COURSE: B.PHARMACY SUBJECT: PHARMACOLOGY-III, CODE: BP602 Module 03 CHEMOTHERAPY

COURSE: B.PHARMACY

SEMESTER: 6TH

SUBJECT: PHARMACOLOGY-III

CODE: BP602T

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Chemotherapy

Antitubercular agents
Antileprotic agents
Antifungal agents
Antiviral drugs
Anthelmintics
Antimalarial drugs
Antiamoebic agents

Antitubercular Drugs

Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries. A new dimension got added in the 1980s due spread of HIV with high prevalence of tuberculosis and Mycobact. avium complex (MAC) infection among these patients. India has a large Load of HIV infected subjects, and these patients are especially vulnerable to severe forms of tubercular /MAC infection

According to their clinical utility the anti-TB drugs can be divided into:

First line: These drugs have high antitubercular efficacy as well as low toxicity; are used routinely.

Second line: These drugs have either low antitubercular efficacy or high toxicity or both; are used in special circumstances only.

First line drugs

1. Isoniazid (H) 4. Ethambutol (E)
2. Rifampin (R) 5. Streptomycin (S)
3. Pyrazinamide (Z)

Second line drugs

1 . Thiacetazone (Tzn)	Newer drugs
2. Paraaminosalicylic acid (PAS)	1. Ciprofloxacin
	2. Ofloxacin
3. Ethionamide (Etm)	3. Clarithromycin
4. Cycloserine (Cys)	4. Azithromycin
5. Kanamycin (Kmc)	5. Rifabutin
6. Amikacin (Am)	
7. Capreomycin (Cpr)	

Mechanism of action: *Isoniazid,* often referred to as *INH*, is a prodrug that is activated by a mycobacterial catalase-peroxidase (KatG). Genetic and biochemical evidence has implicated at least two different target enzymes for *isoniazid* within the unique Type II fatty acid synthase system involved in the production of mycolic acids.

Antibacterial spectrum: For bacilli in the stationary phase, *isoniazid* is bacteriostatic, but for rapidly dividing organisms, it is bactericidal. It is effective against intracellular bacteria. *Isoniazid* is specific for treatment of M. tuberculosis, although Mycobacterium kansasii (an organism that causes three percent of the clinical illness known as tuberculosis) may be susceptible at higher drug levels. When it is used alone, resistant organisms rapidly emerge.

Resistance: This is associated with several different chromosomal mutations, each of which results in one of the following: mutation or deletion of KatG (producing mutants incapable of prodrug activation), varying mutations of the acyl carrier proteins, or overexpression of InhA. Cross-resistance does not occur between *isoniazid* and other antitubercular drugs.

Rifampin (Rifampicin, R) It is a semisynthetic derivative of rifamycin B obtained from Streptomyces mediterranei. Rifampin is bactericidal to M. tu berculosis and many other gram-positive and gram-negative bacteria. Rifampin inhibits DNA dependent RNA synthesis. Probably, the basis of selective toxicity is that mammalian RNA polymerase does not avidly bind rifampin

Mechanism of action: *Rifampin* blocks transcription by interacting with the subunit of bacterial but not human DNA-dependent RNA polymerase.

Pyrazinamide

Pyrazinamide is a synthetic, orally effective, bactericidal, antitubercular agent used in combination with *isoniazid, rifampin,* and *ethambutol*. It is bactericidal to actively dividing organisms, but the mechanism of its action is unknown.

Mechanism of action *Pyrazinamide* must be enzymatically hydrolyzed to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase. *Pyrazinamide* is active against tubercle bacilli in the acidic environment of lysosomes as well as in macrophages. *Pyrazinamide* distributes throughout the body, penetrating the CSF. It undergoes extensive metabolism.

Ethambutol

Ethambutol is bacteriostatic and specific for most strains of M. tuberculosis and M. kansasii.

Mechanism of action: *Ethambutol* inhibits arabinosyl transferase an enzyme that is important for the synthesis of the mycobacterial arabinogalactan cell wall. Resistance is not a serious

problem if the drug is employed with other antitubercular agents. *Ethambutol* can be used in combination with *pyrazinamide, isoniazid*, and *rifampin* to treat tuberculosis. Absorbed on oral administration, *ethambutol* is well distributed throughout the body. Penetration into the centra nervous system (CNS) is therapeutically adequate in tuberculous meningitis.

Streptomycin: This is the first antibiotic effective in the treatment of tuberculosis and is discussed with the aminoglycosides. Its action is directed against extracellular organisms. Infections due to *streptomycin*-resistant organisms may be treated with *kanamycin* or *amikacin*, to which these bacilli remain sensitive.

Capreomycin: This is a peptide that inhibits protein synthesis. It is administered parenterally. *Capreomycin* is primarily reserved for the treatment of multidrug-resistant tuberculosis. Careful monitoring of the patient is necessary to prevent its nephrotoxicity and ototoxicity.

