Program	B. Pharmacy
Semester	VI
Subject /Course	Pharmacology-III
Subject/Course ID	BP602T
Module No.	03
Module Title	Chemotherapy
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Learning Outcome of Module-3

LO	Learning Outcome (LO)	Course Outcome Code
LO1	To explain and compare the mechanism of anti-mycobacterial, anti-fungal, anti-viral,	BP602.3
LO2	Students understand the basic concept regarding pharmacology and chemotherapy of various diseases.	BP602.3
LO3	Know about the different classes of the drugs with their mechanism of action, therapeutic uses and adverse effects.	BP602.3
LO4	To Understand the Pharmacokinetics and pharmacological action of different class of drugs.	BP602.3

Content Table

TUBERCULOSIS (TB)

Tuberculosis (TB) is an infectious disease caused by any one of a group of bacteria collectively known as the Mycobacterium tuberculosis complex. These mycobacteria include:

M. tuberculosis (including subspecies M. canetti)

- M. bovis
- M. bovis BCG
- M. africanum
- M. caprae
- M. microti
- M. pinnipedii

Throughout this manual, bacteria included in the M. tuberculosis complex will be referred to as "TB bacteria". Other mycobacteria (known as non-tuberculous mycobacteria [NTM], atypical mycobacteria, or mycobacteria other than tuberculosis [MOTT]), can cause disease in humans. Signs and symptoms of pulmonary NTM disease can be similar to those of active pulmonary TB disease (e.g., cough, sputum, hemoptysis, weight loss, chest x-ray cavities). Because of the similarities in signs/symptoms, laboratory investigations such as RNA probes and mycobacterial culture are needed to differentiate between disease caused by TB bacteria and disease caused by NTM. From a clinical perspective, it is important to determine whether someone has TB disease or NTM disease because the treatment regimens are different. From a public health perspective, it is important because person-to-person transmission of NTM is thought to be extremely rare.

This is why:

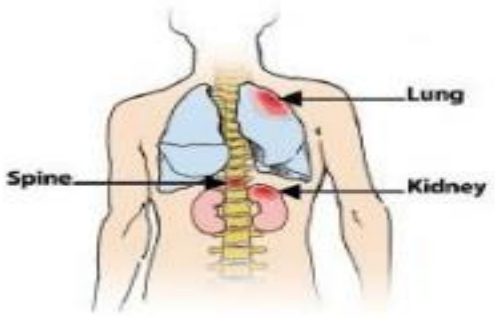
- NTM disease is not a reportable illness.
- Contact investigations for NTM disease are not required.
- Treatment of NTM disease is not mandatory.

Characteristics of TB Bacteria TB bacteria are:

- ✓ Rod-shaped
- ✓ 1-5 microns in size
- ✓ Aerobic
- ✓ Slow-growing (divide once every 15 to 20 hours)
- ✓ The cell walls of TB bacteria also have a high lipid content.

This means that specific laboratory methods are required to identify TB bacteria in smear examinations (acid-fast staining) and in culture (mycobacterial culture versus routine bacterial culture). 4.3 Signs and Symptoms of Active TB Disease To an extent, the signs and symptoms of active TB disease depend on which site(s) are affected. Although TB disease occurs most often as a respiratory illness, it can develop at almost any body site. TB disease can also involve multiple sites at once (disseminated TB disease). A few examples of sites where TB disease can develop are shown in Figure. Other sites of non-respiratory TB disease include:

- Peripheral lymph nodes (TB lymphadenitis)
- Central nervous system (e.g., TB meningitis, tuberculoma)
- Abdominal cavity and/or digestive system
- Genitourinary system
- Bones and/or joints



Generalized signs and symptoms of active TB disease often include:

- ✓ Fever
- ✓ Night sweats
- ✓ Weight loss/loss of appetite
- ✓ Fatigue

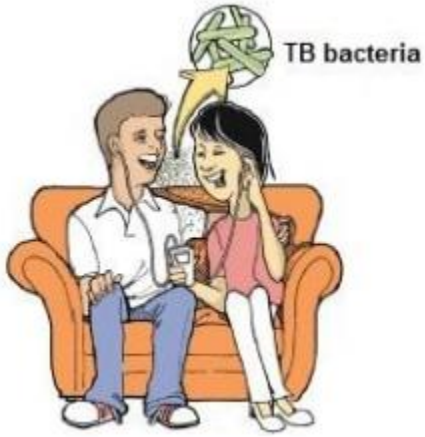
Signs and symptoms of TB disease involving the lungs (pulmonary TB) usually include:

Cough of at least 2 to 3 weeks' duration

- Chest pain
- Abnormalities on chest x-ray (e.g., upper lobe infiltrates, cavitation)

- Hemoptysis (blood in sputum)
- Young children, the elderly, and people with advanced immune suppression might not have typical signs or symptoms of active TB disease.

Transmission Infection with TB bacteria almost always happens from inhalation of tiny droplets of moisture (droplet nuclei) that contain TB bacteria. People with active respiratory TB disease (TB in the lungs or airways) expel TB bacteria when they cough, sneeze, laugh, sing, or play wind instruments. People with laryngeal TB disease (TB laryngitis) can expel TB bacteria when they talk



Transmission of TB

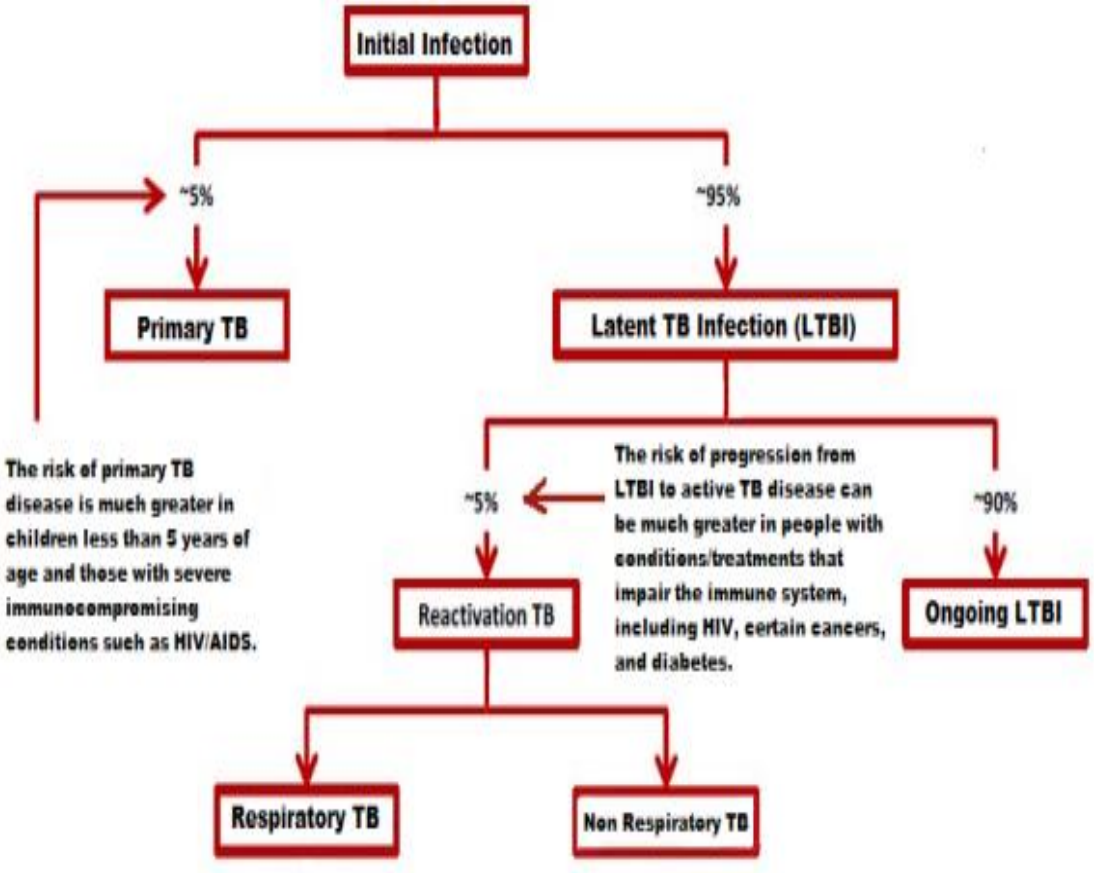
To a large degree, a person's risk for becoming infected with TB bacteria during an exposure to an infectious case depends on the concentration of TB bacteria in the air s/he breathes. This concentration is influenced by: How infectious the case is.

- The degree of air circulation and ventilation
- How close (physical proximity) the person is to the infectious case.
- Whether the person is appropriately protected against inhaling TB bacteria
- (e.g., wearing a fit-checked, disposable N95 respirator). How infectious a case is (the degree of infectiousness) is influenced by: Site and extent of TB disease; Cases with laryngeal involvement and/or
- Cavities on their chest x-rays are considered highly infectious before treatment. Cases with sputum-smear positive/culture-positive pulmonary TB are considered relatively more infectious before treatment than smearnegative/culture-positive cases. Cases with non-respiratory TB

disease are not infectious under most circumstances. Strength and frequency of coughing and other behaviors/activities

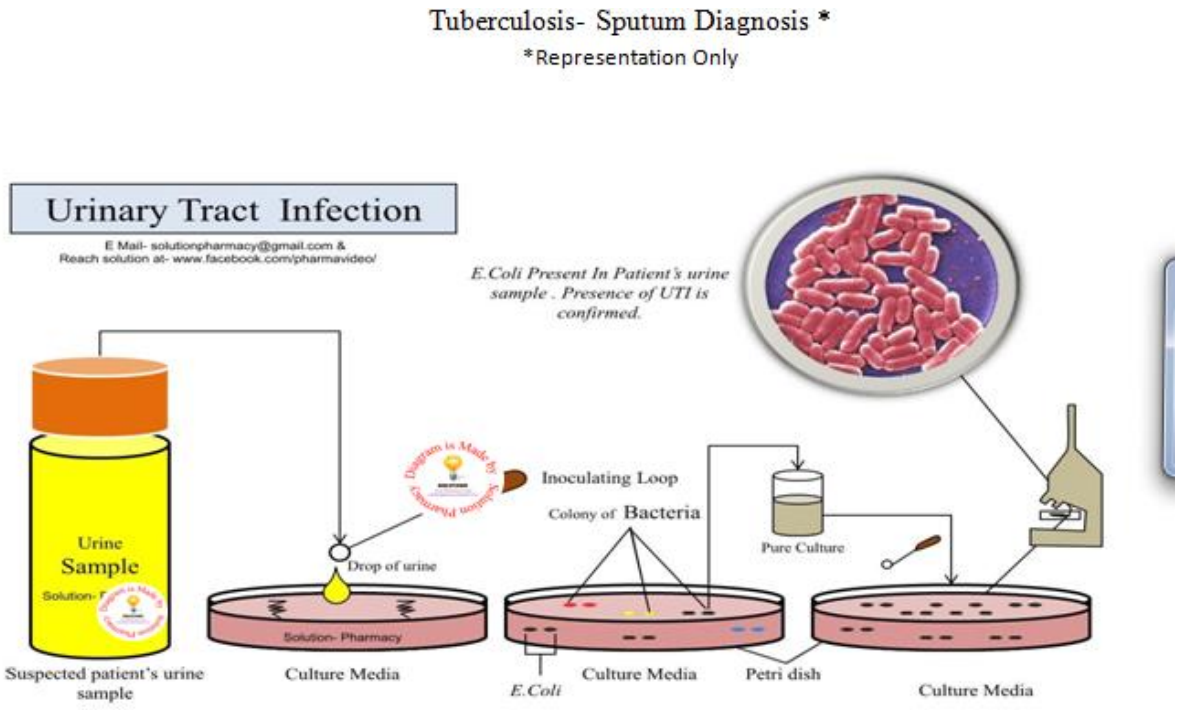
- that produce infectious droplet nuclei; Forceful expiration (e.g., coughing, sneezing, singing, playing wind instruments) can cause TB bacteria to be released into the surrounding airspace, as can certain medical procedures (e.g., sputum induction, bronchoscopy, autopsy, highpressure wound irrigation of a non-respiratory site of TB disease). TB transmission has also been linked to smoking crack cocaine or marijuana. Pathogen factors; some strains of TB bacteria might be more
- Transmissible. Other factors that can influence the risk of transmission include: Frequency and duration of exposure(s) to the case.
- Susceptibility of the exposed person; people with pre-existing TB
- Infection, such as those with LTBI or a history of TB disease, might have some innate immunity to reinfection.

The pathogenesis of TB in humans is described in Figure.



Comparisons between latent TB infection (LTBI) and active TB disease

Latent TB Infection (LTBI)	Active TB Disease
• TB bacteria in the body (TST result usually positive /IGRA result usually reactive) • TB bacteria are inactive (latent) • NO signs/symptoms of active TB disease • NOT infectious • At risk for development of active TB disease in future (reactivation TB disease) • Treatment can prevent development of active TB disease in future • NOT a "case" of active TB disease	• TB bacteria in the body (TST result usually positive /IGRA result usually reactive) • TB bacteria are active (multiplying) • Usually signs/symptoms of active TB disease • Potentially infectious (e.g., with respiratory TB disease) • Almost always curable with timely diagnosis and appropriate treatment • A "case" of active TB disease



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. Clarithro mycin
4. Cycloserine (Cys)	4. Azithromycin
5. Kanamycin (Kmc)	5. Rifabutin
6. Amikacin (Am)	
7. Capreomycin (Cpr)	

ISONIAZID

Isoniazid (isonicotinic acid hydrazide, INH) has been the most commonly used antituberculosis since recognition of its clinical activity in 1952 (Robitzek and Selikoff 1952). Consisting of a pyridine ring and a hydrazide group, INH is a nicotinamide analog, structurally related to the anti-tuberculosis drugs ethionamide and pyrazinamide. Because of its significant bactericidal activity, it has become a critical component of the first-line antituberculous regimens, although in the last two decades resistance to INH has been reported with increasing frequency.

Mechanism of action

INH appears to penetrate host cells readily and diffuses across the M. tuberculosis membrane. INH is a pro-drug, requiring oxidative activation by the M. tuberculosis catalase-peroxidase enzyme KatG. Although the active metabolites of INH have been reported to inhibit multiple essential cellular pathways, including synthesis of nucleic acids, phospholipids, and NAD

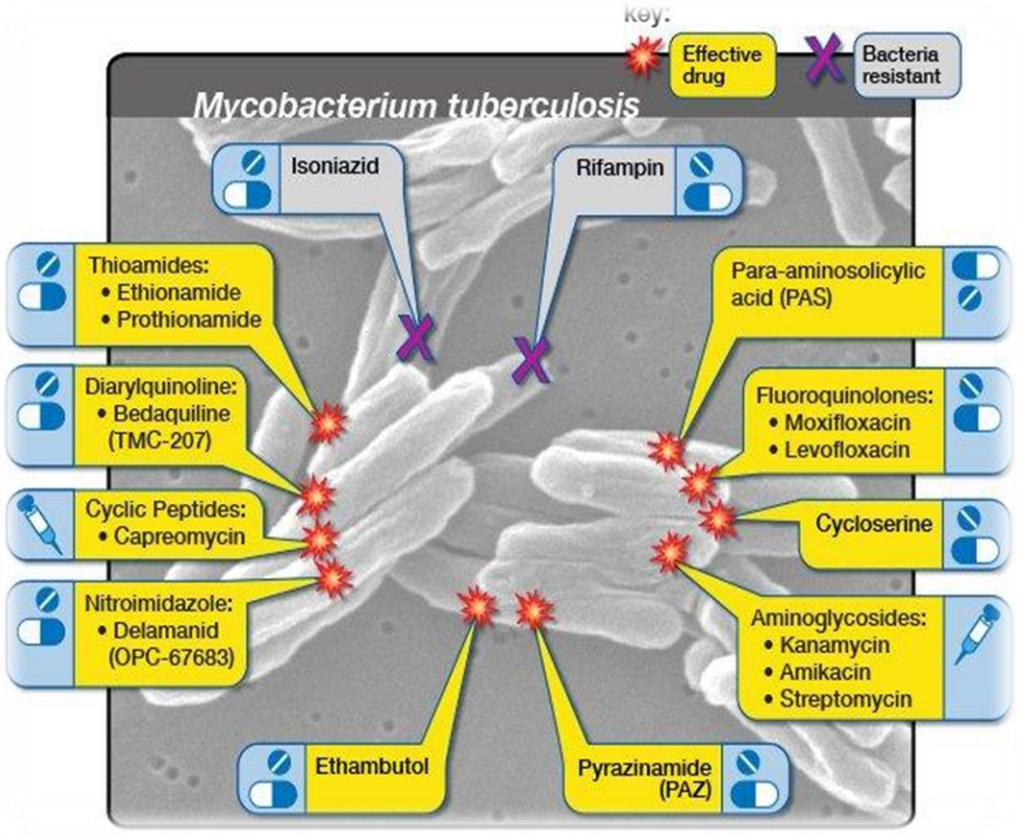
metabolism, the primary pathway responsible for the killing activity of the drug is mycolic acid synthesis. Thus, the activated form of the drug binds tightly to the NADH-dependent enoyl acyl carrier protein (ACP) reductase InhA, a component of the fatty acid synthase II system of

mycobacteria, which is essential for fatty acid elongation INH does not directly interact with InhA, as X-ray crystallographic and mass spectrometry data revealed that the activated form of INH covalently attaches to the nicotinamide ring of NAD bound within the active site of InhA, causing NADH to dissociate from InhA. However, the precise mechanism by which INH kills M. tuberculosis remains to be elucidated.

Mechanism of resistance

Because INH is the most commonly used antituberculosis drug, resistance to INH occurs more frequently among clinical isolates than resistance to any other agent. Mutations in INH-resistant clinical isolates are most commonly detected in the katG gene, occurring in 50–80% of cases, thus reducing the ability of the catalase-peroxidase to activate the INH pro-drug. The katG gene is located in a highly variable and unstable region of the M. tuberculosis genome, with missense and nonsense mutations, insertions, deletions, truncation and, more rarely, full gene deletions observed. Depending on the type of mutation, and the degree to which function of the KatG enzyme is preserved, the ensuing minimum inhibitory concentration (MIC) of isoniazid may range from 0.2 to 256 mg/L. Point mutations in katG are more commonly observed than other types of mutations, and a single point mutation resulting in substitution of threonine for serine at residue 315 (S315T) accounts for the majority of INH resistance among clinical isolates. The S315T mutation results in a significant reduction in catalase and peroxidase activity, and is associated with high-level INH resistance (MIC = 5–10 μg/mL). INH resistance may also arise from mutations in inhA, resulting in reduced affinity of the enzyme for NADH without affecting its enoyl reductase activity, or in the promoter region of the mabAinhA operon, resulting in overexpression of the wild-type enzyme. Generally, mutations in inhA or in the promoter region of its operon usually confer low-level resistance (MIC = 0.2–1 mg/L) (Wade and Zhang 2004). In addition to conferring resistance to INH, mutations in inhA also cause resistance to the structurally related second-line drug ethionamide.

Mutations in the ndh gene, which encodes a NADH dehydrogenase, confer resistance to INH and ethionamide in M. smegmatis and have been detected in INH-resistant M. tuberculosis clinical isolates, which lack mutations in the katG or inhA genes. Defective NADH dehydrogenase could lead to an increased ratio of NADH/NAD, thereby interfering with KatG-mediated peroxidation of INH, or by displacing the INH/NAD adduct from the InhA active site. Furthermore, mutations in kasA and ahpC genes have been associated with INH resistance.



Rifampin and other rifamycins

The rifamycins were first isolated in 1957 from Amycolatopsis (formerly Streptomyces) mediterranei as part of an Italian antibiotic screening program. Their incorporation into the standard anti-tuberculosis regimen allowed reduction of the duration of treatment from 18 to 9 months. Although the early bactericidal activity of the rifamycins is inferior to that of INH, the former are the most potent sterilizing agents available in TB chemotherapy, continuing to kill persistent tubercle bacilli throughout the duration of therapy. Rifampin is a broad-spectrum antibiotic and the most widely used rifamycin to treat TB.

Mechanism of action

Rifamycins contain an aromatic nucleus linked on both sides by an aliphatic bridge. The rifamycins easily diffuse across the M. tuberculosis cell membrane due to their lipophilic profile. Their bactericidal activity has been attributed to their ability to inhibit transcription by binding with high affinity to bacterial DNA-dependent RNA polymerase. Although the molecular target of rifampin has been well characterized, the precise mechanism by which this interaction leads to

mycobacterial killing remains unclear.

Mechanism of resistance

Although INH monoresistance is relatively common in M. tuberculosis, resistance to rifampin alone is rare, and more than 90% of rifampin-resistant isolates are also resistant to INH. Therefore, rifampin resistance has been used as a surrogate marker for MDR-TB. Resistance to rifampin in M. tuberculosis arises at a frequency of 10-7 to 10-8 organisms, most commonly as single point mutations in the rpoB gene, which encodes the β-subunit of RNA polymerase. In over 90% of rifampin-resistant clinical isolates, point mutations cluster in an 81-base pair "hot-spot" region between codons 507 and 533 of the rpoB gene, with mutations in codons 531 [Ser] and 526 [His] predominating. However, a small percentage of rifampin-resistant isolates.

Mechanism of action

PZA is an amide derivative of pyrazine-2-carboxylic acid and nicotinamide analog. Despite recognition of its anti-tuberculosis activity six decades ago, the mechanism of action of PZA remains poorly understood. PZA has been hypothesized to act against bacilli residing in acidified compartments of the lung that are present during the early inflammatory stages of infection, since the drug's sterilizing activity appears to be limited to the first 2 months of therapy. PZA enters tubercle bacilli passively and via an ATP-dependent transport system. Intracellular accumulation of the drug occurs because of an inefficient efflux system unique to M. tuberculosis. PZA, like INH, is a pro-drug, requiring activation to its active form, pyrazinoic acid (POA), by the enzyme pyrazinamidase (PZase). Uptake and intrabacillary accumulation of POA is enhanced when the extracellular pH is acidic. The anti-tuberculosis activity of PZA has been attributed to disruption of the proton motive force required for essential membrane transport functions by POA at acidic pH, although investigation into potential specific cellular targets is ongoing.

