Antitubercular Drugs-I

Dr Shruti V Brahmbhatt

- Tuberculosis is a chronic granulomatous disease
- a major health problem in developing countries.
- About 1/3rd of the world's population is infected with *Mycobact. tuberculosis*

- Remarkable progress has been made in the last 65 years since the introduction of *Streptomycin* in 1947 for the treatment of tuberculosis.
- Its full therapeutic potential could be utilized only after 1952 when *isoniazid was produced to* accompany it.

- According to their clinical utility,
- *First line:*
  - *high anti tubercular* efficacy
  - low toxicity
- *Second line*
  - These drugs have either low anti tubercular efficacy or higher toxicity or both
  - used as reserve drugs.

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

Second line drugs

- Ethionamide (Eto)
- Prothionamide (Pto)
- Cycloserine (Cs)
- Terizidone (Trd)
- Para-aminosalicylic acid (PAS)
- Thiacetazone (Thz)
- Rifabutin

Injectable drugs

- Kanamycin (Km)
- Amikacin (Am)
- Capreomycin (Cm)

Fluoroquinolones

- Ofloxacin (Ofx)
- Levofloxacin (Lvx/Lfx)
- Moxifloxacin (Mfx)
- Ciprofloxacin (Cfx)

Isoniazid (H)

- tuberculocidal.
- Fast multiplying organisms are rapidly killed
- acts on extracellular as well as on intracellular TB (bacilli present within macrophages)
- equally active in acidic or alkaline medium.
- one of the cheapest antitubercular drugs.

- mechanism of action of INH
  - inhibition of synthesis of *mycolic acid*-unique fatty acid components of mycobacterial cell wall
  - Not active against any other microorganism
  - Two gene products labelled ‘InhA’ and ‘KasA’, which function in mycolic acid synthesis are the targets of INH action.

- *Pharmacokinetics*
- *completely absorbed* orally
- penetrates all body tissues, tubercular cavities, placenta and meninges
- It is extensively metabolized in liver-N-acetylation
- Acetylated metabolite is excreted in urine.
- The rate of INH acetylating shows genetic variation.

- Fast acetylators
- (30–40% of Indians) t½ of INH 1 hr.
- Slow acetylators (60–70% of Indians) t½ of INH 3 hr.
- peripheral neuritis is more common in slow acetylators.
- A hepatotoxicity- fast acetylators

- *Interactions*
- *Aluminium hydroxide inhibits* INH absorption.
- INH retards phenytoin, carbamazepine, diazepam, theophylline and warfarin metabolism by inhibiting CYP2C19 and CYP3A4

- *Adverse effects*
- Peripheral neuritis and a variety of neurological manifestations (paresthesias, numbness, mental disturbances, rarely convulsions)
- Interference with production of the active coenzyme pyridoxal phosphate from pyridoxine
- *Pyridoxine given* prophylactically (10 mg/day) prevents the neurotoxicity even with higher doses.
- Prophylactic pyridoxine must be given to diabetics, chronic alcoholics, malnourished, pregnant, lactating and HIV infected patients, but routine use is not mandatory.
- INH neurotoxicity is treated by pyridoxine 100 mg/day.

- Hepatitis, a major adverse effect of INH, is rare in children, but more common in older people and in alcoholics (chronic alcoholism induces CYP2E1 which generates the hepatotoxic metabolite).
- reversible on stopping the drug.
- Other side effects are lethargy, rashes, fever,
- acne and arthralgia.

Rifampin (Rifampicin, R)

- Bactericidal
- efficacious as INH and better than all other drugs.

- Mechanism of Action
- interrupts RNA synthesis by binding to β subunit of mycobacterial DNA-dependent RNA polymerase
- blocking its polymerizing function
- Resistance is nearly always due to mutation in the *rpoB gene reducing its affinity for the drug.*

- *Pharmacokinetics*
- *It is well absorbed orally,* (bioavailability - 70%),
- but food decreases absorption;
- Rifampicin is to be taken in empty stomach.
- It is metabolized in liver
- excreted mainly in bile, some in urine also.