***Cycloserine*:** is an orally effective, tuberculostatic agent that appears to antagonize the steps in bacterial cell wall synthesis involving D-alanine. It distributes well throughout body fluids, including the CSF. *Cycloserine* is metabolized, and both parent and metabolite are excreted in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances, and epileptic seizure activity may be exacerbated.

Ethionamide: This is a structural analog of *isoniazid*, but it is not believed to act by the same mechanism. *Ethionamide* can inhibit acetylation of *isoniazid.* It is effective after oral administration and is widely distributed throughout the body, including the CSF. Metabolism is extensive, and the urine is the main route.

Daily dose 3 x per week dose

DRUG mg/kg For > 50 kg mg/kg For > 50 kg

Isoniazid (H) 5 (4-6) 300 mg 10 (8-12) 600 mg

Rifampin (R) 10 (8-12) 600 mg 10 (8-12) 600 mg

Pyrazinamide (Z) 25 (20-30) 1500 mg 35 (30-40) 2000 mg

Ethambutol (E) 15 (15-20) 1000 mg 30 (25-35) 1600 mg

Streptomycin (S) 15 (12-18) 1000 mg' 15 (12-18) 1000 mg

Category I This category includes:

• New (untreated) smear-positive pulmonaty TB.

• New smear-negative pulmonary TB with extensive parenchymal involvement.

• New cases of severe forms of extra pulmonary TB, viz . meningitis, miliary, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal, genitourinary TB.

Initial phase Four drugs HRZ + E or S are given daily or thrice weekly for 2 months.

- The revised national tuberculosis control programme (RNTCP) has been launched in India in 1997, which is implementing DOTS*. Out of the WHO recommended regimens, the RNTCP has decided to follow thrice weekly regimen, since it is equally effective, saves drugs and effort, and is more practical.
- The RNTCP recommends that if the patient is still sputum-positive at 2 months, the intensive phase should be extended by another month; then continuation phase is started regardless of sputum status at 3 months.

Antileprotic Drugs

Leprosy caused by Mycobacterium leprae, has been considered incurable Due to availability of effective antileprotic drugs now, it is entirely curable, but deformities/ defects already incurred may not reverse.

CLASSIFICATION

Sulfone:Dapsone (DDS)

Phenazine derivative Clofazimine

Antitubercular drugs Rifampin, Ethionamide

Other antibiotics :Ofloxacin, Minocycline,, Clarithromycin

Dapsone (DDS)

It is diamino diphenyl sulfone (DDS), the simplest, oldest, cheapest, most active and most commonly used member of its class.

DAPSONE

Activity and mechanism Dapsone is chemically related to sulfonamides and has the same mechanism of action, *i.e. inhibition of PABA incorporation into folic acid*; its antibacterial action is antagonized by PABA It is leprostatic at low concentrations, and at relatively higher concentrations arrests the growth of many other bacteria sensitive to sulfonamides. Specificity for M. leprae may be due to difference in the affinity of its folate synthase.

Clofazimine (Cio)

It is a dye with leprostatic and anti-inflammatory properties; acts probably by interfering with template function of DNA in M. leprae. When used alone, resistance to clofazimine develops in 1-3 years. Dapsone-resistant M. leprae respond to clofazimine, but apparently after a lag period of about 2 months. Clofazimine is orally active (40-70% absorbed). It accumulates in many tissues, especially in fat, in crystalline form. However, entry in CSF is poor. The t half is 70 days so that intermittent therapy is possible

Two polar types-lepromatous (LL) and tuberculoid (TT) with 4 intermediate formsborderline (BB), borderline lepromatous (BL),

Tuberculoid leprosy	Lepromatous leprosy
Anaesthetic patch	Diffuse skin and mucous membrane infiltration, nodules
Cell mediated immunity (CMI) is normal	CMI is absent
Lepromin test—positive	Lepromin test—negative
Bacilli rarely found in biopsies	Skin and mucous membrane lesions teeming with bacilli
Prolonged remissions with periodic exacerbations	Progresses to anaesthesia of distal parts, atrophy, ulceration, absorption of digits, etc.

For operational purposes, leprosy has been divided into:

Paucibacil/ary leprosy (PBL) (Non-infectious): This includes TT, BT, I and polyneuritic.

Multibacillary leprosy (MBL) (Infectious): This includes LL, BL and BB

Multidrug therapy (MDT) of leprosy

	Multibacillary	Paucibacillary
Rifampin	600 mg once a month supervised	600 mg once a month supervised
Dapsone	100 mg daily self administered	100 mg daily self administered
Clofazimine	300 mg once a month supervised	—
	50 mg daily self administered	—
Duration	12 months	6 months

Doses to be reduced suitably for children.

Reactions in leprosy

Lepra reaction These occur in LL, usually with institution of chemotherapy and/ or intercurrent infection. It is a Jarish Herxheimer (Arthus) type of reaction due to release of antigens from the killed bacilli. It may be mild, severe or lifethreatening (erythema nodosum leprosum).