Ethambutol

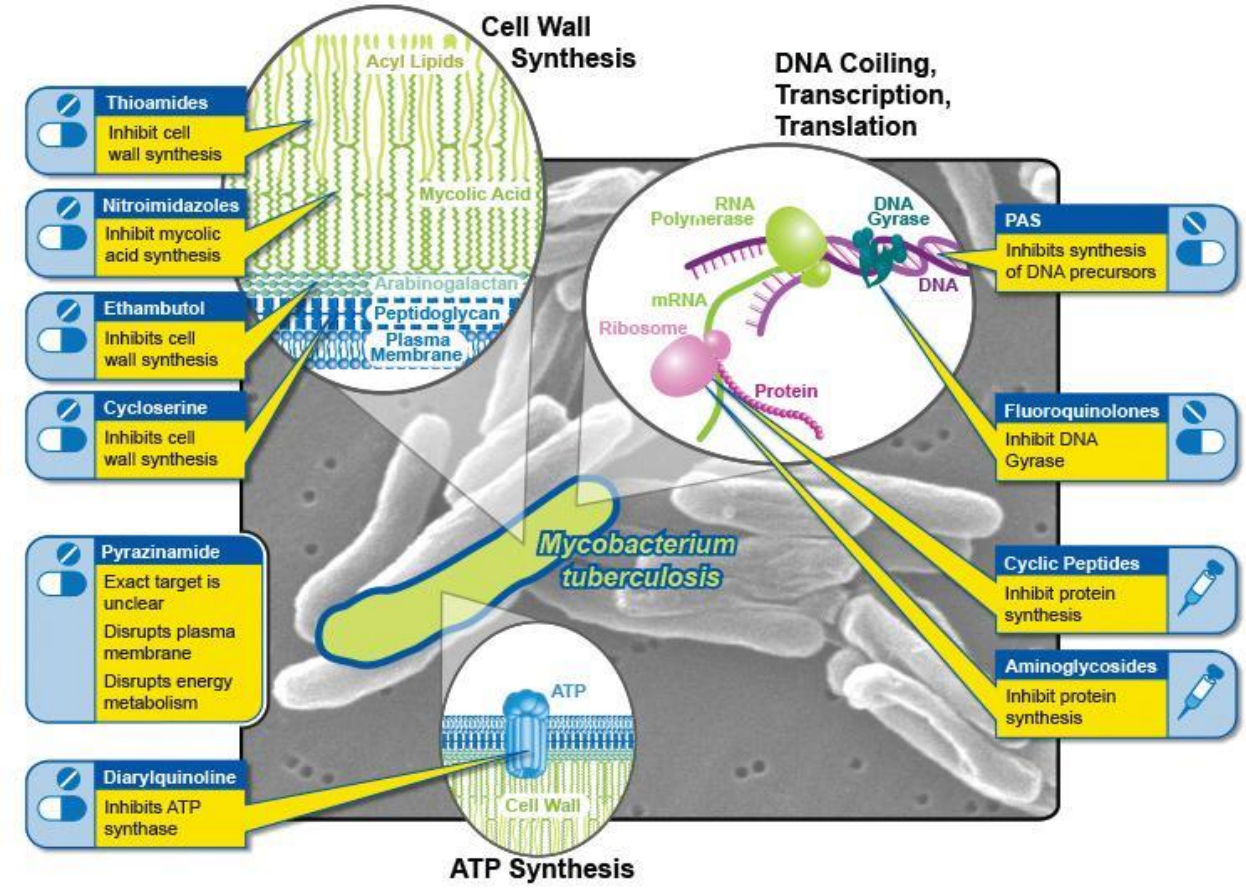
Ethambutol is bacteriostatic and specific for most strains of M. tuberculosis and M. kansasii.

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.

DIRECTLY OBSERVED THERAPY (DOT)

Because the antitubercular drugs must be taken for prolonged periods, compliance with the treatment regimen becomes a problem and increases the risk of the development of resistantstrains of tuberculosis. To help prevent the problem of noncompliance, directly observed therapy (DOT) is used to administer these drugs. When using DOT, the patient makes periodic visits to the office of the primary care provider or the health clinic, where the drug is taken in the presence of the nurse. The nurse watches the patient swallow each dose of the medication regimen.

In some cases, the nurse uses the direct observation method to administer the antitubercular drug in the patient's home, place of employment, or school. DOT may occur daily or two to three times weekly, depending on the patient's health care regimen. Studies indicate that taking the antitubercular drugs intermittently does not cause a drop in the therapeutic blood levels of antitubercular drugs, even if the drugs were given only two or three times a week.

Tuberculosis in pregnant women

The WHO and British Thoracic Society consider H, R, E and Z to be safe to the foetus and recommend the standard 6 month (2HRZE + 4HR) regimen for pregnant women with TB. S is contraindicated because it is ototoxic to the foetus. However, Z is not recommended in the USA (due to lack of adequate teratogenicity data). In India, it is advised to avoid Z, and to treat pregnant TB patients with 2 HRE + 7HR (total 9 months). Treatment of TB should not be withheld or delayed because of pregnancy.

All pregnant women being treated with INH should receive pyridoxine 10–25 mg/day.

Treatment of breastfeeding women

All anti-TB drugs are compatible with breastfeeding; full course should be given to the mother, but the baby should be watched. The infant should receive BCG vaccination and 6 month isoniazid preventive treatment after ruling out active TB.

Multidrug-resistant (MDR) TB

MDR-TB is defined as resistance to both H and R, and may be any number of other (1st line) drug(s). MDR-TB has a more rapid course with worse outcomes. Its treatment requires complex multiple 2nd line drug regimens which are longer, more expensive and more toxic. In India MDRTB accounts for 2.8% of all new TB cases and 12–17% of retreatment cases in different states. These figures are close to the global average incidence. As per WHO, India has the highest number of MDR-TB cases in South-East Asia. The general principles of treatment of MDR-TB are: The regimen should have at least 4 drugs certain to be effective. Often 5–6 drugs are included, since efficacy of some may be uncertain.

• Reliance about efficacy may be placed on survey of similar patients who have been treated, DST results (applicable to H, R, Km, Am, Cm, FQs), and the anti-TB drugs used previously in that individual.

• Avoid combining cross resistance drugs, e.g. two FQs, Km with Am or Eto with Pto, or Cs with terizidone. Include drugs from group I to group IV (alternative classification) in a hierarchial order. Group I drugs (except H and R) can be included, add one injectable drug (group II), One FQ (group III) and one or two group IV drugs. The RNTCP initiated the DOTS-plus programme in the year 2000 to cover the diagnosis and treatment of MDR-TB.

• It has updated its strategy and brought up the revised DOTS-Plus guidelines in 2010, so that they are in consonance with the current WHO guidelines. According to the DOTS-Plus guidelines a case of R resistance is also treated as MDR-TB. The RNTCP has devised a ‘standardized’ treatment regimen (also called category IV regimen), of 6 drugs intensive phase lasting 6–9 months and 4 drugs continuation phase of 18 months, which is used in all confirmed or suspect MDR-TB cases, unless DST results or other specifics (intolerance, etc.) of an individual case necessitate use of an ‘individualized regimen’, which is constructed taking into account these individual specific features.

The minimal 6 month intensive phase is extended by 1 month each time till a maximum of 9 months, if the sputum culture put up at the end of 4th, 5th and 6th month respectively are

positive. PAS is substituted in place of any one of the cidal drugs (Km, Ofx, Z or Eto) or two of the static drugs (E, Cs) when these are not tolerated. Pyridoxine 100 mg/day is given to all patients during the whole course of therapy to prevent neurotoxicity of the anti-TB drugs.

ANTILEPROTIC DEUGS

Leprosy is an infectious disease caused by a acid fast bacillus called as "Mycobacterium leprae".

Leprosy is called ***as "Kushtharog or Maharog"*** in India.

This disease is present from ancient times but,the Gregor Hansen in 1873 discovered the causative organism as "Mycobacterium leprae" hence the disease is called as "Hansen's Disease" also.

The leprosy bacillus attacks the schwan cell nucleus in neuron and hence affects the peripheral nervous system and skin.

Signs of Leprosy:

Leprosy is characterized by presence of patches on skin; the patches of leprosy are characterized by:

- Definite loss of sensation.
- Do not itch or hurt.
- hypopigmentation to reddish or copper red colored.
- No sensation of pain.
- May be flat or elevated.

Two polar types—

Lepromatous (LL) andTtuberculoid (TT) with 4 intermediate forms—

Borderline (BB),

Borderline lepromatous (BL),

Borderline tuberculoid (BT) and

Indeterminate (I) of the disease are recognized.

The important features of the two polar types are:

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.

Diagnosis of Leprosy:

Leprosy patches can easily be identified by checking sensation in comparison to normal skin.

Skin smear test for presence of bacterias.

Chaulmoogra oil with weak antileprotic property had been used in Indian medicine for centuries. Shortly after the demonstration of antibacterial property of sulfonamides, congeners were tested and dapsone, the parent sulfone, was found to be active antileprotic. Demonstration of its efficacy in experimental tuberculosis and leprosy led to clinical trials in the 1940s, and since then it is the sheet-anchor of treatment of leprosy. Few other sulfones were added, but none could excel dapsone. Some antitubercular drugs and clofazimine were subsequently found to be useful adjuncts. Recently good antileprotic activity has been detected in some fluoroquinolones, macrolides and minocycline.

Classification

1. Sulfone: Dapsone (DDS)

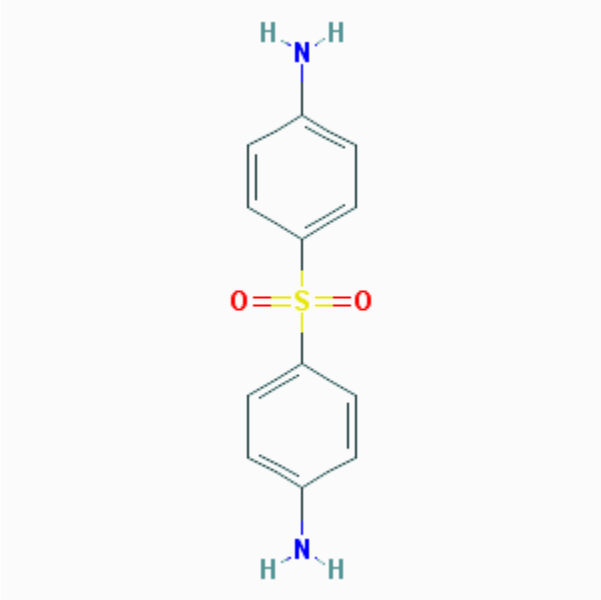
2. Phenazine Derivative: Clofazimine

3. Antitubercular Drugs: Rifampin, Ethionamide

4. 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. All other sulfones are converted in the body to DDS; many have been used, but none is superior.



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. Doses of dapsone needed for the treatment of acute infections are too toxic, so not used.

Dapsone-resistance among *M. leprae*, first noted in 1964, has spread, and has necessitated the use of multidrug therapy (MDT). It may be *primary*—in untreated patients, i.e. they have acquired infection from a patient harbouring resistant bacilli, or *secondary*—which develops during therapy in an individual patient with a single drug. The incidence of primary dapsone resistance reported from different parts of the world, from time-to-time, has varied from 2.5% to 40%; whereas secondary dapsone resistance occurred in about 20% patients treated with monotherapy. The mechanism of secondary resistance appears to be the same as for *M. tuberculosis.* However, the peak serum concentration of dapsone after 100 mg/day dose exceeds MIC for *M. leprae* by nearly 500 times; it continues to be active against low to moderately resistant bacilli.

Pharmacokinetics

Dapsone is completely absorbed after oral administration and is widely distributed in the body, though penetration in CSF is poor. It is 70% plasma protein bound, but more importantly concentrated in skin (especially lepromatous skin), muscle, liver and kidney.

Dapsone is acetylated as well as glucuronide and sulfate conjugated in liver. Metabolites are excreted in bile and reabsorbed from intestine, so that ultimate excretion occurs mostly in urine. The plasma t½ of dapsone is variable, though often > 24 hrs. The drug is cumulative due to retention in tissues and enterohepatic circulation. Elimination takes 1–2 weeks or longer.

DAPSONE 25, 50, 100 mg tab.

Adverse Effects

Dapsone is generally well tolerated at doses 100 mg/day or less.

- Mild haemolytic anaemia is common. It is a dose-related toxicity—reflects oxidising property of the drug. Patients with G6PD deficiency are more susceptible; doses > 50 mg/day produce haemolysis in them.
- Gastric intolerance—nausea and anorexia are frequent in the beginning, decrease later.
- Other side effects are methaemoglobinaemia, headache, paresthesias, mental symptoms and drug fever.
- Cutaneous reactions include allergic rashes, fixed drug eruption, hypermelanosis, phototoxicity and rarely exfoliative dermatitis.
- Hepatitis and agranulocytosis are other rare complications.

Contraindications

Dapsone should not be used in patients with severe anaemia with Hb < 7g%, G6PD deficiency and in those showing hypersensitivity reactions.

Other Use In combination with pyrimethamine, dapsone can be used for chloroquineresistant malaria.

Clofazimine (Clo)

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 t½ is 70 days so that intermittent therapy is possible.

CLOFOZINE, HANSEPRAN 50, 100 mg cap.

Clofazimine is used as a component of multidrug therapy of leprosy. Because of its anti-inflammatory property, it is valuable in lepra reaction.

Occasionally, it is used as a component of MDT for MAC.

Adverse Effects

In the doses employed for multidrug therapy (MDT), clofazimine is well tolerated.

Skin The major disadvantage is reddish-black discolouration of skin, especially on exposed parts. Discolouration of hair and body secretions may also occur. Dryness of skin and itching is often troublesome. Acneform eruptions and phototoxicity have been noted. Conjunctival pigmentation may create cosmetic problem.

GI Symptoms Enteritis with intermittent loose stools, nausea, abdominal pain, anorexia and weight loss can occur, particularly when higher doses are used to control lepra reaction. The early syndrome is a reflection of irritant effect of the drug—subsides with dose adjustment and by taking the drug with meals. A late syndrome occurring after few months of therapy—is due to deposition of clofazimine crystals in the intestinal submucosa.

Clofazimine is to be avoided during early pregnancy and in patients with liver or kidney damage.

Rifampin (R)

It is an important antitubercular drug; also bactericidal to *M. leprae*; rapidly renders leprosy patients noncontagious. Up to 99.99% *M. leprae* are killed in 3–7 days. However, it is not satisfactory if used alone—some bacilli persist even after prolonged treatment—resistance develops. It has been included in the multidrug therapy of leprosy: shortens duration of treatment. The 600 mg monthly dose used in leprosy is relatively nontoxic and does not induce metabolism of other drugs. It should not be given to patients with hepatic or renal dysfunction.

The rifampin congener rifabutin is also cidal against *M. leprae,* but not superior to rifampin.

Ethionamide

This antitubercular drug has significant antileprotic activity, but causes hepatotoxicity in ~ 10% patients. It has been used as an alternative to clofazimine, but other substitutes are preferred. It should be used (250 mg/day) only when absolutely necessary.

Other Antibiotics

Ciprofloxacin is not active against *M. leprae,* but ofloxacin, pefloxacin, gatifloxacin and sparfloxacin are highly active.

Ofloxacin

Many trials have evaluated ofloxacin as a component of MDT and found it to hasten the bacteriological and clinical response. Over 99.9% bacilli were found to be killed by 22 daily doses of ofloxacin monotherapy. However, it is not included in the standard treatment protocols, but can be used in alternative regimens in case rifampin cannot be used, or to shorten the duration of treatment. *Dose:* 400 mg/day.

Minocycline

Because of high lipophilicity, this tetracycline is active against *M. leprae*. A dose of 100 mg/day produces peak blood levels that exceed MIC against *M. leprae* by 10–20 times. Its antibacterial activity is much less than that of rifampin, but greater than that of clarithromycin. In one trial minocycline 100 mg daily monotherapy rendered all 8 patients of lepromatous leprosy negative for *M. leprae* after 8 weeks. It is being tried in alternative MDT regimens.

Clarithromycin

It is the only macrolide antibiotic with significant activity against *M. leprae*. However, it is less bactericidal than rifampin. Monotherapy with clarithromycin 500 mg daily caused 99.9% bacterial killing in 8 weeks. It is being included in alternative MDT regimens.

Multidrug Therapy (MDT) Of Leprosy

To deal with dapsone resistant strains of *M. leprae* and the problem of microbial persisters (dormant forms), multidrug therapy with rifampin, dapsone and clofazimine was introduced by the WHO in 1981. This was implemented under the NLEP. The MDT is the regimen of choice for all cases of leprosy. Its advantages are:

- Effective in cases with primary dapsone resistance.
- Prevents emergence of dapsone resistance.
- Affords quick symptom relief and renders MBL cases noncontagious.
- Reduces total duration of therapy.

Initially under standard MDT, the PBL cases were treated with dapsone + rifampin for 6 months, while the MBL cases were treated with dapsone + rifampin + clofazimine for a minimum of 2 years or till disease inactivity/skin smear negativity was achieved. The MBL cases were kept under surveillance without treatment for the next 5 years. MDT had been highly successful, both in MBL and PBL. The estimated cases of leprosy fell from 10–12 million to 2.7 million.

- Relapse rate after MDT had been 0.74% in MBL and 1.09% in PBL over a period of 9 years.
- The efficacy, safety and acceptability of MDT had been excellent.
- Some reports, mostly from India, had found that for uniformly satisfactory response, treatment of PBL had to be extended beyond the mandatory 6 months (mostly to 12 months). However, no difference in the relapse rate was found among 12000 Indian patients treated with MDT either for 6 months or for 1 year. As such, the WHO expert group recommended continuation of 6 month MDT for PBL.
- No resistance to rifampin developed with MDT: nearly all M. leprae isolated from relapse cases remained fully sensitive to rifampin. No resistance to clofazimine had been reported. New cases of drug resistance were not reported after application of MDT. Retreatment of relapse cases with the same MDT had been successful, and was recommended.
- Drug toxicity had not been a major problem in MDT.

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 life-threatening (erythema nodosum leprosum).

Sufone Syndrome: It is the reaction which develops 4–6 weeks after dapsone treatment: consists of fever, malaise, and 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 anti-inflammatory property.

Other drugs used are—analgesics, antipyretics, antibiotics, etc. according to need. Chloroquine and thalidomide also suppress lepra reaction. Corticosteroids (prednisolone 40–60 mg/day till reaction is controlled, then tapered over 8–12 weeks), should be used only in severe cases.

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. As a result of breakdown of host defence mechanisms, saprophytic fungi easily invade living tissue.

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. Antifungal property of flucytosine was noted in 1970, but it could serve only as a companion drug to amphotericin. The development of imidazoles in the mid 1970s and triazoles in 1980s has been an advancement. Some new compounds like *terbinafine* have been added lately.

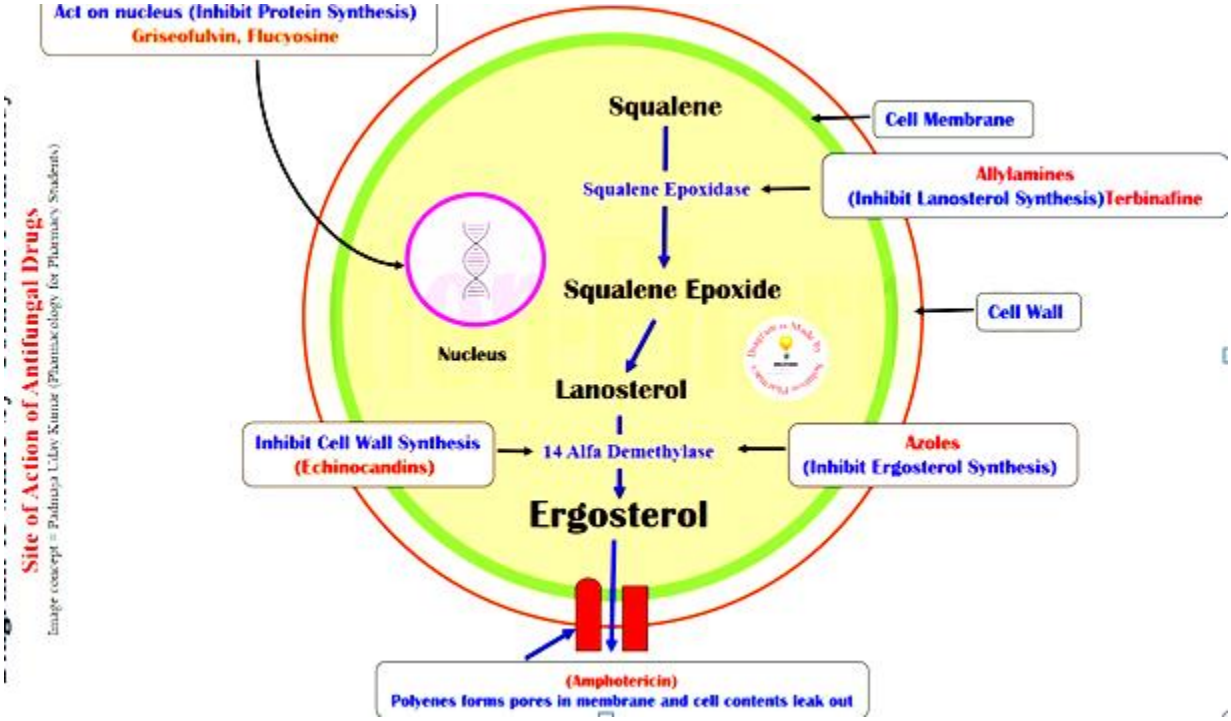


Figure: site of action of antifungal drugs

Classification

1. Antibiotics

Polyenes: Amphotericin B (AMB), Nystatin, Hamycin, Natamycin (Pimaricin)

***Heterocyclic Benzofuran*:** Griseofulvin

2. Antimetabolite Flucytosine (5FC)

3. Azoles

***Imidazoles* (topical):** Clotrimazole, Econazole, Miconazole, Oxiconazole

(systemic): Ketoconazole

***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. A polar amino-sugar and a carboxylic acid group are present at one end in some. They are all insoluble in water and unstable in aqueous medium.

