Pharmacology team

# Pharmacology of drugs used in tuberculosis

Objectives:

- Discuss the etiology of tuberculosis
- Discuss the common route for transmission of the disease
- Discusses the out line for treatment of tuberculosis
- Discuss the drugs used in the first & second line
- Discuss the individual drugs regarding:
  - ⇒ The mechanism of action
  - ⇒ Adverse effects
  - ⇒ Drug interactions
  - ⇒ Contraindication

    Discuss tuberculosis & pregnancy

    Discuss tuberculosis & breast-feeding

Disease information:

- Robert Koch was the first to see *Mycobacterium tuberculosis* with his staining technique in 1882.
- Each year 1% of the global population is infected.

Mycobacterium tuberculosis, an acid fast bacillus with three types known to infect man causing pulmonary TB:

- The human type, commonest
- The bovine type
- The africanum type

Recently, the three are identified as the mycobacterium tuberculosis complex.

Common route of infection is air.

Common site of infection:

Mycobacterium tuberculosis is an aerobic organism → grows in sites that are rich in oxygen

- Apical areas of lung
- Renal parenchyma
- Growing ends of bones

Treatment of tuberculosis:

- Combination of antibiotics should be used → to overcome the bacterial resistance.
- Periods of treatment (minimum 6 months)
- Drugs are divided into two groups:
  - **First line** → **(will be discussed in this lecture)**
  - Second line

First line of drugs:

- Isoniazid (INH)
- Rifampin
- Ethambutol
- Streptomycin
- Pyrazinamide

⇒ Isoniazid –rifampin combination administered for 9 months will cure 95-98% of cases.

⇒ Addition of pyrazinamide for this combination for the first 2 months allows total duration to be reduced to 6 months.

| 1st line drugs | Isoniazid ( INH ) | Rifampin | Ethambutol | Pyrazinamide | Streptomycin |
|---|---|---|---|---|---|
| General information | 1- bacteriostatic for resting bacilli.<br>2- bactericidal for rapidly dividing bacilli.<br>3- is effective against both intracellular and extracellular bacilli. | 1- bactericidal.<br>2- effective against intracellular and extracellular bacilli. | 1- bacteriostatic.<br>2-effective against intracellular and extracellular bacilli. | 1-bactericidal<br>2- prodrug<br>3- **active against intracellular bacilli only.** | 1- Bactericidal.<br>**2- activates mainly on extracellular bacilli.** |
| Mechanism of action | 1-is a prodrug (inactive) then activated by mycobacterial enzyme (enzyme produced by the organism).<br>2- inhibits the synthesis of mycobacterial cell wall by inhibiting the synthesis of mycolic acid. | **inhibits RNA synthesis** by binding to DNA dependent RNA polymerase enzyme. | inhibits mycobacterial cell wall synthesis ( bins to arabinosyl transferase ). | Unknown. | inhibitors of protein synthe by binding to 30s ribosom subunits. |
| Clinical uses | 1-**mycobacterial infections.**<br>2- latent tuberculosis in patients with positive tuberculin test.<br>3-prophylaxis against active TB in individuals who are in great risk. | **1- mycobacterial infections**<br>2- prophylaxis of active tuberculosis.<br>**3- treatment of serious staphylococcal infections.**<br>4- meningitis by highly resistant penicillin pneumococci. | **treatment of tuberculosis in combination with other drugs.** | **1-mycobacterial infections mainly in multidrug resistance cases..**<br>**2- it is important in short – course (6 months) regimen.**<br>3- Prophylaxis of TB. | **severe, life-threating forr of TB as meningitis , disseminated disease.** |

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| **Adverse effects "important"** | 1- Peripheral neuritis (pin & needle sensation in the feet)<br>**2- Optic neuritis & atrophy.**<br>**Pyridoxine (vitamin B6) should be given in both cases)**<br>3- Hepatitis. | 1- Harmless red-orange discoloration of body secretions.<br>2- flu-like syndrome<br>**3- Hemolytic anemia.**<br>4- Hepatitis. | **1- impaired visual acuity.**<br>2- red-green color blindness.<br>3- contraindicated in children under 5 years. | 1- hepatotoxicity<br>2- hyperuricemia (precipitate gouty arthritis).<br>**3- drug fever and skin rash.** | **1- ototoxicity.**<br>2- nephrotoxicity.<br>3- neuromuscular block. |
| **Drug interaction** | Enzyme **inhibitor** (inhibits the hepatic microsomal enzyme especially cytochrome P450). | Enzyme inducer of hepatic microsomal enzymes (cytochrome P450). | | | |

Notes:

- Prodrug= inactive
- Mycolic acid= an important component that forms the cell wall
- Deficiency in vitamin B6 is the cause of peripheral and optic neuritis
- Streptomycin is the last choice we think of in case of tuberculosis (in case of disseminated TB)
- Neuromuscular block= muscle paralysis → streptomycin contraindicated before surgeries because the 2 muscle relaxants will potentiate each other and may cause respiratory failure
- Streptomycin is also contraindicated in pregnancy because it may pass through the placenta and cause deafness to the child

**2nd line treatment of tuberculosis:**

- Used when there is resistance to the drugs of 1st line
- Failure of clinical response
- There is contraindication for the 1st line drug
- Used in typical and **atypical** tuberculosis

Note: the doctor said it is not important to memorize everything about every drug just know them and know the drugs of 2nd line.

| The drug | Ethionamide | Fluoroquinolones (ciprofloxacin) | Refabutin | Aminosalicylic acid (PAS |
|---|---|---|---|---|
| General information | inhibits the synthesis of mycobacterial cell wall through inhibition of mycolic acid<br>- | effictive against multidrug-resistant tuberculosis | 1- RNA inhibitor<br>**2- cross-resistance with Rifampin is complete**<br>**3- enzyme inducer for cytochrome P450** | 1- bacterostatic<br>**2- inhibits folic acid synthesis** |
| Clinical uses | as a secondary line agent | | effective in prevention and treatment of typical and atypical TB | As a second line agent i treatment of pulmonar and other forms of TB |
| Adverse effects | **Poorly tolerated because of:**<br>• **Severe gastric irritation**<br>• Neurological manifistations | | **1- GIT intolerance**<br>2- orange-red discoloration of body secretions | 1- GIT upset<br>**2- hypersensitivity reactions**<br>**3- crystalluria** |

Notes:

- Ethionamide: isn't from the first line drug because of its side effect
- Folic acid is responsible for the growth of the organism

TB and pregnancy:

- **Untreated TB represents a great risk to the pregnant women and her fetus than the treatment itself**
- First line drugs are given for 9 months in normal doses
- Streptomycin is the last alternative in treatment

TB and breast feeding:

- Is not a contraindication to receive drugs, but caution is recommended.

## Notice that:

There is a drug for the 2nd line which not included in the lecture slide but the male's doctor said it

I don't know if it important or not!

Which is:

Cycloserine :

- 2nd line drug.
- MOA: cell wall synthesis inhibitor
- Rout: Taken orally
- Main Adverse effect: peripheral neuropathy + CNS symptoms "depression , psychosis etc.."