Sulfone syndrome It is the reaction which develops 4-6 weeks after dapsone treatment: consists of fever, malaise, lymph node enlargement, desquamation of skin, jaundice and anaemia. It is generally seen in malnourished patients. Lepra reaction is of abrupt onset; existing lesions enlarge, become red, swollen and painful; several new lesions may appear. Malaise, fever and other constitutional symptoms generally accompany and may be marked. Temporary discontinuation of dapsone is recommended only in severe cases. Clofazimine (200 mg daily) is highly effective in controlling the reaction (except the most severe one), probably because of its antiinflammatory property.

Reversal reaction:This is seen in TT -is a manifestation of delayed hypersensitivity to M leprae antigens. Cutaneous ulceration, multiple nerve involvement with pain and tenderness occur suddenly even after completion of therapy. It is treated with clofazimine or corticosteroids.

Antifungal Drugs

These are drugs used for superficial and deep (systemic) fungal infections. A disquietening trend after 1950s is the rising prevalence of more sinister type of fungal infections which are, to a large extent, iatrogenic. These are associated with the use of broad-spectrum antibiotics, corticosteroids, anticancer immunosuppressant drugs, dentures, indwelling catheters and implants, and emergence of AIDS.

Many topical antifungals have been available since the antiseptic era. Two important antibiotics: amphotericin B-to deal with systemic mycosis, and griseofulvin-to supplement attack on dermatophytes were introduced around 1960.

CLASSIFICATION

1. Antibiotics

A. Polyenes:AmphotericinB (AMB),Nystatin, Hamycin, Natamycin (Pimaricin)

B. Heterocyclic benzofuran: Griseofulvin

2. Antimetabolite Flucytosine (5-FC)

3 Azofes

A. lmidazoles (topical): Clotrimazole,Econazole, Miconazole, Oxiconazole (systemic): Ketoconazole

B. Triazoles (systemic): Fluconazole, Itraconazole, Voriconazole

4. Allylamine Terbinafine

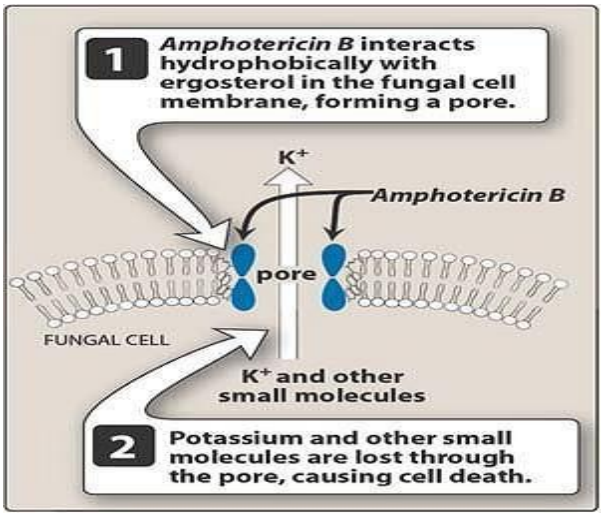
5. Other topical agents Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Butenafine, Sod. thiosulfate.

POLYENE ANTIBIOTICS

The name polyene is derived from their highly double-bonded structure. Amphotericin B is described as the prototype.

Amphotericin B (AMB)

It is obtained from Streptomyces nodosus. Chemistry and mechanism of action The polyenes possess a macrocyclic ring, one side of which has several conjugated double bonds and is highly lipophilic, while the other side is hydrophilic with many OH groups. Several *amphotericin B* molecules bind to ergosterol in the plasma membranes ofsensitive fungal cells. There, they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol. The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.



HETEROCYCLIC BENZOFURAN

Griseofulvin

It was one of the early antibiotics extracted from Penicillium griseofulvum. However, because of lack of antibacterial activity, little attention was paid to it: clinical utility in dermatophytosis was demonstrated only around 1960. Griseofulvin is active against most dermatophytes, including Epidermophyton, Trichophyton, Microsporum.

Griseofulvin interferes with mitosis-multinucleated and stunted fungal hyphae result from its action. It also causes abnormal metaphase configurations. However, unlike the typical mitotic inhibitors (colchicine, vinca alkaloids), it does not cause metaphase arrest; rather the daughter nuclei fail to move apart or move only a short distance.

Flucytosine

Flucytosine [floo-SYE-toe-seen] (*5-FC*) is a synthetic pyrimidine antimetabolite that is often used in combinationwith *amphotericin B.* This combination of drugs is administered for the treatment of systemic mycoses and for meningitis caused by Cryptococcus neoformans and Candida albicans.

Mechanism of action: *5-FC* enters fungal cells via a cytosine-specific permease an enzyme not found in mammalian cells. *5-FC* is then converted by a series of steps to 5 fluorodeoxyuridine 5'-monophosphate. This false *nucleotide inhibits thymidylate synthase*, thus depriving the organism of thymidylic acid an essential DNA component.