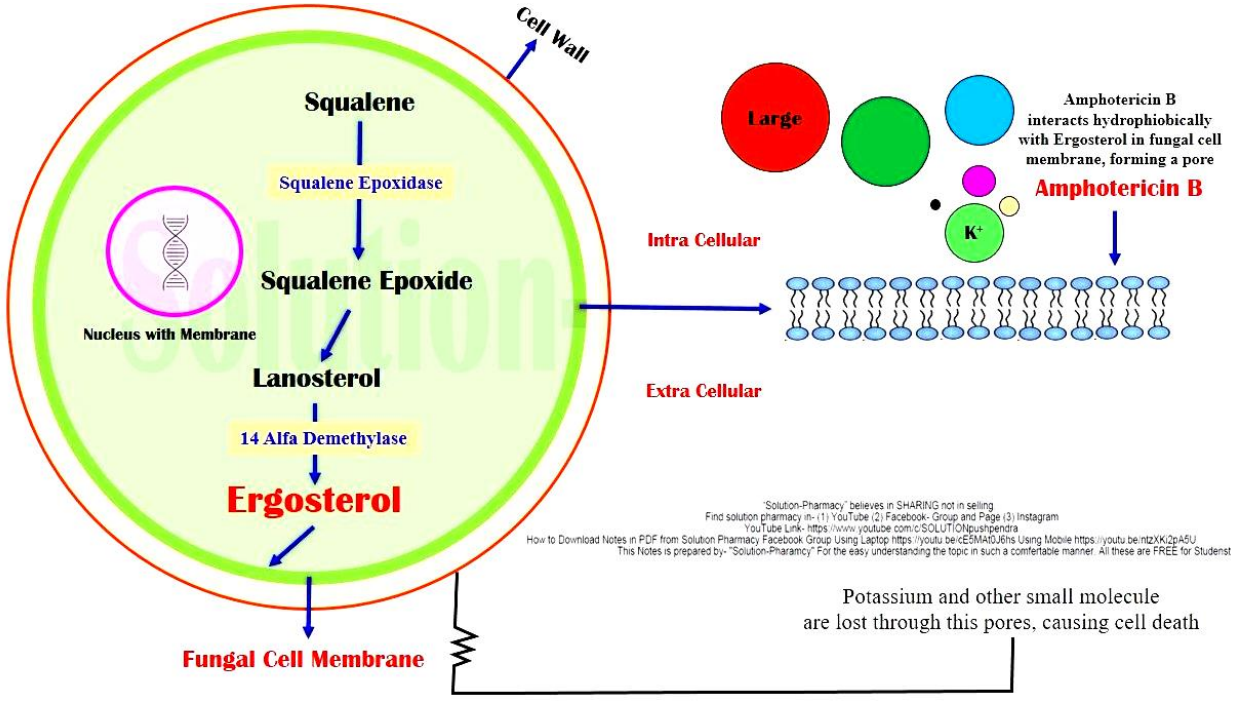


Figure: Mechanism of action of Amphotericin

The polyenes have high affinity for ergosterol present in fungal cell membrane: combine with it, get inserted into the membrane and several polyene molecules together orient themselves in such a way as to form a 'micropore'. The hydrophilic side forms the interior of the pore through which ions, amino acids and other water-soluble substances move out. The micropore is stabilized by membrane sterols which fill up the spaces between the AMB molecules on the lipophilic side—constituting the outer surface of the pore. Thus, cell permeability is markedly increased.

Cholesterol, present in host cell membranes, closely resembles ergosterol; the polyenes bind to it as well, though with lesser affinity. Thus, the selectivity of action of polyenes is low, and AMB is one of the most toxic systemically used antibiotics, though it is the least toxic polyene. Bacteria do not have sterols and are unaffected by polyenes. It has been found that AMB enhances immunity in animals, and this may aid immunocompromised individuals in handling fungal infection.

Antifungal Spectrum

AMB is active against a wide range of yeasts and fungi—Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis, Torulopsis, Rhodotorula, Aspergillus, Sporothrix, etc. Dermatophytes are inhibited in vitro, but concentrations of AMB attained in infected skin are low and ineffective. It is fungicidal at high and static at low concentrations.

Resistance to AMB during therapy has been rarely noted among Candida in a selected group of leucopenic cancer patients, but it is not a problem in the clinical use of the drug. AMB is also active on various species of Leishmania.

Pharmacokinetics

AMB is not absorbed orally; it can be given orally for intestinal candidiasis without systemic toxicity. Administered i.v. as a suspension made with the help of deoxycholate (DOC), it gets widely distributed in the body, but penetration in CSF is poor. It binds to sterols in tissues and to lipoproteins in plasma and stays in the body for long periods. The terminal elimination t½ is 15 days. About 60% of AMB is metabolized in the liver. Excretion occurs slowly both in urine and bile, but urinary concentration of active drug is low.

Administration and Dose

Amphotericin B can be administered orally (50–100 mg QID) for intestinal moniliasis; also topically for vaginitis, otomycosis, etc.: FUNGIZONE OTIC 3% ear drops.

For systemic mycosis, it is available as dry powder along with DOC for extemporaneous dispersion before use: FUNGIZONE INTRAVENOUS, MYCOL 50 mg vial. It is first suspended in 10 ml water and then diluted to 500 ml with glucose solution (saline tends to make the suspension coarse). Initially 1 mg test dose is injected i.v. over 20 minutes. If no serious reaction follows, 0.3 mg/kg is infused over 4–8 hours. Daily dose may be gradually increased to

0.7 mg/kg depending on tolerance of the patient. The total dose of AMB for majority of cases is 3– 4 g given over 2–3 months.

Intrathecal injection of 0.5 mg twice weekly has been given in fungal meningitis.

New Amphotericin B Formulations

In an attempt to improve tolerability of i.v. infusion of AMB, reduce its toxicity and achieve targeted delivery, 3 new lipid formulations of AMB have been produced.

a) Amphotericin B Lipid Complex (ABLC): Contains 35% AMB incorporated in ribbon like pCh. No.s of dimyristoyl phospholipids.

b) Amphotericin B Colloidal Dispersion (ABCD): Disc shaped pCh. No.s containing 50% each of AMB and cholesteryl sulfate are prepared as aqueous dispersion.

c) Liposomal Amphotericin B (Small Unilamellar Vesicles; SUV): Consists of 10% AMB incorporated in uniform sized (60–80 nM) unilamellar liposomes made up of lecithin and other biodegradable phospholipids.

- They can be used in patients not tolerating infusion of conventional AMB formulation.
- They have lower nephrotoxicity.
- They cause minimal anaemia.
- The liposomal preparation delivers AMB particularly to reticulo-endothelial cells in liver and spleen—especially valuable for kala azar and in immuno-compromised patients.

However, some preparations, especially ABLC and ABCD, produce lower AMB levels and their clinical efficacy relative to conventional formulation appears to be lower. Though none of the above formulations is more effective in deep mycosis than conventional AMB, the liposomalAMB produces equivalent blood levels, has similar clinical efficacy with less acute reaction and renal toxicity. It thus appears more satisfactory, can be infused at higher rates (3–5 mg/kg/day), but is many times costlier than conventional AMB. Its specific indications are—as empirical therapy in febrile neutropenic patients not responding to antibacterial antibiotics, critically ill deep mycosis cases and in kala azar.

FUNGISOME (liposomal AMB) 10 mg, 25 mg, 50 mg per vial inj.

Adverse Effects

The toxicity of AMB is high.

a) Acute Reaction: This occurs with each infusion and consists of chills, fever, aches and pain all over, nausea, vomiting and dyspnoea lasting for 2–5 hour, probably due to release of

cytokines (IL, TNFα). When these are severe—the dose is increased gradually. Usually the intensity of reaction decreases with continued medication. Injection of hydrocortisone 0.6 mg/kg with the infusion may reduce the intensity of reaction.Thrombophlebitis of the injected vein can occur.

b) Long-Term Toxicity: Nephrotoxicity is the most important. It occurs fairly uniformly and is doserelated: manifestations are—azotemia, reduced g.f.r., acidosis, hypokalaemia and inability to concentrate urine. It reverses slowly and often incompletely after stoppage of therapy. Anaemia: Most patients develop slowly progressing anaemia which is due to bone marrow depression. It is largely reversible.

CNS toxicity: occurs only on intrathecal injection—headache, vomiting, nerve palsies, etc.

Uses

Amphotericin B can be applied topically for oral, vaginal and cutaneous candidiasis and otomycosis.

It is the most effective drug for various types of systemic mycoses and is the gold standard of antifungal therapy. However, because of higher toxicity of AMB, the azole antifungals are now preferred in conditions where their efficacy approaches that of AMB (see Table 57.1).

Leishmaniasis: AMB is the most effective drug for resistant cases of kala azar and mucocutaneous leishmaniasis.

Interactions

Flucytosine has supra-additive action with AMB in the case of fungi sensitive to both (AMB increases the penetration of 5FC into the fungus).

Rifampin and minocycline, though not antifungal in their own right, potentiate AMB action.

Nystatin

Obtained from S. noursei, it is similar to AMB in antifungal action and other properties. However, because of higher systemic toxicity, it is used only locally in superficial candidiasis and is generally preferred over AMB for these purposes.

MYCOSTATIN 5 lac U tab, 1 lac U vaginal tab, 1 lac U/ g oint, NYSTIN EYE 1 lac U/g ophthalmic oint. Given orally, it is not absorbed; can be used for monilial diarrhoea (due to

superinfection or otherwise), 5 lac U TDS (1 mg = 2000 U). Nausea and bad taste in mouth are the only side effects.

Nystatin is effective (but less than azoles) in monilial vaginitis—1 lac U tab inserted twice daily. For oral thrush, the vaginal tab may be sucked or it may be crushed and suspended in glycerine for application in mouth. Corticosteroid aerosols (e.g. beclomethasone) can cause oral candidiasis: nystatin is effective in preventing as well as treating it.Similarly, it is used for corneal, conjunctival and cutaneous candidiasis in the form of an ointment. No irritation or other side effect is ordinarily seen. Candidal resistance to nystatin is not a clinical problem. It is ineffective in dermatophytosis.

Hamycin

It was isolated from S. pimprina and developed by Hindustan Antibiotics at Pimpri. It is similar to nystatin, but more water soluble. A fraction of the orally administered dose is absorbed, but cannot be relied upon for the treatment of systemic mycosis: use is restricted to topical application for oral thrush, cutaneous candidiasis, monilial and trichomonas vaginitis and otomycosis by Aspergillus.

HAMYCIN, IMPRIMA 5 lac U/g oint, 2 lac U/ ml susp for topical use, 4 lac U vaginal ovules.

Natamycin (Pimaricin)

It is similar to nystatin; has a broader spectrum of action, and is used only topically. A 5% suspension or 1% ointment is nonirritating to the eye, and has been used particularly in Fusarium solani keratitis. Both monilial and trichomonas vaginitis are amenable to natamycin.

NATAMYCIN 2% cream, 25 mg vaginal tab, PIMAFUSIN VAGINAL 100 mg vaginal tab.

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, etc., but not against Candida and other fungi causing deep mycosis. Bacteria are also insensitive. Dermatophytes actively concentrate it: this feature probably accounts for its selective toxicity. Resistance can be induced in vitro and this is associated with loss of concentrating ability. However, emergence of resistance during clinical use is rare.

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. It does not inhibit polymerization of tubulin (microtubular protein which pulls the chromosomes apart), but binds to polymerized microtubules and somehow disorients them.

Pharmacokinetics

The absorption of griseofulvin from g.i.t. is somewhat irregular because of its very low water solubility. Absorption is improved by taking it with fats and by micro-fining the drug particles; now ultra-microfine particle preparations from which absorption is still better are available.

Griseofulvin gets deposited in keratin forming cells of skin, hair and nails; it is especially concentrated and retained in tinea infected cells. Because it is fungistatic and not cidal, the newly formed keratin is not invaded by the fungus, but the fungus persists in already infected keratin, till it is shed off. Thus, the duration of treatment is dependent upon the site of infection, thickness of infected keratin and its turnover rate.

Griseofulvin is largely metabolized, primarily by methylation, and excreted in urine. Plasma t½ is 24 hrs, but it persists for weeks in skin and keratin.

Adverse Effects

Toxicity of griseofulvin is low and usually not serious. Headache is the commonest complaint, followed by g.i.t. disturbances. CNS symptoms and peripheral neuritis are occasional.Rashes, photoallergy may warrant discontinuation.Transient leukopenia and albuminuria (without renal damage) are infrequent.

Use

Griseofulvin is used orally only for dermatophytosis. It is ineffective topically. Systemic azoles and terbinafine are equally or more efficacious; preferred now.

Dose: 125–250 mg QID with meals; duration depends on the site of infection (turnover rate of keratin).

Body skin: 3 weeks

Palm, soles: 4 to 6 weeks
Finger nails: 4 to 6 months
Toe nails: 8 to 12 months

Majority of localized tinea infections are treated with topical agents. Griseofulvin should be reserved for cases with nail, hair or large body surface involvement. It is effective in athlete's foot, but not in pityriasis versicolor.

GRISOVINFP, WALAVIN, GRISORAL 250 mg tab.

Interactions

Griseofulvin induces warfarin metabolism and reduces efficacy of oral contraceptives.

Phenobarbitone reduces the oral absorption and induces the metabolism of griseofulvin—failure of therapy may occur. Griseofulvin can cause intolerance to alcohol.

Flucytosine (5FC)

It is a pyrimidine antimetabolite which is inactive as such. It is taken up by fungal cells and converted into 5fluorouracil and then to 5fluorodeoxyuridylic acid which is an inhibitor of thymidylate synthesis. Thymidylic acid is a component of DNA. The fungal selectivity of 5FC depends on the fact that mammalian cells (except some marrow cells) have low capacity to convert 5FC into 5fluorouracil.

It is a narrow spectrum fungistatic, active against Cryptococcus neoformans, Torula, Chromoblastomyces; and a few strains of Candida. Other fungi and bacteria are insensitive.

Adverse Effects

Toxicity of 5FC is lower than that of AMB; consists of dose-dependent bone marrow depression and gastrointestinal disturbances, particularly enteritis and diarrhoea. Liver dysfunction is mild and reversible.

Use

Flucytosine is not employed as the sole therapy except occasionally in chromoblastomycosis. Rapid development of resistance limits its utility in deep mycosis. In cryptococcosis (both meningeal and nonmeningeal) its synergistic action with AMB is utilized to reduce the total dose of the more toxic latter drug.

Imidazoles and triazoles

These are presently the most extensively used antifungal drugs.

Four imidazoles are entirely topical, while ketoconazole is used both orally and topically. Two triazoles fluconazole and itraconazole have largely replaced ketoconazole for systemic mycosis because of greater efficacy, longer t½, fewer side effects and drug interactions.

The imidazoles and triazoles have broad-spectrum antifungal activity covering dermatophytes, Candida, other fungi involved in deep mycosis (except mucor), Nocardia, some gram-positive and anaerobic bacteria, e.g. Staph. aureus, Strep. faecalis, Bac. fragilis and Leishmania.

The mechanism of action of imidazoles and triazoles is the same. They inhibit the fungal cytochrome P450 enzyme 'lanosterol 14demethylase' and thus impair ergosterol synthesis leading to a cascade of membrane abnormalities in the fungus. The lower host toxicity of triazoles compared to imidazoles has correlated with their lower affinity for mammalian CYP450 enzymes and lesser propensity to inhibit mammalian sterol synthesis. However, because they are active against certain bacteria as well (which do not have ergosterol), other mechanisms of action also appear to be involved. Development of fungal resistance to azoles has been noted among Candida infecting advanced AIDS patients, but has not so far posed significant clinical problem.

Clotrimazole

It is effective in the topical treatment of tinea infections like ringworm: 60–100% cure rates are reported with 2–4 weeks application on a twice daily schedule. Athletes' foot, otomycosis and oral/cutaneous/vaginal candidiasis have responded in >80% cases. It is particularly favoured for vaginitis because of a long lasting residual effect after once daily application. A 7 day course is generally used. For oropharyngeal candidiasis 10 mg troche of clotrimazole is allowed to dissolve in the mouth 3–4 times a day, or the lotion/gel is applied/ swirled in the mouth for as long as possible. It is also effective in skin infections caused by Corynebacteria.

Clotrimazole is well tolerated by most patients. Local irritation with stinging and burning sensation occurs in some. No systemic toxicity is seen after topical use.

Econazole

It is similar to clotrimazole; penetrates superficial layers of the skin and is highly effective in dermatophytosis, otomycosis, oral thrush, but is somewhat inferior to clotrimazole in vaginitis. No adverse effects, except local irritation in few is reported.

ECONAZOLE 1% oint, 150 mg vaginal tab; ECODERM 1% cream.

Miconazole

It is a highly efficacious (>90% cure rate) drug for tinea, pityriasis versicolor, otomycosis, cutaneous and vulvovaginal candidiasis. Because of its good penetrating power, it has been found effective, though partially, even in onychomycosis; single application on skin acts for a few days.

Irritation after cutaneous application is infrequent. No systemic adverse effects are seen. However, a higher incidence of vaginal irritation is reported in comparison to clotrimazole; even pelvic cramps have been experienced.

DAKTARIN 2% gel, 2% powder and solution; GYNODAKTARIN 2% vaginal gel; ZOLE 2% oint, lotion, dusting powder and spray, 1% ear drops, 100 mg vaginal ovules.

Oxiconazole

Another recently marketed topical imidazole antifungal effective in tinea and other dermatophytic infection, as well as vaginal candidiasis. Local irritation can occur in some patients.

OXIZON, ZODERM: oxiconazole 1% with benzoic acid 0.25% cream/lotion; apply topically once or twice daily.

Ketoconazole (KTZ)

It is the first orally effective broad-spectrum antifungal drug, useful in both dermatophytosis and deep mycosis. The oral absorption of KTZ is facilitated by gastric acidity because it is more soluble at lower pH. Hepatic metabolism is extensive; metabolites are excreted in urine and faeces. Elimination of KTZ is dose dependent: t½ varies from 1½ to 6 hours. Penetration in CSF is poor: not effective in fungal meningitis. However, therapeutic concentrations are attained in the skin and vaginal fluid. In spite of relatively short t½, a single daily dose is satisfactory in less severe cases. The usual dose is 200 mg OD or BD; higher doses are sometimes required.

FUNGICIDE, NIZRAL, FUNAZOLE, KETOVATE 200 mg tab.

Adverse Effects

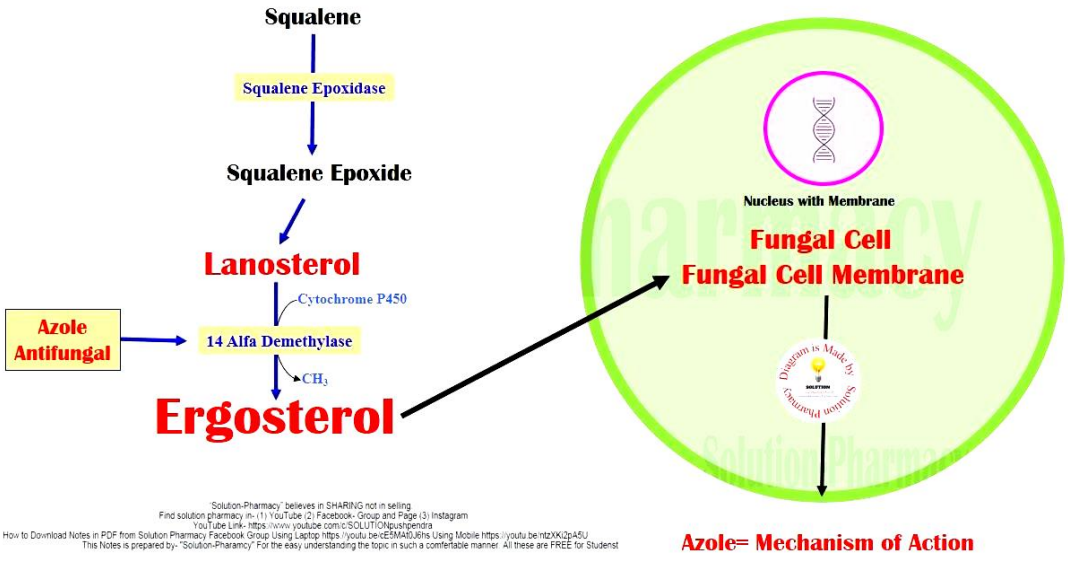
Ketoconazole is much less toxic than AMB, but more side effects occur than with itraconazole or fluconazole, that have largely replaced it for systemic use.

The most common side effects are nausea and vomiting; can be reduced by giving the drug with meals. Others are—loss of appetite, headache, paresthesia, rashes and hair loss.

Ketoconazole decreases androgen production from testes, and it displaces testosterone from protein binding sites. Gynaecomastia, loss of hair and libido, and oligozoospermia may be the manifestations. Menstrual irregularities occur in some women due to suppression of estradiol synthesis.

A dose-dependent decrease in serum hydrocortisone due to synthesis inhibition has also been noted, but without any clinical manifestations in normal individuals.

Mild and asymptomatic elevation of serum transaminases occurs in ~5% patients, but serious hepatotoxicity is infrequent. It is contraindicated in pregnant and nursing women.



Interactions

H2 blockers, proton pump inhibitors and antacids decrease the oral absorption of KTZ by reducing gastric acidity.

Rifampin, phenobarbitone, carbamazepine and phenytoin induce KTZ metabolism and reduce its efficacy. Ketoconazole inhibits cytochrome P450, especially CYP3A4, and raises the blood levels of several drugs including: Phenytoin, Digoxin, Diazepam, Cyclosporine, Haloperidol Nifedipine and other DHPs, Warfarin, HIV protease inhibitors, Sulfonylureas and Statin hypolipidaemics

The dangerous interaction with terfenadine, astemizole and cisapride resulting in polymorphic ventricular tachycardia due to excessive rise in plasma levels of these drugs has resulted in withdrawal of these drugs from the market in many countries.

Use

Orally administered KTZ is effective in dermatophytosis because it is concentrated in the stratum corneum; is an alternative to griseofulvin, but use is restricted due to potential adverse effects.

Though effective in monilial vaginitis, oral therapy (for 5–7 days) with KTZ is reserved for recurrent cases or those not responding to topical agents.

Systemic Mycosis: Administered orally, KTZ is effective in several types of systemic mycosis, but itraconazole and fluconazole, being more active with fewer side effects, have largely replaced it for these indications except for considerations of cost. KTZ is occasionally used in dermal leishmaniasis and kala azar.

Highdose KTZ has been used in Cushing's syndrome to decrease corticosteroid production.

Fluconazole

It is a water-soluble triazole having a wider range of activity than KTZ; indications include cryptococcal meningitis, systemic and mucosal candidiasis in both normal and immunocompromised patients, coccidioidal meningitis and histoplasmosis.

Fluconazole is 94% absorbed; oral bioavailability is not affected by food or gastric pH. It is primarily excreted unchanged in urine with a t½ of 25–30 hr. Fungicidal concentrations are achieved in nails, vagina and saliva; penetration into brain and CSF is good. Dose reduction is needed in renal impairment.

