug action. After release to receptor sites noradrenaline produces its effects. Termination of noradrenergic transmission results from several processes such as reuptake into the nerve terminal (reuptake1), diffusion away from the synaptic cleft and subsequent reuptake into the perisynaptic glia or smooth muscle (reuptake2) or degradation by enzymes. Reuptake into the nerve terminal is the most important mechanism for termination of the effects of noradrenaline.

Receptors that respond to adrenergic nerve transmitter are termed adrenergic receptors. These receptors are subdivided into alpha and beta adrenoreceptor types on the basis of both agonist and antagonist selectivity. The receptors have subclasses depending on drug selectivity. These are alpha 1 and 2 and beta 1, 2 and 3.

Table 2.1: Distribution of adrenoceptor subtypes and their actions

Type	**Tissue**	**Actions**
Alpha$_1$	Most vascular smooth muscles	Contraction
	Pupillary dilator muscle	Mydriasis
	Heart	Increase force of contraction
Alpha$_2$	Adrenergic nerve terminals	Inhibition of transmitter release

There are five key features of neurotransmitter function representing potential targets of pharmacologic therapy. These are synthesis, storage, release, activation of receptors and

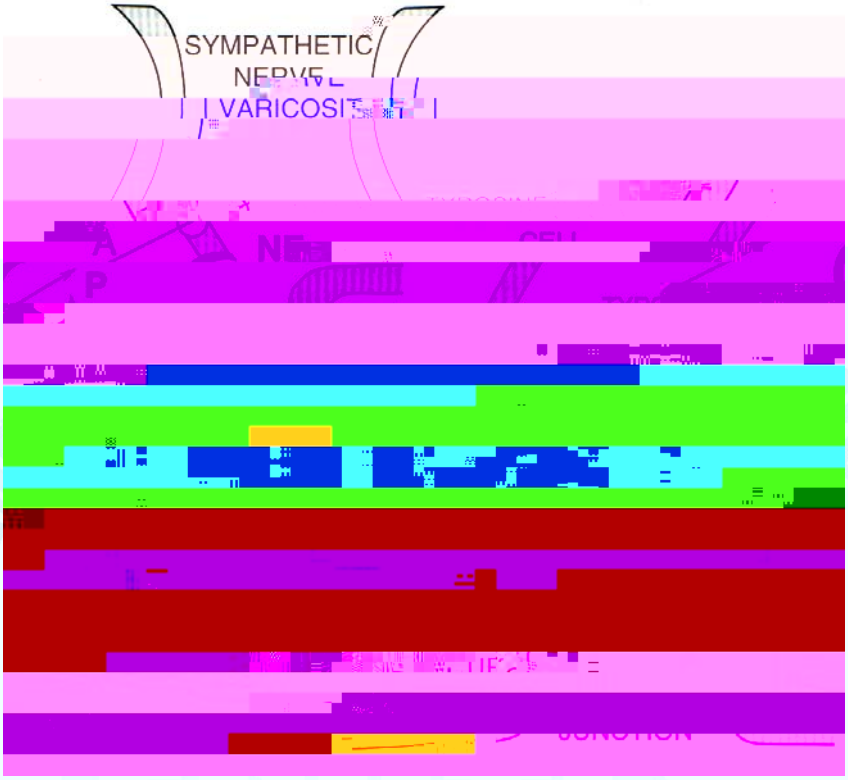


Fig 2.3: Proposed site of action of drugs on the synthesis, action, and fate of norepinephrine at sympathetic neuroeffector junctions

AUTONOMIC DRUGS

There are several drugs affecting the autonomic nervous system which, for a better understanding of specific drugs, are classified into groups.

1. Drugs acting on the sympathetic nervous system

a) Sympathomimetics or adrenergic drugs: are drugs that mimic the effects of sympathetic nerve stimulation.

b) Sympatholytics: are drugs that inhibit the activity of sympathetic nerve or that of sympathomimetics.

2. Drugs acting on the parasympathetic nervous system

a) Parasympathomimetics or cholinergic drugs: are drugs which mimic acetylcholine or the effects of parasympathetic nerve stimulation.

b) Parasympatholytics: are drugs that inhibit parasympathetic nervous system activity or that of cholinergic drugs.

CHOLINERGIC DRUGS

Cholinergic drugs are also called parasympathomimetics because their effect mimics the effect of parasympathetic nerve stimulation. Administration of these drugs will result in an increase in the parasympathetic activities in the systems innervated by cholinergic nerves.

There are two groups of cholinergic drugs:

1. *Direct-acting*: bind to and activate muscarinic or nicotinic receptors (mostly both) and include the following subgroups:
    a. Esters of choline: methacholine, carbachol, betanechol
    b. Cholinergic alkaloids: pilocarpine, muscarine, arecoline, nicotine
2. *Indirect-acting*: inhibit the action of acetylcholinesterase enzyme
    a. Reversible: neostigmine, physostigmine, edrophonium
    b. Irreversible: Organophosphate compounds; echothiophate

The actions of acetylcholine may be divided into two main groups: -

1. Nicotinic actions- those produced by stimulation of all autonomic ganglia and the neuromuscular junction
2. Muscarinic actions- those produced at postganglionic cholinergic nerve endings

ESTERS OF CHOLINE

ACETYLCHOLINE is the prototypical cholinergic agent. It functions as a neurotransmitter at all cholinergic sites in the body; because of its unique pharmacokinetic properties, it has never been used in medical therapeutics; the discussion which follows is for academic exercise.

Pharmacokinetics

Acetylcholine is poorly absorbed from the gastric mucosa; therefore it is ineffective if given orally. The recommended way of administration is parenteral. In the blood it is rapidly hydrolyzed by the enzyme cholinesterase into acetic acid and choline; this makes its duration of action very short and unreliable for therapeutic purposes.

Pharmacodynamics

As mentioned earlier it has two types of actions: nicotinic and muscarinic; the muscarinic actions are of main interest and are discussed below.

Á *Cardiovascular system*

Heart Ą slow heart rate

PHYSOSTIGMINE

Pharmacokinetics

This drug is completely absorbed from the gastrointestinal and is highly distributed throughout the body; it can pass the blood brain barrier.

Pharmacodynamics

Inhibits the enzyme cholinesterase; therefore, it increases and prolongs the effect of endogenous acetylcholine at the different sites.It has no direct effect on cholinergic receptors.

Indications

- Glaucoma
- Atropine over dosage

NEOSTIGMINE

Pharmacokinetics

This drug is poorly absorbed from the gastro intestinal tract and is poorly distributed throughout the body; it cannot pass the blood brain barrier.

Pharmacodynamics

Just like physostigmine, it inhibits cholinesterase enzyme; but unlike physostigmine, it has a direct nicotinic action on skeletal muscles.

Indications

- Myasthenia gravis
- Paralytic Ileus
- Reversal of effect of muscle relaxants, e.g. tubocurarine
- Post operative urine retention

Organophosphates such as echothiophate, isofluorophate, etc. combine with cholinesterase irreversibly and thus hydrolysis is very slow.

They may be used in glaucoma. Other organophosphates like parathion and malathion are used as insecticides. Poisoning with organophosphates is an important cause of morbidity and mortality all over the world. It usually results from:

- Occupational exposure as in persons engaged in spraying insecticides,
- Accidental exposure, and

- Ingestion of any of these compounds with suicidal intent.

ANTICHOLINERGICS

Anticholinergics block the effects of acetylcholine and other cholinergic drugs at cholinergic receptors of effector cells. Anticholinergics fall into two major families:

1. Antinicotinics which include ganglion blockers such as hexamethonium, trimethaphan, etc., and neuromuscular blockers such as gallamine, tubocurarine, pancuronium, etc.
2. Antimuscarinics include tertiary amines such as atropine, scopolamine, tropicamide, etc, andquaternary amines such as propantheline, ipratropium, benztropine, etc.

ATROPINE

Atropine is found in the plant *Atropa belladonna and it is the prototype of muscarinic antagonists.*

Pharmacokinetics

Atropine is absorbed completely from all sites of administration except from the skin wall, where absorption is for limited extent; it has good distribution. About 60% of the drug is excreted unchanged in urine.

Pharmacodynamics

Atropine antagonizes the effect of acetylcholine by competing for the muscarinic receptors peripherally and in the CNS; therefore the effects of atropine are opposite to the acetylcholine effects.

Organ-system Effects:

CNS: - lower doses produce sedation
- higher doses produce excitation, agitation and hallucination

Eyes: - relaxation of constrictor pupillae (mydriasis)
- relaxation or weakening of ciliary muscle (cycloplegia-loss of the ability

Eyes:

Clinical Indications

Pre anesthetic medication -to reduce the amount of secretion and to prevent excessive vagal tone due to anesthesia.

As antispasmodic in cases of intestinal, biliary, and renal colic

Heart block

Hyperhidrosis

Organophosphate poisonings

Side effects

- Dryness of the mouth, tachycardia and blurred vision
-

3. Antiparkinsonian atropine substitute: - drugs like Benztropine, Trihexyphenidyl
4. Atropine substitutes which decrease urinary bladder activity like oxybutynin
5. Atropine substitutes used in bronchial asthma drugs like ipratropium

ADRENERGIC DRUGS

As their name suggests, these drugs resemble sympathetic nerve stimulation in their effects; they may be divided into two groups on the basics of their chemical structure.

1**. Catecholamines**: -these are compounds which have the catechol nucleus.

Catecholamines have a direct action on sympathetic effectors cells through interactions with receptor sites on the cell membrane.

The group includes adrenaline, noradrenaline, dopamine, isoprenaline, and dobutamine.

-

Pharmacokinetics

Adrenaline is rapidly destroyed in the gastrointestinal tract, conjugated, and oxidized in the liver. It is therefore ineffective when given orally and should be given intramuscularly or subcutaneous. Intravenous injection is highly dangerous and is likely to precipitate ventricular

Contra indications

1. Coronary diseases
2. Hyperthyroidism

more selective in their action so that they have fewer side effects than adrenaline and nor adrenaline. Dopamine and dobutamine are very useful drugs for the treatment of shock.

NON- CATECHOLAMINES

Most of the non- catecholamines function by releasing the physiologic catecholamines from the postganglionic nerve endings

EPHEDRINE

Pharmacokinetics

Ephedrine in absorbed from the gastrointestinal tract and from all parenteral sites. It has a good distribution through out the body and is resistant to hydrolysis by the liver enzymes. Major proportion of the drug is excreted unchanged in the urine. Because of its stability to metabolism it has long duration of action than the catecholamines.

Pharmacodynamics

Ephedrine stimulates both α and β receptors. This effect is partly by a direct action on the receptors and partly indirectly by releasing noradrenaline from its tissue stores the effect of the drug to various organs and systems is similar to that of adrenaline. It is also a mild CNS stimulant.

Indications:

1. Bronchial asthma: - usually as a prophylactic for prevention of attacks
2. Nasal decongestion
3. Mydriasis
4. Heart block
5. Nocturnal enuresis

Side effects

The side effects are similar to those of adrenaline; but in addition it may produce insomnia and retention of urine.

Contraindications

They are the same as Adrenaline.

Based on their selectivity to specific receptors the rest of the catecholamines, are classified but it is very difficult to exhaust all the drugs. More over their effect and pharmacology is discussed where they are clinically indicated.

ADRENERGIC BLOCKERS

Adrenergic receptor blockers may be considered in two groups:

1. Drugs blocking the ą adrenergic receptor
2. Drugs blocking theβ Adrenergic receptor

These drugs prevent the response of effectors organs to adrenaline, noradrenaline and other sympathomimetic amines whether released in the body or injected. Circulating catecholamines are antagonized more readily than are the effects of sympathetic nerve stimulation. The drugs act by competing with the catechoamines for α or β receptors on the effectors organs. They don't alter the production or release of the substances.

α- Adrenergic blockers

Alpha adrenergic receptor antagonists may be reversible or irreversible. Reversible antagonists dissociate from the receptors e.g. phentolamine, tolazoline, prazosin,yohimbine, etc. Irreversible antagonists tightly bind to the receptor so that their effects may persist long after the drug has been cleared from the plasma e.g. phenoxybenzamine

Pharmacologic Effects:

Alpha receptor antagonist drugs lower peripheral vascular resistance and blood pressure. Hence, postural hypotension and reflex tachycardia are common during the use of these drugs. Other minor effects include miosis, nasal stuffiness, etc.

Prazosin

This is an effective drug for the management of hypertension. It has high affinity for alpha$_1$ receptor and relatively low affinity for the alpha$_2$

β - ADRENERGIC BLOCKING DRUGS

The β - adrenergic receptor blocking drugs in use may be classified by their selectivity for receptors in different tissues.

1. Drugs blocking all the β receptor effects of adrenaline (non-selective beta blockers) e.g. propanalol, pinadolol, timolol etc
2. Drugs blocking mainly the β1 effects (those on the heart) with less effect on the bronchi and blood vessels (beta1-selective blockers), e.g. atenolol, practalol acebutalol, etc.

PROPRANOLOL

Propranolol is a non- selective β adrenergic blocker; it has also other actions like membrane stabilization.

Pharmacokinetics

Propranolol is almost completely absorbed following oral administration. How ever, the liver, leaving only 1/3 rd of the dose to reach the systemic circulations, metabolizes most of the administered dose. It is bound to plasma to the extent of 90-95%. It is excreted in the urine.

Pharmacodynamics

The drug has the following main actions.

1. Cardiovascular system
   - Bradycardia
   - Reduces force of contraction
   - Reduces blood pressure
2. Respiratory system
   - Bronchoconstriction
3. Metabolic system
   - Hypoglycemia
4. Central nervous system
   - Anti-anxiety action
5. Eye
   - Decrease the rate of Aqueous humor production
6. Kidneys:
   - Decrease renin secretion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Exercice

1. What is the autonomic nervous system?
2. How are drugs affecting the Autonomic nervous system classified?
3. Discuss the effects of Acetylcholine.
4. Discuss the effects and clinical uses of atropine.
5. Discuss the effects of Adrenaline.
6. Discuss the effects and contraindications of propranolol.

CHAPTER THREE

CARDIOVASCULAR AND RENAL DRUGS

Learning objectives

After completing this chapter the student will be able to:

- Describe the different cardiovascular and renal disorders,
- Understand the basic pharmacological principles of cardiovascular and renal drugs,
- Learn the rational use of these drugs,
- Describe the side effects of these drugs,

INTRODUCTION

In the past decades, cardiovascular diseases were considered as major health problems mainly for western countries. However, the problem of cardiovascular disorders is also increasing in developing countries including Ethiopia. The most commonly encountered cardiovascular


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Loop diuretics are indicated in cases of severe hypertension which is associated with renal failure, heart failure or liver cirrhosis.

c) Potassium sparing diuretics, e.g. spironolactone

They are used as adjuncts with thiazides or loop diuretics to avoid excessive potassium depletion and to enhance the natriuretic effect of others. The diuretic action of these drugs is weak when administered alone.

B) Sympathoplegic agents (Depressants of sympathetic activity).

Based on the site or mechanism of action sympathoplegic drugs are divided into:

a) Centrally acting antihypertensive agents e.g. methyldopa, clonidine

Centrally acting sympathetic depressants act by stimulating α_2 - receptors located in the vasomotor centre of the medulla. As a result, sympathetic out flow from the medulla is diminished and either total peripheral resistance or cardiac out put decreases. . Methyldopa is useful in the treatment mild to moderately severe hypertension.

Methyldopa is a prodrug and must be converted in the CNS to active α - methylnorepinephrine to exert the effect on blood pressure.

The side effects of methyldopa include sedation, vertigo, dry mouth, nausea, vomiting, diarrhea, postural hypotension, impotence, haemolytic anemia, weight gain and hypersensitivety reactions (fever, liver damage, thrombocytopenia).

b) Adrenoceptor antagonists, e.g propranolol (beta blocker), prazosin (alpha blocker), labetalol (alpha and beta blocker).

β – Blockers antagonize beta, receptors located on the myocardium and prevent the cardio acceleration, which follows sympathetic stimulation.

The rate and force of myocardial contraction is diminished, decreasing cardiac out put and thus, lowering blood pressure. An additional effect which can contribute to a reduction of blood pressure is that renin release is mediated by β receptors. Therefore, receptor blockade prevents angiotensin II formation and associated aldosterone secretion, resulting in a decrease in total peripheral resistance and blood volume.

The principal action of alpha adrenergic blocking drugs is to produce peripheral vasodilation.

Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels. Treatment with prazosin should be initiated with low dose (1mg 3 times daily) to prevent postural hypotension and syncope or be given at bed time.

c) Adrenergic neuron – blocking agents, e.g. guanethidine

Guanethidine is an adrenergic neuron-blocking drug recommended for treatment of severe forms of hypertension.

Guanethidine blocks adrenergic nerve transmission, preventing the release of transmitter. It lowers blood pressure by reducing both cardiac out put and total peripheral resistance.

d) Drugs which deplete catecholamine stores, e.g. reserpine.

Reserpine interferes with the storage of endogenous catecholamines in storage vesicles as a result of which little neurotransmitter is released upon stimulation. It leads to reduction of cardiac out put and peripheral vascular resistance. Reserpine is a second-line drug for treatment of hypertension.

e) Ganglion blockers, e.g. trimethaphan

Trimethaphan is ganglion blocking drug which is reserved for use in hypertensive emergencies only.

C) Direct vasodilators. These include:-

- Arterial vasodilators, e.g. hydralazine
- Arteriovenous vasodilators, e.g. sodium nitroprusside

Hydralazine:


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- Angiotensin converting enzyme inhibitors
- Central sympathoplegic agents

Beta-blockers are preferred in young patients, high renin hypertension and patients with tachycardia or angina and hypertension. Black patients respond well to diuretics and calcium channel blockers than to beta-blockers and ACE inhibitors.

If mono-therapy is unsuccessful, combination of two drugs with different sites of action may be used. Thiazide diuretics may be used in conjunction with a beta-blocker, calcium channel blocker or an angiotensin converting enzyme inhibitor.

If hypertension is still not under control, a third drug e.g. vasodilator such as hydralazine may be combined.

When three drugs are required, combining a diuretic, a sympathoplegic agents or an ACE inhibitor, and a direct vasodilator or calcium channel block is effective.

The treatment of hypertensive emergencies is usually started with furosemide given by parenteral route at dose of 20-40mg. In addition, parenteral use of diazoxide, sodium nitroprusside, hydralazine, trimethaphan, labetalol can be indicated.

II. Drug used in heart failure

Congestive heart failure occurs when there is an inability of the heart to maintain a cardiac out put sufficient to meet the requirements of the metabolising tissues.

Heart failure is usually caused by one of the following:

- Ischaemic heart disease,
- Hypertension,
- Heart muscle disorders, and
- Valvular heart disease.

Drugs used to treat heart failure can be broadly divided into:

A. *Drugs with positive inotropic effect.*
B. *Drugs without positive inotropic effect.*

A. Drugs with positive inotropic effect:-

Drugs with positive inotropic effect increase the force of contraction of the heart muscle. These include:

- Cardiac glycosides,

- Bipyridine derivatives,
- Sympathomimetics, and
- Methylxanthines

1. Cardiac glycosides.

Cardiac glycosides comprise a group of steroid compounds that can increase cardiac out put and alter the electrical functions. Commonly used cardiac glycosides are digoxin and digitoxin.

The mechanism of inotropic action of cardiac glycosides is inhibition of the membrane-bound Na^+/K^+ ATPase often called the "*Sodium Pump*". This results in an increased intracellular movement of sodium and accumulation of sodium in the cells. As a consequence of the higher intracellular sodium, decreased transmembrane exchange of sodium and calcium will take place leading to an increase in the intracellular calcium that acts on contractile proteins.

All cardiac glycosides exhibit similar pharmacodynamic properties but do differ in their pharmacokinetic properties. For example, digitoxin is more lipid soluble and has long half-life than digoxin.

Therapeutic uses of cardiac glycosides include:

- Congestive heart failure
- Atrial fibrillation,
- Atrial flutter, and
- Paroxysmal atrial tachycardia.