- *Interactions*
- *Microsomal* enzyme inducer
- It thus enhances its own
- as well as that of many drugs including warfarin, oral contraceptives, corticosteroids, sulfonylureas, steroids, HIV protease inhibitors, nonnucleoside reverse transcriptase inhibitor (NNRTIs), theophylline, metoprolol, fluconazole,
- ketoconazole, clarithromycin, phenytoin, etc.

- *Adverse effects*
- Hepatitis, a major adverse effect
- Development of jaundice requires discontinuation of the drug—then it is reversible.
- *Cutaneous syndrome: flushing, pruritus +* rash, redness and watering of eyes.
- *Flu syndrome: with chills, fever, headache* malaise and bone pain.
- *Abdominal syndrome: nausea, vomiting,* abdominal cramps with or without diarrhoea.
- Urine and secretions may become orange-red
- Other serious but rare reactions are: *Respiratory syndrome: breathlessness which may be* associated with shock and collapse
- Purpura, haemolysis, shock and renal failure.

- *Other uses of rifampin*
- 1. Leprosy (*see Ch. 56)*
- 2. Prophylaxis of *Meningococcal and H. influenzae meningitis and carrier state.*
- 3. Second/third choice drug for MRSA, diphtheroids and *Legionella infections.*
- 4. Combination of doxycycline and rifampin is the first line therapy of brucellosis.

Pyrazinamide (Z)

- It is weakly tuberculocidal and more active in acidic medium.

- Mechanism of Action
  - Converted inside the mycobacterial cell into an active metabolite pyrazinoic acid by an enzyme (pyrazinamidase)
  - metabolite gets accumulated in acidic medium
  - probably inhibits mycolic acid synthesis

- Pharmacokinetics
- absorbed orally
- Widely distributed
- good penetration in CSF-useful in meningeal TB
- extensively metabolized in liver and excreted in urine
- plasma t½ is 6–10 hours

- ADR
- Hepatotoxicity -contraindicated in patient with liver disease.
- Safety during pregnancy is uncertain
- Hyperuricaemia is common-inhibition of uric acid secretion in kidney
- abdominal distress,
- arthralgia, flushing, rashes, fever and loss of diabetes control

Ethambutol (E)

- Tuberculostatic
- Inhibit arabinosyl transferases involved in arabinogalactan synthesis
- thereby interfering with mycolic acid incorporation in mycobacterial cell wall.

- About 3/4 of drug absorbed.
- distributed widely, but penetrates meninges incompletely and is temporarily stored in RBCs.
- Less than ½ of E is metabolized
- Excreted in urine
- plasma t½ is ~4 hrs.
- Caution is required in its use in patients with renal disease.

- ADR
- Loss of visual acuity/colour vision, field defects due to optic neuritis is the most important dose and duration of therapy dependent toxicity.
- Patients should be instructed to stop the drug at the first indication of visual impairment.

- Because young children may be unable to report early visual impairment, it was contraindicated, but is now allowed with due precaution.

- contraindicated in patients with optic neuritis.
- nausea, rashes, fever, rarely peripheral neuritis.
- Hyperuricemia is due to interference with urate excretion.
- It is safe during pregnancy

Streptomycin (S)

- The pharmacology of streptomycin is described
- It was the first clinically useful antitubercular drug.
- It is tuberculocidal, but less effective than INH or rifampin; acts only on extracellular bacilli

- Resistance developed rapidly when streptomycin was used alone in tuberculosis—most patients had a relapse.

- Because of need for i.m. injections and lower margin of safety (ototoxicity and nephrotoxicity, especially in the elderly and in those with impaired renal function)
- used only as an alternative to or in addition to other 1st line anti-TB drugs.
- Use is restricted to a maximum of 2 months. It is thus also labelled as a ‘supplemental’ 1st line drug

Reference

1	**K D Tripathi**	**Antitubercular Drugs**	**Essentials of Medical Pharmacology, 8th Edition**	**1**
2	R S Satoskar	Cheotherapy of Tuberculosis	Pharmacology and Pharmacotherapeutics, 25th Edition	1