Adverse Effects

Fluconazole produces few side effects: mostly nausea, vomiting, abdominal pain, rash and headache.

Selectivity for fungal cytochrome P450 is higher; unlike KTZ, it does not inhibit steroid synthesis in man: antiandrogenic and other endocrine side effects have not occurred. Elevation of hepatic transaminase has been noted in AIDS patients. It is not recommended in pregnant and lactating mothers.

Interactions

Though it affects hepatic drug metabolism to a lesser extent than KTZ, increased plasma levels of phenytoin, astemizole, cisapride, cyclosporine, warfarin, zidovudine and sulfonylureas have been observed. A few cases of ventricular tachycardia have been reported when fluconazole was given with cisapride. The same caution as with KTZ or itraconazole needs to be applied in co-administering other drugs. H2 blockers and proton pump inhibitors do not affect its absorption.

Use

Fluconazole can be administered orally as well as i.v. (in severe infections). A single 150 mg oral dose can cure vaginal candidiasis with few relapses.

Oral fluconazole (150 mg/day for 2 weeks) is highly effective in oropharyngeal candidiasis, but is reserved for cases not responding to topical antifungals.

Most tinea infections and cutaneous candidiasis can be treated with 150 mg weekly fluconazole for 4 weeks, while tinea unguium requires weekly treatment for up to 12 months.

For disseminated candidiasis, cryptococcal/ coccidioidal meningitis and other systemic fungal infections the dose is 200–400 mg/day for 4–12 weeks or longer. It is the preferred drug for fungal meningitis, because of good CSF penetration. Long-term fluconazole maintenance therapy is needed in AIDS patients with fungal meningitis.

An eye drop is useful in fungal keratitis. Fluconazole is ineffective in aspergillosis and mucormycosis, and inferior to itraconazole for histoplasmosis, blastomycosis and sporotrichosis.

SYSCAN, ZOCON, FORCAN, FLUZON 50, 100, 150, 200 mg caps, 200 mg/100 ml i.v. infusion. SYSCAN 0.3% eye drops.

Itraconazole

This newer orally active triazole antifungal has a broader spectrum of activity than KTZ or fluconazole; includes some moulds like Aspergillus. It is fungistatic, but effective in immunocompromised patients. Steroid hormone synthesis inhibition is absent in itraconazole, and serious hepatotoxicity is rare.

Oral absorption of itraconazole is variable. It is enhanced by food and gastric acid. Itraconazole is highly protein bound, has a large volume of distribution (10L/Kg), accumulates in vaginal mucosa, skin and nails, but penetration into CSF is poor. It is largely metabolized in liver by CYP3A4; an active metabolite is produced which is excreted in faeces; t½ varies from 30–64 hours. Itraconazole is well tolerated in doses below 200 mg/day. Gastric intolerance is significant at 400 mg/day. Dizziness, pruritus, headache and hypokalaemia are the other common side effects. Unsteadiness and impotence are infrequent. Plasma transaminase may rise transiently. However, antiandrogenic and other hormonal adverse effects are not seen. Impaired left ventricular function has been worsened in some patients.

Drug Interactions

Oral absorption of itraconazole is reduced by antacids, H2 blockers and proton pump inhibitors.

Rifampin, phenobarbitone, phenytoin and carbamazepine induce itraconazole metabolism and reduce its efficacy.

On the other hand, clarithromycin and HIV protease inhibitors reduce the metabolism of itraconazole and raise its blood levels.

Itraconazole inhibits CYP3A4; drug interaction profile is similar to KTZ; ventricular arrhythmias have occurred with terfenadine, astemizole, cisapride and class III antiarrhythmics. Phenytoin, digoxin, sulfonylureas, statins, dihydropyridines, protease inhibitors, warfarin and cyclosporine levels are also increased.

Uses

Itraconazole is the preferred azole antifungal for most systemic mycosis (see Table 57.1) that are not associated with meningitis. It is superior to fluconazole for histoplasmosis, blastomycosis, sporotrichosis and is the drug of choice for para-coccidioidomycosis and chromomycosis. It also affords some relief in aspergillosis. A dose of 200 mg OD/BD with meals is used for 3 months or more.

Vaginal Candidiasis: 200 mg OD for 3 days: as effective as intravaginal clotrimazole. Dermatophytosis: 100–200 mg OD for 7–15 days: more effective than griseofulvin, but less effective than fluconazole.

Onychomycosis: 200 mg/day for 3 months. An intermittent pulse regimen of 200 mg BD for 1 week each month for 3 months is equally effective. Relapses have occurred after itraconazole therapy, though it remains in the nail for few months after completion of the course.

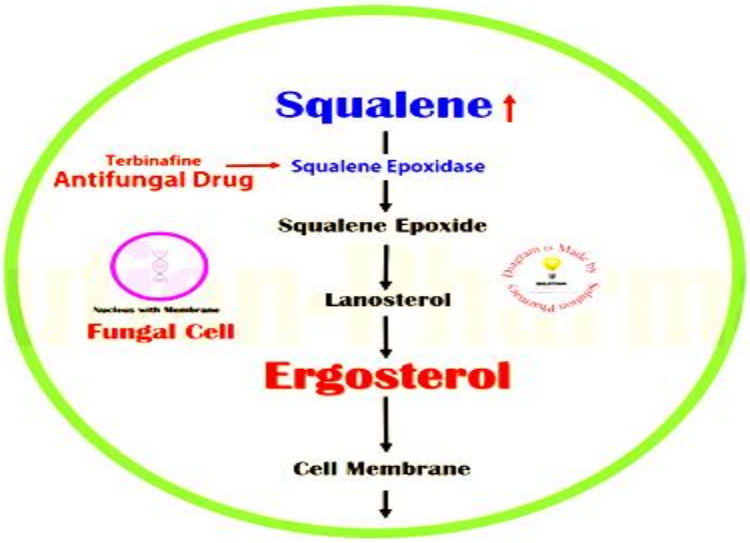
SPORANOX, CANDITRAL, CANDISTAT, ITASPOR, FLUCOVER 100 mg cap.

Terbinafine

This orally and topically active drug against dermatophytes and Candida belongs to a new allylamine class of antifungals. In contrast to azoles which are primarily fungistatic, terbinafine is fungicidal: shorter courses of therapy are required and relapse rates are low. It acts as a noncompetitive inhibitor of ‘squalene epoxidase’, an early step enzyme in ergosterol biosynthesis by fungi. Accumulation of squalene within fungal cells appears to be responsible for the fungicidal action. The mammalian enzyme is inhibited only by 1000fold higher concentration of terbinafine.

Approximately 75% of oral terbinafine is absorbed, but only 5% or less from unbroken skin. First pass metabolism further reduces oral bioavailability. It is lipophilic, widely distributed in the body, strongly plasma protein bound and concentrated in sebum, stratum corneum and nail

plates. It is inactivated by metabolism and excreted in urine (80%) and faeces (20%); elimination t½ of 11–16 hr is prolonged to 10 days after repeated dosing.



Mechanism of Terbinafine

Side effects of oral terbinafine are gastric upset, rashes, taste disturbance. Some cases of hepatic dysfunction, haematological disorder and severe cutaneous reaction are reported. Enzyme inducers lower, and enzyme inhibitors raise its steady-state plasma levels. Terbinafine does not inhibit CYP450.

Topical terbinafine can cause erythema, itching, dryness, irritation, urticaria and rashes.

Use

Terbinafine applied topically as 1% cream or orally 250 mg OD is indicated in tinea pedis/ corporis/cruris/capitis and pityriasis versicolor; 2–6 weeks treatment is required according to the site. Onychomycosis is treated by 3–12 months oral therapy. Efficacy in toe nail infection is 60–80%, which is higher than griseofulvin and itraconazole.

It is less effective against cutaneous and mucosal candidiasis: 2–4 weeks oral therapy may be used as an alternative to fluconazole.

LAMISIL, SEBIFIN, DASKIL 250 mg tab, 1% topical cream. EXIFINE 125, 250 mg tabs, 1% cream; TERBIDERM 1% cream.

Other topical antifungals

All these drugs are used for dermatophytosis.

Tolnaftate

It is an effective drug for tinea cruris and tinea corporis—most cases respond in 1–3 weeks. Because of poor penetrability, it is less effective in tinea pedis and other hyper-keratinized lesions. For the same reason, it is ineffective in tinea capitis—involving scalp and tinea unguium—involving nails.

Symptomatic relief occurs early, but if applications are discontinued before the fungus bearing tissue is shed—relapses are common. Resistance does not occur. Salicylic acid can aid tolnaftate by keratolytic action.

Tolnaftate causes little irritation, but is inferior in efficacy to imidazoles. It is not effective in candidiasis or other types of superficial mycosis.

TINADERM, TINAVATE 1% lotion, TOLNADERM 1% cream.

Ciclopirox Olamine

It is a newer drug effective in tinea infections, pityriasis versicolor and dermal candidiasis: high cure rates are reported. It penetrates superficial layers and reaches hair roots but systemic absorption is negligible. Local tolerance without irritation is good. Sensitization occurs occasionally. Formulated as nail lacquer, it has been used in onychomycosis. Also used for vaginal candidiasis.

BATRAFEN 1% cream, 1% topical solution, 1% vaginal cream, OLAMIN 1% cream.

Benzoic Acid

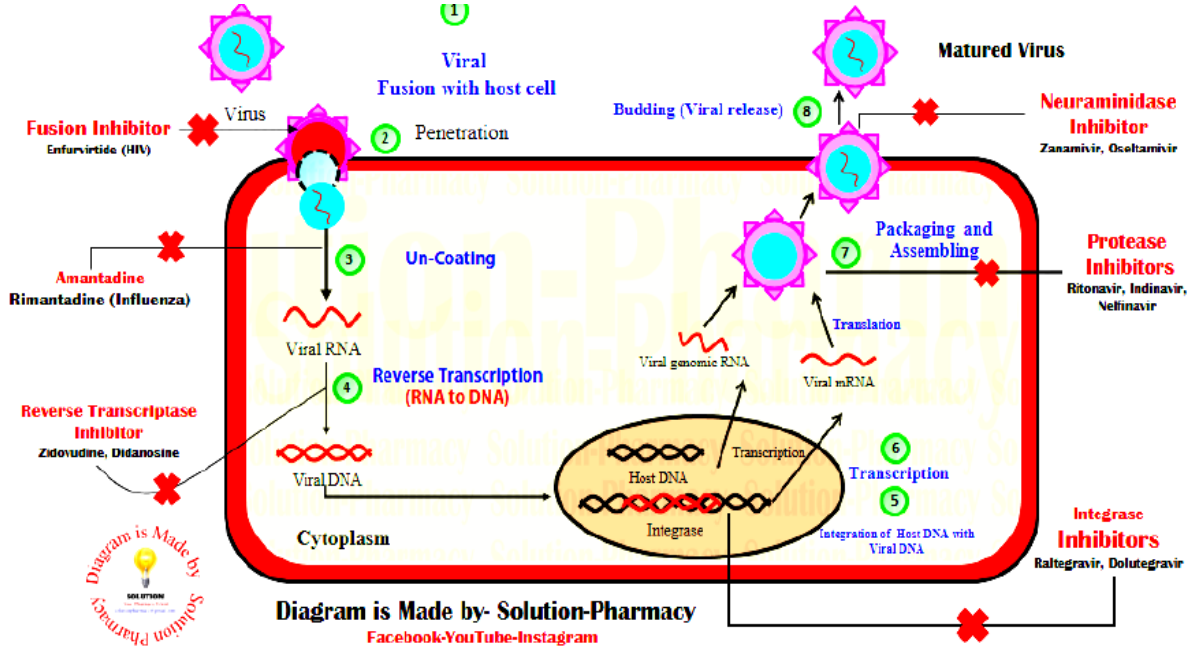
It has antifungal and antibacterial property in slightly acidic medium. It is fungistatic—weaker than tolnaftate; eradication of the fungus needs prolonged application till infected keratin is shed.

On hyperkeratotic lesions, it is used in combination with salicylic acid (as Whitfield's ointment: benzoic acid 5%, salicylic acid 3%). The latter, by its keratolytic action, helps to remove the infected tissue and promotes the penetration of benzoic acid into the lesion. Irritation and burning sensation is experienced by many patients.

RINGCUTTER ointment.

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. Drugs could also target virus specific steps like cell penetration, uncoating, reverse transcription, virus assembly or maturation. Another stumbling block is that in majority of acute infections viral replication is already at its peak when symptoms appear. To be effective, therefore, therapy has to be started in the incubation period, i.e. has to be prophylactic.



Classification

1. Anti-Herpes virus

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

2. Anti-Retrovirus

Nucleoside Reverse Transcriptase Inhibitors (NRTIS): Zidovudine (AZT), Didanosine, Zalcitabine*, Stavudine, Lamivudine, Abacavir

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIS): Nevirapine, Efavirenz, Delavirdine*

Protease Inhibitors: Ritonavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir*, Lopinavir

3. Anti-Influenza Virus: Amantadine, Rimantadine*

4. Nonselective Antiviral Drugs: Ribavirin, Lamivudine, Adefovir dipivoxil, Interferon α

* Not yet marketed in India.

Antiherpes Virus Drugs

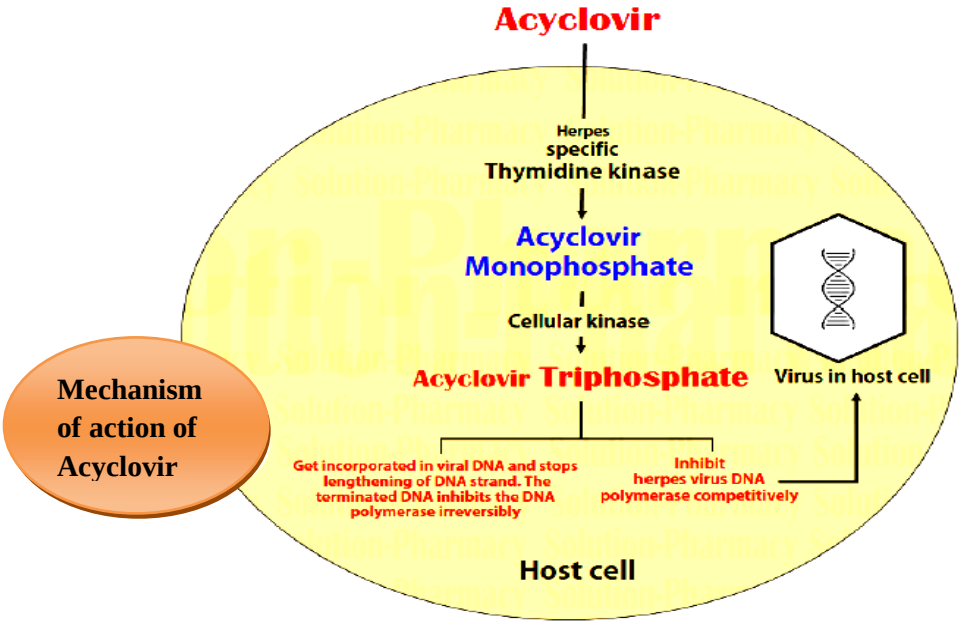
Idoxuridine

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 and clinical utility is limited to topical treatment of Herpes simplex Keratitis, labial and genital herpes. However, because of low virus selectivity, higher local toxicity and rapid development of viral resistance, it has been superseeded by acyclovir.

Trifluridine and vidarabine are other pyrimidine antimetabolites effective against H. simplex.

Acyclovir

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



Acyclovir is preferentially taken up by the virus infected cells. Because of selective generation of the active inhibitor in the virus infected cell and its greater inhibitory effect on viral DNA synthesis, acyclovir has low toxicity for host cells: a several hundredfold chemotherapeutic index has been noted.

Acyclovir is active only against herpes group of viruses; H. simplex type I is most sensitive followed by H. simplex type II > varicellazoster virus=EpsteinBarr virus; while cytomegalovirus (CMV) is practically not affected. Both H. simplex and varicellazoster virus have been found to develop resistance to acyclovir during therapy; the former primarily due to mutants deficient in thymidine kinase activity and the latter primarily by change in specificity of virus directed enzyme so that its affinity for acyclovir is decreased.

Pharmacokinetics

Only about 20% of an oral dose of acyclovir is absorbed. It is little plasma protein bound and is widely distributed attaining CSF concentration that is 50% of plasma concentration. It penetrates cornea well. Acyclovir is primarily excreted unchanged in urine, both by glomerular filtration and tubular secretion; plasma t½ is 2–3 hours. Renal impairment necessitates dose reduction.

Use

Acyclovir is effective in patients with normal as well as deficient immune status.

1. Genital Herpes simplex: Generally caused by type II virus; can be treated by topical, oral or parenteral acyclovir depending on stage and severity of disease.

Primary disease: 5% ointment is applied locally 6 times a day for 10 days. This is effective only if started early and in mild cases. Late and more severe cases should receive oral therapy (1 g/day in 5 divided doses or 400 mg TDS for 10 days) in addition to local therapy. Both local and oral therapies afford symptomatic relief and rapid healing of lesions, but do not prevent recurrences.

Recurrent disease: Topical therapy is totally ineffective. Response to oral treatment is slow and incomplete; severe cases may be treated parenterally—5 mg/kg i.v. infused over 1 hr, repeated 8 hourly for 10 days. Suppressive oral therapy with 400 mg BD has been shown to prevent recurrences as long as given. It is recommended to stop treatment after 1 yr and ascertain whether the patient is still having recurrences; if so restart treatment. After prolonged therapy frequency of recurrences is reduced. Continuous acyclovir prophylaxis is generally advocated in

patients with > 8 recurrences per year. However, suppressive therapy reduces, but does not toally prevent, disease transmission to sexual partner.

2. Mucocutaneous H. simplex is a type I virus disease, remains localized to lips and gums; does not usually require specific treatment, but acyclovir skin cream may provide some relief. Spreading lesions may be treated with 10 day oral acyclovir. Prophylactic oral therapy may prevent sun exposure related recurrences. The disease often gets disseminated in immunocompromised individuals and may be treated with oral or i.v. acyclovir (15 mg/kg/day) for 7 days, but recurrences are not prevented.

3. H. simplex encephalitis (type I virus): Acyclovir 10 to 20 mg/kg/8 hr i.v. for >10 days is the drug of choice. Treatment is effective only if started early: delay precludes salutary effect on mortality and neurological complications.

4. H. simplex (type I) keratitis: Acyclovir is equally effective as idoxuridine in superficial dendritic corneal ulcer, and may be better for deep stromal infections because of good corneal penetration. Though acyclovir eye ointment acts slower than idoxuridine eye drops, blindness can be prevented. The eye ointment should be applied 5 times daily till 3 days after healing.

5. Herpes zoster: The varicella-zoster virus is less susceptible to acyclovir. As such, higher doses are needed and it should be used only in immunodeficient individuals or in severe cases: 10 mg/ kg/8 hr i.v. for 7 days. Oral therapy with 800 mg 5 times daily is beneficial only if started early. It affords symptomatic relief and faster healing of lesions. Postherpetic neuralgia is not prevented, though its duration may be shortened. Acyclovir skin cream may be applied on herpetic ulcers.

6. Chickenpox: in patients with immunodeficiency and in neonate's only calls for specific therapy. Acyclovir (15 mg/kg/day i.v. × 7 days) is the drug of choice: reduces fever, eruptions, hastens healing and prevents visceral complications.

Oral acyclovir 400 mg 4 times a day for 7 days given during the incubation period may abort chickenpox in susceptible contacts.

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.

Dose-dependent decrease in g.f.r. is the most important toxicity; occurs especially in those with kidney disease; normalises on discontinuation of the drug.

Reversible neurological manifestations (tremors, lethargy, disorientation, hallucinations, convulsions and coma) have been ascribed to higher doses.No teratogenic potential has been noted. Valaciclovir It is an ester prodrug of acyclovir with improved oral bioavailability (55–70%) due to active transport by peptide transporters in the intestine. During passage through intestine and liver, it is completely converted to acyclovir in the first passage by esterases. Thus, higher plasma levels of acyclovir are obtained improving clinical efficacy in certain conditions; e.g. it is the drug of choice in herpes zoster. Valaciclovir is excreted in urine as acyclovir with a t½ of 3 hours.

Dose: For genital herpes simplex—first episode 0.5–1.0 g BD × 10 days; recurrent episode 0.5 g BD × 3 days; suppressive treatment 0.5 g OD × 6–12 months.

VALVIR 0.5 g, 1.0 g tabs.

Famciclovir

It is an ester prodrug of a guanine nucleoside analogue penciclovir, which has good oral bioavailability and prolonged intracellular t½ of the active triphosphate metabolite. Like acyclovir, it needs viral thymidine kinase for generation of the active DNA polymerase inhibitor. Famciclovir inhibits H. simplex, H. zoster but not acyclovir-resistant strains. Some activity against hepatitis B virus (HBV) has been noted. It is used as an alternative to acyclovir for genital or orolabial herpes and herpes zoster. Early treatment of herpes zoster reduces the duration of post herpetic neuralgia, but not its incidence.

Dose: Genital herpes (1st episode) 250 mg TDS × 5 days; recurrent cases 250 mg BD for up to 1 year. Herpes zoster and orolabial herpes 500 mg TDS for 7–10 days.

FAMTREX 250, 500 mg tabs.

Famciclovir is a less active alternative to lamivudine in chronic hepatitis B, but not in resistant cases. Side effects are headache, nausea, loose motions, itching, rashes and mental confusion.

Ganciclovir It is an analogue of acyclovir which is active against all herpes viruses including H. simplex, H. zoster,

EB virus and cytomegalovirus (CMV). It is more active than acyclovir against CMV. The active triphosphate metabolite of ganciclovir attains much higher concentrations inside CMV infected cells. The plasma t½ of ganciclovir is 2–4 hrs, but that of its triphosphate inside CMV infected

cells is > 24 hrs. These factors account for its high activity against CMV infections. CMV can develop ganciclovir resistance by mutation.

Systemic toxicity of ganciclovir is high (bone marrow depression, rash, fever, vomiting, neuropsychiatric disturbances) and use is restricted to severe CMV infections (pneumonia/colitis) in immunocompromised (AIDS, transplant recipient) patients. Intravenous infusion of 10 mg/kg/day has prevented blindness in AIDS patients with CMV retinitis. Ganciclovir therapy has been found to lower HBV titre in chronic hepatitis B.