Toxicity of cardiac glycosides include:

- Gastrointestinal effects such as anorexia, nausea, vomiting, diarrhoea
- Cardiac effects such as bradycardia, heart block, arrhythmias
- CNS effects such as headache, malaise, hallucinations, delirium, visual disturbances (yellow vision)

Mild toxicities such as gastrointestinal and visual disturbance can be managed by reducing the dose of the drug.

For the management of arrhythmias or serious toxicity, potassium supplementation, administration of anti-arrhythmic drugs (e.g. lidocaine), and use of digoxin antibodies can be helpful.

2. Bipyridine derivatives, e.g. amrinone, milrinone.

These drugs possess both positive inotropic effect and vasodilator effects.

The suggested mechanism of action is inhibition of an enzyme known as phophodiesterase, which is responsible for the inactivation of cyclic AMP. Inhibition of this enzymes result in an increase in cAMP.

2. Vasodilators.

The vasodilators are effective in acute heart failure because they provide a reduction in preload (through venous dilation), or reduction in after-load (through arteriolar dilation), or both.

Hydralazine has a direct vasodilator effect confined to arterial bed. Reduction in systemic vascular resistance leads to a considerable rise in cardiac out put.

Sodium nitroprusside is a mixed venous and arteriolar dilator used also for acute reduction of blood pressure.

Vasodilator agents are generally reserved for patients who are intolerant of or who have contraindications to ACE inhibitors.

3. ***Angiotensin c*onverting enzyme (ACE) inhibitors.** Because of the pervasive involvement of angiotensin II in the undesirable compensatory responses to heart failure, reduction of this peptide has positive effects on the course of the disease.

These drugs reduce after load by reducing peripheral resistance and also reduce preload by reducing salt and water retention by way of reduction in aldosterone secretion.

They are nowadays considered a head of cardiac glycosides in the treatment of chronic heart failure.

The following are essential for long-term management of chronic heart failure:

Modify cardiovascular risk factor profile, e.g. cigarette smoking, obesity, salt intake Underlying causes should be treated, e.g. anemia, hypertension, valvular disease If this proves inadequate, diuretic should be given.

Give ACE inhibitor and digitalis (ACE inhibitors may be used before digitalis). In patients with persisting symptoms give vasodilators besides increasing the dose of diuretic and ACE inhibitors.

III) Pharmacotherapy of Angina pectoris

Angina pectoris develops as a result of an imbalance between the oxygen supply and the oxygen demand of the myocardium. It is a symptom of myocardial ischemia. When the increase in coronary blood flow is unable to match the increased oxygen demand, angina develops. It has become apparent that spasm of the coronary arteries is important in the production of angina.

Drugs used in angina pectoris

Organic nitrates e.g. nitro-glycerine, isosorbide dinitrate, etc.

Beta adrenergic blocking agents e.g. propranolol, atenolol, etc.

Class – I drugs

Quinidine: It blocks sodium channel so that there is an increase in threshold for excitability. It is well absorbed orally

Adverse effects: It has low therapeutic ratio. Main adverse effects are SA block, cinchonism, severe headache, diplopia and photophobia.

Lidocaine, which is used commonly as a local anaesthetic blocks both open and inactivated sodium channel and decreases automaticity. It is given parenterally.

Adverse effects: excessive dose cause massive cardiac arrest, dizziness, drowsiness, seizures, etc.

Flecainide: It is a procainamide analogue and well absorbed orally. It is used in ventricular ectopic beats in patients with normal left ventricular function.

Class –II drugs: Beta-adrenergic receptor blockers

Propranolol: Myocardiac sympathetic beta receptor stimulation increases automaticity, enhances A.V. conduction velocity and shortens the refractory period. Propranolol can reverse these effects. Beta blockers may potentiate the negative inotropic action of other antiarrhythmics.

Therapeutic uses: This is useful in tachyarrhythmias, in pheochromocytoma and in thyrotoxicosis crisis. It is also useful in patients with atrial fibrillation and flutter refractory to digitalis.

Class – III: Potassium channel blockers

AMIODARONE: This drug is used in the treatment of refractory supraventriculat tachyarrhythmias and ventricular tachyarrhythmias. It depresses sinus, atrial and A.V nodal function.

The main adverse effects of this drug are anorexia, nausea, abdominal pain, tremor, hallucinations, peripheral neuropathy, A.V. block

Class IV drugs: Calcium channel blockers

Verapamil: this drug acts by blocking the movement of calcium ions through the channels. It is absolutely contraindicated in patients on beta blockers, quinidine or disopyramide.

It is the drug of choice in case of paroxysmal supraventricular tachycardia for rapid conversion to sinus rhythm.

Class - V drugs:

Digoxin causes shortening of the atrial refractory period with small doses (vagal action) and a prolongation with the larger doses (direct action). It prolongs the effective refractory period of A.V node directly and through the vagus. This action is of major importance in slowing the rapid ventricular rate in patients with atrial fibrillation

Diuretics

Diuretics are drugs, which increase renal excretion of salt and water: are principally used to remove excessive extracellular fluid from the body.

In order to understand the action of diuretics it is important to have some knowledge of the basic processes that take place in the nephron (unit structure of kidney.

Fig 3.1 Sites of action of diuretics on renal tubule.

Approximately 180 liters of fluid is filtered from the glomerulus into the nephron per day. The normal urine out put is 1-5 liters per day. The remaining is reabsorbed in different areas of nephron. There are three mechanisms involved in urine formation

a) glomerular filtration
b) tubular reabsorption
c) Tubular secretion. These processes normally maintain the fluid volume, electrolyte concentration and PH of the body fluids.

Classification of diuretics:-

Most of the diuretics used therapeutically act by interfering with sodium reabsorption by the tubules. The major groups are:

I. Thiazides and related diuretics: e.g. Hydrochlorothiazide chlorthalidone, bendrofluazide, etc.
II. Loop diuretics: e.g. furosemide, ethacrynic acid, etc.
III. Potassium sparing diuretics e.g. triamterene, amiloride, spironolactone, etc.
IV. Carbonic anhydrase inhibitors e.g. acetazolamide
V. Osmotic diuretics e.g. mannitol, glycerol

I. Thiazide diuretics act by inhibiting NaCl symport at the distal convoluted tubule. They are used in hypertension, edema of hepatic, renal and cardiac origin.

Adverse effects: epigastric distress, nausea, vomiting, weakness, fatigue, dizziness, impotence, jaundice, skin rash, hypokalemia, hyperuricemia, hyperglycaemia and visual disturbance.

II. Loop diuretics: Loop diuretics like frusemde inhibit Na^+- K – 2Cl symporter in the ascending limb.

Adverse effects: Hypokalemia, nausea, anorexia, vomiting epigastric distress, fatigue weakness muscle cramps, drowsiness. Dizziness, hearing impairment and deafness are usually reversible. Therapeutic uses: acute pulmonary edema, edema of cardiac, hepatic and renal disease. Hypertension, cerebral edema, in drug overdose it can be used to produce forced diuresis to facilitate more rapid elimination of drug.

III. Potassium sparing diuretics mechanism of action: Potassium sparing diuretics (spironolactone, triamterene, amiloride) are mild diuretics causing diuresis by increasing the excretion of sodium, calcium and bicarbonate but decrease the excretion of potassium.

Adverse effects: G.I. disturbances, dry mouth, rashes confusion, orthostatic hypotension, hyperkalaemia. Hyponatraemia

Therapeutic uses: used with conjunction with thiazides or loop diuretics in edema due to, cardiac failure nephrotic syndrome and hepatic disease.

IV. Carbonic anhydrase inhibitors: these drugs like acetazolamide inhibit the enzyme carbonic anhydrase in renal tubular cells and lead to increased excretion of bicarbonate, sodium and potassium ions in urine. In eye it results in decrease information of aqueous humor. Therefore these are used in treatment of acute angle glaucoma. Main adverse effects of these agents are drowsiness, hypokalemia, metabolic acidosis and epigastric distress.

V. Osmotic diuretics: these drugs like mannitol and glycerine (glycerol) are freely filtered at the glomerulus and are relatively inert pharmacologically and undergo limited reabsorption by renal tubule. These are administered to increase significantly the osmolality of plasma and tubular fluid. Some times they produce nausea, vomiting, electrolyte imbalances. They are used in cerebral edema and management of poisoning.

Drugs used in hypotensive states and shock

Antihypotensive drugs or agents are used to elevate a low blood pressure and may be classified as follows:

I. ***Agents intended to increase the volume of blood in active circulation***. These include intravenous fluids such as whole blood, plasma, plasma components, plasma substitutes and solution of crystalloids

II. ***Vasoconstrictor drugs*** these include:

- Peripherally acting vasoconstrictors which are further divided into sympathomimetic drugs and direct vasoconstrictors.

Sympathomimetics used to elevate the blood pressure include adrenaline, noradrenaline, methoxamine, phenylephrine, mephentermine and ephedrine.

Direct vasoconstrictors include vasopressin and angiotensin.

Treatment of shock

Shock is a clinical syndrome characterized by decreased blood supply to tissues. Common signs and symptoms include oliguria, heart failure, disorientation, mental confusion, seizures, cold extremities, and comma.

Most, but not all people in shock are hypotensive. The treatment varies with type of shock.

The choice of drug depends primarily on the *patho-physiology involved.*

- For cardiogenic shock and decreased cardiac out put, ***dopamine*** or other ***cardiotonic*** drug is indicated. With severe CHF characterized by decreased CO and high PVR, ***vasodilator drugs*** (nitropruside, nitroglycerine) may be given along with the cardiotonic drug. ***Diuretics*** may also be indicated to treat pulmonary congestion if it occurs.
- For anaphylactic shock or neurogenic shock characterized by ***severe vasodilation*** and decreased PVR, a ***vasoconstrictor*** drug (e.g. levarterenol) is the first drug of choice
- For hypovolemic shock, intravenous fluids that replace the type of fluid lost should be given
- For septic shock, appropriate ***antibiotic therapy*** in addition to other ***treatment measures***.


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CHAPTER FOUR

AUTACOIDS

Learning Objectives:


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3. Less potent and less sedative: such as pheniramine
4. Non-sedative: such as terfenadine, loratadine, and cetrizine.

The newer generation agents are relatively free of central depressant effects.

These agents may also possess anti-emetic effects.

Pharmacological Actions:

1. Antihistaminic Actions:-they block histamine effects at various sites.
2. Other Effects: are independent of the antihistaminic effects and vary widely according to the drug used.

Most of them produce CNS depression resulting in sedation, drowsiness, inability to concentrate, and disturbances of coordination. But very few agents such as phenindamine may produce stimulation.Anti-motion sickness effects are exhibited by promethazine, diphenhydramine, and dimenhydinate.Promethazine and mepyramine have significant local anesthetic effect.Majority possess atropine-like effects.Some have central antimuscarinic actions which is useful in the treatment of Parkinsonism.

Pharmacokinetics:

They are well-absorbed following oral and parenteral administration. And are mainly metabolized by the liver; degradation products are removed in the urine.

Therapeutic Uses:

1. ***Allergic Disorders***:-Including urticaria, seasonal hay fever, atopic and contact dermatitis, mild blood transfusion reactions.

N.B. Their topical use is not recommended because of the risk of sensitization and a high tendency to cause eczematous reactions.

They are not effective in bronchial asthma and common cold.

2. ***Other uses:***

Diphehydramine and promethazine are used as hypnotics. Diphenhydramine and orphenadrine are effective in the treatment of Parkinsonism .Dimehydrinate and promethazine are employed in the prevention and treatment of motion sickness, other vomiting disorders associated with labyrinthine dysfunction as well as nausea and vomiting associated with pregnancy. Diphenhydramine is frequently used in the treatment of cough as combination preparation with other agents.

Adverse Effects:

- Are usually mild. Most common is sedation. The most common anticholinergic adverse effect is dryness of the mouth. They may themselves occasionally cause allergic reactions.

2. 5-Hydroxytreptamine (Serotonin)

It is widely distributed in plants and animals. Highest concentration in mammals is found in the pineal gland, acting as a precursor for melatonin. It is synthesized from the amino acid tryptophan and acts on several types of receptors.

Pharmacolocial Actions:

5-HT causes constriction of renal, splanchnic, meningeal, and pulmonary arteries and veins and venules, but dilatation of the blood vessels of skeletal musles, coronaries, and skin capillaries. It has weak direct ino-chronotropic effect on the myocardium. It also stimulates smooth muscles, especially of the intestines. Serotonin is widely distributed in the CNS, serving as a neurotransmitter. Altered functions may be responsible for disturbances in sleep, mood, sexual behavior, motor activity, pain perception, migraine, temperature regulation, endocrine control, psychiatric disorders and extra-pyramidal activity.

Serotonin Agonists:

Sumatriptan is a selective agonist of 5-HT_1 receptors and is highly effective in treating acute attacks of migraine, but is not useful in the prevention. It relieves the nausea and vomiting, but the headache may recur, necessitating repeated administrations.

It is administered orally or by the subcutaneous route. The bioavailability of oral dose is only 14 %; thus, the oral dose is several times larger than the subcutaneous dose.

Adverse effects include flushing and heat at the injection site, neck pain, dizziness, and tingling of the hands.

The drug is contraindicated with symptomatic ischemic heart diseases, angina, and hypertension as it may cause coronary vasoconstriction.

Buspirone, another serotonin agonist, is a useful effective anxiolytic agent.

Serotonin Antagonists:

a. ***Methysergide:*** blocks the actions of 5-HT on a variety of smooth muscles. It also has a weak direct vasoconstrictor effect. It is an effective prophylactic agent for migrainous headaches. But has no effect in treating acute attacks, even may worsen the condition. Adverse reactions include gastrointestinal irritation, drowsiness, vertigo, and psychic disturbances.

b. ***Cyproheptadine:*** is a potent antagonist of 5-HT and to a smaller extent of histamine and acetylcholine. It stimulates appetite probably by acting directly on the hypothalamus. It can block the release of hydrocortisone, and the production of aldosterone. It is mainly used to relieve the itching associated with skin disorders such as allergic dermatitis. The common adverse reaction is drowsiness.

c. ***Ondansetron***: is specific 5-HT_3 receptor antagonist. Given orally or intravenously, it is useful in the management of nausea and vomiting associated with cytotoxic therapy. Adverse reactions include headache, constipation, and allergic reactions.

d. Prochlorperazine and haloperidol have anti-5-HT activity and are sometimes used for resistant acute attacks.

3. Prostaglandins:

They were named so because of their presumed origin from the prostate gland. Human seminal fluid is the richest known source, but they are also present in various tissues. The prostaglandins are synthesized from polyunsaturated fatty acids at their sites of action. PG E_2 and PG F_2 are the two main prostaglandins. They are released in the body by mechanical, chemical, and infectious insults.

They play an important role in the development of the inflammatory response in association with other mediators.

Synthesis of important prostaglndins and leukotriens:

Essential Fatty Acids in the diet

Cell membrane phospholipids

Arachidonic acid

5-Lipooxygenaseu

Exercise

1. Explain the antagonistic effects of histamine and adrenaline.

2. Discuss the consequences of inhibition of prostaglandin synthesis.

CHAPTER FIVE

DRUGS ACTING ON THE RESPIRATORY SYSTEM

Learning Objectives

At the end of the chapter the students will be able to learn:

- Detail description of drug used to treat bronchial asthma, cough, nasal congestion as a result of some disorders and allergic condition.
- Broad classification of drugs used to treat bronchial asthma
- The pharmacokinetics, mechanism of action, side effects of each group of drugs used to treat bronchial asthma.

INTRODUCTION

The respiratory system includes the upper airway passages, the nasal cavities, pharynx and trachea as well as the bronchi and bronchioles. Respiration is the exchange of gases between the tissue of the body and to outside environment. It involves breathing in of an air through the respiratory tract, uptake of oxygen from the lungs, transport of oxygen through the body in the blood stream, utilization of oxygen in the metabolic activities (cells and removal of carbon dioxide from the body.

Drug therapy of pulmonary disorders is generally directed towards altering a specific physiologic function. The chapter will focus on drugs used to treat some of the more common disorders affecting the respiratory system particularly bronchial asthma, allergies and congestions associated with certain respiratory disorders.

1.1 Bronchial asthma

Asthma is physiologically characterized by increased responsiveness of the trachea and bronchi to various stimuli and by wide spread narrowing of the airways that changes in severity either spontaneously or as a result of therapy

Impairment of airflow in bronchial asthma is caused by three bronchial abnormalities.

i. Contraction of airway smooth muscles
ii. Thickening of bronchial mucosa from edema and cellular infiltration
iii. Inspissations in the airway lumen of abnormally thick, viscid plugs of excessive mucus.

Pathogenesis

There are two types of bronchial asthma i.e extrinsic and intrinsic.

Extrinsic asthma is associated with history of allergies in childhood, family history of allergies, hay fever, or elevated IgE.

Intrinsic asthma occurs in middle-aged subjects with no family history of allergies, negative skin tests and normal serum IgE.

Immunologic model

Asthma is a disease mediated by reaginic (IgE) antibodies bound to mast cells in the airway mucosa. But not all features of asthma can be accounted for by antigen-challenge model. Non-antigenic stimuli like viral infections, exercise, and cold air stimulate bronchial spasm.

In allergic asthma, the immediate phase, i.e the initial response to allergen provocation, occurs abruptly and is due mainly to spasm of the bronchial muscle.Allergen interaction with mast cell-fixed IgE release histamine, LTC4 and LTD4 which cause bronchial spasm.

PHARMACOTHERAPY OF BRONCHIAL ASTHMA

Drug used in the treatment of bronchia asthma can be grouped into three main categories:

1. Bronchodilators
   a. β- Adrenergic agonists which include:
      - Non selective β-agonists e.g. adrenaline
      - Selective β

Mechanism of Action

β-Agonists stimulate adenyl cyclase and increase formation of cAMP in the airway tissues.

They have got several pharmacological actions important in the treatment of asthma

- Relax smooth muscles
- Inhibit release of inflammatory mediator or broncho constricting substances from mast cells.
- Inhibit microvasculature leakage
- Increase mucociliary transport

a. Non-selective β- agonists

- Cause more cardiac stimulation (mediated by a β1 receptor), they should be reserved for special situation.
- Epinephrine: very effective, rapidly acting bronchodilator especially preferable for the relief of acute attack of bronchial asthma.
- Administered by inhalation or subcutaneously.

Side effects include arrhythmia and worsening of angina pectoris, increase blood pressure, tremors etc

Contraindication: - hypertension, arrhythmia,

Ephedrine: compared to epinephrine, it has longer duration of action but more pronounced central effect and lower potency. It can be given orally. The drug is currently infrequently used because of development of more efficacious and beta$_2$-selective agents.

b. Selective β_2- selective agonists

Largely replaced non – selective β_2- agonists, are effective after inhaled or oral administration and have got longer duration of action. They are the most widely used sympathomimetics. Commonly used drugs both by oral and inhalation are Salbutamol, terbutaline, metaproterenol, pirbuterol and bitolterol.

Salmeterol and formeterol are new generation, long acting β_2- selective agonists (with duration of action 12 hrs or more). These drugs appear to interact with inhaled corticosteroids to improve asthma control.

Delivery of adrenoreceptor agonists through inhalation results in the greatest local effect on airway smooth muscle with least systemic toxicity.

Side effects

Tremors, anxiety, insomnia, tachycardia, headache, hypertension and etc.

Contraindications: Sympathomimetics are contraindicated in patients with known hypersensitivity to the drugs

Precautions: They should be used cautiously in patients with hypertension, cardiac dysfunction, hyperthyroidism, glaucoma, diabetes, pregnancy.

2. METHYLXANTHINES

- The three important methylxanthines are theophylline, theobromine, and caffeine. The theophylline preparations most commonly used for therapeutic purposes is aminophylline (theophylline plus diethylamine).

Mechanism of Action

i. Competitively inhibit phosphodiesterase (PDE) enzyme leading to increased cAMP level.

ii. They competitively inhibit the action of adenosine on adenosine (A1 and A2) receptors (adenosine has been shown to cause contraction of isolated airway smooth muscle and to provoke histamine release from airway mast cells.

iii. Inhibit the release of histamines and leukotriens from the mast cells

Of the three natural xanthines, agents theophylline is most selective in its smooth muscle effect, while caffeine has the most marked central effect.