Pharmacokinetics: *5-FC* is well absorbed by the oral route. It distributes throughout the body water and penetrates well into the CSF. *5-FU* is detectable in patients and is probably the result of metabolism of *5-FC* by intestinal bacteria. Excretion of both the parent drug and its metabolites is by glomerular filtration, and the dose must be adjusted in patients with compromised renal function.

Adverse effects: *5-FC* causes reversible neutropenia, thrombo-cytopenia, and dose-related bone marrow depression.

Ketoconazole

Ketoconazole was the first orally active azole available for the treatment of systemic mycoses.

Mechanism of action: Azoles are predominantly fungistatic. They inhibit C-14 ±-demethylase (a cytochrome P450 enzyme), thus blocking the demethylation of lanosterol to ergosterol the principal sterol of fungal membranes *This inhibition disrupts membrane structure and function and, thereby, inhibits fungal cell growth.*

For example, in addition to blocking fungal ergosterol synthesis, the drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production.

Pharmacokinetics: *Ketoconazole* is only administered orally. It requires gastric acid for dissolution and is absorbed through the gastric mucosa. Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as H2-histamine receptor blockers and proton-pump inhibitors, impair absorption.

Adverse effects: In addition to allergies, dose-dependent gastrointestinal disturbances, including nausea, anorexia, and vomiting, are the most common adverse effects of *ketoconazole* treatment.

Endocrine effects, such as gynecomastia, decreased libido, impotence, and menstrual irregularities, result from the blocking of androgen and adrenal steroid synthesis by *ketoconazole.*

Antiviral Drugs

Viruses are the ultimate expression of parasitism: they not only take nutrition from the host cell but also direct its metabolic machinery to synthesize new virus particles. Viral chemotherapy, therefore, is difficult, as it would require interference with cellular metabolism in the host. However, virus directed enzymes have been identified in the infected cell and some viruses have few enzymes of their own which may have higher affinities for some antimetabolites or inhibitors than the regular cellular enzymes.

CLASSIFICATION

Anti-Herpes virus

Idoxuridine, Acyclovir, Valacyclovir, Famciclovir, Ganciclovir*, Foscarnet*

Anti-Retrovirus

(a) Nucleoside reverse transcriptase inhibitors (NRTis): Zidovudine ((AZT), Didanosine, Zalcitabine*, Stavudine, Lamivudine, Abaca vir

(b) Nonnucleoside reverse transcriptase inhibitors (NNRTis): Nevirapine, Efavirenz, Delavirdine*

(c) Protease inhibitors: Ritonavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir*, Lopinavir

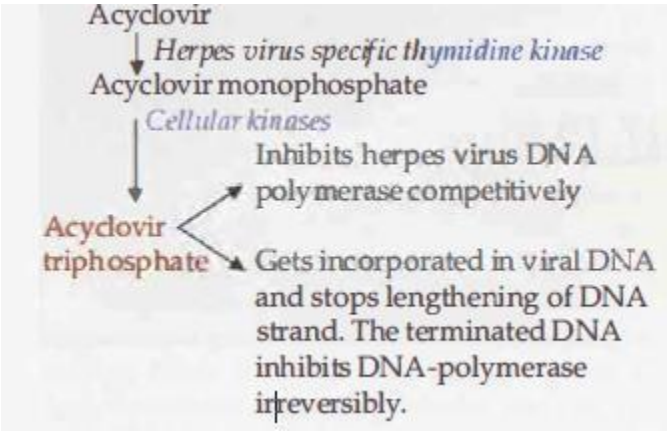
Anti-Influenza virus Amantadine, Rimantadine*

NonselectiVe antiviral drugs Ribavirin, Lamivudine, Adefovir dipivoxil, Interferon a * Not yet marketed in India.

ldoxuridine It is 5-iodo-2-deoxyuridine (IUDR); acts as a thymidine analogue. It was the first pyrimidine antimetabolite to be used as antiviral drug. It competes with thymidine, gets incorporated in DNA so that faulty DNA is formed which breaks down easily. It is effective only against DNA viruses.

Acyclovir

This deoxiguanosine analogue antiviral drug requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication.



Use

1 . Genital Herpes simplex

2. Mucocutaneous H.

3. H. simplex encephalitis (type I virus):

4. H. simplex (type I) keratitis:

5. Herpes zoster

6. Chickenpox:

Adverse effects

Topical: stinging and burning sensation after each application.

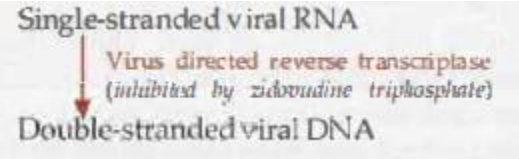
Oral: The drug is well tolerated; headache, nausea, malaise and some CNS effects are reported.

Intravenous: rashes, sweating, emesis and fall in BP occur only in few patients.

Nucleoside reverse transcriptase inhibitors (NRTis)

Zidovudine It is a thymidine analogue (azidothymidine, AZT), the prototype NRTI. After phosphorylation in the host cell-zidovudine triphosphate selectively inhibits viral reverse transcriptase (RNA-dependent DNA polymerase) in preference to cellular DNA polymerase.