Foscarnet It is a simple straight chain phosphonate unrelated to any nucleic acid precursor which inhibits viral DNA polymerase and reverse transcriptase. It is active against H. simplex (including strains resistant to acyclovir), CMV (including ganciclovir resistant ones) and HIV. Viral resistance to foscarnet is minimal. However, viral selectivity of foscarnet is low. Oral absorption is poor. Its t½ is 4–8 hours, and it is not metabolised.

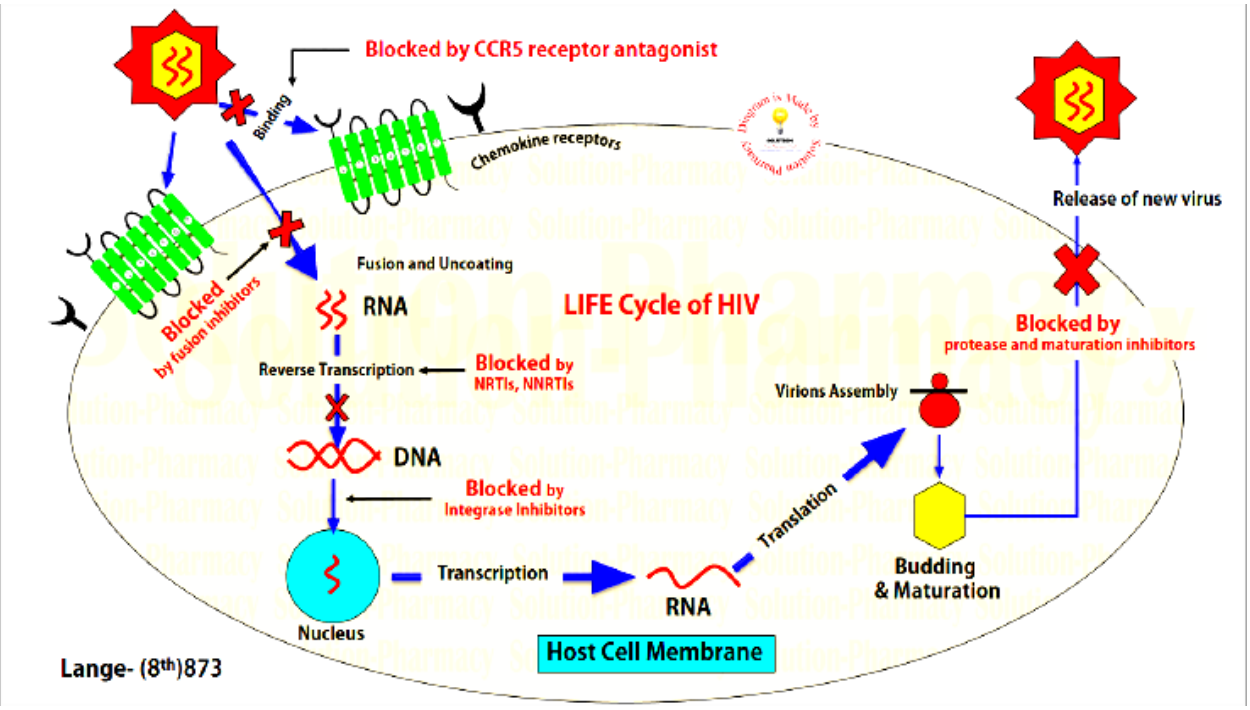
Toxicity of foscarnet is high: damages kidney— produces a renal diabetes like condition, acute renal failure can also occur. Anaemia, phlebitis, tremor, convulsions and other neurological as well as constitutional symptoms due to hypocalcaemia are frequent. Administered by i.v. infusion, foscarnet has been used for:

1. CMV retinitis and other CMV infections in AIDS patients; efficacy is similar to ganciclovir, but includes resistant cases.
2. Acyclovir-resistant mucocutaneous H. simplex type and varicella-zoster infections in AIDS patients. When used to treat associated CMV/H. simplex/Varicella-zoster infection in AIDS patient, it decreases HIV viral titre, but is not used primarily for HIV infections.

ANTI-RETROVIRUS DRUGS

These are drugs active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC), but do not cure the infection. The clinical efficacy of anti-retrovirus drugs is monitored primarily by plasma HIV-RNA assays and CD4 lymphocyte count carried out at regular intervals.

The first antiretrovirus (ARV) drug Zidovudine was developed in 1987. Over the past 20 years, 20 drugs belonging to 3 classes have been introduced and a large number of others are under development.

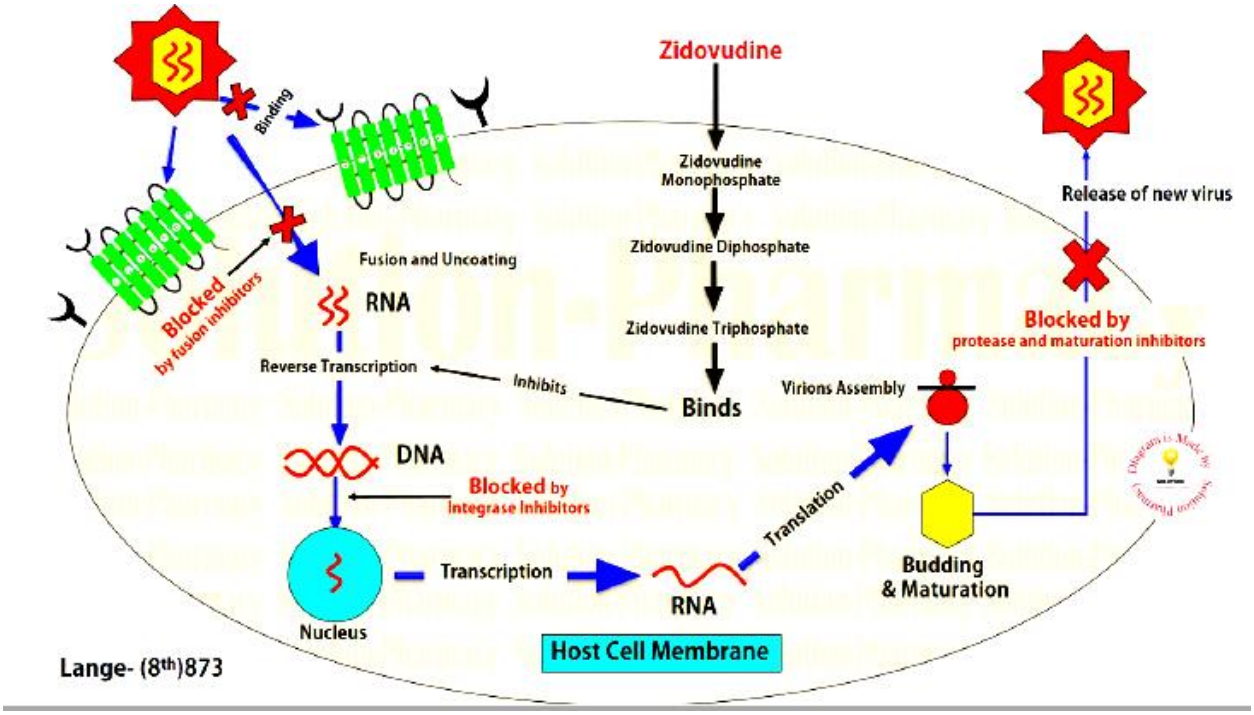


Nucleoside Reverse Transcriptase Inhibitors (NRTIS)

Zidovudine It is a thymidine analogue (azidothymidine, AZT), the prototype NRTI. After phosphorylation in the host cell—zidovudine triphosphate selectively inhibits viral reverse transcriptase (RNAdependent 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. This DNA translocates to the nucleus and is integrated with chromosomal DNA of the host cell, which then starts transcribing viral genomic RNA as well as viral mRNA. Under the direction of viral mRNA, viral regulatory and structural proteins

are produced. 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. It is effective only against retroviruses. Zidovudine itself gets incorporated into the growing viral DNA and terminates chain elongation. Resistance to AZT occurs by point mutations which alter reverse transcriptase enzyme. In the past, when AZT was used alone, >50% patients became nonresponsive to AZT within 1–2 years therapy due to growth of resistant mutants.



Pharmacokinetics

The oral absorption of AZT is rapid, but bioavailability is ~65%. It is quickly cleared by hepatic glucuronidation (t½ 1 hr); 15–20% of the unchanged drug along with the metabolite is excreted in urine. Plasma protein binding is 30% and CSF level is ~50% of that in plasma. It crosses placenta and is found in milk.

Dose Adults 300 mg BD; Children 180 mg/m2 (max 200 mg) 6–8 hourly.

RETROVIR, ZIDOVIR 100 mg cap, 300 mg tab, 50 mg/5 ml syr VIROZ, ZIDOMAX, ZYDOWIN 100 mg cap, 300 mg tab. (to be taken with plenty of water).

Adverse Effects Toxicity is mainly due to partial inhibition of cellular DNA polymerase. Anaemia and neutropenia are the most important and doserelated adverse effects.

Nausea, anorexia, abdominal pain, headache, insomnia and myalgia are common at the start of therapy but diminish later.

Myopathy, lactic acidosis, hepatomegaly, convulsions and encephalopathy are infrequent.

Interactions Paracetamol increases AZT toxicity, probably by competing for glucuronidation. Azole antifungals also inhibit AZT metabolism. Other nephrotoxic and myelosuppressive drugs and probenecid enhance toxicity. Stavudine and zidovudine exhibit mutual antagonism by competing for the same activation pathway.

Use

Zidovudine is used in HIV infected patients only in combination with at least 2 other ARV drugs. However, its efficacy as monotherapy in AIDS has been confirmed in the past. HIVRNA titer is reduced to undetectable levels and CD4 count increases progressively. Immune status is improved and opportunistic infections become less common. There is a sense of wellbeing and patients gain weight. AZT also reduces neurological manifestations of AIDS and new Kaposi's lesions do not appear. Mortality among AIDS patients is reduced. It has also been shown to slow the progression of HIV infection, including escalation of ARC to full blown AIDS. However, beneficial effects are limited from a few months to a couple of years after which progressively non-responsiveness develops.

AZT, along with one or two other ARV drugs is the standard choice for post exposure prophylaxis of HIV, as well as mother to offspring transmission.

Didanosine (ddI) It is a purine nucleoside analogue which after intracellular conversion to didanosine triphosphate competes with ATP for incorporation in viral DNA, inhibits HIV reverse transcriptase and terminates proviral DNA. Antiretroviral activity of didanosine is equivalent to AZT. Mutational resistance develops, but only few AZT resistant mutants are nonresponsive to didanosine also. Now it is used only in combination regimens.

Dose: 200 mg BD (for > 60 kg BW), 125 mg BD (< 50 kg BW) 1 hour before or 2 hour after meals.

DINEX EC, DDRETRO, VIROSINE DR 250 mg, 400 mg tabs.

Oral absorption of didanosine is somewhat erratic due to acid lability. It is metabolized as well as excreted unchanged; t½ 1 to 1.5 hr. In contrast to AZT, it does not cause myelosuppression. The major doserelated toxicity is peripheral neuropathy and rarely pancreatitis. Diarrhoea, abdominal pain and nausea are the side effects.

Stavudine (d4T) It is also a thymidine analogue which acts in the same way as AZT. By utilizing the same thymidine kinase for activation, AZT antagonises the effect of stavudine. Resistance to stavudine develops as for other NRTIs.

It is well absorbed orally and rapidly metabolized (t½ 1.5 hr). The antiHIV efficacy of stavudine is comparable to AZT, and it is used in combination regimens. Peripheral neuropathy, lipodystrophy and rarely pancreatitis are the serious toxicies which have restricted its use.

Dose: 40 mg BD (> 60 kg BW), 30 mg BD (< 60 kg BW) STAG, STAVIR, VIROSTAV 30, 40 mg caps.

Lamivudine (3TC) This deoxycytidine analogue is phosphorylated intracellularly and inhibits HIV reverse transcriptase as well as hepatitis B virus (HBV) DNA polymerase. Its incorporation into DNA results in chain termination. Most human DNA polymerases are not affected and systemic toxicity of 3TC is low. Point mutation in HIVreverse transcriptase and HBVDNA polymerase gives rise to rapid lamivudine resistance. Certain lamivudineresistant mutants become slow growing. Some crossresistance with ddI has been noted among HIV.

Oral bioavailability of 3TC is high and plasma t½ longer (6–8 hours). Intracellular t½ is still longer (> 12 hr). It is mainly excreted unchanged in urine.

Lamivudine is used in combination with other antiHIV drugs, and appears to be as effective as AZT. It is also frequently used for chronic hepatitis B. HBVDNA titre is markedly reduced and biochemical as well as histological indices of liver function improve. However, viral titres rise again after discontinuation. Even with continued medication HBV viraemia tends to return after 1 year due to emergence of resistant mutants.

Dose: For chronic hepatitis B—100 mg OD For HIV infection— 150 mg BD.

LAMIVIR 150 mg tab, 150 mg/ 5 ml soln; LAMIVIRHBV 100 mg tab; HEPTAVIR, LAMIDAC, LAMUVID, VIROLAM 100, 150 mg tabs;

Lamivudine is generally well tolerated. Side effects are few—headache, fatigue, nausea, anorexia, abdominal pain. Pancreatitis and neuropathy are rare. Hematological toxicity does not occur.

Abacavir (ABC)

This guanosine analogue is a potent ARV drug that acts after intracellular conversion to carbovir triphosphate. Resistance to ABC develops slowly, and it exhibits little cross resistance with other NRTIs. Its oral bioavailability is 80% and it is mainly eliminated by metabolism. The plasma t½

is 1–1.5 hour, but intracellular t½ of active metabolite is >12 hours. Hypersensitivity reactions such as rashes, fever, flulike symptoms are the major problems. Some fatalities have occurred when patients developing the reaction were given further doses of ABC. Avoidance of alcohol is advised.

Dose: 300 mg BD or 600 mg OD.

ABAVIR, ABAMUNE 300 mg tab.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIS)

Nevirapine (NVP) and Efavirenz (EFV) These are nucleoside unrelated compounds which directly inhibit HIV reverse transcriptase without the need for intracellular phosphorylation. Their locus of action on the enzyme is also different. They are more potent than AZT on HIV1, but do not inhibit HIV2. Viral resistance to these drugs develops by point mutation and cross resistance is common among different NNRTIs, but not with NRTIs or PIs.

Nevirapine is well absorbed orally and is extensively metabolized in liver with a t½ of 30 hours. Oral absorption of efavirenz is incomplete (50%), but t½ is longer (48 hours) and it is totally metabolized. Both NVP and EFV modestly induce CYP 3A4, 2D6 enzymes and enhance their own metabolism as well as that of other drugs.

The NNRTIs are indicated in combination regimens for HIV, and have succeeded in reducing HIVRNA levels when an earlier regimen has failed.

Nevirapine Dose 200 mg/day, may be increased later to 200 mg BD.

NEVIMUNE, NEVIVIR, NEVIPAN, NEVIRETRO 200 mg tab

Side effects

Rashes (commonest), nausea, headache are the usual side effects. Fever and rise in liver enzymes can occur. Nevirapine is potentially hepatotoxic. Avoid enzyme inducers (rifampin) and enzyme inhibitors (ketoconazole).

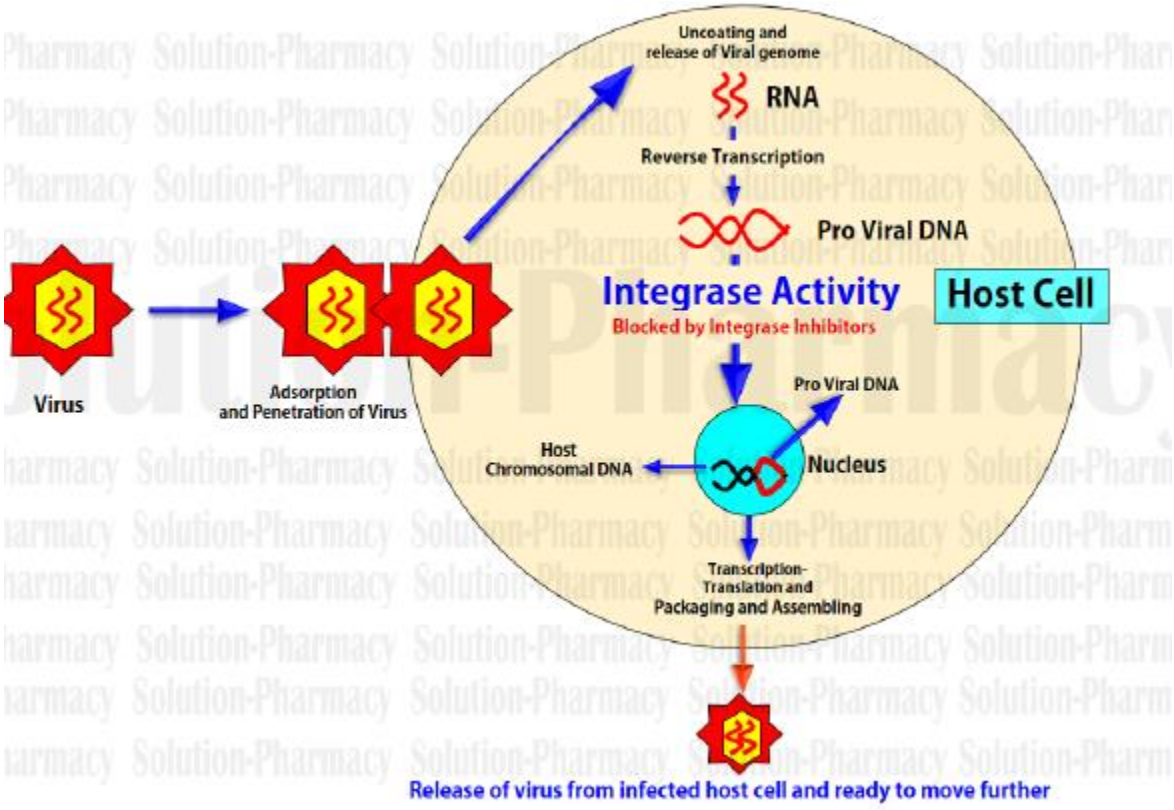
Efavirenz: Dose 600 mg OD on empty stomach. Side effects are headache, rashes, dizziness, insomnia and a variety of neuropsychiatric symptoms. It induces the metabolism of certain drugs and inhibits that of others.

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 pCh. No.s when the RNA genome acquires the core proteins and enzymes. Five protease inhibitors—Indinavir (IDV), Nelfinavir (NFV), Saquinavir (SQV), Ritonavir (RTV) and Lopinavir (in combination with ritonavir LPV/r) have been marketed in India for use against HIV. They bind to the protease molecule, interfere with its cleaving function, and are more effective viral inhibitors than AZT. Because they act at a late step of viral cycle, they are effective in both newly and chronically infected cells. Under their influence, HIV-infected cells produce immature noninfectious viral progeny—hence prevent further rounds of infection.

Oral bioavailability of PIs is variable (IDV and RTV ~65%, NFV >20%, SQV 15%) and their plasma t½ ranges from 2–5 hours. All are extensively metabolized by CYP3A4 and other CYP isoenzymes. All (especially ritonavir and lopinavir) are potent inhibitors of CYP3A4, while few other CYP isoenzymes are induced. The PIs interact with many drugs. Nelfinavir and ritonavir induce their own metabolism.



Monotherapy with one of these drugs in previously AZT treated patients reduced HIV viral levels, increased CD4 cell count and improved the clinical condition. However, viral resistance developed against the PIs over months due to selection of resistant mutants in a stepwise manner.

Combination of NRTIs with PIs has been found more effective than either drug given alone, and triple therapy is more effective than double therapy. Current recommendations are to use a PI in combination with two NRTIs or one NRTI + one NNRTI.

Because different PIs both inhibit and induce specific CYP isoenzymes to different extents, drug interactions with them are common and often unpredictable. Manufacturer's package inserts should be consulted while co-prescribing any other drug. Specifically, metabolism of PIs is induced by rifampin and other enzyme inducers rendering them ineffective. Another problem in their use is the large tablet load. In case of different PIs, 6–18 tablets are to be taken daily, some on empty stomach, but others with meals; and this has to go on for months and years. Patient acceptability and compliance are often low. One of the strategies adopted to reduce the dose of IDV, LPV and SQV is to combine them with a low and subtherapeutic dose (100 mg) of ritonavir. By reducing first pass metabolism, ritonavir increases the bioavailability of the companion PI. This 'boosted PI regimen' permits reduction in the number/frequency of tablets to be taken each day. Lopinavir is marketed only in combination with ritonavir. Nelfinavir is not to be combined with ritonavir.

The most prominent adverse effects of PIs are gastrointestinal intolerance, asthenia, headache, dizziness, limb and facial tingling, numbness and rashes. Of particular concern are lipodystrophy (abdominal obesity, buffalo hump with wasting of limbs and face) and dyslipidaemia (raised triglycerides and cholesterol) which may necessitate hypolipidaemic drugs. Diabetes may be exacerbated. Indinavir crystalises in urine and increases risk of urinary calculi.

Indinavir It is to be taken on empty stomach; g.i. intolerance is common; excess fluids must be consumed to avoid nephrolithiasis.

Dose: 800 mg TDS (BD if taken with 100 mg RTV).

Nelfinavir

It is to be taken with meals and bioavailability is erratic. Often produces diarrhoea and flatulence; clinical efficacy may be somewhat lower than other PIs.

Dose: 750 mg TDS; NELFIN, NELVIR, NEIVEX 250 mg tab.

Ritonavir

It is a potent PI; also a potent CYP3A4 inhibitor. Drug interactions, nausea, diarrhoea, paresthesias, fatigue and lipid abnormalities are prominent.

Dose: 600 mg BD, to be taken with food.

RITOMUNE, RITOMAX 100 mg cap; RITOVIR 250 mg tab.

Saquinavir

Two types of formulations (hard gel and soft gel capsules) with differing, but low oral bioavailability have been produced. The tablet load is large and side effects are frequent; photosensitivity can occur. It is a weak inhibitor of CYP3A4.

Dose: 1200 mg TDS on full stomach; 1000 mg BD (with RTV 100 mg).

Lopinavir

It is available only in combination with RTV to improve bioavailability. Diarrhoea, abdominal pain, nausea and dyslipidaemias are more common.

Dose: 400 mg (with ritonavir 100 mg) BD with food.

FUSION INHIBITOR

Enfuvirtide This recently introduced HIV-derived synthetic peptide acts by binding to HIV1 envelope glycoprotein (gp41) and preventing fusion of viral and cellular membranes. Entry of the virus into the cell is thus blocked. It is not active against HIV2. No cross resistance with other classes of ARV drugs occur. Administered s.c., it is used as add on drug to an optimized regimen in patients who have failed many earlier regimens.

