Anti-tubercular drugs

Contents

Antitubercular drugs

- Classification
- Pharmacology of individual drugs

At the end of this lecture, the student will be able to:

- Describe the mechanism of action and pharmacokinetics of First line and second line anti-TB drugs
- Discuss the adverse effects and drug interactions of anti-TB drugs
- Explain the DOTS therapy based on WHO guidelines

Anti-tubercular Agents

- Tuberculosis is a chronic granulomatous disease
- In developing countries it is a major health problem
- 30% of world population is infected with *M. tuberculosis* infection
- In India > 2 million people develop active disease every year & half million die.
- Anti-tubercular drugs used in chemotherapy of tuberculosis, a disease caused by *Mycobacterium tuberculosis*
- Many drugs were developed to treat tuberculosis and they are often used in combinations to reduce the emergence of resistant strains of the mycobacterium
- Combination chemotherapy is also used in the treatment of leprosy, caused by *Mycobacterium leprae*

Classification

First-line (High efficacy, low toxicity)

- Isoniazid
- Rifampicin
- Ethambutol
- Pyrazinamide
- Streptomycin

Second-line (Low efficacy, high toxicity)

- Clarithromycin
- Ciprofloxacin
- Capreomycin
- Cycloserine

- Kanamycin
- Amikasin
- Para amino salicylic Acid

Isoniazid (Isonicotinic Acid Hydrazid)

- Isoniazid is an effective anti-tubercular drug and is essential component of all anti tubercular regimens
- It is more potent among the anti-tubercular drugs, but it is not used alone in treatment of active tuberculosis
- It acts on extracellular as well as on intercellular tubercule bacilli present within macrophages

Mode of Action

- Acts only on mycobacteria
- Interferes with mycolic acid synthesis (unique to mycobacterial cell wall)
- Passes freely to mammalian cell wall
- Effective for intracellular organism
- Bacteriostatic – to resting organism
- Bactericidal – to multiplying organism

Pharmacokinetics

- Well absorbed from GIT
- Fatty food & aluminium-containing antacids may reduce absorption
- CSF penetration: 20% of plasma concentration with non-inflamed meninges
- Penetrate well into caseous material
- Excretion – urine
- Plasma half-life 3 hrs

Adverse Effects

- Hepatotoxicity
  - Elderly, slow acetylators more prone
- Polyneuropathy
  - Prevented by concurrent pyridoxine
- Rashes, acne
- Heamatological – haemolytic anaemia in G6PD deficiency

Drug Interactions

- Absorption of Isoniazid is impaired if taken with food consisting carbohydrates or with aluminium-containing antacids
- It inhibits the metabolism of phenytoin, carbamazepine, diazepam and warfarin and raised their blood levels

- Para amino salicylic acid inhibits its metabolism and increases its metabolism

Rifampicin

- Rifampicin is semisynthetic derivative of refamycin B, obtained from *Streptomyces mediterannei*
- It is one of the most active anti tubercular drugs
- It is active against many other Gram-positive and Gram-negative bacteria

Mechanism of Action

- Rifampicin acts by inhibiting DNA- dependent RNA polymerase thus inhibiting RNA synthesis by suppressing the initiation step in prokaryotic but not in eukaryotic cells
- It also enters phagocytic cells and kill intercellular microorganism including tubercule bacilli
- It is the only drug which acts on the persisters

Pharmacokinetics

- It is well absorbed orally and is widely distributed in the tissues and body fluids
- It gives an orange tinge to saliva, sputum, tears and sweat
- The drug is taken up by liver and undergoes enterohepatic cycling
- The metabolite retains antibacterial activity but less absorbed from the GIT tract
- Mainly Excreted in bile and also in urine

Adverse Effects

- Unwanted effects are infrequent and include skin eruptions, fever and GIT disturbances
- The drug should be used carefully in patients with hepatic failure as it may lead to jaundice

Drug Interactions

- Rifampicin is an inducer of cytochrome P-450 enzymes and decreases the half-life of drugs such as warfarin, glucocorticoids, antidiabetic, oral-contraceptives leading to their failure

Anti-TB Therapy

- Multiple drugs are used to reduce the emergence of resistance
- Given as combination tablets
- Taken 30 min before the breakfast as absorption of rifampicin is influenced by food
- For pulmonary TB – 6 months treatment
- For renal, bone and CNS infection – longer treatment

Summary

- Isoniazid – bactericidal to rapidly dividing bacteria
- Rifampicin - kill intracellular bacteria
- Ethambutol – bacteriostatic against multiplying bacteria

- Pyrazinamide - kill dormant mycobacteria
- Adverse effects:

✓ INH- Hepatotoxicity and Polyneuropathy

✓ Rifampicin- inducer of cytochrome P-450 enzymes and decreases the half-life of drugs such as warfarin, glucocorticoids, antidiabetic, oral-contraceptives

✓ Pyrazinamide- GI disturbances, Hepatotoxicity, gout

✓ Streptomycin- Ototoxicity, vestibular toxicity, nephrotoxicity