Pharmacokinetics

Only slightly soluble in water so has been administered as several salts containing varying amounts of theophylline base. Most preparations are well absorbed from gastro intestinal tract and metabolized by liver. Doses should be decreased in cases of liver disease and heart failure.

Adverse Effects:

Anorexia, nausea vomiting, abdominal discomfort, headache, anxiety, insomnia, seizures, arrhythmias

Theophylline is now largely reserved for patients in whom symptoms remain poorly controlled despite the combination of regular treatment with an inhaled anti- inflammatory agent and as needed use of a ß2 agonist.

3. MUSCRANIC RECEPTOR ANTAGONISTS

Mechanism of Action

Muscarinic antagonist competitively inhibit effect of acetylcholine at muscarinic receptors – hence block the contraction of air way smooth muscle and the increase in secretion of mucus that occurs in response to vagal activity e.g atropine sulfate

Systemic adverse effects as a result of rapid absorption include urinary retention, tachycardia, loss of accommodation and agitation and local effects like excessive dryness of mouth limits the quantity of atropine used. Ipratropium bromide is poorly absorbed and does not readily enter the central nervous system thus permits the delivery of high doses to muscarinic receptor in the airways; hence, it can safely be used for bronchial asthma.

Antimuscranic antagonist drugs appear to be slightly less effective than β- agonists agents in reversing asthmatic bronchospasm, The addition of ipratropium enhances the bronchodilation produced by nebulized albuterol in acute sever asthma. The antimuscarinic agents appear to be of significant value in chronic obstructive pulmonary diseases - perhaps more than asthma. They are useful as alternative therapies for patients intolerant of β - agonists

4. ANTI-INFLAMMATORY AGENTS: CORTICOSTEROIDS

bronchodilator. Aerosol treatment is the most effective way to decrease the systemic adverse effect of corticosteroid therapy. Abrupt discontinuation should be discouraged because of the fear of adrenal insufficiency. Doses should be decreased after improvement. Regular or controlled therapy is better maintained with aerosol corticosteroids.

Clinical uses in bronchial asthma

- Urgent treatment of severe asthma not improved with bronchodilator
    - IV, inhalation or oral.
- Nocturnal asthma prevention
    - oral or inhalation
- Chronic asthma
    - Regular aerosol corticosteroids

Side effects:

- Suppression of the hypothalamic-pituitary-adrenal axis
- Osteoporosis
- Sodium retention and hypertension
- Cataract
- Impairment of growth in children
- Susceptibility to infection like oral candidiasis, tuberculosis

5. MAST CELL STABILIZERS

e.g cromolyn sodium

Mechanism of action

Stabilize the mast cells so that release of histamine and other mediators is inhibited through alteration in the function of delayed chloride channel in cell membrane. It has no role once mediator is released and is used for casual prophylaxis.

Clinical uses

-

TREATMENT OF STATUS ASTHMATICS

Status asthmatics

Very sever and sustained attack of asthma which fails to respond to treatment with usual measures

Management includes:

- Administration of oxygen
- Frequent or continuous administration of aerosolized ß2 agonists like salbutamol
- Systemic corticosteroid like methyl prednisolone or hydrocortisone IV
- Aminophylline IV infusion
- Iv fluid to avoid dehydration
- Antibiotics in the presence of evidence of infection

ANTI-TUSSIVES

Cough is a protective reflex, which serves the purpose of expelling sputum and other irritant materials from the respiratory airway.

Types:

- Useful productive cough
    - Effectively expels secretions and exudates
- Useless cough
    - Non-productive chronic cough
    - Due to smoking and local irritants

Anti-tussives are drugs used to suppress the intensity and frequency of coughing.

Two Types of Anti-tussives:

1. Central anti- tussives
    - Suppress the medullay cough center and may be divided into two groups:
        - Opoid antitussive e.g. codeine, hydrocodeine, etc
        - Non opoid antitussives e.g. dextromethorphan
2. Peripheral antitussives
    - Decrease the input of stimuli from the cough receptor in the respiratory passage.

e.g: Demulcents e.g. liquorices lozenges, honey

Local anesthetics e.g. lidocaine aerosol

Demulcents coat the irritated pharyngeal mucosa and exert a mild analgesic effect locally.

CODEINE

Codeine is a narcotic relatively less addicting drug and central antitussive agen and it's main side effects are dryness of mouth, constipation and dependence.

DEXTROMETROPHAN

Dextromethorphan is an opoid synthetic antitussive, essentially free of analgesic and addictive properties and the main side effects are respiratory depression

Expectorant is a drug that aid in removing thick tenacious mucus from respiratory passages, e.g. Ipecac alkaloid, sodium citrate, saline expectorant, guanfenesin, potassium salts

Mucolytics are agents that liquefy mucus and facilitate expectoration, e.g.acetylcysteine.

DECONGESTANTS

Decongestants are the drugs that reduce congestion of nasal passages, which in turn open clogged nasal passages and enhances drainages of the sinuses.

e.g phenylephrine, oxymetazoline etc.

Mechanism of Action

Mucus membrane decongestants are α_1 agonists, which produce localized vasoconstriction on the small blood vessels of the nasal membrane. Reduce congestion in nasal passages.

Clinical uses:

Used in congestion associated with rhinitis, hay fever, allergic rhinitis and to a lesser extent common cold.

Drugs can be administered nasally or orally for longer duration of action.

Classification:

Side effects:

1. Rebound nasal congestion
2. Ischemic changes in mucus membranes
3. Nasal burning, stinging, dryness
4. Tachycardia, arrhythmia, nervousness, restlessness, insomnia, blurred vision

Contraindications

1. Hypertension, severe coronary artery disease

Exercice

1. What are the drugs used to treat bronchial asthma and how are they classified?
2. Explain mechanism of action and pharmacokinetic properties of methylxanthines.
3. What are the side effects and contraindications of glucocorticoids?
4. What are differences between antitussives and expectorants? Give example.
5. Give examples of decongestant drugs and their side effects.

CHAPTER SIX

DRUGS USED IN GASTROINTESTINAL DISEASES

Learning objectives

After completing this chapter the student will be able to:

-

Zollinger-Ellison syndrome is caused a tumor of gastrin secreting cells of pancreas characterized by excessive secretion of gastrin that stimulates gastric acid secretion.

The disorders can be treated by drugs, which are able to:

- Neutralize gastric acid (HCl) e.g. magnesium hydroxide
- Reduce gastric acid secretione.g. cimetidine
- Enhance mucosal defences e.g sucralfate
- Exert antimicrobial action against H.pylori e.g. clarithromycin

The effective therapeutic approach of ucler is based on the adage:

“no acid, no ulcer”

Anti – ulcer drugs: drugs used in the prevention and treatment of peptic ulcer disease act mainly to decrease cell-destructive effects, increase cell – protective effects or both.

A: Gastric acid neutralizers (antacids)

Antacids are alkaline substances (weak bases) that neutralize gastric acid (hydrochloric acid)

They react with hydrochloric acid in the stomach to produce neutral or less acidic or poorly absorbed salts and raise the PH of stomach secretion, and above PH of 4, pepsin is inactive. Antacids are divided into systemic and nonsystemic

Systemic, e.g. sodium bicarbonate are absorbed into body fluids and may alter acid – base balance. It can be used in the treatment of metabolic acidosis.

Non systemic, do not alter acid – base balance significantly. They are used as gastric antacids; and include aluminium, magnesium and calcium compounds e.g. ($Al(OH)_3$, MgS_2O_3 , $Mg(OH)_2$, $CaCO_3$)

Á Gastric antacids differ in their potency, in onset of action, du.9891 0 panalinc(mayJ- miMTc003 Tj/TT

•

The most commonly used antacids, are mixtures of aluminium hydroxide and magnesium hydroxide (e.g. Gelusil, Maalox etc).

Antacids act primarily in the stomach and are used to prevent and treat peptic ulcer. They are also used in the treatment of Reflux esophagitis and Gastritis

B. Gastric acid secretion inhibitors (antisecretory drugs):

HCl is secreted by parietal cells of the gastric mucosa which contain receptors for acetylcholine, histamine and gastrin that stimulate the secretion.

Fi

F

Cimetidine dosage: PO 400mg 2 times/day, with meals and at bed time, or 800mg once daily at bed time for 6-8 weeks.

Prophylaxis of recurrent ulcer, PO 400mg at bed time. High doses are used in the treatment of Zollinger-Ellison syndrome.

Common adverse effects: muscular pain, headache, dizziness,

- Colloidal bismuth compounds additionally exert bactericidal action against H.pylori

  Other drugs that can to eradicate H.pylori such as amoxicillin, metronidazole, clarithromycin and tetracycline are included in the anti-ulcer treatment regimens.

- Protaglandins have both antisecretory and mucosal protective effects.

  Example: **Misoprostol**- used for prevention of NSAID – induced ulcer.

II. Laxatives and cathartics (purgatives)

Laxatives and ***cathartics*** are drugs used orally to evacuate the bowels or to promote bowel elimination (defecation).

The term ***laxative*** implies ***mild effects***, and eliminative of soft formed stool. The term cathartic implies ***strong effects*** and ***elimination of liquid*** or ***semi liquid*** stool. Both terms are used interchangeably because it is the ***dose*** that determines the effects rather than a particular drug.

Example:- castor oil laxative effect= 4ml
Cathartic effect = 15-60ml

Laxative and cathartics are arbitrarily classified depending on mode of action as:

- Bulk forming laxatives: are substances that are largely unabsorbed from the intestine. They include hydrophilic colloids such as psyllium, bran, methylcellulose, etc. When water is added, the substances swell and become gel-like which increases the bulk of the fecal mass that stimulates peristalsis and defecation.

Osmotic laxatives such as magnesium sulfate, magnesium hydroxide, sodium phosphate, etc. also belong to bulk – forming laxatives.

These substances mod th TDen

- Fecal softners – Decrease the surface tension of the fecal mass to allow water to penetrate into the stool. They have detergent – like property e.g. ***docusate***.
- They may also decrease water absorption through intestinal wall.
- Lubricant laxatives e.g. ***liquid paraffin*** (mineral oil). It lubricates the intestine and is thought to soften stool by retarding colonic *absorption of fecal water*.

- Used as retention enema.

Indications for use

Laxatives and cathartics are used:

1. To relieve constipation – bulk – forming
2. To prevent straining – stool softeners
3. To empty the bowel in preparation for bowel surgery or diagnostic procedures (saline or stimulant)
4. To accelerate elimination of potentially toxic substances from the GI tract (saline or stimulant)
5. To accelerate excretion of parasite after anthelmintic drugs (saline or stimulant) have been administered.

- Constipation is a common problem in older adults and laxatives are often used or overused. Non drug measures to prevent constipation (e.g. ***increasing intake of fluid*** and ***high –fiber foods, exercise***) are much ***preferred to laxatives***.

III. Antidiarrhoeals:

- Are used in the treatment of diarrhea, defined as the *frequent expulsion* of liquid or semi liquid stools → hinders absorption of fluids and electrolytes.
- In many instances, drug intervention is not required because is a protective mechanism used in an attempt by the body to flush out the offending pathogen or agent.

  Antidiarrheal drugs may be given to relive the symptom (non-specific therapy) or may be given to treat the underlying cause of the symptom (specific therapy).

- For symptomatic treatment of diarrhoea, opiates and opiate derivatives are the most effective. They decrease diarrhea by slowing propulsive movements in small and large intestine.

Morphine is effective but not used because of serious potential adverse effects, other synthetic drugs such as diphenoxylate and loperamide are commonly used

- Adsorbent – demulcent products such as kaolin – pectin preparation may be included in antidiarrheal preparations, unfortunately, they may adsornutrient and other drugs, including the antidiarrheal agents if given concurrently
- Anticholinergic agents e.g. atropine are occasionally used to decrease abdominal cramping and pain associated with diarrhea.
    - Specific therapy may include the use of antibacterial, which are recommended for use in carefully selected cases of bacterial enteritis.
    - Severe diarrhea by salmonella, shigella, campylobacter and clostridia. Species can be treated by antibiotics (ampicillin, chloramphinicol, colistin, co-trimoxazole etc.

Indications for use

1. severe or prolonged diarrhea (>2-3 days)
2. when specifice causes have been determined

Glucose – electrolyte solution should be given in severe cases for electrolyte and fluid replacement. It contains:

Glucose	20 gm
NaCl	3.5gm
$NaHCO_3$	2.5gm

- Vomiting occurs when the vomiting center in the medulla oblongata is stimulated. Dopamine and acetylcholine play a major role in stimulating the vomiting center. To a certain extent, vomiting is a protective mechanism which can result from various noxious stimuli.

Drugs used in nausea and vomiting belong to several different therapeutic classifications.

- Most antiemetic agents relieve nausea and vomiting by acting on the vomiting center, CTZ, cerebral cortex, vestibular apparatus, or a combination of these.
- Antiemetic drugs are generally more effective in prophylaxis than treatment. Antiemetic drugs include:

Phenothiazines (neuroleptics) such as chlorpromazine

- Acts on CTZ and vomiting center
- Block dopamine receptors
- Are effective in prevention or treating nausea and vomiting induced by drugs, radiation therapy, surgery and most other stimuli
  (e.g. pregnancy).
- Are generally ineffective in motion sickness.

Antihistamines – such as promothazine, dimehydrinate etc.

- Are especially effective in prevention and treatment of motion sickness (but they may cause concurrent drowsiness, that may be troublesome for travellers)

Miscellaneous antiemetics

Metoclopramide has both central and peripheral antiemetic effects. Centrally, metoclopoamide antagonizes the action of dopamine.

Peripherally metoclopoamide stimulates the release of acetylcholine, which in turn, increases the rate of gastric emptying (used in esophapeal reflux)

Indication as chlorpromazine

- ***Scopolamine,*** an anticholinergic drug is very effective in reliving nausea & vomiting associated with motion sickness.
- Ondansetron- is serotonin antagonist (5-HT_3 receptors) found on the afferent fibers of the vagus nerve and in parts of the brain associated with CTZ.
- Controls chemical induced vomiting and nausea)

CHAPTER SEVEN

DRUGS ACTING ON THE BLOOD

INFLAMMATION AND GOUT

Learning Objectives

After reading and studying this chapter the student should be able to

- Discuss the pharmacokinetics of iron, Vit B_{12} and folic acid.
- Explain the mechanisms of action of major anti anemic drugs
- Discuss the use of iron to treat iron deficiency anemia, the use of Vit B_{12} and folic acid to treat megaloblastic anemia.
- Describe how heparin and oral anticoagulants produce their effect.
- Discuss the indication of heparin and oral anticoagulants
- Identify major adverse reactions associated with heparin and oral anticoagulants

INTRODUCTION

Hematopoiesis, the production of circulating erythrocytes, platelets and leukocytes from undifferentiated stem cells, is a remarkable process that produces over 200 billion new cells per day in the normal person and even greater number of blood cells in people with conditions that causes loss or destruction of blood cells. The hemopoietic machinery resides primarily in the bone marrow in adults, and requires constant supply of three essential nutrients – iron, vitamin B12 and folic acid

ANEMIA – a deficiency in oxygen carrying erythrocytes and very common in developing countries

In this section anemia due to deficiency of iron, vit B_{12} or a folic acid will be dealt with.

AGENTS USED IN ANEMIAS

IRON

Iron forms the nucleus of the iron porphyrin heme ring, which together with globin chains forms hemoglobin that reversibly binds oxygen and provides the critical mechanism for oxygen

delivery from lungs to other tissues. In the absence of adequate iron, small erythrocytes with insufficient hemoglobin are formed resulting in microcytic hypochromic anemia.

Causes of Iron Deficiency Anemia

1. Nutritional deficiency

Low intake of iron containing foods, reduced absorption as a result of mucosal damage, co-administration of drugs that chelate iron e.g. antacids and after gastrectomy iron deficiency will take place.

2. Chronic blood loss

Chronic nose bleeding, Menorrhagia, Occult GI bleeding, Worm infestation and Ulers, e.g. PUD.

Pharmacokinetics of Iron

Daily requirement of Iron - Male 10mg
- Female 15 mg

Increases in growing children, pregnant and lactating women

Sources

- Dietary - mostly in the organic form from meat, cereals, etc.

Body composition of Iron

Total content of Iron in the body is about 4000mg in an adult male, of which about 2/3 – 2500 mg is present in circulating red blood cells see table.

Table: Iron distribution in normal adults

	Iron content (mg)	
	Men	**Women**
Hemoglobin	3050	1700
Myoglobin	430	30
Enzymes	10	8
Transport (transferin	8	6
Storage (ferritin and other form)	750	other form(
Total	4246	

The average male adult weighs 80 kg and has a mean Hb level of 16 g/dL and the female adult weighs 55 kg and has a mean Hb level of 14 g/dL.

Absorption

Iron is absorbed in duodenum and proximal jejunum. A normal individual with out iron deficiency absorbs 5-10 % of daily intakes.

Absorption is increased in states with increased requirements or deficiencies (low iron stores, pregnancy, menstruation, growing children, and blood loss) and/or dietary factors such as heme-iron (from meat, etc), HCl and vitamin C.

Absorption is decreased from non heme iron (Fe^{3+}), in the presence of phytates, antacids and other chelates, and following gastric resection.

Iron crosses the stinal mucosal cell by active transport; then according to mucosal iron store, it can either be available to transferrin to be transported to plasma or be stored in the mucosal cell as ferritin.

Storage: Iron is stored primarily as ferritin in intestinal mucosal cells and in macrophages in the liver, spleen and bone.

Elimination:

Very small amount are execrated in stool by exfoliation of intestinal mucosal cells and trace amounts are execrated in bile, urine and sweat with total daily excretion not more than 1mg/day.

TREATMENT OF IRON DEFICIENCY ANEMIA

The cause should always be identified and treated whenever possible. Treatment of iron deficiency anemia consists of administration of oral or parenteral iron preparation.

1. Oral Iron Therapy:

Only ferrous salts should be used because of most efficient absorption. Ferrous sulfate, ferrous gluconate, ferrous fumarate are the most commonly used oral iron preparations. About 25% of oral iron given as ferrous salt can be absorbed; therefore 200-400mg elemental irons should be given daily to correct iron deficiency most rapidly. Treatment should be continued for 3-6 months to replenish iron stores.

Side effects: Oral iron therapy can cause nausea, vomiting, epigastric discomfort, abdominal cramps, constipation and diarrhea.


EPHTI

Pharmacokinetics

Absorbed in distal ileum after combined with intrinsic factor secreted by stomach through a highly specific receptor mediated transport system once absorbed vit B_{12} is transported to various cells of the body bound to plasma glycoprotein, transcobalamin II. Excess vitamin B_{12} is

Physiologic functions

It plays a role in the biosynthesis of purines and pyrimidines, i.e., DNA.

Folic acid Ą dehydrofolate Ą tetrahdyroflate

$ $

pyrmidens purine

$ $

Phamacokinetics

Unaltered folic acid is readily and completely absorbed in the proximal jejunum. 5 -20 mg of folates are stored in the liver and other tissues. Body stores of folates are relatively low and daily requirement is high and hence folic acid deficiency and magaloblasitc anemia can develop within 1 -6 months after the in take of folic acid stops. Folates are excreted in the urine and stool.

Deficiency:

Common among elderly patients, poor patients, pregnant ladies. It results in megaloblasiic anemia. Congenital malformation in newborn like spina bifida are also consequences of folate deficiency during pregnancy.

Causes

Dietary deficiency, alcoholics with liver disease, hemolytic anemia, malabsorption syndrome,

- The administration of folic acid in the setting of vitB_{12} deficiency will not prevent neurological manifestation even though it will largely correct the anemia caused by the vitamin B_{12} deficiency.

Drugs used in Disorder of coagulation

Introduction

Hemostasis is spontaneous arrest of bleeding from a damaged blood vessel. Steps: Vascular injury Ą vasospasm Ą platelate adhesion Ą platelate aggregation Ą coagulation cascades Ą fibrin formation

Anticoagulants are the drugs which inhibit fibrin formation.