Some Antiretroviral Combinations

1. Lamivudine 150 mg + Zidovudine 300 mg tab (1 tab BD); COMBIVIR, CYTOCOM, DUOVIR, LAMUZID tab.

2. Lamivudine 150 mg + Stavudine 30 mg or 40 mg tab (1 tab BD); LAMIVIRS, LAMOSTAD, VIROLIS tab.

3. Lamivudine 150 mg + Zidovudine 300 mg + Nevirapine 200 mg tab (1 tab BD); DUOVIRN, CYTOCOMN, NEXIVIRZ.

4. Lamivudine 150 mg + Stavudine 30 mg or 40 mg + Nevirapine 200 mg tab (1 tab BD); LAMOSTADN, TROMUNE, VIROLANS.

5. Lamivudine 150 mg + Zidovudine 300 mg 2 tab and Efavirenz 600 mg 1 tab kit; CYTOCOME kit.

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. A protein designated 'M2' which acts as an ion channel has been identified as one of its targets of action. Resistance to amantadine develops by mutation causing amino acid substitutions in the M2 protein. Amantadine is well absorbed orally and excreted unchanged in urine over 2–3 days (t½ 16 hr).

Adverse effects

Generally well tolerated; nausea, anorexia, insomnia, dizziness, nightmares, lack of mental concentration, rarely hallucinations have been reported. Ankle edema occurs due to local vasoconstriction.

Uses

1. Prophylaxis of influenza A2 during an epidemic or seasonal, especially in high risk patients. It does not interfere with antibody response to influenza vaccination; both may be given together. If the vaccine is given, amantadine can be stopped after 2 weeks. It is quite virus specific: influenza B is unaffected.
2. Treatment of influenzal (A2) illness: a modest therapeutic effect (reduction in fever, congestion and cough) occurs if the drug is given quickly after the symptoms appear. A 5 day treatment is advised.
3. Parkinsonism

Dose: 100 mg BD, elderly—half dose, children 5 mg/kg/ day; AMANTREL, NEAMAN 100 mg tab.

Contraindications: epilepsy and other CNS disease; gastric ulcer, pregnancy.

Rimantadine

It is a more potent, long-acting (t½ 30 hr) and better tolerated congener of amantadine. Oral bioavailability is higher and it is largely metabolized. Dose and clinical application is similar to amantadine. Amantadine resistant virus is resistant to rimantadine as well.

Oseltamivir (TAMIFLU)

This recently developed anti-influenza virus drug has a broader-spectrum activity covering influenza A (amantadine sensitive as well as resistant), influenza B and avian-influenza (bird flu) H5N1 and other strains. It is an ester prodrug that is rapidly and nearly completely hydrolysed during absorption in intestine and by liver to the active form oseltamivir carboxylate. The active metabolite is not further metabolized and is excreted by the kidney with a t½ of 6–10 hours. It acts by inhibiting influenza virus neuraminidase enzyme which is needed for release of progeny virions from the infected cell. Spread of the virus in the body is thus checked.

Oseltamivir is indicated both for prophylaxis as well as treatment of influenza A, B and bird flu. Started at the onset of symptoms, it reduces the severity and duration illness. However, considering the cost, and to preserve its efficacy, use should be restricted to high risk subjects.

Dose: therapeutic 75 mg oral BD for 5 days; prophylactic 75 mg OD.

Side effects

Nausea and abdominal pain due to gastric irritation (reduced by taking the drug with food), headache, diarrhoea, cough and insomnia. Skin reactions have been reported.

Zanamivir (RELENZA)

Another influenza virus (A, B, avian strains) neuraminidase inhibitor that is administered by inhalation as a powder due to very low oral bioavailability. Small amount that is absorbed after inhalation is excreted by the kidney with a t½ of 2–5 hours. The mechanism of action, clinical utility and efficacy of zanamivir are similar to that of oseltamivir. Though viral resistance against both is not clinically significant, some variants resistant to oseltamivir remain sensitive to zanamivir and vice versa.

Dose: 10 mg through breath actuated inhaler, BD × 5 days for treatment, and OD for prophylaxis.

The inhaled powder can induce bronchospasm in some individuals. This may be severe in asthmatics; contraindicated in them. Headache, dizziness, nausea and rashes are mild and infrequent side effects.

Nonselective Antiviral Drugs

Ribavirin

This purine nucleoside analogue has broadspectrum antiviral activity, including that against influenza A and B, respiratory syncytial virus and many other DNA and double stranded RNA viruses. Its mono and triphosphate derivatives generated intracellularly inhibit GTP and viral RNA synthesis and have other sites of action as well. No viral resistance to ribavirin has yet been observed.

Oral bioavailability of ribavirin is ~50%. It is partly metabolized and eliminated in a multiexponential manner; accumulates in the body and persists months after discontinuation.

Administered orally or i.v. ribavirin has been used in influenza A/B and measles in immunosuppressed patients as well as for herpes virus infections, acute hepatitis, but is not a first line drug for any of these. Combined with interferon α, ribavirin is the standard treatment for chronic hepatitis C. Nebulized ribavirin has been used for respiratory syncytial virus broncholitis in infants and children, particularly those with congenital heart disease, prematurity or other high risk conditions. It has also shown efficacy in some rare viral infections.

Dose: 200 mg QID (children 10 mg/kg/day).

Prominent toxic effects are anaemia, haemolysis, CNS and g.i. symptoms. It is also teratogenic. The aerosol can cause irritation of mucosae and bronchospasm.

Adefovir dipivoxil

It is the diester prodrug of AMP analogue adefovir which is active against hepatitis B virus (HBV) and some other DNA viruses. Esterases in the intestine and liver release the active drug during absorption to attain oral bioavailability of ~60% in terms of adefovir, which is then distributed in whole body water. On entering cells, adefovir (a monophosphate) is phosphorylated to the diphosphate which has high affinity for HBV DNA polymerase. This enzyme is inhibited and adefovir itself gets incorporated in the viral DNA resulting in termination of the DNA chain. While plasma t½ of adefovir is ~7 hours (due to renal excretion), intracellular t½ of the diphosphate is upto 18 hours.

Adefovir is indicated in chronic hepatitis B, including lamivudineresistant cases and those having concurrent HIV infection. There is no cross resistance between adefovir and lamivudine. Clinical, biochemical (liver function tests), histological, serological and virological response

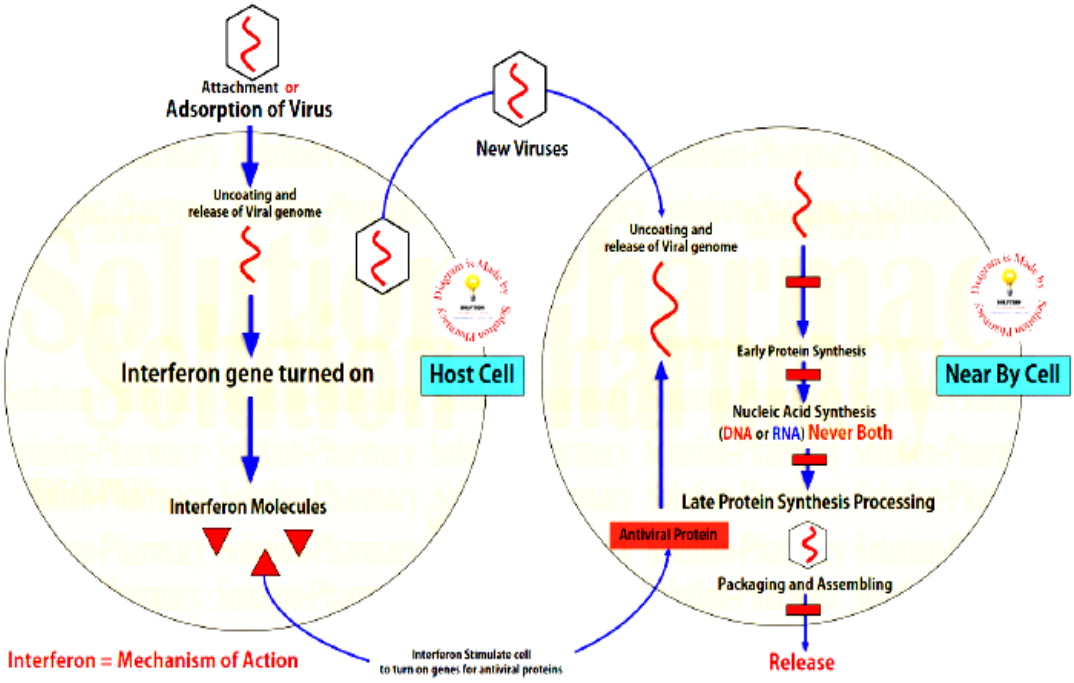
occurs in nearly 50% patients within 1 year. More cases respond with continued treatment. The optimum duration of treatment is uncertain at present.

Dose: 10 mg/day; ADESERA, ADFOVIR 10 mg tab.

At 10 mg/day dose adefovir is well tolerated. Side effects are sore throat, headache, weakness, abdominal pain and flu syndrome. Nephrotoxicity occurs at higher doses and in those with preexisting renal insufficiency. Lactic acidosis is a risk in patients receiving antiHIV drugs.

Interferon α

Interferons are low molecular weight glycoprotein cytokines produced by host cells in response to viral infections and some other inducers. They have nonspecific antiviral as well as other complex effects on immunity and cell proliferation. Interferons bind to specific cell surface receptors and affect viral replication at multiple steps: viral penetration, synthesis of viral mRNA, assembly of viral particles and their release, but the most widespread effect is direct or indirect suppression of viral protein synthesis, i.e. inhibition of translation.



Interferon receptors are JAKSTAT tyrosine protein kinase receptors which on activation phosphorylate cellular proteins. These then migrate to the nucleus and induce transcription of ‘interferon-induced-proteins’ which exert antiviral effects.

Interferons inhibit many RNA and DNA viruses, but they are host specific: those produced by another species have poor activity in man. Three types of human interferons (α, β and γ) have been produced by recombinant DNA technology. Only interferon α2A and α2B have antiviral activity.

After i.m./s.c. injection, interferon is distributed to tissues and is degraded; may be detectable in plasma for 24 hours. However, cellular effects are longer lasting and it is generally administered thrice weekly. Complexed with polyethylene glycol (pegylated interferon), it is absorbed more slowly—exerts more sustained effects, permiting weekly administration and improving clinical efficacy.

Uses; Chronic hepatitis B and C: Interferon causes disappearance of HBVDNA from plasma and improvement in liver function tests/histology in nearly half of the patients. High doses (10 MU) injected thrice weekly for 6 months often produce prolonged remission, but relapses do occur. The newer pegylated interferons produce better and more sustained responses. Addition of ribavirin has the potential to further decrease chances of relapse.

1 AIDS-related Kaposi's sarcoma (but not to treat HIV as such). However, interferon accentuates haematological toxicity of zidovudine.

2. Condyloma acuminata caused by papilloma virus is usually treated with topical podophyllin. Intralesional interferon injection may be used in refractory cases.

3. H. simplex, H. zoster and CMV infections in immunocompromised patients: interferon is inferior to acyclovir/ganciclovir; may be used as second line/adjuvant drug.

4. Rhinoviral cold: intranasal interferon is prophylactic, but not beneficial in those already having cold.Interferons are also used in chronic myelogenous leukaemia and multiple myeloma.

Interferon is not effective orally. Clinical utility of s.c. or i.m. injected interferon is limited by substantial adverse effects.

Adverse Effects

Flulike symptoms—fatigue, aches and pains, malaise, fever, dizziness, anorexia, taste and visual disturbances: develop a few hours after each injection, but become milder later.

Neurotoxicity—numbness, neuropathy, tremor, sleepiness, rarely convulsions. Myelosuppression (dose limiting)—neutropenia, thrombocytopenia.

Thyroid dysfunction (hypo as well as hyper). Hypotension, transient arrhythmias, alopecia and liver dysfunction.

ANTIMALARIAL DRUGS

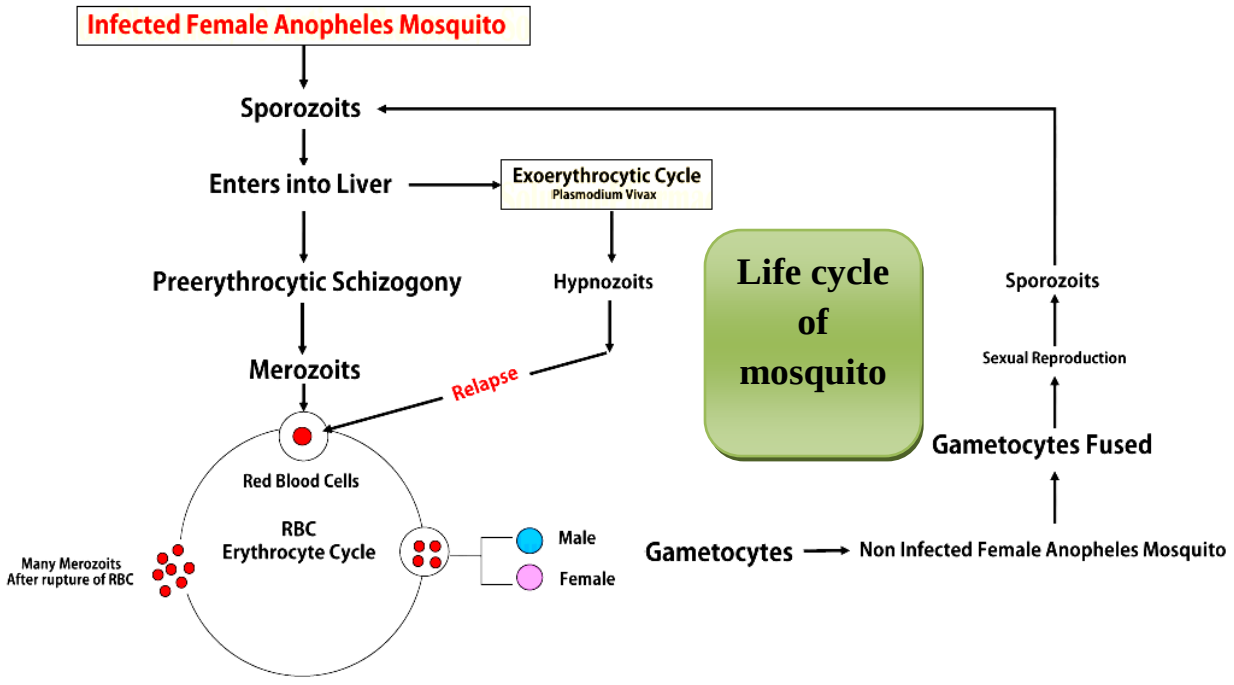
These are drugs used for prophylaxis, treatment and prevention of relapses of malaria.

Malaria, caused by 4 species of the protozoal parasite Plasmodium, is endemic in most parts of India and other tropical countries. It is one of the major health problems. As per latest WHO estimates there are 300–500 million new clinical cases globally and >1 million deaths occur due to malaria each year, 90% of which are in Africa. In India the National Malaria Eradication Programme (NMEP), started in 1958, achieved near complete disappearance of the disease in 1960s (from 75 million cases in 1950s to 0.1 million cases in 1960s). However, due to the development of insecticide resistance among mosquitoes and other factors, it staged a comeback in the mid 1970s (6.47 million cases in 1976), and continues to prevail in endemic/subendemic proportions in different areas. Conceding that eradication of malaria is not possible, NMEP was renamed National Antimalaria Programme (NAMP). Its scope has now been widened to include other vector borne diseases, and it is called 'National vector borne diseases control programme' (NVBDCP). For the year 2005, the NVBDCP has reported 1.8 million slide proven malaria cases in India, out of which ~ 44% were falciparum malaria with 963 deaths. The WHO estimates that actual number of malaria cases in India is 6 times more, i.e. ~12 million.

The bark of Cinchona tree, growing in Peru, was introduced in Europe in the early 17th century as a cure for fevers. Later it was realized to be a specific remedy for malaria. Quinine, isolated from Cinchona bark in 1820, replaced the crude preparation and continued to be the major antimalarial drug till 1942. The world's supply of Cinchona bark for producing quinine was met by Java and neighbouring countries. This was cut off from the Germans during World War I and from the Allies during World War II. Due to enormous military importance of malaria and its treatment, intense activity was initiated for the development of antimalarial drugs. Mepacrine was produced in Germany in 1926 and extensively field tested by the Allies during World War II. Chloroquine was produced in USA soon after as a less toxic alternative to mepacrine. It had already been synthesized and used by Germans in 1934 as 'Resochin'. Proguanil was introduced in 1945 by the British as a well tolerated clinical curative.

None of the above drugs were found to be capable of preventing relapses in vivax malaria. Pamaquine was the first 8aminoquinoline to be tested in Germany in the 1920s. However, no attention was paid to it because of its poor schizontocide action. This class of drugs was retested

during World War II as radical curative and Primaquine emerged as the most desirable drug. Pyrimethamine was produced in 1951 under a planned postwar research programme for antimalarial drugs. The important additions of the recent years are Mefloquine, Artemisinin and its derivatives/congeners, pyronaridine and few other synthetic compounds for resistant falciparum malaria.



Classification

1. 4-Aminoquinolines: Chloroquine, Amodiaquine, Piperaquine.

2. Quinoline-methanol: Mefloquine.

3. Cinchona alkaloid: Quinine, Quinidine

4. Biguanides: Proguanil (Chloroguanide), Chlorproguanil

5. Diaminopyrimidines: Pyrimethamine

6. 8-Aminoquinoline: Primaquine, Bulaquine

7. Sulfonamides and sulfone: Sulfadoxine, Sulfamethopyrazine, Dapsone

8. Tetracyclines: Tetracycline, Doxycycline

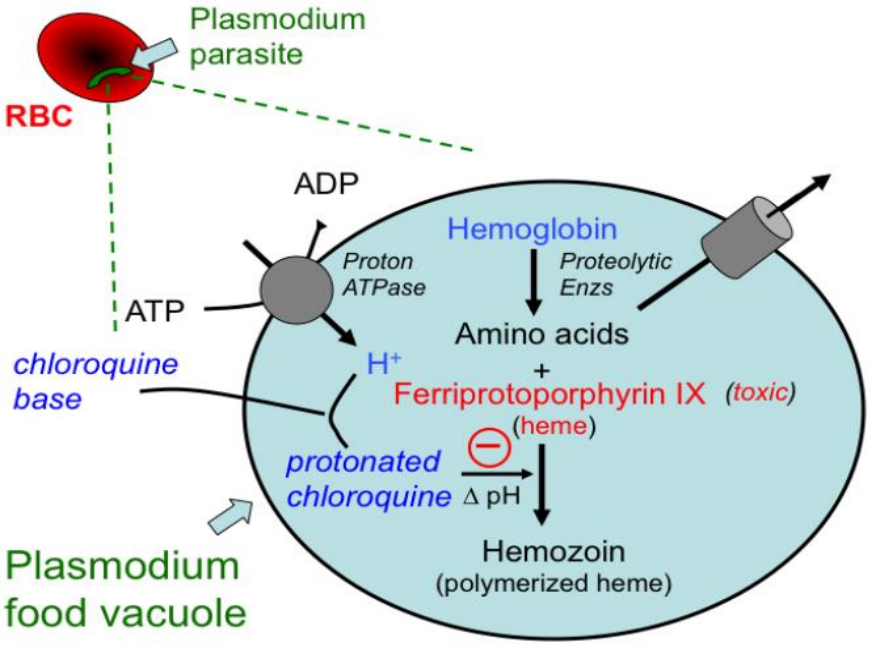
9. Sesquiterpine Lactones : Artesunate, Artemether, Arteether

10.Amino Alcohols: Halofantrine, Lumefantrine

11. Mannich Base: Pyronaridine

12. Naphthoquinone: Atovaquone

Antimalarials that act on erythrocytic schizogony are called erythrocytic schizontocides, those that act on preerythrocytic as well as exoerythrocytic (P. vivax) stages in liver are called tissue schizontocides, while those which kill gametocytes in blood are called gametocides. Antimalarial drugs exhibit considerable stage selectivity of action (see Table 59.1). Antimalarial therapy is given in the following forms.



Mechanism of action of anti-malarial drugs

1. Causal Prophylaxis

The preerythrocytic phase (in liver), which is the cause of malarial infection and clinical attacks, is the target for this purpose.

Proguanil is a causal prophylactic, primarily for P. falciparum, but is not employed routinely because it has to be given daily and is not very effective against P. vivax.

Primaquine is a causal prophylactic for all species of malaria, but has not been used in mass programmes, because of its toxic potential. Trials in Kenya and Irian Jaya have successfully used primaquine 0.5 mg/kg daily against both P. falciparum and P. vivax in subjects with normal

G6PD levels. The CDC (USA) recommends it only for subjects who cannot take any other prophylactic drug.

2. Suppressive Prophylaxis

The schizontocides which suppress the erythrocytic phase and thus attacks of malarial fever can be used as prophylactics. Though the exoerythrocytic phase in case of vivax and other relapsing malarias continues, clinical disease does not appear.

Chloroquine 300 mg (base*) or 5 mg/kg weekly. In travellers, start one week before with a loading dose of 10 mg/kg and continue till one month after return from endemic area. The last dose should be 25 mg/kg over 3 days along with primaquine 15 mg/day for 14 days. It should not be given for > 3 yr for fear of cumulative toxicity.

Proguanil 200 mg daily with chloroquine 300 mg weekly affords substantial protection against moderately chloroquine-resistant P. falciparum, but less than that afforded by mefloquine. This has been successfully used in Africa. In India NVBDCP recommends it for visitors to areas with chloroquine resistance.

Mefloquine 250 mg weekly till 4 weeks after return from endemic area has been used for areas where chloroquine-resistant P. falciparum is prevalent. In India use of mefloquine for prophylaxis is not allowed among residents, but may be used by travellers.

Doxycycline 100 mg daily starting day before travel and taken till 4 weeks after return from endemic area for chloroquine resistant P. falciparum, is an alternative regimen for individuals unable to take mefloquine. It is contraindicated in pregnant women and children < 8 yr.

Chemoprophylaxis of malaria should be limited to short-term use in special risk groups, such as — nonimmune travellers, nonimmune persons living in endemic areas for fixed periods (army units, labour forces) and pregnant women (falciparum malaria has serious consequences in the pregnant). Start prophylaxis after 1st trimester and continue till 1 month after delivery.

