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Lecture (24)
Drug therapy of Tuberculosis

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(Pharmacology)

ILOs:

1. Name the classification of drugs used for treatment of tuberculosis.
2. Describe the mechanism of action of different antituberculous drugs.
3. Enumerate the adverse effects and contraindications of antituberculous drugs.
4. Describe the therapeutic regimen for treatment of TB case.

1- Which one of the following antitubercular drugs induce metabolic liver enzyme?

a) Rifampin

b) Isoniazid

c) Streptomycin

d) Ethambutol

2- Which one of the following antitubercular drugs act best in acidic Ph?

a) Isoniazid

b) Pyrazinamide

c) Streptomycin

d) Rifampin

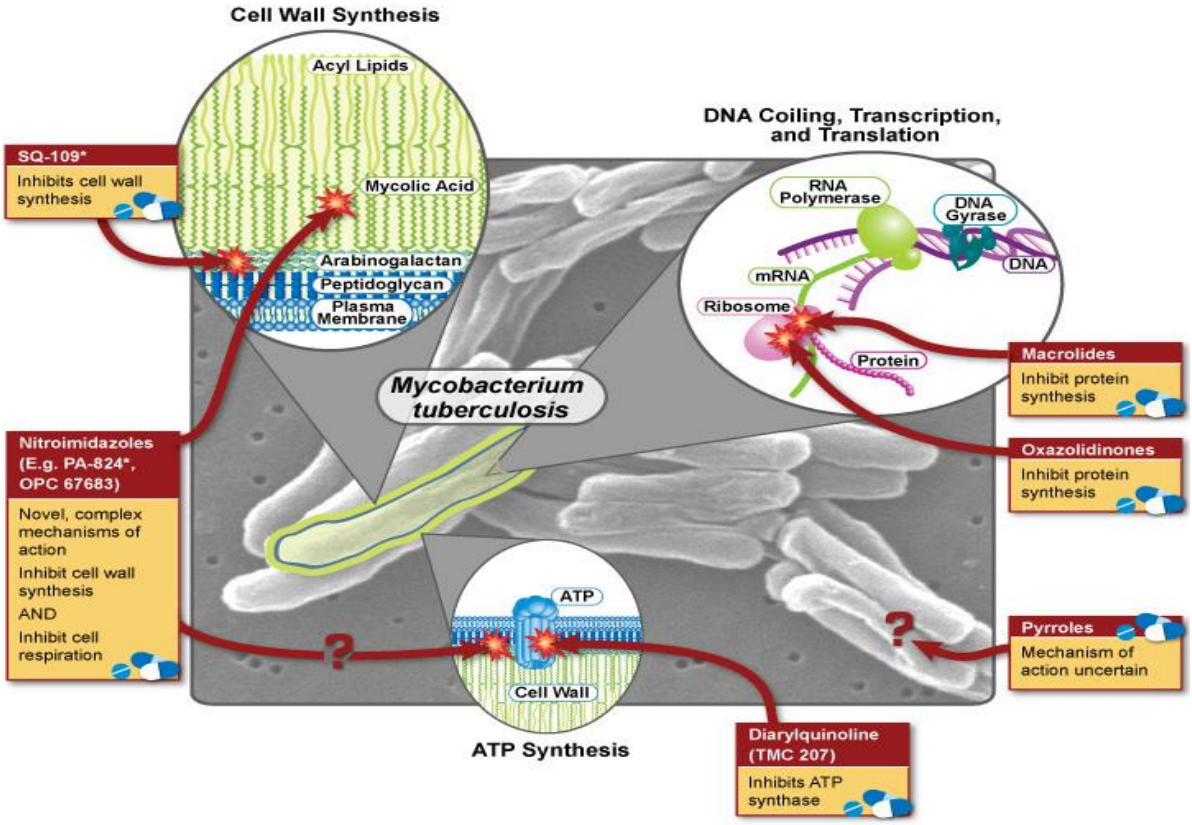
background

- More than **one-quarter** of the world's population has been infected with *M. tuberculosis.*
- **Tuberculosis (TB)** is an infectious disease caused by Mycobacterium tuberculosis bacteria.
- Tuberculosis generally affects **the lungs**, but it can also affect other organs of the body.
- **The first line drugs for treatment of TB: Isoniazid, Rifampin, Pyrazinamide, Ethambutol.**

Antituberculous drugs

First line drugs	Second line drugs
1-Rifampin 2-Isoniazid (INH) 3-Pyrazinamide 4-Ethambutol	1- Streptomycin and other aminoglycosides like amikacin and kanamycin 2- Ethionamide 3- p-aminosalicylic acid (PAS) 4- Imipenem-cilastatin 5- Fluroquinolones.