Classification

Based on mechanism of action

1. Fast and direct acting
   e.g: Heparin
2. Slow and indirect acting
   - Oral anticoagulants
     e.g Warfarin and Dicumarol

Heparin

It is a heterogeneous mixture of sulfated mucopolysaccharides

Mechanism of action

Heparin activates antithrobimin III (AT III) which inhibits clotting factor proteases and hence it inhibits the formation of fibrin clots, inhibits the conversion of fibrinogen to fibrin, and inactivates

Side effects:

Bleeding is the major side effect, allergy, alopecia, osteoporosis and thrombocytopenia

Contraindications

Contraindicated in patients who are hypersensitive to the drug, are actively bleeding or have hemophilia, thrombocytopenia, purpura, sever hypertension, intracranial hemorrhage, infective endocarditis, active tuberculosis, etc.

ORAL ANTICOAGULANTS

WARFARIN

This compound was originally employed as a rodent poison. It is the most widely used coumarin anticoagulant and may be considered to be the drug of choice as an oral anticoagulant.

Mechanism of action

- The anticoagulant prevents reductive metabolism of the inactive vitamin K epoxide back to its active form

Pharmacokinetics:

- It is administered orally as sodium salt and has 100% bioavailability.
- The drug has slow onset of action, and long half-life in plasma (36hr) because 99% of the drug is bound to albumin.

Clinical uses

Prevention and treatment of deep vein thrombosis, treatment of atrial fibrillation with thrombus formation, prevention and treatment of pulmonary embolus, as part of the treatment of coronary occlusion and prevention of thrombus formation after value replacement

Side effects

Birth defect in pregnancy, hemorrhagic disease of newborn, hemorrhagic infarcts and cutaneous necrosis

Contraindications – similar to heparin and the drug should never be administered during pregnancy.

Drug interactions

Á The effect of warfarin will be increased when it is used with the following drugs.

Cimitidine, dsulfiram, metronidazole, phenylbutazone, ASA and cephalosporin (3rd generations)

- The effect of warfarin will be decreased when it is used with the following drugs.

Barbiturates, Cholestyramine, Rifampincin, Diuretics, vit K

THROMBOLYTIC AGENTS

Fibrinolytic agents rapidly lyse thrombi by catalyzing the formation of plasmin from plasminogen. All thrombolytic agents currently in use act directly or indirectly as plasminogen activators. The presently used plasminogen activators are:

a. Streptokinase- a protein synthesized by streptococci, combines with plasminogen to convert it to active plasmin.

b. Urokinase-human enzyme synthesized by the kidneys that directly converts plasminogne to active plasmin

c. Anistreptase (Acylated plasminongen -streptokinase activator)- bacterial streptokinase plus human plasminogen

d. Tissue plaminogen activator (tPA)-this activates preferentially plasminogen that is bound to fibrin.

Indications:

Multiple pulmonary emboli, central deep vein thrombosis and acute myocardial infarction.

Adverse Reactions:

Bleeding and allergic reactions are most common adverse effects thrombolytics.

Contra-indications:

Severe hypertension, recent cranial trauma and history of cerebrovascualr accident.

ANTIPLATELET DRUGS

Platelet function is regulated by three categories of substances

1. Agents outside the platelet that interact with platelet membrane receptors, e.g. catecholamines, prostacyclin
2. Agents generated within the platelets and interact with the membrane receptors, e.g. prostaglandin E_2 and serotonin

3. Agents generated within the platelet and act within the platelet, e.g. thromboxane A_2 and calcium ions

Antiplatelets act on any one of the above processes. They include aspirin, ticlopidine, dipyridamole.

ASPIRIN (ASA)

Thromoboxane A2 is an arachidonate product that causes platelet to change shape, to release their granules and to aggregate. Drugs that antagonize this pathway interfere with platelet aggregation and prolong bleeding time. Asprin at low dose is the prototype of this class of drugs. It inhibits the synthesis of thromboxane A2 by irreversible acetylation of the enzyme cyclo-oxygenase.

Therapeutic Uses:

Prophylaxis against myocardial infarction and prevention of stroke in patients at risk, e.g. those with transient ischemic attacks.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Aspirin

Aspirin and other nonsteroidal anti-inflammatory drugs are weak organic acids. They all inhibit prostaglandin biosynthesis. They decrease the production of free radicals and of superoxide and may interact with adenylyl cyclase to alter the cellular concentration of cAMP. Aspirin is the drug of choice for treating the majority of articular and musculoskeletal disorders. It is also the standard against which all anti-inflammatory agents are compared.

Pharmacokinetics: The salicylates are rapidly absorbed from the stomach and upper small intestine. The acid medium in the stomach keeps a large fraction of the salicylate in the nonionized form, promoting absorption. However, the drug may damage the mucosal barrier. Aspirin is absorbed as such and is rapidly hydrolyzed to acetic acid and salicylate by esterases in tissue and blood. Salicylate is bound to albumin. Ingested salicylate and that generated by the hydrolysis of aspirin may be excreted unchanged, but most is converted to water-soluble conjugates that are rapidly cleared by the kidney. Alkalinization of the urine increases the rate of excretion of free salicylate.

Pharmacodynamics

Mechanism of Action: Aspirin irreversibly blocks the enzyme cyclooxygenase; the drug decreases the formation of both the prostaglandins and thromboxane A_2 but not the leukotrienes.

Anti-inflammatory Effects: In addition to reducing the synthesis of eicosanoid mediators, aspirin also interferes with the chemical mediators of the kallikrein system. Thus, aspirin inhibits granulocyte adherence to damaged vasculature, stabilizes lysosomes, and inhibits the migration of polymorphonuclear leukocytes and macrophages into the site of inflammation.

Analgesic Effects: Aspirin is most effective in reducing pain of mild to moderate intensity. Muscular, vascular, and dental origin, postpartum states, arthritis, and bursitis are alleviated by aspirin. Aspirin acts peripherally through its effects on inflammation but probably also inhibits pain stimuli at a subcortical site.

Antipyretic Effects: Aspirin reduces elevated temperature. The fall in temperature is related to increased dissipation of heat caused by vasodilation of superficial blood vessels. The antipyresis may be accompanied by profuse sweating. Aspirin blocks the pyrogen-induced production of prostaglandins and the central nervous system response to interleukin-1.

Platelet Effects:

Diclofenac

Diclofenac is a potent cyclooxygenase inhibitor with antiinflammatory, analgesic, and antipyretic properties. The drug is rapidly absorbed following oral administration and has a half-life of 1-2 hours. It accumulates in the synovial fluid. The potency of diclofenac as a cyclooxygenase inhibitor is greater than that of naproxen. The drug is recommended for chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis and for the treatment of acute musculoskeletal pain. Adverse effects include gastrointestinal distress, occult gastrointestinal bleeding, and gastric ulceration.

Sulindac

Sulindac is a prodrug. Its active metabolite is, like diclofenac, an acetic acid derivative. The drug is effective only after it is converted by liver enzymes to a sulfide, which is excreted in bile and then reabsorbed from the intestine. The enterohepatic cycling prolongs the duration of action to 12-16 hours. The indications and adverse reactions are similar to those of other NSAIDs. Among the more severe reactions, Stevens-Johnson epidermal necrolysis syndrome, thrombocytopenia, agranulocytosis, and nephrotic syndrome have all been observed. Like diclofenac, sulindac may have some propensity to cause elevation of serum aminotransferase; it is also sometimes associated with cholestatic liver damage.

Mefenamic Acid

Mefenamic acid, another fenamate, possesses analgesic properties but is probably less effective than aspirin as an anti-inflammatory agent and is clearly more toxic.

Piroxicam

It is rapidly absorbed in the stomach and upper small intestine and reaches 80% of its peak plasma concentration in 1 hour. Gastrointestinal symptoms are encountered in 20% of patients. Other adverse reactions include dizziness, tinnitus, headache, and rash.

Nimesulide: It is a new NSAID and after oral administration it is rapidly and almost completely absorbed. Highly bound to plasma proteins. It is a weak inhibitor of prostaglandin synthesis.The advantage of nimesulide over other NSAIDs is that it causes minimal gastric irritation.

Rofecoxib: Rofecoxib is a highly selective and specific COX-2 inhibitor. It inhibits prostaglandin synthesis via inhibiting cyclooxygenase- 2. It is about 90% bound to plasma proteins. The main adverse effects are nausea, dyspepsia, epigastric discomfort, heart burn, diarrhea, fluid

retention etc. It is mainly useful in osteoarthritis, acute pain like dental pain & primary dysmenorrhoea.

NSAIDS FOR SPECIAL INDICATIONS

Indomethacin

Indomethacin is slightly more toxic but in certain circumstances more effective than aspirin. Indomethacin is well absorbed after oral administration and highly bound to plasma proteins. Metabolism occurs in the liver and unchanged drug and inactive metabolites are excreted in bile and urine.

Clinical Uses: treatment of patent ductus arteriosus, acute gouty arthritis and ankylosing spondylitis, pericarditis and pleurisy.

Adverse Effects: The gastrointestinal effects may include abdominal pain, diarrhea, gastrointestinal hemorrhage, and pancreatitis. CNS effects include be associated with dizziness, confusion, and depression. Serious hematologic reactions' including thrombocytopenia and aplastic anemia has been reported.

Acetaminophen

Acetaminophen is the active metabolite of phenacetin responsible for its analgesic effect. It is a weak prostaglandin inhibitor in peripheral tissues and possesses no significant anti-inflammatory effects.

Pharmacokinetics: Acetaminophen is administered orally. Absorption is related to the rate of gastric emptying. Acetaminophen is slightly bound to plasma proteins and is partially metabolized by hepatic microsomal enzymes.

Indications: It is an effective analgesic and antipyretic agent, but it lacks of anti-inflammatory properties. The drug is useful in mild to moderate pain such as headache, myalgia, and postpartum pain.

Adverse Effects: It is hepatotoxic (contraindicated in patients with known liver diseases), and also causes hemolytic anemia and methemoglobinemia

DRUGS USED IN GOUT

Gout is a familial metabolic disease characterized by recurrent episodes of acute arthritis due to


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not to precipitate the formation of uric acid calculi. Uricosuric drugs are organic acids and act at the anionic transport sites of the renal tubule.

Pharmacokinetics: Probenecid is completely reabsorbed by the renal tubules and is metabolized very slowly. Sulfinpyrazone or its active hydroxylated derivative is rapidly excreted by the kidneys. Its effect after oral administration is almost that of probenecid.

Pharmacodynamics: Uric acid is freely filtered at the glomerulus. Like many other weak acids, it is also both reabsorbed and secreted in the middle segment of the proximal tubule. Uricosuric drugs probenecid, sulfinpyrazone, and large doses of aspirin affect these active transport sites so that net reabsorption of uric acid in the proximal tubule is decreased. Because aspirin in small doses causes net retention of uric acid by inhibiting the secretory transporter, it should not be used for analgesia in patients with gout.

Indications: Uricosuric therapy should be initiated if several acute attacks of gouty arthritis have occurred, when evidence of tophi appears, or when plasma levels of uric acid in patients with gout are so high that tissue damage is almost inevitable.

Adverse Effects: Both drugs cause gastrointestinal irritation, but sulfinpyrazone is more active in this regard. Probenecid is more likely to cause allergic dermatitis, but a rash may appear after the use of either compound. Nephrotic syndrome has resulted from the use of probenecid. Both sulfinpyrazone and probenecid may cause aplastic anemia.

Allopurinol

An alternative to increasing uric acid excretion in the treatment of gout is to reduce its synthesis by inhibiting xanthine oxidase with allopurinol.

Allopurinol is absorbed after oral administration. Like uric acid, allopurinol is itself metabolized by xanthine oxidase. The resulting compound, alloxanthine, retains the capacity to inhibit xanthine oxidase and has a long duration of action.

Pharmacodynamics: Dietary purines are not an important source of uric acid. The quantitatively important amounts of purine are formed from amino acids, formate, and carbon dioxide in the body. Those purine ribonucleotides not incorporated into nucleic acids and those derived from the degradation of nucleic acids are converted to xanthine or hypoxanthine and oxidized to uric acid. When this last step is inhibited by allopurinol, there is a fall in the plasma urate level and a decrease in the size of the urate pool with a concurrent rise in the more soluble xanthine and hypoxanthine.

Indications

- in chronic tophaceous gout
- for recurrent renal stones
- in patients with renal functional impairment;
- When serum urate levels are grossly elevated.

Adverse Effects: Gastrointestinal intolerance, including nausea, vomiting, and diarrhea, may occur. Peripheral neuritis and necrotizing vasculitis, depression of bone marrow elements may occur. Hepatic toxicity and interstitial nephritis have been reported.

Exercice

1. Discuss in detail the pharmacokinetics of iron?
2. Discuss various types of iron formulations with their side effects?
3. Explain the mechanism of action and effect of vit B_{12} and folic acid and the relation of the latter?
4. What are the effects and adverse reaction of heparin and oral anticoagulants?
5. What is the role of aspirin as an antiplatelet agent?

CHAPTER EIGHT

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

Learning Objectives

At the end this section the student will be able to:

1. Describe the major adverse effects of sedative hypnotic drugs.
2. Describe the drugs used in epilepsy.
3. Illustrate the approaches in the management of parkinsonism.
4. Explain the site of action, uses and adverse effects of antipsychotic drugs.
5. Describe the major adverse effects opioid analgesics.

INTRODUCTION

To facilitate the understanding of the pharmacological and unwanted effects of CNS drugs, the physiological functions of the main CNS neurotransmitters are discussed briefly.

Noradrenaline. Noradrenergic transmission is important in control of mood (functional deficiency resulting depression) controlling wakefulness, and alertness.

Dopamine. Dopamine is important in motor control (Parkinsonism is due to dopamine deficiency), has behavioural effects (excessive dopamine activity is implicated in schizophrenia), important in hormone release (prolactin, GH) and dopamine in chemoreceptor trigor zone causes nausea and vomiting.

5-HT. Physiological functions associated with 5-HT pathways include; feeding behaviour, behavioural response (hallucinatory behaviour), control of mood and emotion, control of body temperature and vomiting.

Acetylcholine(Ach). Ach has effects on arousal, on learning, and on short-term memory. Dementia and parkinsonism are associated with abnormalities in cholinergic pathways.

GABA. GABA is an inhibitory neurotransmitter in CNS.

Glycine. is an inhibitory neurotransmitter, acts on GABA like receptor in the spinal cord.

GENERAL ANESTHETICS

General anesthesia involves the physiological changes: Reversible loss of response to painful stimuli, loss of consciousness and loss of motor and autonomic reflexes. Loss of consciousness is associated with inhibition of the activity of reticular formation.

General anesthetics are administered by *inhalation* or by *intravenous* routes. They are classified into two on the basis of their route of administration as inhalation and intravenous anesthetics.

Inhalation anesthetics

The main agents are: Halothane, nitrous oxide, enflurane and ether.

1. Halothane: Is the most widely used agent, highly lipid soluble, potent. It causes arrhythmia, hangover and the risk of liver damage is high if used repeatedly.

2. Nitrous oxide: Oderless and colourless gas. It is rapid in action and also an effective analgesic agent. Its potency is low, hence must be combined with other agents. It is a relatively free of serious unwanted effects.

3. Enflurane: Halogenated ether (similar to halothane). Poorly metabolized in the liver, thus less toxic than halothane. It is faster in its action, less liable to accumulate in the body fat compared to halothane. It causes seizure during induction and following recovery from anaesthesia.

4. Ether: Has analgesic and muscle relaxant properties. It is highly explosive, causes respiratory tract irritation, postoperative nausea and vomiting. It is not widely used currently.

INTRAVENOUS ANESTHETICS

Intravenous anesthetics act much more rapidly, producing unconsciousness in about 20

Etomidate: It is more quickly metabolized and the risk of cardiovascular depression is less compared to thiopentone. Etomidate suppresses the adrenal cortex, which has been associated with an increase in mortality in severely ill patients.

Ketamine: acts more slowly than thiopentone and produces a different effect, known as dissociative anaesthesia in which there is a marked sensory loss and analgesia, as well as amnesia and paralysis of movement, without actual loss of consciousness. Ketamine causes dysphoria, hallucinations during recovery.

Benzodiazepines including diazepam, lorazepam, and midazolam are used in general anesthetic procedures. Compared with intravenous barbiturates, benzodiazepines produce a slower onset of central nervous system effects. Benzodiazepines prolong the postanesthetic recovery period but also cause a high incidence of amnesia for events occurring after the drug is administered.The benzodiazepines are useful in anesthesia as premedication and intraoperative sedation.

Opioid analgesic anesthesia: Opioid analgesics can be used for general anesthesia, in patients undergoing cardiac surgery and fentanyl and its derivates are commonly used for these purposes.

Preanesthetic medication:

5. *Miscellaneous drugs* (chloral hydrate, paraldehyde,

5 - HT_{1A} receptor agonist

Buspirone is a potent agonist of. *5 - HT_{1A}* receptors. Anxiolytic effects take days to weeks to develop. Buspirone does not cause sedation, motor incoordiation and withdrawal effects. The main side effects are nausea, dizziness, headache, and restlessness.

Barbiturates

They are non-selective CNS depressants, which produce effects ranging from sedation and reduction of anxiety, to unconsciousness and death from respiratory and cardiovascular failure.

Barbiturates act by enhancing action of GABA, but less specific than benzodiazepines. They are potent inducers of hepatic drug metabolizing enzymes, hence likely to cause drug interaction. Tolerance and dependance occur, more than benzodiazepines.

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Main side effects are sedation, confusion, gum hyperplasia, skin rash, anaemia, nystagmus, and diplopia.

Carbamazepine

It is derived from tricyclic antidepressant. Its pharmacological action resembles those of phenytoin, however, it is chiefly effective in the treatment of partial seizure. It is also used in the treatment of trigeminal neuralgia and manic-depressive illness.

It is powerful inducer of liver microsomal enzymes, thus accelerates the metabolism of phenytoin, warfarin, oral contraceptives and corticosteroids.

Carbamazepine causes sedation, mental disturbances and water retention.

Valproate

Valproate is chemically unrelated to the other antiepileptic drugs. The mechanism of action is unknown. It is used in grand mal, partial, petit mal and myoclonic seizure.

Relatively has few side effects, however, it is potentially hepatotoxic. It is non sedating.

Ethosuximide

Has fewer side effects and used in the treatment of absence seizures.

Phenobarbitone

It is well absorbed after oral administration and widely distributed. Renal excretion is enhanced by acidification of the urine. Phenobarbitone is liver enzyme inducer and hence accelerates the metabolism of many drugs like oral contraceptives and warfarin.

The clinical use of phenobarbitone is nearly the same as that of phenytoin. The most important unwanted effect is sedation.

Benzodiazepines: Clonazepam and related compounds, clobazam are claimed to be relatively selective as antiepileptic drugs. Sedation is the main side effect of these compounds, and an added problem may be the withdrawal syndrome, which results in an exacerbation of seizures if the drug is stopped.

MANAGEMENT OF PARKINSONISM

Parkinsonism: Parkinsonism is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability. It is due to the imbalance between the cholinergic and dopaminergic influences on the basal ganglia. Thus, the aim of the treatment is either to increase

dopaminergic activity (by dopamine agonist) or to decrease cholinegic (antimuscarinic drugs) influence on the basal ganglia.

Levodopa

Levodopa, the immediate metabolic precursor of dopamine, does penetrate the blood brain barrier, where it is decarboxylated to dopamine. Levodopa is rapidly absorbed from the small intestine. Food will delay the appearance of levodopa in the plasma. It is extensively metabolized by peripheral dopa decarboxylase, hence given in combination with carbidopa, a peripheral dopa decarboxylase inhibitor.

When levodopa is given without carbidopa it causes vomiting (which is due to stimulation of emetic center to dopamine) and CVS disorder (tachycardia, ventricular extrasystoles, atrial fibrillation and due to increased catecholamine formation peripherally).

Dopamine agonists

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Adverse Effects

Antimuscarinic drugs have a number of central nervous system effects, including drowsiness, mental slowness, inattention, restlessness, and confusion, agitation, delusions, hallucinations, and mood changes. Other common effects include dryness of the mouth, blurring of vision, mydriasis, urinary retention, nausea and vomiting, constipation, tachycardia, tachypnea, increased intraocular pressure, palpitations, and cardiac arrhythmias.