3. Clinical Cure

The erythrocytic schizontocides are used to terminate an episode of malarial fever. The available drugs can be divided into:

Fast-Acting High-Efficacy Drugs: Chloroquine, amodiaquine, quinine, mefloquine, halofantrine, lumefantrine, atovaquone, artemisinin; they can be used singly to treat attacks of malarial fever.Slow-Acting Low-Efficacy Drugs: Proguanil, pyrimethamine, sulfonamides, tetracyclines; they are used only in combination for clinical cure.

The faster acting drugs are preferred, particularly in falciparum malaria where delay in treatment may result in death even if the parasites are cleared from blood by the drug. The exoerythrocytic phase of vivax and ovale persists which can cause relapses subsequently without reinfection. Thus, the above drugs are radical curatives for falciparum, but not for relapsing malaria. Recrudescences occur in falciparum infection if the blood is not totally cleared of the parasites by the drug.

The drugs and regimens used for uncomplicated falciparum and vivax malaria are detailed in the box. Only oral drugs are used for uncomplicated malaria.

Treatment of Uncomplicated Malaria

Vivax malaria

1. Chloroquine 600 mg (10 mg/kg) followed by 300 mg (5 mg/kg) after 8 hours and then for next 2 days (total 25 mg/kg over 3 days) + Primaquine 15 mg (0.25 mg/kg) daily × 14 days

In occasional case of chloroquine resistance

2. Quinine 600 mg (10 mg/kg) 8 hourly × 7 days + Doxycycline 100 mg daily × 7 days + Primaquine (as abov)

Chloroquine-sensitive Falciparum malaria

1. Chloroquine (as above) + Primaquine 45 mg (0.75 mg/kg) single dose (as gametocidal)

In case of intolerance to chloroquine

2. Sulfadoxine 1500 mg (25 mg/kg) + Pyrimethamine 75 mg (1.25 mg/kg) single dose + Primaquine 0.75 mg/kg single dose

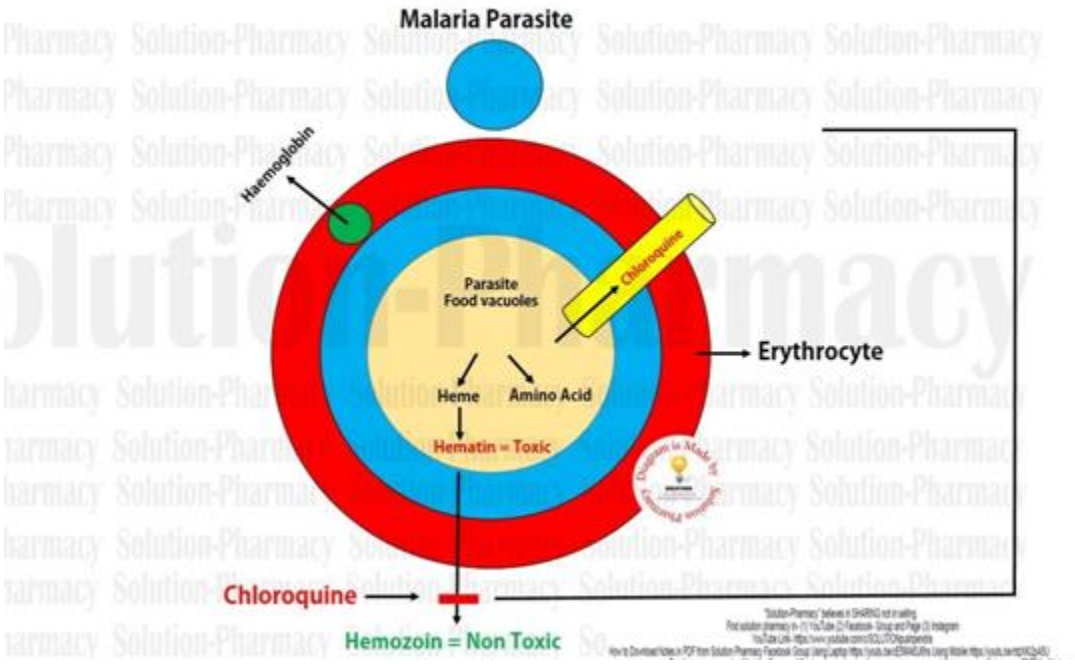
Chloroquine-Resistant Falciparum malaria

1.* Artesunate 100 mg BD (4 mg/kg/day) × 3 days + Sulfadoxine# 1500 mg (25 mg/kg) + Pyrimethamine 75 mg (1.25 mg/kg) single dose or

2. Artesunate 100 mg BD (4 mg/kg/day) × 3 days + Mefloquine# 750 mg (15 mg/kg) on 2nd day and 500 mg (10 mg/kg) on 3rd day. or

3. Artemether 80 mg + Lumefantrine 480 mg twice daily × 3 days (child 25–35 kg BW ¾ dose; 15–25 kg BW ½ dose; 5–15 kg BW ¼ dose) or

4. $ Quinine 600 mg (10 mg/kg) 8 hourly × 7 days + Doxycycline 100 mg daily × 7 days.



Mechanism of action of chloroquine

***First line ACT under NVBDCP, $Second line drug under NVBDCP, #Sulfadoxine-pyrimethamine (S/P) alone and mefloquine alone are also used, but should preferably be combined with artesunate**.

Relapses of vivax/ovale malaria are treated in the same way as the primary attack because the parasite remains sensitive to the drug. Recrudescence in falciparum malaria indicates resistant infection: should be treated with an alternative drug as per local needs.

Severe and Complicated Falciparum malaria

This includes P. falciparum infection attended by any one or more of—hyperparasitaemia, hyperpyrexia, fluid and electrolyte imbalance, acidosis, hypoglycaemia, prostration, cardiovascular collapse, jaundice, severe anaemia, spontaneous bleeding, pulmonary edema, haemoglobinuria, black water fever, renal failure and cerebral malaria. Parenteral (i.m./i.v.) drugs have to be used; oral drugs may be substituted when the condition improves. Drugs and regimens employed are detailed below.

Treatment of Severe and Complicated Falciparum Malaria*

Artesunate: 2.4 mg/kg i.v. or i.m., followed by 2.4 mg/kg after 12 and 24 hours, and then once daily for 7 days. Switchover to 3 day oral ACT inbetween whenever the patient can take and tolerate oral medication. or

Artemether: 3.2 mg/kg i.m. on the 1st day, followed by 1.6 mg/kg daily for 7 days. Switchover to 3 day oral ACT inbetween whenever the patient is able to take oral medication. or

4. Arteether: 3.2 mg/kg i.m. on the 1st day, followed by 1.6 mg/kg daily for the next 4 days. Switchover to 3 day oral ACT inbetween whenever the patient is able to take oral medication. or

5. Quinine diHCl: 20 mg/kg (loading dose) diluted in 10 ml/kg 5% dextrose/dextrosesaline and infused i.v. over 4 hours, followed by 10 mg/kg (maintenance dose) i.v. infusion over 4 hours (in adults) or 2 hours (in children) every 8 hours, untill patient can swallow. Switchover to oral quinine 10 mg/kg 8 hourly to complete the 7 day course.

(Volume of fluid for i.v. infusion of quinine should be reduced in patients with volume overload/pulmonary edema).

4. Radical Cure

Drugs which attack the exoerythrocytic stage (hypnozoites) given together with a clinical curative achieve total eradication of the parasite from the patient's body. A radical curative is needed in relapsing malaria, while in falciparum malaria — adequate treatment of clinical attack leaves no parasite in the body (there is no secondary exoerythrocytic tissue phase).

Drug of choice for radical cure of vivax and ovale malaria is:

Primaquine 15 mg daily for 14 days. A shorter course of 5 days used earlier by NAMP in India has been found inadequate, and is no longer recommended. This treatment should be given concurrently with or immediately after chloroquine/other schizontocide only to individuals who test negative for G6PD deficiency.

There is no point in antirelapse treatment in highly endemic areas, because chances of reinfection would be high; a subsequent attack may be erroneously labelled as failure of radical cure. Antirelapse treatment of vivax malaria should be restricted to:

- Areas with very low level of transmission (where only sporadic cases occur).
- Patients treated during an epidemic along with effective vector control measures to cut down transmission.

5. Gametocidal

This refers to elimination of the male and female gametes of Plasmodia formed in the patient's blood. Gametocidal action is of no benefit to the patient being treated, but will reduce the transmission to mosquito.

Primaquine and artemisinins are gametocidal to all species of Plasmodia, while chloroquine and quinine are active against vivax but not falciparum gametes. Gametes exposesd to proguanil or pyrimethamine fail to carry on the life cyle normally in the mosquito. Adequate control of clinical attacks will reduce formation of gametes.

A single 45 mg (0.75 mg/kg) dose of primaquine is employed immediately after clinical cure of falciparum malaria to kill the gametes and cut down transmission to mosquito. This is not necessary when an artemisinin is used for clinical cure.

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. However, it has no effect on pre and exoerythrocytic phases of the parasite—does not prevent relapses in vivax and ovale malaria.

Mechanism of action

The mechanism of action of chloroquine is not completely known. It is actively concentrated by 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. Clumping of pigment and changes in parasite membranes follow. Other related antimalarials like quinine, mefloquine, lumefantrine appear to act in an analogous manner.

Chloroquine-resistance among P.vivax has been slow in developing. However, P. falciparum has acquired significant resistance and resistant strains have become prevalent especially in eastern part of India, South East Asia, Africa and South America. Some of these have also acquired resistance to proguanil and S/P (multidrug resistant strains). Because P. falciparum produces the

more severe forms of malaria with considerable mortality, emergence of such strains is the biggest threat to the antimalaria programmes, and is the focus of attention for current research efforts.

Chloroquine-resistance among P. falciparum is now widespread in India, but is mostly low grade (RI or late clinical failure). Higher grade resistance (RII, RIII or early treatment failure) averaged 8.7% over the period 1978–2002. The largest number of chloroquine-failures are reported from the North eastern part of India where 24–83% P. falciparum cases are resistant to chloroquine, and some of these (particularly in areas bordering Myanmar) are multidrug resistant. In 73 districts (mostly North eastern states, Orissa, Karnataka, Gujarat) the NVBDCP has switched over to the 2nd line treatment (sulfa-pyrimethamine ACT), due to high rates of chloroquine resistance.

Resistance in P. falciparum is associated with a decreased ability of the parasite to accumulate chloroquine. Verapamil, a Ca2+ channel blocker, has been found to restore both the chloroquine concentrating ability as well as sensitivity to this drug.

A chloroquine transporter glycoprotein encoded by the Pf mdr1 gene appears to play a role in chloroquine-resistance of P. falciparum but not that of P. vivax. However, other mechanisms of resistance also appear to be involved.

Other Actions: Chloroquine is active against Entamoeba histolytica and Giardia lamblia also.

It has anti-inflammatory, local irritant and local anaesthetic (on injection), weak smooth muscle relaxant, antihistaminic and antiarrhythmic properties.

Pharmacokinetics

Oral absorption of chloroquine is excellent. About 50% gets bound in the plasma. It has high affinity for melanin and nuclear chromatin: gets tightly bound to these tissue constituents and is concentrated in liver, spleen, kidney, lungs (several hundredfold), skin, leucocytes and some other tissues. Its selective accumulation in retina is responsible for the ocular toxicity seen with prolonged use. Absorption after i.m. injection is also good.

Chloroquine is partly metabolized by liver and slowly excreted in urine. The early plasma t½ varies from 3–10 days. Because of tight tissue binding, small amounts persist in the body with a terminal t½ of 1–2 months.

Adverse Effects

- ✓ Toxicity of chloroquine is low, but side effects are frequent and unpleasant: nausea, vomiting, anorexia, uncontrollable itching, epigastric pain, uneasiness, difficulty in accommodation and headache. Suppressive doses have been safely given for 3 years.
- ✓ Parenteral administration can cause hypotension, cardiac depression, arrhythmias and CNS toxicity including convulsions (more likely in children).
- ✓ Prolonged use of high doses (as needed for rheumatoid arthritis, DLE, etc.) may cause loss of vision due to retinal damage. Corneal deposits may also occur and affect vision, but are reversible on discontinuation.
- ✓ Loss of hearing, rashes, photoallergy, mental disturbances, myopathy and graying of hair can occur on long-term use.

Chloroquine can be used for treatment of malaria during pregnancy: no abortifacient or teratogenic effects have been reported.

Caution is to be exercised in the presence of liver damage, severe g.i., neurological and haematological diseases. Attacks of seizures, porphyria and psoriasis may be precipitated.

Chloroquine should not be co-administered with mefloquine, amiodarone and other antiarrhythmics.

Uses

- Chloroquine is the drug of choice for clinical cure and suppressive prophylaxis of all types of malaria, except that caused by resistant P. falciparum. Uncomplicated cases are treated orally, while i.v. chloroquine is rarely employed for complicated/cerebral malaria in adults. It completely cures sensitive falciparum disease, but relapses in vivax and ovale malaria are not prevented. In short time visitors to chloroquine-sensitive endemic areas, suppressive doses should be started 1 week before and continued for 4 weeks after returning.
- Extraintestinal amoebiasis
- Rheumatoid arthritis
- Discoid lupus erythematosus—very effective; less valuable in systemic LE.
- Lepra reactions
- Photogenic reactions.
- Infectious mononucleosis: affords symptomatic relief.

Amodiaquine

It is almost identical to chloroquine in properties and is less bitter.

In the mid 1980s some fatal cases of toxic hepatitis and agranulocytosis were reported among travellers using amodiaquine for prophylaxis, and WHO in 1990 recommended that it should not be used for prophylaxis of malaria as well as for treatment of chloroquine failures.

Dose: for treatment of acute attack of malaria: 25–35 mg/ kg over 3 days; CAMOQUIN 200 mg (as HCl = 150 mg base) tab; BASOQUIN 150 mg (base) per 5 ml susp.

Piperaquine

Mefloquine

It is a drug developed to deal with the problem of chloroquine resistant P. falciparum, and has emerged from reinvestigation of quinoline methanols that were originally tested during World War II. Mefloquine is a relatively fastacting erythrocytic schizontocide, slower than chloroquine or quinine; effective against chloroquine-sensitive as well as resistant plasmodia. In field trials, single dose (15 mg/kg, max 1 g) has rapidly controlled fever and eliminated circulating parasites in infections caused by P. falciparum or P. vivax in partially immune as well as nonimmune individuals. However, like chloroquine, relapses occur subsequently in vivax malaria. It is also an efficacious suppressive prophylactic for multiresistant P. falciparum and other types of malaria. Mefloquine-resistance among P. falciparum has become common in Thailand, Cambodia and Myanmar, but is sporadic in Africa, South America and Middle east. Since it has not been extensively used in India, mefloquine-resistance is not a problem yet, but due to its long t½ chances of selection of resistant strains are high; mefloquine-resistant P. falciparum isolates have been reported from Gujarat and Andhra Pradesh. Resistance to mefloquine confers cross resistance to quinine and halofantrine.

Mechanism of action

The mechanism of action of mefloquine is not known, but the morphological changes produced in the intraerythrocytic parasite resemble quinine. It is actively taken up even by chloroquine-resistant P. falciparum and, like chloroquine raises intravesicular pH. It appears to bind to haeme and the complex damages membranes of the parasite. Resistant organisms accumulate less mefloquine.

Pharmacokinetics

Oral absorption of mefloquine is good but quite slow. It is highly plasma protein bound and concentrated in many organs including liver, lung and intestines. Extensive metabolism occurs in liver and it is primarily secreted in bile. Considerable enterohepatic circulation of mefloquine and its tissue binding accounts for the long t½ which is 2–3 weeks.

Adverse Effects

Mefloquine is bitter in taste; common reaction is dizziness, nausea, vomiting, diarrhoea, abdominal pain and sinus bradycardia. These are usually mild and largely dose related, but may be severe in some. Major concern has been a variety of neuropsychiatric reactions (disturbed sense of balance, ataxia, errors in operating machinery, strange dreams, anxiety, hallucinations, rarely convulsions) occurring in some recipients. These are dose related and subside in 1–3 weeks. Rare events are haematological, hepatic and cutaneous toxicity. Mefloquine appears to be safe during pregnancy, but should be avoided in 1st trimester unless absolutely essential.

Use

Mefloquine is an effective drug for multiresistant P. falciparum. Because of its potential toxicity, cost and long t½, its use is being restricted to areas where such strains are prevalent. To check the spread of mefloquine-resistance, current recommendation is to use it only along with the rapidly acting drug artesunate, as ACT for uncomplicated chloroquine as well as S/P resistant falciparum malaria. For vivax malaria, it should be used only in the rare case of the parasite being both chloroquine and quinine + doxycycline resistant. Mefloquine cannot be given parenterally and is not used in complicated/ cerebral malaria.

For prophylaxis of malaria among travellers to areas with multidrug resistance; 5 mg/kg (adults 250 mg) per week is started preferably 2–3 weeks before travel to assess side effects in the individual. Not recommended for prophylaxis in residents of the endemic area.

Mepacrine (Quinacrine, Atabrine)

It is an acridine derivative erythrocytic schizontocide, more toxic and less effective than chloroquine. It is obsolete as an antimalarial, but is also active against giardia and tapeworms.

Quinine

Quinine is the levo rotatory alkaloid obtained from cinchona bark. Its disomer quinidine is used as an antiarrhythmic (and for malaria in some countries).

Quinine is an erythrocytic schizontocide for all species of plasmodia; less effective and more toxic than chloroquine. Resurgence of interest in quinine is due to the fact that most chloroquine and multi-drug-resistant strains of P. falciparum still respond to it. However, even quinine-resistance has been described in certain parts of Southeast Asia and Brazil where quinine + tetracycline has been the standard treatment of complicated malaria. Quinine-resistance has been encountered sporadically in India, particularly along Myanmar border where in a sample study 6% falciparum malaria cases did not respond sequentially to chloroquine, S/P and quinine. There is partial cross resistance between quinine and mefloquine, but many mefloquine-resistant cases respond to quinine. Though effective in terminating an acute attack of falciparum malaria, it may not prevent recrudescence — indicating incomplete clearance of the parasites.

Quinine has no effect on pre-erythrocytic stage and on hypnozoites of relapsing malaria, but kills vivax gametes. Like chloroquine, it is a weak base: gets concentrated in the acidic vacuoles of the blood schizonts and causes pigment changes; inhibits polymerization of haeme to hemozoin; free haeme or haemequinine complex damages parasite membranes and kills it. However, the exact mechanism of action is not known.

Quinine Has Many Other Actions:

1. Local irritant and anaesthetic Quinine is intensely bitter and irritant. Orally it causes nausea, vomiting, epigastric discomfort. Injections can cause pain and local necrosis in the muscle and thrombosis in the vein. Local inflammation may be followed by fibrosis.

2. Systemic actions Gastric secretion is increased. Quinine is a weak analgesic and antipyretic; affects hearing and vision at higher doses. Cardiodepressant, antiarrhythmic and hypotensive actions are similar to quinidin. Rapid i.v. injection can produce marked fall in BP and cardiovascular collapse.

Quinine directly decreases contractile power of the muscle fibre. It stimulates the myometrium and can cause abortion in early pregnancy. However, it is not a dependable abortifacient. Blood sugar is slightly lowered due to release of insulin from the pancreas. Rapid i.v. injection of quinine has caused hypoglycaemia.

Pharmacokinetics

Quinine is rapidly and completely absorbed orally. It is 70% bound to plasma proteins, especially α1 acid glycoprotein. Such binding increases during acute malarial infection. CSF concentrations

are low. A large fraction of the dose is metabolized in the liver by CYP3A4 and excreted in urine with a t½ of 10–12 hours. Quinine is noncumulative.

Adverse Effects

Toxicity of quinine is high and dose related; 8–10 g taken in a single dose may be fatal.

Cinchonism: A large single dose or higher therapeutic doses taken for a few days produce a syndrome called cinchonism. It consists of ringing in ears, nausea, vomiting (due to both gastric irritation and CTZ stimulation), headache, mental confusion, vertigo, difficulty in hearing and visual defects (due to direct neurotoxicity as well as constriction of retinal and auditory vessels). Diarrhoea, flushing and marked perspiration may also appear. The syndrome subsides completely if the drug is stopped.

Few individuals are idiosyncratic/hypersensitive to quinine; cinchonism may appear after a single therapeutic dose. Purpura, rashes, itching, angioedema of face and bronchoconstriction may also develop.

Quinine occasionally causes haemolysis, especially in pregnant women and in patients of falciparum malaria, resulting in haemoglobinuria (black water fever) and kidney damage.

During pregnancy it should be used only for life-threatening infection, with special care to prevent hypoglycaemia.

Uses

1. Malaria Quinine is used orally for uncomplicated chloroquine-resistant malaria, and i.v. for complicated/cerebral malaria (chloroquine-sensitive or resistant).
2. Uncomplicated resistant falciparum malaria: Quinine may be used orally as an alternative to S/PACT in uncomplicated chloroquine-resistant falciparum malaria. It acts more rapidly than S/P alone. The 7 day quinine + doxycycline regimen is the 2nd line treatment of chloroquine-resistant malaria (both falciparum and vivax) under NVBDCP. Certain chloroquine-resistant strains are also resistant to S/P, but respond to quinine.
3. Complicated and severe malaria including cerebral malaria: Quinine (i.v.) has been used as the drug of choice for cerebral malaria (falciparum malaria with impaired consciousness) and other forms of complicated malaria. However, some recent studies indicate that parenteral artemisinins are faster acting, more effective, better tolerated and more conveniently administered. Many experts now prefer i.v./i.m. artesunate/artemether/ arteether over quinine for severe malaria. The dosage and schedule for i.v. infusion of

quinine for severe malaria is given in the box on p. 784. Hypoglycaemia due to hyperinsulinemia is the most important side effect: can be prevented by 5% dextrose infusion.

1. Supportive treatment — cooling for fever, i.v. diazepam for convulsions, correction of fluid and electrolyte balance and acidosis is of vital importance. Corticosteroids have been used but are of no benefit; may be harmful — avoid them.

2. Nocturnal muscle cramps: a single tablet of quinine (300 mg) at bed time affords benefit in some but not all cases. It is also effective in myotonia congenita.

3. Diagnosis of myasthenia gravis: a single dose of quinine precipitates weakness in myasthenia gravis. However, this provocative test is dangerous — not recommended.

4. Varicose veins: injected along with urethane, it causes thrombosis and fibrosis of the varicose vein mass.

BIGUANIDES

Proguanil (Chloroguanide)

It is a slowacting erythrocytic schizontocide which also inhibits the preerythrocytic stage of falciparum. Gametocytes exposed to proguanil are not killed but fail to develop properly in the mosquito. It is cyclized in the body to a triazine derivative (cycloguanil) which inhibits plasmodial DHFRase in preference to the mammalian enzyme. Resistance to proguanil develops rapidly due to mutational changes in the plasmodial DHFRase enzyme.