On the template of single-stranded RNA genome of HIV a double-stranded DNA copy is produced by viral reverse transcriptase. Finally, viral particles are assembled and matured. Zidovudine thus prevents infection of new cells by HIV, but has no effect on virus directed DNA that has already integrated into the host chromosome



Non-nucleoside reverse transcriptase inhibitors (NNRTis)

Nevirapine (NVP) and Efavirenz (EFV): *These are nucleoside unrelated compounds which directly inhibit HlV reverse transcriptase without the need for intracellular phosphorylation.*

Retroviral protease Inhibitors (Pis)

An aspartic protease enzyme encoded by HIV is involved in the production of structural proteins and enzymes (including reverse transcriptase) of the virus. The large viral polyprotein is broken into various functional components by this enzyme. This protease acts at a late step in HIV replication, i.e. maturation of the new virus particles when the RNA genome acquires the core proteins and enzymes. Five protease inhibitors-Indinavir (IDV), Nelfinavir (NFV), Saquinavir (SQV), Ritonavir (RTV) and Lopinavir.

ANTI-INFLUENZA VIRUS DRUGS

Amantadine

Chemically, it is a tricyclic amine unrelated to any nucleic acid precursor, but inhibits replication of influenza A virus (a myxovirus). It appears to *act at an early step (possibly uncoating) as well as at a late step (viral assembly) in viral replication*.

Antimalarial Drugs

These are drugs used for prophylaxis, treatment and prevention of relapses of malaria.

Malaria, caused by 4 species of the protozoal parasite Plasmodium, is endemic in most parts of India and other tropical countries.

CLASSIFICATION

4-Aminoquino/ines Chloroquine, Amodiaquine, Piperaquine.

Quinoline-methanol Mefloquine.