***Contraindications**:* Acetylcholine-blocking drugs should be avoided in patients with prostatic hyperplasia, obstructive gastrointestinal disease, or angle-closure glaucoma.

ANTIPSYCHOTIC AGENTS

Adverse Effects:

concentrations in tissues that are highly perfused. The opioids are converted in large part to polar metabolites, which are then readily excreted by the kidneys.

Pharmacodynamics

A. Mechanism of Action: Opioid agonists produce analgesia by binding to specific receptors, located primarily in brain and spinal cord regions involved in the transmission and modulation of pain.

Effects of morphine and its synthetic derivatives

1. **Central nervous system effects-**The principal effects of the opioid analgesics with affinity for mu receptors are on the central nervous system; the more important ones include analgesia, euphoria, sedation, and respiratory depression. With repeated use, a high degree of tolerance occurs to all of these effects except respiratory depression. They also cause addiction and dependence.

    a. *Analgesia*-Pain consists of both sensory and affective (emotional) components. Opioids can change both aspects of the pain experience. In most cases, these drugs have a relatively greater effect on the affective component.

    b. *Euphoria***-**After a dose of morphine, a typical patient in pain experiences a pleasant floating sensation and freedom from anxiety and distress. Dysphoria is a state characterized by restlessness and a feeling of malaise.

    c. *Sedation***-**Drowsiness and clouding of mentation are frequent concomitants of opioid action.

    d. *Respiratory depression***-**All of the opioid analgesics can produce significant respiratory depression by inhibiting brain stem respiratory mechanisms.

    e. *Cough suppression***-**Suppression of the cough reflex is a well-recognized action of opioids. However, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis. e.g. codeine

    f. *Miosis***-**Constriction of the pupil is seen with virtually all opioid agonists.

    g. *Nausea and vomiting***-**The opioid analgesics can activate the brain stem chemoreceptor trigger zone to produce nausea and vomiting.

2. Peripheral effects


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The main drugs of abuse are given the following table:

Type	example	dependence liability

Table 1. Shows the methods of administration and clinical uses of local aesthetics.

Methods of administration	Uses	Drugs
Surface anaesthesia	Nose, mouth, urinary tract	Lidocaine
Infiltration anaesthesia	Direct injection into tissues to reach nerve braches and terminals. Minor surgery	Most
Regionanl anaesthesia	LA injected IV distal to a pressure cuff, limb surgery	Mainly lidocaine
Nerve block anaesthesia	LA injected close to nerve trunks. Dentistry	Most
Spinal anaesthesia	LA injected into subarachinoid space. Pelvis surgery	Mainly lidocaine
Epidural anaesthesia	LA injected into epidural space. Labour.	Mainly lidocaine

Exercice

CHAPTER NINE

ENDOCRINE PHARMACOLOGY

Learning objective

At the end of this chapter the student is expected to learn the following:

- The effects of insulin on different organ/systems
- The types of insulin with their therapeutic uses and adverse reactions
- The mechanism of action, uses and side effects of oral hypoglycemic agents
- Drugs used as oxytocic agents
- Types of hormonal contraception with their uses and adverse effects including preparations
- Actions, therapeutic uses and adverse effects of glucocorticoids

I. ANTIDIABETIC DRUGS

INTRODUCTION

Diabetes Mellitus *is a* disease that occurs as a result of absolute or relative deficiency of insulin that results in metabolic and vascular abnormalities.

The ***etiologies*** include Obesity (because chronic calorie intake and prolonged stimulation of β cell causes a decrease in insulin receptor and also adipose tissue and muscle are less sensitive),hereditary,damrgo1(eso rece4uT4 1 Tf)5.5(a 12 90 N),.5(t).4(12 90eH2 Tlo59 -1.79n79 -1.79n79 -1.

It can *be* ***classified*** *as:* Type I: ***IDDM*** *(*or Juvenile type) occurs predominantly in children and young adults who have no insulin secretion and Type II: ***NIDDM*** (or maturity onset type) usually occur after the age of 40years.

Diabetic ketoacidosis (DKA) is serious complication of diabetes. It is severe metabolic disturbance due to insulin deficiency, which results in hyperglycemia, ketonimia and later acidosis. It is characterized by headache, nausea, vomiting, rapid pulse, dry skin, deep breathing, and change in mentation. Management includes Regular (soluble) insulin IV infusion, treatment of dehydration and precipitating factor.

Hypoglycemic Coma is more serious complication which usually occurs due to excess dose of insulin which produces severe lowering of blood glucose that may leads to coma.

The Sign /Symptom are mental confusion, in coordination, paresthesia, convulsion, coma and Signs of sympathetic over activity. *The aim of treatment* is to restore blood glucose to normal by giving glucose 50% 20 – 100 ml IV, or glucagon 1mg iv, im, sc

Antidiabetogenic drugs

I. INSULIN

Sources include pork or beef, combination of pork and beef and also human insulin (Recombinant DNA technique)

Actions:

- Insulin lower blood glucose level through increasing utilization of glucose by peripheral

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Protein metabolism

Liver: it increases protein catabolism

Muscle: it increases aminoacid uptake and protein synthesis

Other metabolic effect:

It increases uptake of K^+ and Ca^{++} into cells and synthesis of nucleic acids

There are some factors that increase insulin demand: like Infection, surgery, pregnancy and drugs (those that antagonize actions of insulin glucocorticoids, thyroid hormone, adrenaline)

Type of insulin preparation:

A. Short acting (rapid onset): Eg Regular Insuline
B. Intermediate acting Eg Lente insuline,NPH insuline
C. Long acting E.g Protamine Zn insuline

Types	Route	Onset (hrs)	Duration (hrs)
Regular insulin	IV, SC, IM	¼ - 1	5 – 7
Lente insulin	SC, IM	1 – 1½	18 – 24
Protamine Zn insulin	SC, IM	4 – 8	36

N.B. *It is only regular insulin that can be given by intravenous route.*

Therapeutic use -IDDM, NIDDM (not controlled by diet and oral hypoglycemic agents), diabetic ketoacidosis, Control of diabetes in pregnancy, during surgery and in infections.

They are also used in the treatment of hyper kalmia due to renal failure

Adverse Reaction*:* can be categorized as

Local: Atrophy or hypertrophy at site of injection, local hypersensitivity and secondary infections.

Systemic: Hypoglycemic coma and Immunologic reaction like hypersensitive and insulin resistance

II. ORAL HYPOGLYCEMICS

These are drugs administered orally to lower blood glucose level used in mild diabetes.

They are grouped as Sulphonylureas and Biguinides.

Sulphonyl ureas

These compounds are chemically related to sulphonamides.

First generation: Tolbutamide, Chlorpropamide

Second generation: Glibenclamide, Glipizide

Pharmacokinetics: Phenformin and metformin are rapidly absorbed from the gastrointestinal tract. Metformin is largely excreted unchanged in the urine and has a longer duration of action.

Side effects: Nausea, vomiting, anorexia, diarrhea, abdominal cramp, lactic acidosis (esp. phenformin)

Use: Obese diabetics (uncontrolled by diet alone), Supplement to sulphonyl urea

Contraindication: Diabetes with hepatic, renal insufficiency, In IDDM, NIDDM (with infection, fever, surgery) and during pregnancy

They have no value in diabetes complicated by acidosis or coma

II .OXYTOCICS

These are group of drugs that cause contraction of the uterus.

Oxytocin

Actions: 1. Oxytocin stimulates the uterus and cause physiologic type of contraction

2. It also causes ejection of milk through contraction of the myo-epithelial cells around the alveoli of the mammary gland.

Pharmacokinetics: It is inactivated orally and absorbed rapidly after intramuscular administration. It can also be absorbed from nasal and buccal membrane.

Use: Induction of labor in women with uterine inertia, Relief of breast engorgement during lactation (few minutes before breast feeding) as nasal spray, Postpartum hemorrhage.

Side effect: Oxytocin may cause over stimulation and leads to rupture of the uterus in the presence of cephalo-pelvic disproportion. Therefore it's contraindicated in woman with uterine scar. When given intravenously may cause water retention leading to water intoxication.

Prostaglandins

They induce labor at anytime during pregnancy but most effective at the third trimester. In female reproductive system prostaglandin E & F are found in ovaries, endometrium and menstrual fluid which is responsible for initiating and maintaining normal birth process. PGF, $PGF_{2\acute{\alpha},}$ PGE stimulate both the tone and amplitude of the uterine contraction.

Adverse reaction: nausa, vomiting, headache, diarrhea, fever, etc.

PGs should be used cautiously in the presence of hypertension, angina, and diabetes. They are contraindicated in the presence of cardiac, renal, pulmonary or hepatic disease

Ergometrine

It is one of the ergot alkaloids with the ability to cause contraction of the uterine smooth muscle.

It causes sustained uterine contraction. It is completely absorbed after subcutaneous and intravenous administration. It is metabolized in the liver and eliminated in the urine .Liver damage enhances the toxicity of ergot alkaloid.

Use: after delivery of placenta if bleeding is severe (Prevent postpartum bleeding)

Adverse effect: Nausa, vomiting but serious toxic effects are rare.

III. Female Sex Hormones and Hormonal Contraception

Oestrogens

These drugs can be classified into three groups.

1. Natural – estradiol, esterone, estriol
2. Semisynthetic – Ethnylestradiol
3. Synthetic: Diethylstibosterol

Natural

Estradiol: Estradiol is most potent, major secretory product of ovary.It is oxidized into esterone by liver; estrone is hydrated to estriol and synthesized by ovarian follicle, adrenal cortex, fetoplacental unit, and testis. Androgen and testestrone are precursor for estrogen. Certain tissue can make estrone from androgen.

Semisynthetic

Ethylestadiol: Highly potent, effective orally

Absorption and Fate: It is absorbed from GI and skin and rapidly metabolized in the liver

Physiologic actions:

Genital system

Ovary: estrogen affects the ovary through indirectly influencing the secretion of gonadotrophin

Uterus: it affects the 'proliferative phase' of the endometrium and also increases the growth and sensitivity of myometrium for oxytocin.

Cervix: it makes cervical mucus thin and alkaline

Vagina: Stratification, cornification and glycogen deposit is affected by estrogen.

Breast

Estrogen causes the growth of gland and duct system

Anterior pitutary

Estrogen inhibit release of gonadotrophins (FSH, LH)

Metabolic action:

a) Retention of salt and water
b) Plasma lipid level: it increases the level of high density lipoprotein and triglycerides while decreases the level of low density lipoprotein and cholesterol.
c) Increases Ca^{tt} bone deposition
d) It has a mild anabolic action

Blood coagulation

Enhance level of factor II, VII, IX, X so, increase the coagulability of blood and may predispose to thromboembolic condition

Therapeutic use: contraceptive in combination with progestogens, Functional uterine bleeding, Dysmenorrhea, Alleviation of menopausal disorder, Osteoporosis, Replacement therapy in ovarian failure, Prevents senile and atrophic vaginitis

Side effects: Thromboembolism, Sodium and water retention, Withdrawal bleeding, nausea, endometrial carcinoma

Contraindication: History of thromboembolism condition, Undiagnosed uterine bleeding, endometrial Carcinoma, liver disease

PROGESTOGENS

Progestrone is natural occuring progestational hormone.it is synthesized by corpus luteum, placenta, adrenal cortex, testis. It is less effective orally due to complete metabolism by liver so it's given through intramuscular route.

*Actions on g*enital organs:

Ovary - Inhibition of ovulation

Uterus - converts the endometrum for secretory phase and makes the myometrium less sensitive to oxytocin. It also causes relaxation of the uterus in late pregnancy.

Metabolic actions:

(a) Thermogenic action

(b) Competes with aldosterone at renal tubule so inhibits sodium reabsorption.

Synthetic /Senisynthetic progestogens:

Derivative of progestrone: Hydroxyprogesterone capriot/medroxyprogestrone

Derivative of testestrone: Dimethisterone

Nortestrone: Norethisterone

Therapeutic use: Hormonal contraception**,** functional uterine bleeding**,** dymennorrhea Ammenorrhea**,** Endometrial Carcinoma**,** Premenustral tension

ORAL CONTRACEPTIVEs

These are drugs taken orally to prevent conception. They are available in the following forms:

1. Combined regimen type
2. sequential regimen type
3. triphasic pill regimen

Combined regimen: involves the administration of pills containing combination of Estrogen and Progestogen. They are administered starting 5th day of menustral cycle for 21 days.

They can also be classified as fixed dose combination (monophasic), biphasic and triphasic pills. Fixed dose combination: the commonest procedure is to administer one pill containing both an estrogen and progestin daily at bed time for 21 days. In biphasic and triphasic pills: these are combined oral contraceptive pills containing varying proportion of an estrogen and a progesterone designed to stimulate the normal pattern of menustral cycle.

Formulation:

a) low estrogen, low progesterone(0.03mg ethinylestradiol+0.15 mg norgestril

b) Low esterogen, high progestogen
(0.03 mg ethinylestradiol + 1.5 mg norethindrone)

c) High estrogen, high progestrone

(0.05 mg ethinylestradiol + 0.5 mg norgestril)

Mechanism: includes inhibition of release of FSH and LH, increase viscosity of cervical mucus endometrial changes, interfere with contraction of cervix, uterus and fallopian tube

Single Entity preparation

A. Continuous progestrone

i) Oral progestrone

Norethindone (Norgestril)

ii) Depot

IM injection of long acting progestogen. ( )]TJe–estogd4H, incr7

Drug interaction:

1. Effect reduced when taken with enzyme inducers like Rifampicin, Phenytoin, Phenobarbitone etc. It may result in unexpected pregnancy and spotting.

Dexamethasone and betamethasone have got a high glucorticoid activity while cortisone and hydrocortisone have high mineralocorticoid action. Therapeutic activity in inflammatory disorder is proportional to the glucocorticoid activity.

Actions on CHO metabolism:

- antinsulinic effect
- decreases Peripheral utilization of glucose,
- increases gluconeogenesis
- promote glycogen storage

Protein metabolism:

- Inhibit protein synthesis,
- Increases catabolism

Fat metabolism:

- Interferes with fat storage causing deposits with characteristic distribution (neck, supraclavicular area, and face

Electrolyte and H_2O metabolism

- Sodium and water retention
- Hypokalmia

Suppression of pitutary adenocortical system

CNS: Euphoria and stimulation

CVS: Restore vascular reactivity

GIT: Increase gastric acid secretion

Blood: Increase number of RBC, Hypercoagulability

Uric acid: Increased excretion

Calcium metabolism: increased Ca^{++}excretion, interfere with Ca^{++} absorption

Antinflammatory: Inhibit exudation, capillary dilatation, migration of phagocyte, fibroblast, inhibit fibrous tissue formation

Antiallergic: through inhibition of antibody production suppress tissue inflammatory response.

Absorption and fate: It has fair absorption, bound to α -globuin (transcortin).And in the liver, cortisone is converted into hydrocortisone.

Therapeutic use

1) Replacement therapy: In Addisons disease and Addisonian crisis

2) Antinflammatory: in conditions like Collagen disease (rheumatoid carditis, arthritis),

Antithyroid drugs include:

1. Thiourea compounds, e.g. , propylthiouracil, methimazole, carbimazole
2. Ionic inhibitors, e.g. , potassium percholate, potassium thiocyanate
3. Iodide, e.g. , Lugol's iodine, potassium iodide
4. Radioactive iodine (^{131}I)

Thiourea Compounds

Inhibit the formation of throid hormone through inhibiting the oxidation of iodide to iodine by peroxidase enzyme and blocking the coupling of iodothryosines to form iodothyronines.

They are contraindicated in pregnant and lactating women.

Toxicities include drug fever, skin rashes, increased size and vascularity of the thyroid gland, and agranulocytosis.

Ionic Inhibitors

Potassium percholate prevents the synthesis of thyroid hormones through inhibition of uptake and concentration of iodide by the gland. It has the risk of aplastic anemia, therefore no longer used in the treatment of hyperthyroidism.

Iodides:

Improve manifestations of hyperthyroidism by decreasing the size and vascularity of the gland so they are required for preoperative preparation of the patient for partial thyroidectomy.

Iodides act through inhibition of the "protease" enzyme which releases T_3 and T_4 from thyroglobulin, and organification.

Radioactive Iodine:

It is used in hyperthyroidism as sodium ^{131}I orally. It is trapped and concentrated as ordinary iodine, which emits beta rays that act on parenchymal cells of the gland.

It is contraindicated in pregnancy and lactation as it affects thyroid gland in the fetus and the infant. Its important toxicity is hypothyroidism.

Propranolol

This is an important drug which controls the peripheral manifestations of hyperthyroidism (tachycardia, tremor). In addition, it decreases the peripheral conversion of T_4 to T_3.

Thryoid Storm (Crisis)

This is a sudden acute exacerbation of all the symptoms of thyrotoxic which rarely occur after thyroidectomy. Manifestations include hyperpyrexia, gastrointestinal symptoms, dehydration, tachycardia, arrhythmia, restlessness, etc. which may progress to shock and death.

Management: It consists of infusion of intravenous fluids, supportive management, and also administration of propylthiouracil, sodium iodide, hydrocortisone, and propranolol.

Exercise

1. List the important organ/system effects of insulin.
2. Write about the clinical aspects of oral antidiabetic drugs.
3. Discuss the mechanism and beneficial effects of combined oral contraceptive pills.
4. Discuss the pharmacological action and adverse effects of glucorticoids.
5. Write about anti thyroid drugs.

CHAPTER TEN

CHEMOTHERAPEUTIC DRUGS

Learning Objectives

At the end this section the student will able to:

1. Describe the general mechanisms of action of antimirobial drugs.
2. Illustrate the mechanims of antimicrobial drug resistance.

Chemotherapeutic agents: are chemical which are intended to be toxic for parasitic cell but non toxic to the host, such selective toxicity depends on the existence of exploitable biochemical difference between the parasite and the host cell.

Antimicrrobials: are chemical agents (synthetic/natural) usa

2. Alteration of the drug-binding site: this occurs with penicillins, aminoglycosides and erythromycin.
3. Reduction of drug uptake by the bacterium: eg. Tetracyclines
4. Alteration of enzymes: eg. Dihydrofolate reductase becomes insensitive to trimethoprim.

Anibacterial agents

Cell wall synthesis inhibitors

Members the group: Beta-lactam antibiotics, vancomycin, bacitracine, and cycloserine

Beta-lactam antibiotics: Penicillins, cephalosporins, carbapenems, and monobactams are members of the family. All members of the family have a beta-lactam ring and a carboxyl group resulting in similarities in the pharmacokinetics and mechanism of action of the group members. They are water-soluble, elimination is primary renal and organic anion transport system is used.

Penicillins

Penicillins have similar structure, pharmacological and toxicological properties. The prototype of penicillins is penicillin G and is naturally derived from a genus of moulds called penicillium.

Classification: Penicillins can be classified into three groups: *Natural Penicillins, Antistaphylococcal penicillins,* and *Extended-spectrum penicillins.*

Mechanism of Action: Penicillins inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis (block the transpeptidation reaction). Sensitive pencillins are inactivatived by betalactamase enzymes.

Pharmacokinetics: Penicillin G is unstable in acid media, hence destroyed by gastric juice. Ampicillin, amoxicillin, and dicloxacillin are acid-stable and relatively well absorbed after oral adminstraion. Oral penicillins should be given 1-2 hours before or after meals to minimize binding to food proteins and acid inactivation (except ampicilin). The absorption of most penicillin is complete and rapid after IM administration. The kidneys rapidly excrete penicillin. Renal excretion is by glomerular filtration (10%) and by tubular secretion (90%). Blood levels of all penicillins can be raised by simultaneous administration of probenecid orally, which impairs tubular secretion of weak acids.

Clinical Uses

Natural Penicillins: Penicillin G and penicillin V are natural penicillins. Penicillin G is the drug of choice for infections caused by streptococci, meningococci, enterococci, penicillin-susceptible pneumococci, non-beta-lactamase-producing staphylococci, Treponema pallidum and many other spirochetes, Bacillus anthracis, Clostridium species, Actinomyces, and other gram-positive rods and non-beta-lactamase-producing gram-negative anaerobic organisms. Penicillin V is acid stable but it is less potent than penicillin G.