Proguanil is slowly but adequately absorbed from the gut; is partly metabolized and excreted in urine; t½ is 16–20 hr; noncumulative. It is very well tolerated; side effects are less compared to chloroquine; mild abdominal upset, vomiting, occasional stomatitis, haematuria, rashes and transient loss of hair are reported. Current use of proguanil is restricted to prophylaxis of malaria in combination with chloroquine in areas of low level chloroquineresistance among P. falciparum. It can be employed during pregnancy.

Dose for malaria prophylaxis: 200 mg daily with chloroquine 300 mg weekly till 4 weeks after exposure; LAVERAN, PROGUNAL 100 mg tab.

Because it potentiates atovaquione, a combination of the two has been used in Thailand and some other countries for treatment of multi-drugresistant falciparum malaria.

Chlorproguanil

It is proguanil with an additional chlorine substitution, but with similar properties. Combined with dapsone, it has been used for prophylaxis and treatment of chloroquine-resistant malaria. Along with artesunate, the combination is being evaluated as ACT.

PYRIMETHAMINE

It is a directly acting inhibitor of plasmoidal DHFRase (does not require conversion to a cyclic triazine, as is the case with proguanil). Selective antimalarial action depends on high affinity for plasmodial enzyme (~2000 times greater than for the mammalian enzyme). In contrast to trimethoprim, it has very poor action on bacterial DHFRase. Under the influence of pyrimethamine, schizogony of malarial parasite in blood gradually stops. At high doses, it inhibits Toxoplasma gondii.

Pyrimethamine is more potent. It is a slowly acting erythrocytic schizontocide, but does not eliminate the preerythrocytic phase of P. falciparum. It is not a radical curative, but by extended treatment, the secondary tissue phase of P. vivax may be exhausted. If used alone, resistance develops rather rapidly by mutation in the DHFRase enzyme of the parasite. These organisms exhibit cross resistance to proguanil.

Pharmacokinetics

Absorption of pyrimethamine from g.i.t. is good but slow. Certain organs like liver, spleen, kidney and lungs concentrate pyrimethamine. It is metabolized and excreted in urine with a t½ of 4 days. Prophylactic concentrations remain in blood for 2 weeks.

Adverse Effects

Pyrimethamine is relatively safe. The only side effects are occasional nausea and rashes. Folate deficiency is rare; megaloblastic anaemia and granulocytopenia may occur with higher doses, especially in those with marginal folate stores. This can be treated by folinic acid.

Use

Pyrimethamine is used only in combination with a sulfonamide (S/P) or dapsone (see below) for treatment of falciparum malaria.

PRIMAQUINE

In contrast to other antimalarial drugs, primaquine is a poor erythrocytic schizontocide: has weak action on P. vivax, but blood forms of P. falciparum are totally insensitive. On the other hand, it is more active against the preerythrocytic stage of P. falciparum than that of P. vivax. Primaquine differs from all other available antimalarials in having a marked effect on primary as well as secondary tissue phases of the malarial parasite. It is highly active against gametocytes and hypnozoites.

Mechanism of action

The mechanism of action of primaquine is not known. However, it is different from that of chloroquine. Though, resistance among P. vivax against primaquine can be induced, it is not a clinical problem.

Pharmacokinetics Primaquine is readily absorbed after oral ingestion. It is oxidized in liver with a plasma t½ of 3–6 hrs and excreted in urine within 24 hours. It is not a cumulative drug.

Adverse Effects The usual doses of primaquine produce only abdominal pain, g.i. upset, weakness or uneasiness in chest as side effect. These can be minimized by taking the drug with meals. CNS and cardiovascular symptoms are infrequent. Leucopenia occurs rarely with larger doses.

The most important toxic potential is dose related haemolysis, methaemoglobinaemia, tachypnoea and cyanosis. These are due to the oxidant property of primaquine. Its metabolites are more potent in this regard. However, in normal individuals doses < 60 mg (base) produce little haemolysis. Those with G6PD deficiency are highly sensitive and haemolytic anaemia can occur with 15–30 mg/day. The incidence of G6PD deficiency is low among Indians, except in some tribal people of Jharkhand, Andhra Pradesh, Madhya Pradesh and Assam. It is high among black races and Mediterranean people. Spot tests are available for detecting G6PD deficiency. Passage of dark urine is an indication of haemolysis; primaquine should be promptly stopped if it occurs. The risk of haemolysis and leucopenia is increased in patients of rheumatoid arthritis, SLE and in those acutely ill.

Primaquine should be avoided during pregnancy, because foetus is G6PD deficient.

Use

The primary indication of primaquine is for radical cure of relapsing (vivax) malaria: 15 mg (children 0.25 mg/kg) daily for 2 weeks is given with full curative dose of chloroquine (to cover the erythrocytic phase). Relapse rate with 5 day primaquine treatment employed earlier by

NAMP (India) has been found similar to no treatment; therefore not recommended now. The G6PD status of the patient should be tested before giving 14 day primaquine course.

Bulaquine

This congener of primaquine, developed in India, has shown comparable antirelapse activity in vivax malaria when administered for 5 days along with a course of chloroquine. It is partly metabolized in the body to primaquine. Whether the activity is due to bulaquine itself or due to primaquine produced from it is not clear. Bulaquine is claimed to be better tolerated, especially by G6PD deficient individuals, but without any convincing evidence. Precautions and contraindications are the same as for primaquine. Since 5 day antirelapse treatment has been discontinued, the status of bulaquine is uncertain. Dose: 25 mg/day for 5 days starting on 2nd day of chloroquine therapy.

ARTEMISININ DERIVATIVES

Artemisinin is the active principle of the plant Artemisia annua used in Chinese traditional medicine as 'Quinghaosu'. It is a sesquiterpine lactone active against P. falciparum resistant to all other antimalarial drugs as well as sensitive strains. Potent and rapid blood schizontocide action is exerted eliciting quicker defervescence and parasitaemia clearance (<48 hr) than chloroquine or any other drug. In the erythrocytic schizogony cycle of the malarial parasite, artemisinins exert action on a wide range of stages—from ring forms to early schizonts; thus have the broadest time window of antimalarial action.

Artemisinin is poorly soluble in water as well as oil. Several derivatives have been produced, of which three are marketed in India: Artemether is soluble in oil, while Artesunate (sod.) is water soluble. Another compound Arteether has been developed in India. Artemisinins do not kill hypnozoites but have some action on falciparum gametes. The duration of action is short and recrudescence rate is high when they are used alone in short courses. Recrudescence depends upon the dose and duration of therapy as well as severity of disease. So far no resistance among P. falciparum patients to artemisinin has been noted, but can be developed in animal models.

Because artemisinins are short acting drugs, monotherapy needs to be extended beyond the disappearance of the parasites to prevent recrudescence. After 5 days treatment recrudescence rate is ~10%, while with a 3 day course it is ~50%. Recrudescence can be totally prevented by combining 3 day artesunate/artemether with a long-acting drug (see ACT later).

Mechanism of Action

Mechanism of Action of artemisinin is not definitely known. The endoperoxide bridge in its molecule appears to interact with haeme in the parasite. Iron-mediated cleavage of the bridge releases a highly reactive free radicals species that binds to membrane proteins, causes lipid peroxidation, damages endoplasmic reticulum, inhibits protein synthesis and ultimately results in lysis of the parasite.

Pharmacokinetics

Data on pharmacokinetics of artemisinin derivatives is limited and incomplete. Both artesunate and artemether are prodrugs.

Artesunate: Its sodium salt is water-soluble and is administered by oral, i.m. or i.v. routes. After oral ingestion, absorption is incomplete but fast, reaching peak in <60 min. It is rapidly converted to the active metabolite dihydro-artemisinin (DHA) with a t½ of 30–60 min. The t½ of DHA is 2–4 hours. After repeated dosing, artesunate causes autoinduction of its own metabolism.

Artemether: It is lipid-soluble and is administered orally or i.m., but not i.v. Oral absorption is slower taking 2–4 hours, but is enhanced by food. It undergoes substantial first pass metabolism and is converted to DHA. Extensive metabolism by CYP3A4 yields a variable t½ of 3–10 hours.

α/β Arteether: This compound developed in India has been released for institutional use only, for i.m. administration in complicated/cerebral malaria. Because of its longer elimination t½ (23 hours), it is effective in a 3 day schedule with a recrudescence rate of 5%.

[Note: The recent (2006) WHO Regional guidelines for South East Asia recommend a 5 day course of i.m. arteether (3.2 mg/kg on 1st day, followed by 1.6 mg/kg daily for the next **4 days)].**

Use

Oral artemisinins are indicated only for the treatment of uncomplicated chloroquine/ multidrug-resistant falciparum malaria. Parenterally they are used in severe and complicated falciparum malaria. There is no justification of using them for uncomplicated chloroquine or S/P sensitive falciparum malaria or for vivax malaria. Because of their short duration of action and availability of better tolerated/cheaper drugs, use of artemisinins for prophylaxis of malaria is irrational, and is not allowed.

Uncomplicated resistant falciparum malaria: Oral artemisinins are almost 100% effective, but recrudescence rates are high. In order to protect their powerful antimalarial activity and to reduce recrudescence rates, current recommendation is to use them only in combination with a longeracting drug (see box on p. 783 and ACT below). Their gametocidal action cuts down transmission and spread of resistant P. falciparum.

Severe and complicated falciparum malaria: Parenteral artemisinins are higly effective and are indicated irrespective of chloroquine-resistant status. Though i.v. quinine is still advocated as the 1st line drug in complicated/cerebral malaria, i.v. artesunate offers several advantages:

- It causes faster parasite clearance than i.v. quinine.
- It is safer and better tolerated than i.v. quinine.
- Its dosing schedule is simpler.
- Recent evidence indicates higher efficacy and lower mortality.

AMINOALCOHOLS

Halofantrine It is a phenanthrene methanol blood schizontocide having activity comparable to mefloquine with which it exhibits cross resistance. It is effective against P. falciparum resistant to chloroquine and S/P, as well as against P. vivax. It is not active against gametocytes or hepatic stages of the malarial parasite.

Oral absorption of halofantrine is low and erratic. The plasma t½ is 1 day, but that of its active metabolite is 3 days. Side effects are abdominal pain, diarrhoea, itching, rashes and occasional elevation of serum transaminase. Prolongation of QTc interval is seen even at therapeutic doses and few cases of serious ventricular arrhythmia (some fatal) are on record.

It is not approved in India, but in other countries it has been used for multiresistant falciparum malaria when no other effective alternative is available.

Lumefantrine

Pyronaridine

Atovaquone

This synthetic naphthaquinone is a rapidly acting erythrocytic schizontocide for P. falciparum and other plasmodia. Pneumocystis jiroveci and Toxoplasma gondii are also susceptible to atovaquone. It collapses plasmodial mitochondrial membranes and interferes with ATP production. Proguanil potentiates its antimalarial action and prevents emergence of resistance. A

fixed dose oral combination of the two drugs is used for 3 day treatment of uncomplicated chloroquine-resistant P. falciparum as well as P. vivax malaria in the USA and some other countries, but not in India.

Atovaquone is also approved as a second line drug for opportunistic infections with P. jiroveci and T. gondii in AIDS patients. It produces few side effects—diarrhoea, vomiting, headache, rashes and fever.

ANTIAMOEBIC DRUGS

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

Amoebiasis has a worldwide distribution (over 40 million people are infected), but it is endemic in most parts of India and other developing countries. Poor environmental sanitation and low socioeconomic status are important factors in the spread of the disease, 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 commensals— form cysts that pass into the stools (luminal cycle) and serve to propagate the disease, or invade the mucosa—form amoebic ulcers (Fig. 60.1) and cause acute dysentery (with blood and mucus in stools) or chronic intestinal amoebiasis (with vague abdominal symptoms, amoeboma).

Occasionally the trophozoites pass into the blood stream, reach the liver via portal vein and cause amoebic liver abscess. Other organs like lung, spleen, kidney and brain are rarely involved in extraintestinal amoebiasis. In the tissues, only trophozoites are present; cyst formation does not occur. Tissue phase is always secondary to intestinal amoebiasis, which may be asymptomatic. In fact, most chronic cyst passers are asymptomatic. In the colonic lumen, the Entamoebae live in symbiotic relationship with bacteria, and a reduction in colonic bacteria reduces the amoebic population.

The ‘Brazil root’ or Cephaelis ipecacuanha was used for the treatment of dysentery in the 17th century. The pure alkaloid emetine obtained from it was found to be a potent antiamoebic in 1912 and remained the most efficacious and commonly used drug till 1960. Many 8hydroxyquinolines (quiniodochlor, etc.) became very popular drugs for diarrhoeas and amoebic dysentery, but have come under a cloud since they were held responsible for causing epidemics of SMON in Japan in 1970. Soon after its triumph as an antimalarial in 1948, chloroquine was found to be an effective and safe drug for hepatic amoebiasis. Diloxanide furoate was a useful

addition in 1960, covering mainly chronic intestinal form of the disease. However, the most remarkable development was the demonstration of antiamoebic property of metronidazole in the early 1960s. This drug had been introduced a few years back as a well tolerated, orally effective agent for trichomonas vaginitis. Of the many congeners of metronidazole that were tested, tinidazole has emerged in the 1970s as a good alternative, and others have been added subsequently.

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 lamblia 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. Though, it does not directly inhibit the helminth Dracunculus medinensis, extraction of the worm from under the skin is facilitated. Metronidazole does not affect aerobic bacteria. Clinically significant resistance has not developed among E. histolytica, but decreased responsiveness of T. vaginalis has been observed in some areas. Anaerobic bacteria and G. lamblia also can develop metronidazole resistance, but this is a clinical problem only in the case of H. pylori.

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 cytotoxicity. The nitro radical of

metronidazole acts as an electron sink which competes with the biological electron acceptors of the anaerobic organism for the electrons generated by the pyruvate : ferredoxin oxidoreductase (PFOR) enzyme pathway of pyruvate oxidation. The energy metabolism of anaerobes is, thus, disrupted. Aerobic environment attenuates cytotoxicity of metronidazole by inhibiting its reductive activation. Anaerobes which develop metronidazole resistance become deficient in the mechanism that generates the reactive nitro radical from it.

Metronidazole has been found to inhibit cell mediated immunity, to induce mutagenesis and to cause radio-sensitization.

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 primarily by oxidation and glucuronide conjugation, and excreted in urine. Plasma t½ 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.
- Less frequent side effects are—headache, glossitis, dryness of mouth, dizziness, rashes and transient neutropenia.
- Prolonged administration may cause peripheral neuropathy and CNS effects. Seizures have followed very high doses.
- Thrombophlebitis of the injected vein occurs if the solution is not well diluted.

Contraindications

Metronidazole is contraindicated in neurological disease, blood dyscrasias, first trimester of pregnancy (though no teratogenic effect has yet been demonstrated, its mutagenic potential warrants caution), and chronic alcoholism.

Interactions

A disulfiram-like intolerance to alcohol occurs in some patients taking metronidazole; they should be instructed to avoid drinking. Enzyme inducers (phenobarbitone, rifampin) may reduce its therapeutic effect.

Cimetidine can reduce metronidazole metabolism: its dose may need to be decreased. Metronidazole enhances warfarin action by inhibiting its metabolism. It can decrease renal elimination of lithium.

Preparations

Uses

Amoebiasis:

Metronidazole is a first line drug for all forms of amoebic infection. Many dosage regimens have been tried; the current recommendations are:

- For invasive dysentery and liver abscess—800 mg TDS (children 30–50 mg/kg/day) for 7–10 days. In serious cases of liver abscess 1 g may be infused i.v. slowly followed by 0.5 g every 8–12 hr till oral therapy is instituted.

- For mild intestinal disease—400 mg TDS for 5–7 days. Metronidazole is less effective than many luminal amoebicides in eradicating amoebic cysts from the colon, because it is nearly completely absorbed from the upper bowel.

Giardiasis

It is highly effective in a dose of 400 mg TDS for 7 days. A shorter course of 3 days with 2 g/day is equally effective.

Trichomonas Vaginitis

It is the drug of choice; 400 mg TDS for 7 days achieves nearly 100% cure. Additional intravaginal treatment has been given, but is not necessary except in refractory cases. The male partner should be treated concurrently in cases of recurrent infections. Nonspecific bacterial vaginosis also responds.

Anaerobic Bacterial Infections

They occur mostly after colorectal or pelvic surgery, appendicectomy, etc. Brain abscesses and endocarditis may be caused by anaerobic organisms.

Metronidazole is an effective drug for these and is generally used in combination with gentamicin or cephalosporins (many are mixed infections). For serious cases i.v. administration is recommended: 15 mg/kg infused over 1 hr followed by 7.5 mg/kg every 6 hrs till oral therapy can be instituted with 400–800 mg TDS. Prophylactic use in high risk situations (colorectal surgery) is recommended.

Other drugs effective in anaerobic infections are clindamycin and chloramphenicol.

Pseudomembranous Enterocolitis due to Cl. difficile is generally associated with use of antibiotics. Oral metronidazole 800 mg TDS is more effective, more convenient, less toxic, and therefore preferred over vancomycin.

Ulcerative Gingivitis, Trench Mouth 200–400 mg TDS (15–30 mg/kg/day) is quite effective because anaerobes are involved. Metronidazole/ tinidazole are the drugs of choice for acute necrotizing ulcerative gingivitis, in which they are often combined with amoxicillin, tetracycline or erythromycin. The response is rapid with disappearance of the spirochetefuso-bacterium complex from the lesions and resolution of pain, bleeding, ulceration and bad breath within 2–3 days; but treatment must be continued for at least 5 days.

Helicobacter Pylori Gastritis/Peptic Ulcer

Metronidazole or tinidazole alone are relatively ineffective in eradicating H. pylori; resistance develops. However, metronidazole 400 mg TDS or tinidazole 500 mg BD is frequently used along with amoxicillin/clarithromycin and a proton pump inhibitor in triple drug 2 week regimens.

Guinea worm infestation Niridazole is considered to

be the drug of choice, but because it is not available in India, metronidazole is used. A 7 day course with 200– 400 mg TDS produces symptomatic relief. The local reaction to the worm may be suppressed by its anti-inflammatory action, and extraction is facilitated.

Tinidazole

It is an equally efficacious congener of metronidazole, similar to it in every way except:

Metabolism is slower; t½ is ~12 hr; duration of action is longer; dosage schedules are simpler. Thus, it is more suited for single dose or once daily therapy. Some comparative trials in amoebiasis have reported higher cure rates. It appears to be better tolerated; the incidence of side effects is lower: metallic taste (2%), nausea (1%), rash (0.2%).

Ornidazole

Activity similar to metronidazole, but it is slowly metabolized—has longer t½ (12–14 hr). Dose and duration of regimens for amoebiasis, giardiasis, trichomoniasis, anaerobic infections and bacterial vaginosis resemble those for tinidazole. Side effect profile is also similar.

EMETINE

An alkaloid from Cephaelis ipecacuanha. Emetine is a potent and directly acting amoebicide—kills trophozoites but has no effect on cysts. It acts by inhibiting protein synthesis in amoebae by arresting intra-ribosomal translocation of tRNA-amino acid complex.

The stool in acute dysentery is rapidly cleared of the trophozoites and symptomatic relief occurs in 1–3 days (even faster than metronidazole), but it is not curative in the sense that the patient continues to pass cysts in the stool. It is highly efficacious in amoebic liver abscess also.

Emetine cannot be given orally because it will be vomited out. It is administered by s.c. or i.m. injection: 60 mg OD. It should be given only till acute symptoms subside; not more than 10 days in any case. It is concentrated in liver, kidney, spleen and lungs. Emetine is very slowly excreted in urine taking 1–2 months. Thus, a second course should not be repeated within 6 weeks, otherwise cumulative toxicity can occur. Toxicity of emetine is high.

Local: It is an irritant; pain, stiffness and eczematous lesions occur at the site of injection.

- ✓ Nausea and vomiting are frequent. After parenteral administration this is central in origin due to stimulation of CTZ. Vomiting due to oral dose of emetine is primarily because of gastric irritation.
- ✓ Abdominal cramps and diarrhoea due to emetine toxicity may be confused with that due to intestinal amoebiasis itself.
- ✓ Weakness and stiffness of muscles; a myositis like picture may be present.
- ✓ Hypotension, tachycardia, ECG changes and myocarditis are the most serious complications. To avoid these, strict bed rest must be imposed during emetine therapy and exercise should be prohibited for another 1–2 months.
- ✓ Emetine is contraindicated in presence of cardiac or renal disease and during pregnancy.

Use

Because of the above drawbacks, emetine is now seldom used as a reserve drug in severe intestinal or extraintestinal amoebiasis, or for patients not responding to or not tolerating metronidazole. A luminal amoebicide must always follow emetine to eradicate the cyst forming trophozoites. It is also effective in liver fluke infestation.

IMPORTANT QUESTIONS

Very short answer question (2 marks)

1. Define Jerish Herxeimer reactions.
2. What are opportunistic infections?
3. What are the toxicities of amphotericin?
4. Write drugs used for candidiasis and gonorrhea?
5. What is DOTS?
6. Give MOA acyclovir.
7. Outline treatment for paucibacilary leprosy.
8. Give drugs for superficial fungal infections.
9. What are different types of TB?
10. Write drugs used for AIDS.
11. What is helminthiasis?
12. Write the MOA of zidovudine.
13. Write the MOA of terbinfine.
14. What are tropical infections?
15. What is DDS?

Short answer questions (5 marks)

1. Write a note on amphotericin B.
2. Classify the first line anti tubercular drugs and their pharmacology.
3. Discuss clinical manifestations and drugs used for leprosy.
4. Explain the chemotherapy of anti amoebic agents.
5. Write a note on NNRTIs.
6. Write the mechanism, uses and side effects of metronidazole and ketoconazole.

Long answer questions (10 marks)

1. Classify anti tuberculosis drugs. Discuss their mechanism of actions and therapeutic uses.
2. Classify anti HIV drugs. Discuss about actions, mechanism, uses and side effects of anti Herpes, protease inhibitors.
3. Explain the mechanism of actions, uses and side effects of anti anthelmintcs drugs.
4. Discuss in detail about the anti fungal drugs with their mechanism, uses and side effects.
5. Classify anti malarial drugs. Discuss pharmacology of chloroquine and artemether.