Cinchona alkaloid Quinine, Quinidine

Biguanides Proguanil, (Chloroguanide), Chlorproguanil

Diaminopyrimidines Pyrimethamine

8-Aminoquino/ine Primaquine, Bulaquine

Sulfonamides Sulfadoxine and sulfone Sulfamethopyrazine, Dapsone

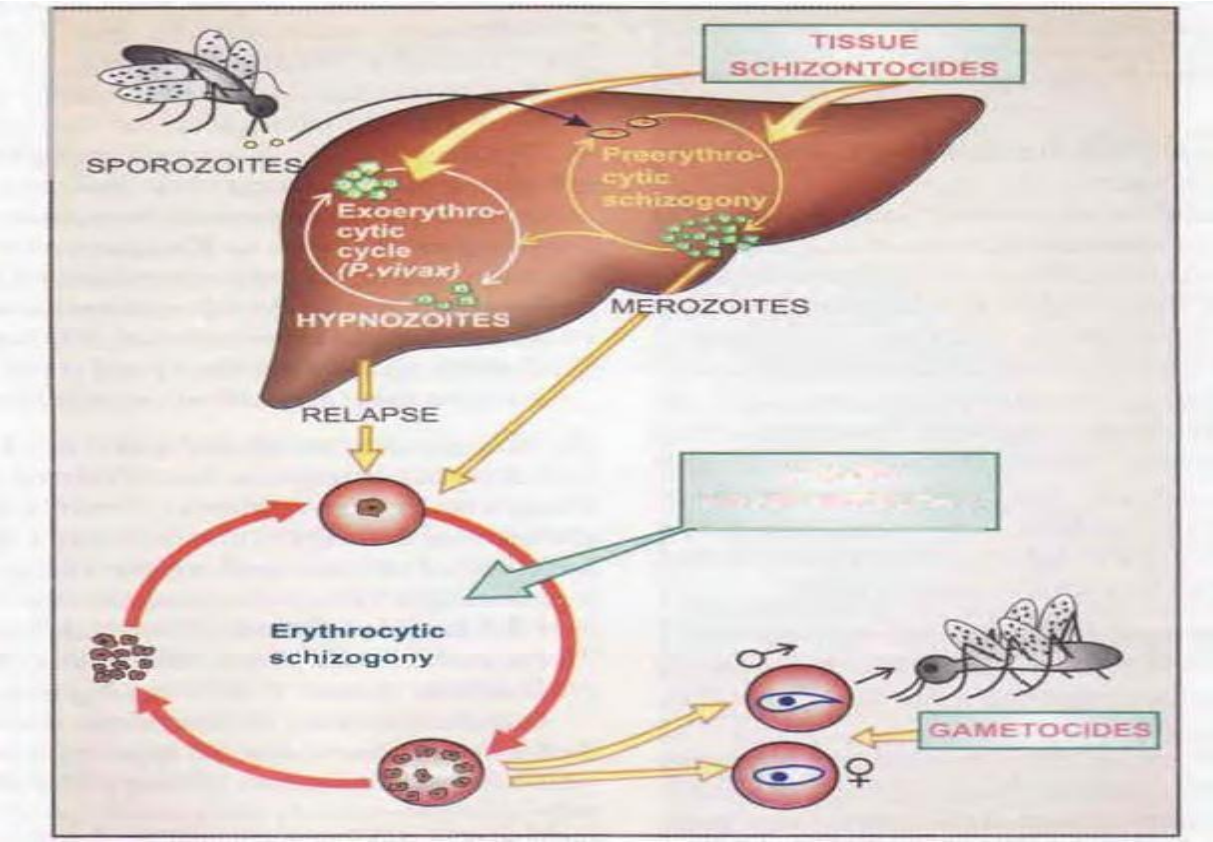
Tetracyclines Tetracycline, Doxycycline

Sesquiterpine lactones Artesunate, Artemether, Arteether

Amino alcohols Halofantrine, Lumefantrine

Mannich base Pyronaridine

Naphthoquinone Atovaquone



CHLOROQUINE

It is a rapidly acting erythrocytic schizontocide against all species of plasmodia; controls most clinical attacks in 1-2 days with disappearance of parasites from peripheral blood in 1-3 days. Therapeutic plasma concentrations are in the range of 15-30 ng/ml.

The mechanism of action of chloroquine is not completely known. It is actively concentrated sensitive intraerythrocytic plasmodia: higher concentration is found in infected RBCs. *By accumulating in the acidic vesicles of the parasite and because of its weakly basic nature, it raises the vesicular pH and thereby interferes with degradation of haemoglobin by parasitic lysosomes.* Polymerization of toxic haeme to nontoxic parasite pigment hemozoin is inhibited by formation of chloroquine-heme complex. Heme itself or its complex with chloroquine then damages the plasmodial membranes

Blood schizonticide: Mefloquine

Mefloquine [MEF-lo-kween] appears to be promising as an effective single agent for suppressing and curing infections caused by multidrug-resistant forms of P. falciparum. Its exact mechanism of action remains to be determined, but like *quinine*, it can apparently damage the parasite's membrane.

Mefloquine is absorbed well after oral administration and concentrates in the liver and lung. It has a long half-life (17 days) because of its concentration in various tissues and its continuous circulation through the enterohepatic and enterogastric systems. The drug undergoes extensive metabolism. Its major excretory route is the feces.

Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. Electrocardiographic abnormalities and cardiac arrest are possible if *mefloquine* is taken concurrently with *quinine* or *quinidine*.

Blood schizonticides: Quinine and quinidine

Quinine and its stereoisomer, quinidine interfere with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. These drugs are reserved for severe infestations and for malarial strains that are resistant to other agents, such as *chloroquine*. Taken orally, *quinine* is well distributed throughout the body and can reach the fetus. Alkalinization of the urine decreases its excretion.

The major **adverse effect** of *quinine* is cinchonisma syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not considered to be reasons for suspending therapy. However, *quinine* treatment should be suspended if a positive Coombs' test for hemolytic anemia occurs.

Drug interactions include potentiation of neuromuscular-blocking agents and elevation of *digoxin* levels if taken concurrently with *quinine*. *Quinine* absorption is retarded when the drug is taken with aluminum-containing antacids. *Quinine* is fetotoxic.

Blood schizonticide: Artemisinin ***Artemisinin*** is derived from the qinghaosu plant, which has been used in Chinese medicine for more than two millennia in the treatment of fevers and malaria. *Artemisinin* (or one of its derivatives) is available for the treatment of

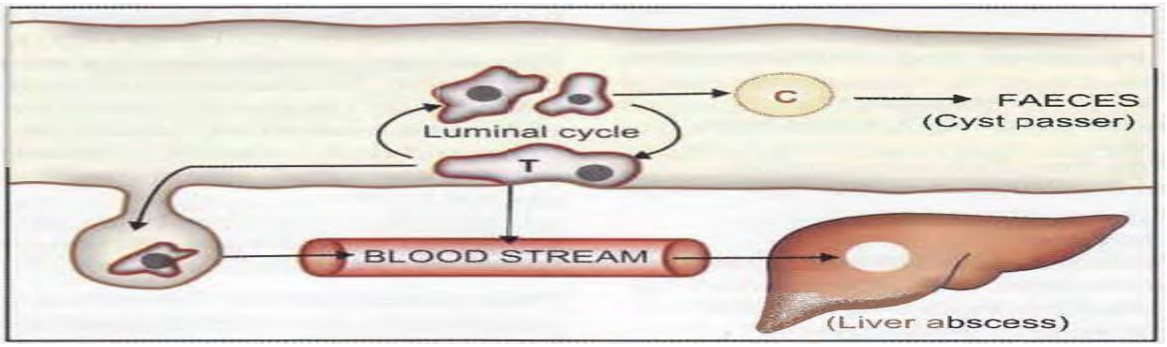
severe, multidrug-resistant P. falciparum malaria. Its *antimalarial action involves the production of free radicals within the plasmodium food vacuole, following cleavage of the drug's endoperoxide bridge by heme iron in parasitized erythrocytes*. It is also believed to covalently bind to and damage specific malarial proteins. Oral, rectal, and intravenous preparations are available, but the short half-lives precludetheir use in chemoprophylaxis. They are metabolized in the liver and are excreted primarily in the bile. Adverse effects include nausea, vomiting, and diarrhea, but overall, *artemisinin* is remarkably safe. Extremely high doses may cause neurotoxicity and prolongation of the QT interval.