Antistaphylococcal Penicillins: [Methicillin, Nafcillin, isoxazolyl penicillins (Oxacillin, cloxacillin, and dicloxacillin)]. The only indication is infections caused by beta-lactamase-producing staphylococci. Oral isoxazolyl penicillin is suitable for treatment of mild localized staphylococcal infections, for serious systemic staphylococcal infections, oxacillin or nafcillin, is given by intermittent intravenous infusion.

Extended Spectrum Penicillins: Aminopenicillins (ampicillin, amoxicillin), Carboxypenicillins (Carbenicillin, ticarcillin, effective at lower doses), and Ureidopenicillins (piperacillin, mezlocillin, and azlocillin): Spectrum of activity similar to penicillin G, though having greater activity against gram-negative bacteria due to their enhanced ability to penetrate the gram-negative outer membrane. The aminopenicillins have the same spectrum and activity, but amoxicillin is better absorbed from the gut. These drugs are given orally to treat urinary tract infections, sinusitis, otitis, and lower respiratory tract infections. Ampicillin IV is useful for treating serious infections caused by penicillin-susceptible organisms, including anaerobes, enterococci, Listeria monocytogenes, and susceptible strains of gram-negative cocci and bacilli such as E coli, H influenzae, and Salmonella species. Carboxypenicillins extend the ampicillin spectrum of activity to include Pseudomonas aeruginosa and Enterobacter species. The ureidopenicillins resemble ticarcillin except that they are also active against selected gram-negative bacilli, such as Klebsiella pneumoniae. Because of the tendency of P aeruginosa to develop resistance during monotherapy, antipseudomonal penicillins generally is used in combination with an aminoglycoside for pseudomonal infections.

Adverse Reactions: Grouped into three: *Allergy*: Cross sensitivity and cross reactivity among beta-lactams is common. Reactions include: Skin rashes, fever, bronchospasm, Oral lesions, interstitial nephritis (autoimmune reaction to penicillin-protein complex), eosinophilia, hemolytic anemia, vasculitis and anaphylactic shock. *Biological:* antibiotic assoicated enterocolitis (ampicillin), and *Toxic:* diarrhea (ampicillin), nephritis, especially methicillin, and platelet dysfunction (antipseudomonal penicillins).

Cephalosporins

Cephalosporins can be classified into four generations depending mainly on the spectrum of antimicrobial activity. First-generation compounds have better activity against gram-positive organisms and the later compounds exhibit improved activity against gram-negative aerobic organisms.

First-generation cephalosporins

Members: Cefadroxil, cefazolin, cephalexin, and cephalothin. These drugs are very active against gram-positive cocci (pneumococci, streptococci, and staphylococci). Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis are often sensitive, but activity against Pseudomonas aeruginosa, indole-positive Proteus, Enterobacter, Serratia marcescens, Citrobacter, and Acinetobacter is poor. Anaerobic cocci (eg, Peptococcus, Peptostreptococcus) are usually sensitive, but B fragilis is not.

Cephalexin, and cefadroxil are absorbed from the gut to a variable extent. Urine concentration is usually very high, but in most tissues levels are and generally lower than in serum. Cefazolin is given IM/IV (the only first generation administered parentrally). Excretion is via the kidney and probenecid may increase serum levels substantially.

Antimicrobial activity: The major features of these drugs are the ability of some to cross the blood-brain barrier and their expanded gram-negative coverage (active against Citrobacter, Serratia marcescens, Providencia, and beta-lactamase-producing strains of Haemophilus and Neisseria). Ceftazidime is effective in pseudomonas infections.

They can be given orally or IM or IV. They penetrate body fluids and tissues well. Cefotaxime, ceftazidim, and ceftriaxone crosses blood brain barrier, hence inhibit most pathogens, including gram-negative rods.

Clinical uses: Gonorrhea (ceftriaxone and cefixime), meningitis (pneumococci, meningococci, H influenzae, and susceptible enteric gram-negative rods), penicillin-resistant strains of pneumococci (ceftriaxone, cefotaxime), and sepsis

Fourth-generation cephalosporins (e.g.cefepime)

It is similar to third-generation agents; however, it is more resistant to hydrolysis by beta-lactamases. It has good activity against P aeruginosa.

Adverse Effects: Cephalosporins are sensitizing and may elicit a variety of hypersensitivity reactions that are identical to those of penicillins. Overgrowth of resistant organisms and fungi may induce superinfection.

Monobactams contain a monocyclic beta-lactam ring(e.g. aztreonam). They are relatively resistant to beta-lactamases and active against gram-negative rods. It resembles aminoglycosides in its spectrum of activity.

Carbapenems include imipenem and meropenem and have a broad spectrum of activity (against most Gram-positive and negative bacteria). Imipenem is inactivated by a renal proteolytic enzyme and must therefore be combined with cilastatin which inhibitati8 TD.0013 of activity.

Vancomycin

Vancomycin is active only against gram-positive bacteria, particularly staphylococci. It inhibits cell wall synthesis.

Vancomycin is poorly absorbed from the intestinal tract and is administered orally only for the treatment of antibiotic-associated enterocolitis caused by Clostridium difficile. Parenteral doses must be administered intravenously. The drug is widely distributed in the body. Ninety percent of the drug is excreted by glomerular filtration.

Clinical Uses: Parenteral vancomycin is indicated for sepsis or endocarditis caused by methicillin-resistant staphylococci. It irritates the tissues surrounding the injection site and is known to cause a red man or red neck syndrome.

Bacitracin

Bacitracin is active against gram-positive microorganisms. It inhibits cell wall formation. It is markedly nephrotoxic if administered systemically, thus limited to topical use. Bacitracin is poorly absorbed.

Cycloserine

Cycloserine inhibits many gram-positive and gram-negative organisms, but it is used almost exclusively to treat tuberculosis caused by strains of M tuberculosis resistant to first-line agents. It is widely distributed in tissues. Most of the drug is excreted in active form into the urine. Cycloserine causes serious dose-related central nervous system toxicity with headaches, tremors, acute psychosis, and convulsions.

Cell Membrane Function Inhibitors

Antimirobials such as polymyxins acting on gram negative bacteria and affects the functional integrity of the cytoplasmic membrane, macromolecules and ions escape from the cell and cell damage and death occurs. The two most well known agents are poymyxin B and colistin. Polymyxins are effective against Gram-negative bacteria, particularly pseudomonas species. The major adverse effects are nephrotoxicity dizziness, alterd sensation and neuromuscular paralysis.

Protien Synthesis Inhibitors

Bacteria have two ribosomal subunits; 30S and 50S. The 30S subunit binds mRNA in initiation and holds growing peptide chain. The 50S subunit accepts / translocates charged tRNAs. Protien synthesis inhibitors are divided into two groups: bacteriostatic and bactericidal. Chloramphenicol, macrolides, clindamycin (Lincosamides), and tetracyclines are bacteriostatic whereas aminoglycosides are bactericidal**.**

Mechanisms of action:

Chloramphenicol blocks proper binding of 50S site which, stops protein synthesis. It does inhibit mitochondrial ribosomal protein synthesis because these ribosomes are 70S, the same as those in bacteria. It does not bind to the 80S mammalian ribosomes. This may be responsible for the dose related anemia caused by chloramphenicol.

Macrolides, clindamycin, prevent transfer of the growing polypeptide chain within the 50S site so a new charged tRNA cannot bind to the ribosome so, stops protein synthesis.

Tetracyclines bind to 30S ribosomal subunit at a site that blocks binding of charged tRNA to the 50S site of the ribosome. Tetracyclines can inhibit mammalian protein synthesis, but because they are "pumped" out of most mammalian cells do not usually reach concentrations needed to significantly reduce mammalian protein synthesis.

Aminoglycosides: Protein synthesis is inhibited by aminoglycosides in at least three ways: (1) They interfere with the "initiation complex" of peptide formation; (2) they induce misreading of mRNA, which causes incorporation of incorrect amino acids into the peptide, resulting in a non-functional or toxic protein; and (3) they cause a breakup of polysomes into nonfunctional monosomes. These activities occur more or less simultaneously, and the overall effect is irreversible and lethal for the cell.

Chloramphenicol

Chloramphenicol is a bacteriostatic broad-spectrum antibiotic that is active against both aerobic and anaerobic gram-positive and gram-negative organisms. It is active also against rickettsiae*. Haemophilus influenzae, N. meningitidis,* and some strains of *Bacteroides* are highly susceptible, and for them chloramphenicol may be bactericidal. Clinically significant resistance emerges and may be due to production of chloramphenicol acetyltransferase, an enzyme that inactivates the drug.

Pharmacokinetics: Following oral administration, chloramphenicol is rapidly and completely absorbed. It is widely distributed to virtually all tissues and body fluids. The drug penetrates cell membranes readily. Excretion of active chloramphenicol and of inactive degradation products occurs by way of the urine. A small amount of active drug is excreted into bile or feces. Newborns less than a week old and premature infants clear chloramphenicol inadequately.

Clinical Uses: Because of potential toxicity, bacterial resistance, and the availability of other effective drugs, chloramphenicol may be considered mainly for treatment of serious rickettsial infections, bacterial meningitis caused by a markedly penicillin-resistant strain of pneumococcus or meningococcus, and thyphoid fever.

Adverse Reactions

Gastrointestinal disturbances: Adults occasionally develop nausea, vomiting, and diarrhea. Oral or vaginal candidiasis may occur as a result of alteration of normal microbial flora.

Bone marrow disturbances: Chloramphenicol commonly causes a dose-related reversible suppression of red cell production at dosages exceeding 50 mg/kg/d after 1-2 weeks. Aplastic anemia is a rare consequence of chloramphenicol administration by any route. It is an idiosyncratic reaction unrelated to dose, though it occurs more frequently with prolonged use. It tends to be irreversible and can be fatal.

Toxicity for newborn infants: Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol. Consequently, when infants are given dosages above 50 mg/kg/d, the drug may accumulate, resulting in the gray baby syndrome, with vomiting, flaccidity, hypothermia, gray color, shock, and collapse.

Interaction with other drugs: Chloramphenicol inhibits hepatic microsomal enzymes that metabolize several drugs. Like other bacteriostatic inhibitors of microbial protein synthesis, chloramphenicol can antagonize bactericidal drugs such as penicillins or aminoglycosides.

Tetracyclines

The tetracyclines are a large group of drugs with a common basic structure and activity. Tetracyclines are classified as short acting (chlortetracycline, tetracycline, oxytetracycline), intermediate acting (demeclocycline and methacycline), or long-acting (doxycycline and minocycline) based on serum half-lives.

Antimicrobial activity: Tetracyclines are broad-spectrum antibiotics. They are active against for many gram-positive and gram-negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasmas, and are active against some protozoa. The main mechanisms of resistance to tetracycline is decreased intracellular accumulation due to either impaired influx or increased efflux by an active transport protein pump.

Pharmacokinetics: Tetracyclines mainly differ in their absorption after oral administration and their elimination. Doxycycline better absorbed after oral administration than tetracycline. A portion of an orally administered dose of tetracycline remains in the gut lumen, modifies intestinal flora, and is excreted in the feces. Absorption occurs mainly in the upper small intestine and is impaired by food (except doxycycline and minocycline); by divalent cations (Ca^{2+} , Mg^{2+}, Fe^{2+}) or Al^{3+}

Bony structures and teeth: Tetracyclines are readily bound to calcium deposited in newly formed bone or teeth in young children. It causes discoloration, and enamel dysplasia; they can also be deposited in bone, where it may cause deformity or growth inhibition. If the drug is given to children under 8 years of age for long periods, similar changes can result.

They are hepato and nephrotoxic drug, the also induce sensitivity to sunlight (demeclocycine) and vestibular reactions (doxycycline, and minocycline).

Macrolides: include erythromycin, clarithromycin and azithromycin.

Erythromycin

Erythromycin is poorly soluble in water but dissolves readily in organic solvents. They Erythromycins are usually dispensed as various esters and salts.

Antimicrobial Activity: Erythromycin is effective against gram-positive organisms, especially pneumococci, streptococci, staphylococci, and corynebacteria. Mycoplasma, Legionella, Chlamydia trachomatis, Helicobacter, Listeria, Mycobacterium kansasii, and Mycobacterium scrofulaceum are also susceptible. Gram-negative organisms such as Neisseria species, Bordetella pertussis, Treponema pallidum, and Campylobacter species are susceptible.

Pharmacokinetics: Erythromycin base is destroyed by stomach acid and must be administered with enteric coating. Food interferes with absorption. Stearates and esters are fairly acid-resistant and somewhat better absorbed. Large amounts of an administered dose are excreted in the bile and lost in feces. Absorbed drug is distributed widely except to the brain and cerebrospinal fluid.

Clinical Uses: Erythromycin is the drug of choice in corynebacterial infections (diphtheria, corynebacterial sepsis, erythrasma); in respiratory, neonatal, ocular, or genital chlamydial infections; and in treatment of community-acquired pneumonia because its spectrum of activity includes the pneumococcus, Mycoplasma, and Legionella. Erythromycin is also useful as a penicillin substitute in penicillin-allergic individuals with infections caused by staphylococci, streptococci, or pneumococci.

Adverse Reactions

Gastrointestinal Effects: Anorexia, nausea, vomiting, and diarrhea.

Liver Toxicity: Erythromycins, particularly the estolate, can produce acute cholestatic hepatitis (reversibile).

Drug Interactions: Erythromycin metabolites inhibit cytochrome P450 enzymes; hence increase the serum concentrations of theophylline, oral anticoagulants, and terfenadine. It increases serum concentrations of oral digoxin by increasing its bioavailability.

Clarithromycin

Clarithromycin is derived from erythromycin. It is better absorbed compared with erythromycin. Clarithromycin and erythromycin are virtually identical with respect to antibacterial activity except that clarithromycin has high activity against H. influenzae, *M. leprae* and *T. gondii.* Clarithromycin penetrates most tissues, with concentrations equal to or exceeding serum concentrations. It is metabolized in the liver. A portion of active drug and major metabolite is eliminated in the urine. It has drug interactions similar to those described for erythromycin. The advantages of clarithromycin compared with erythromycin are lower frequency of gastrointestinal intolerance and less frequent dosing.

Azithromycin

The spectrum of activity and clinical uses of azithromycin is identical to those of clarithromycin.It is rapidly absorbed and well tolerated orally. Azithromycin does not inactivate cytochrome P450 enzymes like erythromycin.

Clindamycin

Clindamycin is active against streptococci, staphylococci, bacteroides species and other anaerobes, both grampositive and gram-negative. It resembles erythromycin in activity and mechanisms of resistance. Clindamycin is well absorbed orally and about 90% protein-bound. Excretion is mainly via the liver, bile, and urine. It penetrates well into most tissues.

Clinical uses: Clindamycin is used for the treatment of severe anaerobic infection caused by Bacteroides. It is used for prophylaxis of endocarditis in patients with valvular heart disease who are undergoing certain dental procedures. Clindamycin plus primaquine is an effective for moderate to moderately severe Pneumocystis carinii pneumonia. It is also used in combination with pyrimethamine for AIDS-related toxoplasmosis of the brain.

Adverse effects: Diarrheas, nausea, and skin rashes, impaired liver functions are common. Severe diarrhea and enterocolitis is caused by toxigenic C difficile (infrequently part of the normal fecal flora but is selected out during administration of oral antibiotics).

Aminoglycosides:

Members: Streptomycin, neomycin, kanamycin, amikacin, gentamicin, netilmicin.

Pharmacokinetics: Aminoglycosides are absorbed very poorly from the intact gastrointestinal tract. After intramuscular injection, aminoglycosides are well absorbed. They are highly polar compounds that do not enter cells readily. The kidney clears aminoglycosides, and excretion is directly proportionate to creatinine clearance.

Adverse effects: Aminoglycosides damage the VIII nerve and the kidneys. Ototoxicity can manifest itself either as auditory damage, resulting in tinnitus and high-frequency hearing loss initially; or as vestibular damage, evident by vertigo, ataxia, and loss of balance. Nephrotoxicity results in rising serum creatinine levels or reduced creatinine clearance. Neomycin, kanamycin, and amikacin are the most ototoxic agents. Streptomycin and gentamicin are the most vestibulotoxic.

Streptomycin

Streptomycin is mainly used as a first-line agent for treatment of tuberculosis.

Adverse Reactions: Disturbance of vestibular function (vertigo, loss of balance) is common. The frequency and severity of this disturbance are proportionate to the age of the patient, the blood levels of the drug, and the duration of administration. Vestibular dysfunction may follow a few weeks of unusually high blood levels or months of relatively low blood levels. Vestibular toxicity tends to be irreversible. Streptomycin given during pregnancy can cause deafness in the newborn.

Gentamicin

Gentamicin inhibits many strains of staphylococci and coliforms and other gram-negative bacteria. It is a synergistic companion with beta-lactam antibiotics, against *Pseudomonas, Proteus, Enterobacter, Klebsiella, Serratia, Stenotrophomonas,* and other gram-negative rods that may be resistant to multiple other antibiotics.

Gentamicin is also used concurrently with penicillin G for bactericidal activity in endocarditis due to viridans streptococci. Creams, ointments, or solutions gentamicin sulfate are for the treatment of infected burns, wounds, or skin lesions.

Amikacin

Amikacin is a semisynthetic derivative of kanamycin; it is less toxic than the parent molecule. It is resistant to many enzymes that inactivate gentamicin and tobramycin, and it therefore can be employed against some microorganisms resistant to the latter drugs. Strains of multidrug-resistant Mycobacterium tuberculosis, including streptomycin-resistant strains, are usually susceptible to amikacin.

Kanamycin, Neomycin, Paromomycin

These drugs are closely related is also a member of this group. All have similar properties. Neomycin and kanamycin are too toxic for parenteral use and are now limited to topical and oral use. Neomycin is given orally in preparation for elective bowel surgery. In hepatic coma, the coliform flora can be suppressed for prolonged periods by giving 1 g every 6-8 hours together with reduced protein intake, thus reducing ammonia intoxication. Paromomycin has been effective in intestinal amebiasis.

Spectinomycin

Spectinomycin is an aminocyclitol antibiotic that is structurally related to aminoglycosides. Spectinomycin is used almost solely as an alternative treatment for gonorrhea in patients who are allergic to penicillin or whose gonococci are resistant to other drugs. It is rapidly absorbed

Pharmacokinetics: After oral administration, the fluoroquinolones are well absorbed and distributed widely in body fluids and tissues. Oral absorption is impaired by divalent cations, including those in antacids. The fluoroquinolones are excreted mainly by tubular secretion and by glomerular filtration. All fluoroquinolones accumulate in renal failure.

Clinical Uses: Fluoroquinolones are effective in urinary tract infections even when caused by multidrug-resistant bacteria, eg, Pseudomonas. Norfloxacin 400 mg, ciprofloxacin 500 mg, and ofloxacin 400 mg given orally twice daily and all are effective. These agents are also effective for bacterial diarrhea caused by Shigella, Salmonella, toxigenic E coli, or Campylobacter. Fluoroquinolones (except norfloxacin, which does not achieve adequate systemic concentrations) have been employed in infections of soft tissues, bones, and joints and in intra-abdominal and respiratory tract infections, including those caused by multidrug-resistant organisms such as Pseudomonas and Enterobacter. Ciprofloxacin and ofloxacin are effective for gonococcal infection, including disseminated disease, and ofloxacin is effective for chlamydial urethritis or cervicitis.

Adverse Effects: The most common effects are nausea, vomiting, and diarrhea. Concomitant administration of theophylline and quinolones can lead to elevated levels of theophylline with the risk of toxic effects, especially seizures. Fluoroquinolones may damage growing cartilage and cause an arthropathy. Thus, they are not routinely recommended for use in patients under 18 years of age. Since fluoroquinolones are excreted in breast milk, they are contraindicated for nursing mothers.

Rifampin

Rifampin binds strongly to the bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis. It is well absorbed after oral administration and excreted mainly through the liver into bile. Rifampin is distributed widely in body fluids and tissues. It is relatively highly protein-bound, and so adequate cerebrospinal fluid concentrations are achieved only in the presence of meningeal inflammation. Rifampin is used in the treatment of mycobacterial infections.