The site of action of (anti-TB drugs)



Isoniazid (Isonicotinylhydrazide) (INH)

- Isoniazide **inhibits mycolic acid synthesis** (one of mycobacterial cell wall components) of the **mycobacterial cell wall**.
- Bacterial catalaseperoxidase (encoded by KatG) is needed to **convert INH to active metabolite.**
- This explains **the activity of INH** on certain bacterial cells like **mycobacterial tuberculosis**.

Clinical uses of Isoniazid

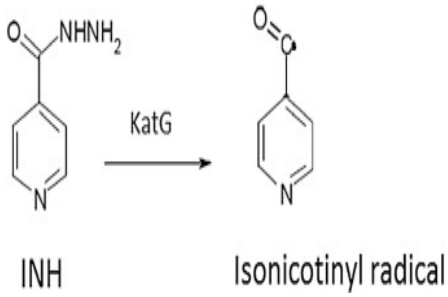
1-**Treatment of Mycobacterium tuberculosis infections (with Rifampin and other drugs).**

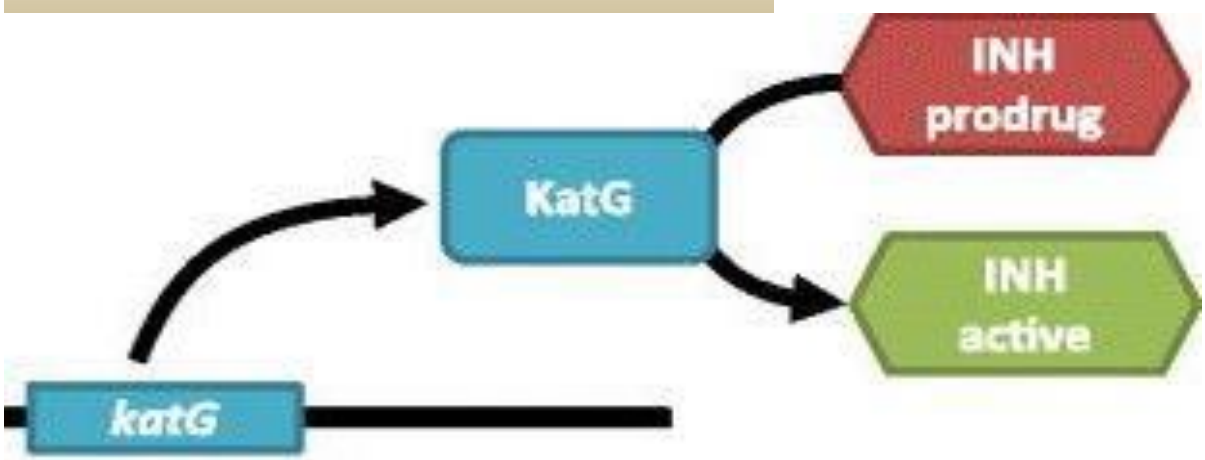
2- **Prophylaxis against tuberculosis among contacts to patients suffering from disease** (Isoniazid is the only agent that can be used alone).

3- **As monotherapy** Isoniazid is used for **latent TB control.**

Resistance of mycobacterial cell to INH

KatG mutation or deletion is the main source of developing resistance to INH.





Adverse effects of isoniazid

1- **Hepatotoxicity.**

2- **Drug interactions** **(isoniazid inhibit cytochrome** P-450)

3-**Drug-induced systemic lupus erythematous** (SLE).

4- **Metabolic acidosis.**

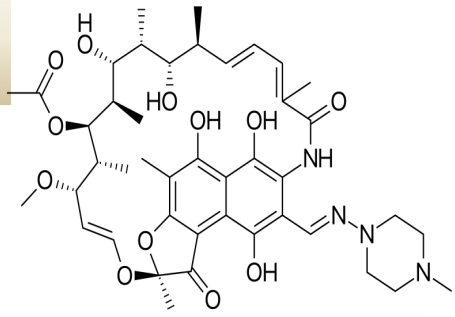
5-**Vitamin B6 deficiency** (which may lead to peripheral **neuropathy and anemia).**

6-**Seizures** **(in high doses, refractory to** benzodiazepines).