ANTIAMOEBIC DRUGS

These are drugs useful in infection caused by the protozoa Entamoeba histolytica.

INTESTINAL LUMEN ULCER

(Dysentery) which occurs by faecal contamination of food and water. Amoebic cysts reaching the intestine transform into trophozoites which either live on the surface of colonic mucosa as commensalsform cysts that pass into the stools (luminal cycle) and serve to propagate the disease, or invade the mucosa-form amoebic ulcers and cause acute dysentery (with blood and mucus in stools) or chronic intestinal amoebiasis (with vague abdominal symptoms, amoeboma).



CLASSIFICATION

1. Tissue amoebicides

(a) For both intestinal and extraintestinal amoebiasis: Nitroimidazoles: Metronidazole, Tinidazole, Secnidazole, Ornidazole, Satranidazole

Alkaloids: Emetine, Dehydroemetine

(b) For extraintestinal amoebiasis only: Chloroquine

2. Luminal amoebicides

(a) Amide : Diloxanide furoate, Nitazoxanide

(b) 8-Hydroxyquinolines: Quiniodochlor (Iodochlorohydroxyquin, Clioquinol), Diiodohydroxyquin (Iodoquinol)

(c) Antibiotics: Tetracyclines

METRONIDAZOLE

It is the prototype nitroimidazole introduced in 1959 for trichomoniasis and later found to be a highly active amoebicide. It has broad-spectrum cidal activity against protozoa, including Giardia Iamblia in addition to the above two. Many anaerobic bacteria, such as Bact. fragilis, Fusobacterium, Clostridium perfringens, Cl. difficile, Helicobacter pylori, Campylobacter, peptococci, spirochetes and anaerobic Streptococci are sensitive.

Metronidazole is selectively toxic to anaerobic microorganisms. After entering the cell by diffusion its nitro group is reduced by certain redox proteins operative only in anaerobic microbes to highly reactive nitro radical which exerts cytotoxicityThe energy metabolism of anaerobes is, thus, disrupted Metronidazole has been found *to inhibit cell mediated immunity, to induce mutagenesis and to cause radiosensitization.*

Pharmacokinetics Metronidazole is almost completely absorbed from the small intestines; little unabsorbed drug reaches the colon. It is widely distributed in the body, attaining therapeutic concentration in vaginal secretion, semen, saliva and CSF. It is metabolized in liver primarilyby oxidation and glucuronide conjugation, and excreted in urine. Plasma t half is 8 hrs.

Adverse effects Side effects to metronidazole are relatively frequent and unpleasant, but mostly nonserious. Anorexia, nausea, metallic taste and abdominal cramps are the most common. Looseness of stool is occasional.

AMIDES

Diloxanide furoate

It is a highly effective luminal amoebicide: directly kills trophozoites responsible for production of cysts. The furoate ester is hydrolysed in intestine and the released diloxanide is largely absorbed Diloxanide is a weaker amoebicide than its furoate ester : no systemic antiamoebic activity is evident despite its absorption. It is primarily metabolized by glucuronidation and is excreted in urine. Diloxanide furoate exerts no antibacterial action. It is less effective in invasive amoebic dysentery, because of poor tissue amoebicidal action.

However, a single course produces high (80-90%) cure rate in mild intestinal amoebiasis and in asymptomatic cyst passers.

Luminal amebicides

After treatment of invasive intestinal or extraintestinal amebic disease is complete, a luminal agent, such as *iodoquinol*, *diloxanide furoate*, or *paromomycin*, should be administered for treatment of asymptomatic colonization state.

Iodoquinol: *Iodoquinol* a halogenated 8-hydroxy quinolone, is amebicidal against E. histolytica, and is effective against the luminal trophozoite and cyst forms. Side effects from *iodoquinol* includerash, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. Long-term use of this drug should be avoided.

Paromomycin: *Paromomycin* an aminoglycoside antibiotic, is only effective against the intestinal (luminal) forms of E. histolytica and tapeworm, because it is not significantly absorbed from the gastrointestinal tract. It is an alternative agent for cryptosporidiosis. *Although directly amebicidal, paromomycin also exerts its antiamebic actions by reducing the population of intestinal flora*. Its direct amebicidal action is probably due to the effects it has on cell membranes, causing leakage.

ANTI HELMINTIC

Three major groups of helminths (worms) the nematodes, trematod, and cestodes ”infect humans. As in all antibiotic regimens, the anthelmintic drugs are aimed at metabolic targets that are present in the parasite but are either absent from or have different characteristics than those of the host.