Rifampin causes a harmless orange color to urine, sweat, and tears. Occasional adverse effects include rashes, thrombocytopenia, nephritis, cholestatic jaundice and occasionally hepatitis. Rifampin induces microsomal enzymes (cytochrome P450), which increases the elimination of anticoagulants, anticonvulsants, and contraceptives. Administration of rifampin with ketoconazole, or chloramphenicol results in significantly lower serum levels of these drugs.

Topical Agents: Sodium sulfacetamide ophthalmic solution or ointment is effective treatment for bacterial conjunctivitis and as adjunctive therapy for trachoma. Silver sulfadiazine is a much less toxic topical sulfonamide and is preferred to mafenide for prevention of infection of burn wounds.

Adverse Reactions: The most common adverse effects are fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, and diarrhea. Stevens-Johnson syndrome, crystalluria, hematuria, hemolytic or aplastic anemia, granulocytopenia, and thrombocytopenia occur less frequently. Sulfonamides taken near the end of pregnancy increase the risk of kernicterus in newborns.

Trimethoprim

Trimethoprim inhibits bacterial dihydrofolic acid reductase. Dihydrofolic acid reductases convert dihydrofolic acid to tetrahydrofolic acid, a stage leading to the synthesis of purines and ultimately to DNA.

Trimethoprim is usually given orally. It is absorbed well from the gut and distributed widely in body fluids and tissues, including cerebrospinal fluid. Trimethoprim concentrates in prostatic fluid and in vaginal fluid, which are more acid than plasma. Therefore, it has more antibacterial activity in prostatic and vaginal fluids than many other antimicrobial drugs.

Trimethoprim can be given alone in acute urinary tract infections, because most community-acquired organisms tend to be susceptible to the high concentrations.

Trimethoprim produces the predictable adverse effects of an antifolate drug, especially megaloblastic anemia, leukopenia, and granulocytopenia. This can be prevented by the simultaneous administration of folinic acid, 6-8 mg/d.

Trimethoprim-Sulfamethoxazole(Cotrimoxazole)

The half-life of trimethoprim and sulfamethoxazole is similar. Trimethoprim, given together with sulfamethoxazole, produces sequential blocking in this metabolic sequence, resulting in marked enhancement of the activity of both drugs. The combination often is bactericidal, compared to the bacteriostatic activity of a sulfonamide alone.

Clinical uses: Trimethoprim-sulfamethoxazole is effective treatment for Pneumocystis carinii pneumonia, shigellosis, systemic Salmonella infections, urinary tract infections, and prostatitis. It is active against many respiratory tract pathogens; P*neumococcus, Haemophilus species, Moraxella catarrhalis, and Klebsiella pneumoniae.*

ANTIMYCOBACTERIAL DRUGS

Mycobacterial infections are the most difficult of all bacterial infections to cure. Mycobacteria are slowly growing organisms (can also be dormant) and thus completely resistant to many drugs, or killed only very slowly by the few drugs that are active. The lipid-rich mycobacterial cell wall is impermeable to many agents. A substantial proportion of mycobacterial organisms are intracellular, residing within macrophages, and inaccessible to drugs that penetrate poorly. Finally, mycobacteria are notorious for their ability to develop resistance to any single drug. Combinations of drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy. The response of mycobacterial infections to

Adverse Reactions: The incidence and severity of untoward reactions to INH are related to

adverse effects of pyrazinamide include hepatotoxicity, nausea, vomiting, drug fever, and hyperuricemia. Hyperuricemia may provoke acute gouty arthritis.

Streptomycin

Most tubercle bacilli are inhibited by streptomycin. Streptomycin penetrates into cells poorly, and thus it is active mainly against extracellular tubercle bacilli. Streptomycin crosses the blood-brain barrier and achieves therapeutic concentrations with inflamed meninges. It is employed principally in individuals with severe, possibly life-threatening forms of tuberculosis (meningitis and disseminated disease), and in treatment of infections resistant to other drugs.

Combination Chemotherapy of Tuberculosis

The duration of therapy for a patient with tuberculosis depends upon the severity of the disease, the organ affected and the combination of agents. There are two phases in the treatment of tuberculosis; the intensive phase, which lasts 8 weeks, makes the patients noninfectious. The continuation phase, which lasts 6 months or more and at least two drugs should be taken. Four types of drug regimen are currently employed in Ethiopia; Directly Observed Treatment Short Course (DOTS), Re- treatment Regimen, and Short course Chemotherapy and long course chemotherapy (LCC)

Drug Regimens and Treatment Categories

1. Directly Observed Treatment Short Course (DOTS)

Used in new Pulmonary TB smear positive patients; new Pulmonary TB smear negative and Extrapulmonary TB patients who are seriously ill; TB in children < 6 years. It consists of 8 weeks of treatment with Streptomycin, Rifampicin, Isoniazid and Pyrazinamide during the intensive phase followed by 6 monthes of Ethambutol and Isoniazid or 4 months of rifampin and isoniazid (RH). (2S (RHZ)/6(EH). Children <6 years receive 4 monthes of Rifampicin and INH (RH) in the continuation phase. Drugs have to be collected daily during the intensive phase of DOTS and taken under direct observation by the health worker. During the continuation phase drugs have to be collected every month and self-administered by the patient.

2. Re- treatment Regimen

Used for patients previously treated for more than one month with short course chemotherapy (SCC) and Long course chemotherapy (LCC) and are still smear positive. These patients are: - Relapses; Treatment failures; Returns after default who are pulmonary tuberculosis positive. It consists of 2 months of treatment using Streptomycin, INH, Ethambutol, Rifampicin and

Pyrazinamide then 1month of INH, Ethambutol, Rifampicin and Pyrazinamide in the intensive phase, Followed by 5 months of ethambutol, Rifampicin and INH. [2SE (RH) Z/1E (RH) Z/$5E_3$ (RH) $_3$].

Dapsone

Dapsone (diaminodiphenylsulfone) is the most widely used drugs in the treatment of leprosy and it inhibits folate synthesis. Resistance can emerge in large populations of M leprae. Therefore, the combination of dapsone, rifampin, and clofazimine is recommended for initial therapy. Sulfones are well absorbed from the gut and widely distributed throughout body fluids and tissues. Excretion into urine is variable, and most excreted drug is acetylated.

Dapsone is usually well tolerated. Gastrointestinal intolerance, fever, pruritus, and rashes occur. Erythema nodosum often develops during dapsone therapy in lepromatous leprosy. Erythema nodosum leprosum may be suppressed by corticosteroids. Hemolysis and methemoglobinemia can occur.

Rifampin

This drug is effective in lepromatous leprosy. Because of the probable risk of emergence of rifampin-resistant M leprae, the drug is given in combination with dapsone or another antileprosy drug.

Clofazimine

The absorption of clofazimine from the gut is variable, and a major portion of the drug is excreted in feces. Clofazimine is stored widely in reticuloendothelial tissues and skin. Clofazimine is given for sulfone-resistant leprosy or when patients are intolerant to sulfone. A common dosage is 100 mg/d orally. The most prominent untoward effect is skin discoloration ranging from red-brown to nearly black.

ANTIFUNGAL AGENTS

Fungal infections have increased in incidence and severity in recent years, due to increased in the use of broad-spectrum antimicrobials and the HIV epidemic. The antifungal drugs fall into two groups: antifungal antibiotics and synthetic antifungals.

Antifungal antibiotics

Amphotericin B

Amphotericin B is poorly absorbed from the gastrointestinal tract. Oral amphotericin B is thus effective only on fungi within the lumen of the tract. The drug is widely distributed in tissues, but only 2-3% of the blood level is reached in CSF, thus occasionally necessitating intrathecal therapy for certain types of fungal meningitis.

Mechanism of Action: Amphotericin B binds to ergosterol (a cell membrane sterol) and alters the permeability of the cell by forming amphotericin B-associated pores in the cell membrane. The pore allows the leakage of intracellular ions and macromolecules, eventually leading to cell death.

Adverse Effects: The toxicity of amphotericin B which may occur immediately or delayed include fever, chills, muscle spasms, vomiting, headache, hypotension (related to infusion), renal damage associated with decreased renal perfusion (a reversible) and renal tubular injury (irreversible). Anaphylaxis, liver damage, anemia occurs infrequently.

Antifungal Activity: Amphotericin B is a broad-spectrum antifungal agent. It has activity against yeasts including; Candida albicans and Cryptococcus neoformans; molds, Aspergillus fumigatus.

Clinical Use: Amphotericin B remains the drug of choice for nearly all life-threatening mycotic infections. Used as the initial induction regimen for serious fungal infections (immunosuppressed patients, severe fungal pneumonia, and cryptococcal meningitis with altered mental status).

Nystatin

Nystatin has similar structure with amphotericin B and has the same pore-forming mechanism of action. It is too toxic for systemic use and is only used topically. It is not absorbed from skin, mucous membranes, or the gastrointestinal tract. Nystatin is active against most Candida species and is most commonly used for suppression of local candidal infections. Nystatin is used in the treatment of oropharyngeal thrush, vaginal candidiasis, and intertriginous candidal infections.

Griseofulvin

Griseofulvin is a fungistatic and used is in the treatment of dermatophytosis. Absorption is improved when it is given with fatty foods. Griseofulvin is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection. It must be administered for 2-6 weeks for skin and hair infections to allow the replacement of infected keratin by the resistant structures. Nail infections may require therapy for months to allow regrowth of the new protected nail and is often followed by relapse. Adverse effects include an allergic syndrome


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therapeutic window. Fluconazole is the azole of choice in the treatment and secondary prophylaxis of cryptococcal meningitis. It is also effective for mucocutaneous candidiasis.

ANTIVIRAL AGENTS

Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cell. Viral replication consists of several steps: (1) adsorption to and penetration into susceptible host cells; (2) uncoating of viral nucleic acid; (3) synthesis of early, regulatory proteins, eg, nucleic acid polymerases; (4) synthesis of RNA/ DNA; (5) synthesis of late, structural proteins; (6) assembly (maturation) of viral particles; and (7) release from the cell.

Antiviral agents can potentially target any of these steps. Most of the antiviral agents currently available act on synthesis of purines and pyrimidines (step 4); reverse transcriptase inhibitors block transcription of the HIV RNA genome into DNA, thereby preventing synthesis of viral mRNA and protein. The protease inhibitors act on synthesis of late proteins and packaging (steps 5 and 6). In this section drugs used in the treatment of herps, human immunodeficiency virus and other antiviral agents will be discussed.

Antiherpes Agents

Acyclovir

Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms: competitive inhibition of the viral DNA polymerase and by binding to the DNA template as an irreversible complex..

Acyclovir is available in oral, intravenous, and topical formulations. Acyclovir diffuses into most tissues and body fluids to produce concentrations that are 50-100% of those in serum. Cerebrospinal fluid concentrations are 50% of serum values.

Clinical Uses: Oral acyclovir is effective for treatment of primary infection and recurrences of genital and labial herpes. Intravenous acyclovir is the treatment of choice for herpes simplex encephalitis, neonatal HSV infection and for severe primary, recurrent HSV genital and labial infections and for those who cannot ingest oral pills

Adverse Reactions: Acyclovir is generally well tolerated. Nausea, diarrhea, and headache have occasionally been reported. IV infusion may be associated with renal insufficiency or neurologic toxicity.

Idoxuridine

Idoxuridine (IDU, IUDR) is a substituted pyrimidine analog that was the first antiviral agent to be approved. It is used topically in the treatment of herpes keratitis (0.1% solution), but because of its lack of selectivity it is too toxic for systemic administration.

Vidarabine

Vidarabine as a 3% ointment is effective treatm


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Adverse Effects: The most common adverse effects reported thus far are indirect hyperbilirubinemia and nephrolithiasis. Thrombocytopenia, nausea, diarrhea, and irritability have also been reported in some patients. Indinavir and ritonavir are inhibitors of as well as substrates for cytochrome P450 CPY3A4. Serum levels of indinavir will increase in the

Delavirdine (DLV)

Delavirdine a synthetic antiretroviral agent, is a nonnucleoside reverse transcriptase inhibitor.Delavirdine differs structurally from nevirapine, a dipyridodiazepinone derivative nonnucleoside reverse transcriptase inhibitor. The drug inhibits replication of HIV-1 by interfering with viral RNA- and DNA-directed polymerase activities of reverse transcriptase. The mechanism of action of DLV derivatives appears to be similar to that of other nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine, loviride, efavirenz). All nonnucleoside reverse transcriptase inhibitors appear to bind to a common region of reverse transcriptase and exhibit similar kinetic characteristics in their mode of retroviral inhibition.

Spectrum: Delavirdine is a highly specific antiretroviral agent with a very limited spectrum of activity. The drug has in vitro virustatic activity against HIV-1, but is inactive against HIV-2.

Resistance: Strains of HIV-1 with reduced susceptibility to delavirdine (i.e., 10- to 100-fold decrease in susceptibility from baseline) have been produced in vitro by serial passage of the retrovirus in the presence of increasing concentrations of the drug. The mechanism of resistance or reduced susceptibility to delavirdine has not been fully determined, but mutation of HIV reverse transcriptase appears to be involved.

Clinical Uses: Oral delavirdine is used in combination with other antiretroviral agents for the management of human immunodeficiency virus type 1 (HIV-1) infection in adults.

Adverse reactions: Rash is the major toxicity associated with delavirdine therapy. Severe or life-threatening rash (e.g., erythema multiforme, Stevens-Johnson syndrome) have been reported rarely and resolved after the drug was discontinued. Rash usually is evident within 1-3 weeks (median: 11 days) following initiation of delavirdine therapy and typically is diffuse, maculopapular, erythematous, and often pruritic; rash occurs mainly on the upper body and proximal arms with decreasing intensity of the lesions on the neck and face and progressively less on the rest of the trunk and limbs.

Nevirapine

Nevirapine is a nonnucleoside reverse transcriptase inhibitor. The drug inhibits replication of human immunodeficiency virus type 1 (HIV-1) by interfering with viral RNA- and DNA-directed polymerase activities of reverse transcriptase. Nevirapine binds directly to HIV-1 reverse transcriptase and exerts a virustatic effect by acting as a specific, noncompetitive HIV-1 reverse transcriptase inhibitor. Nevirapine is a highly specific antiretroviral agent with a very limited spectrum of activity.


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Antineoplastic agents

Cancer refers to a malignant neoplasm or new growth. Cancer cells manifest uncontrolled *proliferation, loss of function due to loss of capacity to differentiate, invasiveness, and the ability to metastasize.*

Cancer arises as a result of genetic changes in the cell, the main genetic changes being; *inactivation of tumor suppressor genes and activation of oncogenes*.

There are three approaches for the management of cancer:

1. Radiotherapy
2. Surgery
3. Chemotherapy

Most anticancer drugs are antiproliferative, and hence affect rapidly growing dividing normal cells. Anticancer drugs are broadly classified into two: *cytotoxic* drugs and *hormones.*

Cytotoxic drugs are further classified into:

- *Alkylating agents and related compounds* (e.g. cyclophosphamide, lomustine, thiotepa, cisplatin): These groups of drugs act by forming covalent bonds with DNA and thus impending DNA replication.
- *Antimetabolites* (e.g. methotrexate, fluorouracil, mercaptopurine): These drugs blocks or destabilize pathways in DNA synthesis.
- *Cytotoxic antibiotics (e.g.* Doxorubucin, bleomycin, dactinomycin): These drugs inhibit DNA or RNA synthesis or cause fragmentation to DNA chains or interfere with RNA polymerase and thus inhibit transcription.
- *Plant derivatives (e.g.* vincristine): Inhibits mitosis

Hormones and their antagonists are used in hormone sensitive tumors (eg. glucocorticoids for lymphomas, oestrogens for prostatic cancer, tamoxifen for breast tumors).

General toxic effects of anticancer drugs:

- Bone marrow toxicity.
- Impaired wound healing.
- Sterility.
- Loss of hair.
- Damage to gastrointestinal epithelium.

TREATMENT OF PROTOZOAL INFECTIONS

1. Treatment of Malaria

4) Sporonticidal agents are drugs that render gametocytes noninfective in the mosquito (eg, pyrimethamine, proguanil).

None of these drugs prevent infection except for pyrimethamine and proguanil which prevent maturation of P falciparum hepatic schizonts. Blood schizonticides do destroy circulating plasmodia. Primaquine destroys the persisting liver hypnozoites of P vivax and P ovale.

1.3. Individual antimalarial drugs

1.3.1. Chloroquine

Pharmacokinetics: Chloroquine is a synthetic 4-aminoquinoline. It is rapidly and almost completely absorbed from the gastrointestinal tract, and is rapidly distributed to the tissues. From these sites it is slowly released and metabolized. The drug readily crosses the placenta. Renal excretion is increased by acidification of the urine.

Antimalarial Action: Chloroquine is a highly effective blood schizonticide and is most widely used in chemoprophylaxis and in treatment of attacks of vivax, ovale, malariae, or sensitive falciparum malaria. It is moderately effective against gametocytes of P. vivax, P. ovale, and P. malariae, but not against those of P falciparum. Chloroquine is not active against the preerythrocytic plasmodium and does not effect radical cure.

The exact mechanism of action has not been known. Selective toxicity for malarial parasites depends on a chloroquine-concentrating mechanism in parasitized cells. Chloroquine's concentration in normal erythrocytes is 10-20 times that in plasma; in parasitized erythrocytes, its concentration is about 25 times that in normal erythrocytes.

Clinical uses: Acute Malaria Attacks (it clears the parasitemia of acute attacks of P vivax, P ovale, and P malariae and of malaria due to nonresistant strains of P falciparum), and chemoprophylaxis (It is the preferred drug for prophylaxis against all forms of malaria except in regions where P falciparum is resistant to 4-aminoquinolines).

Adverse Effects: Gastrointestinal symptoms, mild headache, pruritus, anorexia, malaise, blurring of vision, and urticaria are uncommon. A total cumulative dose of 100 g (base) may, contribute to the development of irreversible retinopathy, ototoxicity, and myopathy.

Contraindications: It is contraindicated in patients with a history of liver damage, alcoholism, or neurologic or hematologic disorders, psoriasis or porphyria, in whom it may precipitate acute attacks of these diseases.

1.3.2. Primaquine

Primaquine phosphate is a synthetic 8-aminoquinoline derivative. After oral administration, the drug is usually well absorbed, completely metabolized, and excreted in the urine.

Primaquine is active against the late hepatic stages (hypnozoites and schizonts) of P vivax and P ovale and thus effects radical cure of these infections. Primaquine is also highly active against the primary exoerythrocytic stages of P falciparum. When used in prophylaxis with chloroquine, it protects against P vivax and P ovale. Primaquine is highly gametocidal against the four malaria species.

Clinical Uses

1. Terminal prophylaxis of vivax and ovale malaria.
2. Radical cure of acute vivax and ovale malaria.
3. Gametocidal action.
4. Pneumocystis carinii pneumonia

Adverse Effects: Primaquine is generally well tolerated. It infrequently causes nausea, epigastric pain, abdominal cramps, and headache. Se

4. Other Uses: Quinine sulfate sometimes relieves night time leg cramps.

Adverse Effects: Quinine often causes nausea, vomiting, hypoglycemia. Cinchonism; a less common effect and manifested by headache, nausea, slight visual disturbances, dizziness, and mild tinnitus and may subside as treatment continues. Severe toxicity like fever, skin eruptions, gastrointestinal symptoms, deafness, visual abnormalities, central nervous system effects (syncope, confusion), and quinidine-like effects occurs rarely.

1.3.4. Proguanil and Pyrimethamine

Pyrimethamine and proguanil are dihydrofolate reductase inhibitors. They are slowly but adequately absorbed from the gastrointestinal tract.

Pyrimethamine and proguanil are slow acting blood schizonticides against susceptible strains of all four malarial species. Proguanil (but not pyrimethamine) has a marked effect on the primary tissue stages of susceptible P falciparum and therefore may have causal prophylactic action.

Resistance to pyrimethamine and proguanil is found worldwide for P falciparum and somewhat less ubiquitously for P vivax.