Isoniazid and pyridoxine (vit. B6)

- **pyridoxine (B6)** should be given with **isoniazid** to prevent certain adverse effects like **peripheral neuropathy** especially in **slow acetylates**.
- **Isoniazid** is **contraindicated** in patients with **acute liver failure**, **severe uncontrolled diabetes**, **anemia** from pyruvate kinase and G6PD deficiencies and **severe neuropathy**.

Rifamycins (Rifampin)



- **Rifampin (U.S), rifampicin (Europe), rifapentine and rifabutin.**
- Rifampin **binds** to the **β-subunit of DNA-dependent RNA polymerase** (*rpoB*) to form a **stable drug-enzyme complex**. This binding **inhibits RNA synthesis.**

Clinical uses of Rifampin

1- Rifampin has **antibacterial activity** against ***M. tuberculosis*** and ***M. leprae*** (causing leprosy).

2- **Staphylococcal endocarditis** or **osteomyelitis**

3- Used for **meningococcal prophylaxis and chemoprophylaxis** in contacts of children with ***H. influenzae*** type b.

Adverse effects of Rifampin

1- **Hepatotoxicity.**

2- **Orange-tan discoloration** of **skin, urine, feces, saliva, and tears.**

3- **Drug interactions:** it **induces cytochrome P-450** with concomitantly given drugs decreasing their $t_{½}$ (e.g. **propranolol, cyclosporine, corticosteroids, oral contraceptives**)

Resistance to Rifampin in mycobacterial infections

- 1- **Mutation** in the **rpoB gene** reduce drug binding to RNA polymerase.

N.B. **Monotherapy** leads to resistance.

Remember
Rifampin's 4 R's

1.RNA polymerase inhibitor.

2.Ramps up microsomal cytochrome P-450.

3.Red/orange body fluids

4.Rapid resistance if used alone

Pyrazinamide

- Pyrazinamide is a **prodrug** that is converted to the active compound **pyrazinoic acid.**
- Pyrazinamide **inhibits mycobacterial cell membrane** after being **converted into pyrazinoic acid** by **acidic medium induced by inflammatory cells.**
- **It works best at acidic pH**
- **Clinical use**: ***Mycobacterium tuberculosis*** (with other drugs).
- **Adverse effects**: **Hyperuricemia**, **hepatotoxicity**.

Ethambutol

- **Mechanism of action: decreases carbohydrate polymerization** of **mycobacterium cell wall** by blocking **arabinosyltransferase**.

Arabinose —(arabinosyl transferase III)→ **arabinogalactan**

- **Clinical uses:** Mycobacterium tuberculosis (with other drugs).
- **Adverse effects:**

1-Optic neuropathy (red-green color blindness, may be reversible).

2-Hyperuricemia.

Streptomycin

- **Mechanism of action:** It is a member of aminoglycosides (**interferes with 30s** component of **ribosome** leading to **irreversible inhibition of bacterial protein synthesis).**
- **Clinical use:** **mycobacterium tuberculosis** (2nd line).
- **Adverse effects**: **tinnitus**, **vertigo**, **ataxia**, **nephrotoxicity.**
- **Contraindicated** in **pregnancy** and **renal failure.**

Therapeutic regimen for TB

- **Six months of treatment with isoniazid (INH), pyridoxine (vitamin B6), and rifampin**, **supplemented during the first 2 months with pyrazinamide and ethambutol.**

(A current global challenge is the rise of multidrug-resistant (MDR) and, more recently, extensively drug-resistant (XDR) Tuberculosis).

- **MDR-TB** is resistant to at least **rifampin and isoniazid. XDRTB** is additionally **resistant to several second-line therapies.**
- The treatment of **drug-resistant TB** depends heavily on **culture sensitivities.**

❖**Latent tuberculosis infection (LTBI) treatment for** individuals with a positive PPD but no active disease generally consists of 9 months of **INH plus pyridoxine.**

❖**Note that** this is not an appropriate regimen for active TB (active TB needs combination of TWO or more anti-TB rugs).

REFERENCES:

1- First aid for the basic sciences organ systems: Chapter 10 page 827 - 8 29.

2- First aid USML page 196- 1 98.