II. Drugs for the Treatment of Nematodes

Nematodes are elongated roundworms that possess a complete digestive system, including both a mouth and an anus. They cause infections of the intestine as well as the blood and tissues.

A. Mebendazole

Mebendazole a synthetic benzimidazole compound, is effective against a wide spectrum of nematodes. It is a drug of choice in the treatment of infections by whipworm (Trichuris trichiura), pinworm (Enterobius vermicularis), hookworms (Necator americanus and Ancylostoma duodenale), and roundworm (Ascariasis lumbricoides).

Mebendazole **acts by binding to and interfering with the assembly of the parasites' microtubules and also by decreasing glucose uptake**.

Affected parasites are expelled with the feces. *Mebendazole* is nearly insoluble in aqueous solution. Little of an oral dose (that is chewed) is absorbed by the body, unless it is taken with a high-fat meal. It undergoes first-pass metabolism to inactive compounds. *Mebendazole* is relatively free of toxic effects,although patients may complain of abdominal pain and diarrhea. It is, however, contraindicatedin pregnant women because it has been shown to be embryotoxic and teratogenic in experimental animals.

B. Pyrantel pamoate

Pyrantel pamoate along with *mebendazole*, is effective in the treatment of infections caused by roundworms, pinworms, and hookworms. *Pyrantel pamoate* is poorly absorbed orally and exerts its effects in the intestinal tract.

It acts as a depolarizing, neuromuscular-blocking agent, causing persistent activation of the parasite's nicotinic receptors. The paralyzed worm is then expelled from the host's intestinal tract. Adverse effects are mild and include nausea, vomiting, and diarrhea.

C. Thiabendazole

Thiabendazole, like the other benzimidazoles, affects microtubular aggregation. Although nearly insoluble in water, the drug is readily absorbed on oral administration. It is hydroxylated in the liver and excreted in the urine. The adverse effects most often encountered are dizziness, anorexia, nausea, and vomiting. There have been reports of central nervous system (CNS) symptomatology.

D. Ivermectin

Ivermectin [eye-ver-MEK-tin] is the drug of choice for the treatment of onchocerciasis (river blindness) caused by Onchocerca volvulus and is a drug of first choice for cutaneous larva migrans and strongyloides. *Ivermectin* targets the parasite's glutamate-gated Cl- channel receptors.

Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis of the worm. The drug is given orally. It does not cross the blood-brain barrier and, thus, has no pharmacologic effects in the CNS. However, it is contraindicated in patients with meningitis, because their blood-brain barrier is more permeable and CNS effects might be expected.

E. Diethylcarbamazine

Diethylcarbamazine [dye-eth-il-kar-BAM-a-zeen] is used in the treatment of filariasis because of its ability to immobilize microfilariae and render them susceptible to host defense mechanisms. It is rapidly absorbed following oral administration with meals and is excreted primarily in the urine. Urinary alkalosis or renal impairment may require dosage reduction. Adverse effects are primarily caused by host reactions to the killed organisms. The severity of symptoms is related to the parasite load and include fever, malaise, rash, myalgias, arthralgias, and headache.

III. Drugs for the Treatment of Trematodes

The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect. For example, they may be categorized as liver, lung, intestinal, or blood flukes

A. Praziquantel

Trematode infections are generally treated with *praziquantel.* This drug is an agent of choice for the treatment of all forms of schistosomiasis and other trematode infections and for cestode infections like cysticercosis. Permeability of the cell membrane to calcium is increased, causing contracture and paralysis of the parasite.

Praziquantel is rapidly absorbed after oral administration and distributes into the cerebrospinal fluid. High levels occur in the bile. The drug is extensively metabolized oxidatively, resulting in a short half-life. The metabolites are inactive and are excreted through the urine and bile. Common adverse effects include drowsiness, dizziness, malaise, and anorexia, as well as gastrointestinal upsets.

IV. Drugs for the Treatment of Cestodes

The cestodes, or tapeworms typically have a flat, segmented body and attach to the host's intestine Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle.

A. Niclosamide

Niclosamide is the drug of choice for most cestode (tapeworm) infections. Its action has been ascribed to inhibition of the parasite's mitochondrial phosphorylation of adenosine diphospate, which produces usable energy in the form of adenosine triphospate. Anaerobic metabolism may also be inhibited. The drug is lethal for the cestode's scolex and segments of cestodes but not for the ova. A laxative is administered prior to oral administration of *niclosamide*. This is done to purge the bowel of all dead segments and so preclude digestion and liberation of the ova, which may lead to cysticercosis. Alcohol should be avoided within 1 day of *niclosamide*.

B. Albendazole

Albendazole is a benzimidazole that, like the others*, inhibits microtubule synthesis and glucose uptake in nematodes*. Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as cysticercosis (caused by Taenia solium larvae) and hydatid disease (caused by Echinococcus granulosis).

Albendazole is erratically absorbed after oral administration, but absorption is enhanced by a high-fat meal. It undergoes extensive first-pass metabolism, including formation of the sulfoxide, which is also active. *Albendazole* and its metabolites are primarily excreted in the urine.