Clinical uses

1. Chemoprophylaxis
2. Treatment of Chloroquine-Resistant Falciparum Malaria
3. Toxoplasmosis treatment

Adverse Effects: In malaria treatment, pyrimethamine and proguanil are well tolerated. In the high doses pyrimethamine causes megaloblastic anemia, agranulocytosis and thrombocytopenia (leucovorin calcium is given concurrently).

1.3.5. Sulfones and Sulfonamides

Sulfonamides and sulfones have blood schizonticidal action against P falciparum by inhibition of dihydrofolic acid synthesis. But, the drugs have weak effects against the blood schizonts of P vivax, and they are not active against the gametocytes or liver stages of P falciparum or P vivax. When a sulfonamide or sulfone is combined with an antifol, synergistic blockade of folic acid synthesis occurs in susceptible plasmodia. Sulfadoxine with pyrimethamine (Fansidar) and dapsone with pyrimethamine (Maloprim) are the most used combination.

1.3.6. Pyrimethamine-Sulfadoxine (Fansidar)

Pyrimethamine-Sulfadoxine (Fansidar) is well absorbed. Its components display peak plasma levels within 2-8 hours and are excreted mainly by the kidneys. Average half-lives are about 170 hours for sulfadoxine and 80-110 hours for pyrimethamine.

Pyrimethamine-Sulfadoxine is effective against certain strains of falciparum malaria. But, quinine must be given concurrently in treatment of seriously ill patients, because fansidar is only slowly active. It is not effective in the treatment of vivax malaria.

Clinical uses

1. Treatment of Chloroquine-Resistant Falciparum
2. Presumptive Treatment of Chloroquine-Resistant Falciparum Malaria

Adverse Effects: Rare adverse effects to single-dose Fansidar are those associated with sulfonamide allergy, including the hematologic, gastrointestinal, central nervous system, dermatologic, and renal systems. Fansidar is no longer used in prophylaxis because of severe reactions. However, in our situation, it used for prevention of malaria in pregnant women after the first trimester.

Contraindications: Fansidar is contraindicated in patients who have had adverse reactions to sulfonamides, in pregnancy at term, in nursing women, or in children less than 2 months of age. Fansidar should be used with caution in those with severe allergic disorders, and bronchial asthma.

1.3.7. Mefloquine

Mefloquine is used in prophylaxis and treatment of chloroquine-resistant and multidrug-resistant falciparum malaria. It is also effective in prophylaxis against P. vivax, P. ovale, P. malariae, and P. falciparum.

Mefloquine hydrochloride is chemically related to quinine. It can only be given orally because intense local irritation occurs with parenteral use. It is well absorbed. The drug is highly bound to plasma proteins, concentrated in red blood cells, and extensively distributed to the tissues, including the central nervous system. Mefloquine is cleared in the liver. Its acid metabolites are slowly excreted, mainly in the feces. Its elimination half-life, which varies from 13 days to 33 days, tends to be shortened in patients with acute malaria.

Mefloquine has blood schizonticidal activity against P falciparum and P vivax. Sporadic and low levels of resistance to mefloquine have been reported from Southeast Asia and Africa. Resistance to the drug can emerge rapidly, and resistant strains have been found in areas where the drug has never been used.

Clinical uses: Prophylaxis of Chloroquine-Resistant Strains of P falciparum and Treatment of Chloroquine-Resistant P falciparum Infection

Adverse Reactions: The frequency and intensity of reactions are dose-related. In rophylactic doses it causes; gastrointestinal disturbances, headache, dizziness, syncope, and extra systoles and transient neuropsychiatric events

of extraintestinal infection. The choice of drug depends on the clinical presentation and on the desired site of drug action, ie, in the intestinal lumen or in the tissues.

All of the antiamebic drugs act against Entamoeba histolytica trophozoites, but most are not effective against the cyst stage. Antiamebic drugs are classified as tissue amebicides and luminal amebicides.

2.1. Tissue amebicides eliminate organisms primarily in the bowel wall, liver, and other extraintestinal tissues and are not effective against organisms in the bowel lumen.

2.1.1. Metronidazole, and tinidazole are highly effective against amebas in the bowel wall and other tissues.

2.1.2. Emetine and dehydroemetine act on organisms in the bowel wall and other tissues but not on amebas in the bowel lumen.

2.1.3. Chloroquine -Active principally against amebas in the liver.

2.2. Luminal Amebicides act primarily in the bowel lumen.

2.2.1. Diloxanide furoate

2.2.2. Iodo-quinol

2.2.3. Tetracyclines, paromomycin and erythromycin

2.3. Treatment of Amebiasis

2.3.1. Asymptomatic Intestinal Infection: The drugs of choice, diloxanide furoate and iodoquinol. Alternatives are metronidazole plus iodoquinol or diloxanide.

2.3.2. Intestinal Infection: The drugs of choice, metronidazole and a luminal amebicide.

2.3.3. Hepatic Abscess: The treatment of choice is metronidazole. Diloxanide furoate or iodoquinol should also be given to eradicate intestinal infection whether or not organisms are found in the stools. An advantage of metronidazole is its effectiveness against anaerobic bacteria, which are a major cause of bacterial liver abscess. Dehydroemetine and emetine are potentially toxic alternative drugs.

2.3.4. Ameboma or Extraintestinal Forms of Amebiasis: Metronidazole is the drug of choice. Dehydroemetine is an alternative drug; chloroquine cannot be used because it does not reach high enough tissue concentrations to be effective D.hhepg9nnot is eapness79.4.ecai5 T

2.4. Antiamoebic drugs

2.4.1. Metronidazole

Pharmacokinetics : Oral metronidazole is readily absorbed and permeates all tissues including cerebrospinal fluid, breast milk, alveolar bone, liver abscesses, vaginal secretions, and seminal fluid. Intracellular concentrations rapidly approach extracellular levels whether administered orally or intravenously. Protein binding is low. The drug and its metabolites are excreted mainly in the urine.

Mechanism of Action: The nitro group of metronidazole is chemically reduced by ferredoxin within sensitive organisms. The reduction products appear to be responsible for killing the organisms by reacting with various intracellular macromolecules.

Clinical Uses: Metronidazole is active against amebiasis, urogenital trichomoniasis, giardiasis, anaerobic infections, acute ulcerative gingivitis, cancrum Oris, decubitus ulcers, and bacterial vaginitis and Helicobacter pylori infection.

Adverse effects: Nausea, headache, dry mouth, or metallic tastes occur commonly. Rare adverse effects include vomiting, diarrhea, insomnia, weakness, dizziness, stomatitis, rash, urethral burning, vertigo, and paresthesias. It has a disulfiram-like effect.

2.4.2. Other Nitroimidazoles

Other nitroimidazole derivatives include tinidazole, and ornidazole. They have similar adverse effects Because of its short half-life, metronidazole must be administered every 8 hours; the other drugs can be administered at longer intervals. However, with the exception of tinidazole, the other nitroimidazoles have produced poorer results than metronidazole in the treatment of amebiasis.

2.4.3. Chloroquine

Chloroquine reaches high liver concentrations and is highly effective when given with emetine in the treatment and prevention of amebic liver abscess. Chloroquine is not active against luminal organisms.

2.4.4. Dehydroemetine Emetine

Emetine and dehydroemetine are administered parenterally. They are stored primarily in the liver, lungs, spleen, and kidneys. They are eliminated slowly via the kidneys.These drugs act only against trophozoites, which they directly eliminate.

Clinical Uses: Severe Intestinal Disease (Amebic Dysentery): Parenterally administered emetine and dehydroemetine rapidly alleviate severe intestinal symptoms but are rarely curative even if a full course is given.

Adverse Effects: Sterile abscesses, pain, tenderness, and muscle weakness in the area of the injection are frequent. Emetine and dehydroemetine should not be used in patients with cardiac or renal disease, in patients with a history of polyneuritis, or in young children or liver abscess. They should not be used during pregnancy.

2.4.5. Diloxanide Furoate

Diloxanide furoate is directly amebicidal, but its mechanism of action is not known. In the 2gut, diloxanide furoate is split into diloxanide and furoic acid; about 90% of the diloxanide is rapidly absorbed and then conjugated to form the glucuronide, which is rapidly excreted in the urine. The unabsorbed diloxanide is the active antiamebic substance. Diloxanide furoate is the drug of choice for asymptomatic infections. For mild intestinal disease, and other forms of amebiasis it is used with another drug.

2.4.6. Iodoquinol

Iodoquinol is effective against organisms in the bowel lumen but not against trophozoites in the intestinal wall or extraintestinal tissues. The mechanism of action of iodoquinol against trophozoites is unknown. Iodoquinol is an alternative drug for the treatment of asymptomatic or mild to moderate intestinal amebiasis.

Adverse Effects: Reversible severe neurotoxicity (optic atrophy, visual loss, and peripheral neuropathy). Mild and infrequent adverse effects that can occur at the standard dosage include diarrhea, which usually stops after several days, anorexia, nausea and vomiting, gastritis, abdominal discomfort, slight enlargement of the thyroid gland, headache, skin rashes, and perianal itching.

2.4.7. Paromomycin Sulfate

Paromomycin is an alternative drug for the treatment of asymptomatic amebiasis. In mild to moderate intestinal disease, it is an alternative luminal drug used concurrently with metronidazole. Paromomycin is both directly and indirectly amebicidal; the indirect effect is caused by its inhibition of bowel bacteria. It can be used only as a luminal amebicide and has no effect in extraintestinal amebic infections.

2.4.8. Other Antibiotics

Adverse Effects: Pain at the injection site is common; infrequently, a sterile abscess develops and ulcerates. Occasional reactions include rash, gastrointestinal symptoms, neutropenia, abnormal liver function tests, serum folate depression, hyperkalemia, and hypocalcemia. Severe hypotension, hypoglycemia, hyperglycemia, hyponatremia, and delayed nephrotoxicity.

Adverse Reactions: Mild and transient epigastric distress, diarrhea, headache, nausea, dizziness. In 3-month treatment courses causes jaundice, nausea, vomiting, abdominal pain, alopecia, rash or pruritus occurs.

Diethylcarbamazine Citrate

Diethylcarbamazine is a drug of choice in the treatment of filariasis, loiasis, and tropical eosinophilia.

Anthelmintic Actions: Diethycarbamazine immobilizes microfilariae and alters their surface structure, making them more susceptible to destruction by host defense mechanisms. The mode of action of diethylcarbamazine against adult worms is unknown.

Clinical Uses:

1. Wuchereria bancrofti, Loa loa: Diethycarbamazine is the drug of choice for treatment of infections with these parasites, given its high order of therapeutic efficacy and lack of serious toxicity. Microfilariae of all species are rapidly killed; adult parasites are killed more slowly, often requiring several courses of treatment.
2. Onchocerca volvulus: Diethylcarbamazine temporarily kills microfilariae but are poorly effective against adult worms. If diethylcarbamazine is used in onchocerciasis treatment, suramin (a toxic drug) must be added to the regimen to kill the adult worms.

Adverse Reactions

Reactions to the drug itself are mild and transient includes: headache, malaise, anorexia, and weakness are frequent. Reactions Induced by dying Parasites: As a result of the release of foreign proteins from dying microfilariae or adult worms in sensitized patients. Reactions in onchocerciasis affect the skin and eyes in most patients. The reactions may be severe, if infection is heavy. Vision can be permanently damaged as a result of dying microfilariae in the optic disks and retina. Reactions in W bancrofti, and L loa infections are usually mild in W bancrofti, and occasionally severe in L loa infections. Reactions include fever, malaise, papular rash, headache, gastrointestinal symptoms, cough, chest pains, and muscle or joint pains.

Ivermectin

Ivermectin is the drug of choice in individual and mass treatment of onchocerciasis and for strongyloidiasis. The drug is rapidly absorbed. The drug has a wide tissue distribution. It apparently enters the eye slowly and to a limi

Anthelmintic Actions: Ivermectin paralyze nematodes and arthropods by intensifying GABA-mediated transmission of signals in peripheral nerves. In onchocerciasis, ivermectin is microfilaricidal and affects embryogenesis. The mode of action of ivermectin on microfilariae is uncertain.

Clinical Uses: Onchocerciasis, Bancroftian Filariasis, Strongyloidiasis, scabies and cutaneous larva migrans

Adverse Reactions: The adverse effects of ivermectin are the Mazotti reaction, which starts on the first day after a single oral dose and peaks on the second day. The reaction is due to killing of microfilariae and its intensity correlates with skin microfilaria loads. The Mazotti reaction includes fever, headache, dizziness, somnolence, weakness, rash, increased pruritus, diarrhea, joint and muscle pains, hypotension, tachycardia, lymphadenitis, lymphangitis, and peripheral edema. The Mazotti reaction diminishes with repeated dosing. Steroids may be necessary for several days.

Levamisole

Levamisole hydrochloride is highly effective in eradicating Ascaris and moderately effective against both species of hookworm.

Mebendazole

Mebendazole has a broad spectrum of anthelmintic activity and a low incidence of adverse effects. Poorly absorbed after oral adminstration. It rapidly metabolized and excreted mostly in the urine, either unchanged or as decarboxylated derivatives.

Mebendazole inhibits microtubule synthesis in nematodes, thus irreversibly impairing glucose uptake. As a result, intestinal parasites are immobilized or die slowly.

Clinical Uses: The drug can be taken before or after meals; the tablets should be chewed before swallowing.

1. Pinworm Infection: Give 100 mg once and repeat the dose at 2 and 4 weeks
2. Ascaris lumbricoides, Trichuris trichiura, and Hookworm
3. Hydatid Disease: Mebendazole is the alternative.
4. Taeniasis: In Taenia solium infection, mebendazole has a theoretic advantage over niclosamide in that proglottids are expelled intact.
5. Strongyloidiasis.


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Clinical Uses: Oxamniquine is safe and effective in all stages of S mansoni disease, including advanced hepatosplenomegaly. It is better tolerated if given with food, although food delays absorption. In mixed infections with S mansoni and S haematobium, oxamniquine has been successfully used in combination with metrifonate.

Adverse Reactions: Central nervous system symptoms are most common; nausea and vomiting, diarrhea, colic, pruritus, and urticaria also occur.

Piperazine

The piperazine salts are alternative drugs in the treatment of ascariasis. Piperazine is readily absorbed from the gastrointestinal tract, and maximum plasma levels are reached in 2-4 hours. Most of the drug is excreted unchanged in the urine in 2-6 hours.

Anthelmintic Actions: Piperazine causes paralysis of Ascaris by blocking acetylcholine at the myoneural junction. The paralyzed roundworms are unable to maintain their position in the host and are expelled live by normal peristalsis.

Clinical Uses: Ascariasis

Adverse Reactions: Piperazine cause nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache.

Praziquantel

Praziquantel is effective in the treatment of schistosome infections of all species and most other trematode and cestode infections, including cysticercosis. The drug's safety and effectiveness as a single oral dose have also made it useful in mass treatment of several of the infections. It is rapidly absorbed after oral administration. Most of the drug is rapidly metabolized to inactive products after a first pass in the liver. Excretion is mainly via the kidneys and bile.

Anthelmintic Actions: Praziquantel drug increases cell membrane permeability to calcium, resulting in marked contraction, followed by paralysis of worm musculature. Vacuolization and disintegration of the tegumen occur, and parasite death follows.

Clinical Uses:

1. Schistosomiasis: Praziquantel is the drug of choice for all forms of schistosomiasis.
2. Taeniasis and Diphyllobothriasis: A single dose of praziquantel, 10 mg/kg.
3. Neurocysticercosis: The praziquantel dosage is 50 mg/kg/d in three divided doses for 14 days.

available. Thiabendazole is rapidly absorbed after ingestion. The drug is almost completely metabolized in the liver. Ninety percent of the drug is excreted in the urine.

Anthelmintic Actions: Thiabendazole has anti-inflammatory properties, which may be an important factor in its ability to relieve symptoms in some parasitic diseases. It also has immunomodulating effects on T cell function appears to be an immunorestorative agent.

Exercise

1. Describe the mechanisms of action of antimicrobials
2. What is the difference between bacteriostatic and bactericidal drug action?
3. What are the potential adverse effects of aminoglycosides?
4. How can chloroquine - resistant Falciparum malaria be treated?
5. Discuss the antiretroviral drugs with regard to their efficacy and safety.

CHAPTER ELEVEN

TOXICOLOGY

Learning objectives:

After completing this chapter the student will be able to:

1. describe commonly encountered poisons
2. understand the measures employed for the management of poisoning

INTRODUCTION

Toxicology is concerned with the deleterious effects of chemical and physical agents on all living systems. The terms poison, toxic substance and toxicant are synonymous. The most important axiom of toxicology is that “the dose makes the poison”, indicating that any chemical or drug can be toxic if the dose or exposure becomes high enough. Poisoning occurs by non-therapeutic substances such as household and environmental agens, and due to over-dosage of therapeutic substances. Poison may be ingested accidentally or deliberately. A difficult challenge to the health care provider is the identification of the toxicant and limited availability of antidotes. Thus, the health care provider in most cases, may be limited with symptomatic therapy.

“Treat the patient, not the poison” remains the most basic and important principle of clinical toxicology.

A toxic response can occur with in minutes or after a delay of hours, days, months or years. Acute toxicities are of particular interest for practicing health care provider.

General measures in poisoning

The treatment of a poisoned patient requires a rapid and genuine approach.

There are three principles underlying the management of poisoning:

- Life support
- Drug identification
- Drug detoxification

Drug overdose or poisoning by other chemicals can often manifest itself as an acute clinical emergency. The kinds of life-threatening emergencies include seizures, cardiac arrhythmias, circulatory shock and coma. Massive damage to liver, lungs or kidneys can also lead to death with in a relatively short period of time. Immediate supportive measures may take precedence over identification and detoxification of the offending agent. Therefore, maintenance of vital functions such as respiration, circulation, suppression of seizures, etc. is given priority.

Drug identification and the amount taken may have to be deduced frrm a combination of client history, clinical manifestations and laboratory findings.

The first action for drug detoxification is to cease the administration of the offending agent until the crisis is under control. The effectiveness of the approaches employed for detoxification may depend on the route of administration of the poison.

The general approaches employed to reduce systemthe clie festill hf as icett a gag3(flex(n is t5(adminindes g

Exercises

1. Describe poisoning management measures that hinder the absorption of the poison from the gut.
2. List down heavy metal chelators

3. **Constructin of a prescription:** A ideal prescription should contain a) the name, qualification, registration number, full address, telephone number and working hours of the physician; b) the full name, sex, age and address of the patient; c) the diagnosis, the drug preparation, total amount, frequency of administration advises and signature of the prescriber.

The name of the drug preparation begins with the symbol Rx means *take thou* derived from a Roman symbol for Jupiter.

4. **Prescription incompatibility:** In competency or careless of the prescriber results incompatable prescription.It may lead to failure of desired therapeutic goal, may prove harmful or even death to the patient. Incompatibility may be pharmaceutical, chemical or therapeutic.

5. **Patient's compliance:** A matter of concern for prescriber with regard to prescription is patient's noncompliance i.e patient's failure to take medication as intended by their physicians. Noncompliance includes taking of inadequate doses, improper timing, preterm discontinuation of drug.

6. **Rational use of drugs:** According WHO rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements for an adequate period of time, and lowest cost to them and their community.

Criteria for rational prescribing: Rationa prescribing should meet the certain criteria such as appropriate diagnosis, indication, drug, patient, dosage, duration, route of administration, information and monitoring.

7. **Irrational prescription**: Over use of antibiotics, indiscriminate use of injections, excessive use of drugs, use of anabolic steroids for growth and use of tonics and multivitamins for malnutrition are some of irrational practices.

Prevention of irrational prescribing: To prevent irrational prescription the following measures should be taken-a) making correct diagnosis b) limiting the number of the drugs c) encouraging the availability of essential drugs d)providing adequate training,drug information and standard treatment guidelines(STG) to the prescribers incorporating the concept of essential drugs e) teaching of rational prescribing into the curricula of medicine,pharmacy,dentistry and nursing and f) finally providind effective public education to the consumers.

Exercise

1. What is meant by compliance?

2. What do you understand by irrational prescribing, dispensing and use of drugs?

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