Drug Treatment of Tuberculosis

EDITED SLIDES

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Edited by: Anas Ananzeh

Dr Munir Gharaibeh, MD, PhD, MHPE
Department of Pharmacology
School of Medicine
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Drug Treatment of Tuberculosis

Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 (above HIV/AIDS). In 2018, 1.7 billion people were infected by TB bacteria.

Recommended Duration of Therapy

TB needs prolonged treatment, also a combination treatment.
one drug isn't enough

Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥24

not for memorization

Antituberculous Agents

Primary or First Line Drugs:

we use first line drugs first, then if they didn't work we can try other drugs

Isoniazid (INH) الأهم

Rifampin "Rifadin" or "Rimactane" مهم

Ethambutal

Pyrazinamide

أقل أهمية

Streptomycin: in patients that have previously been treated for TB.

Isoniazid(INH)

- Most active.
- Small molecule, water soluble, -> easily absorbed
- Structurally related to Pyridoxine. (vitamin B6)

it's prodrug in human body, but when it reaches the mycobacterium it's converted to active drug -> So, Low toxicity

- Prodrug, activated by KatG(the mycobacterial catalase-peroxidase).
- Blocks mycolic acid synthesis, and consequently mycobacterial cell wall synthesis, leading to a bactericidal effect in growing TB cells. (very specific)

isonicotinic acid hydrazide

Isoniazid (INH)

- When used alone, resistance is 1 in 10^6.
- A TB lesion usually contains more than 10^8 cells.
- When used in combination, the probability of resistance will be 1 in

$$10^6 * 10^6 = 10^{12}.$$

(more than the quantity of cells found in the lesion) so resistance is negligible.

- Readily absorbed
- Widely distributed, penetrates into macrophages.
- Metabolized by acetylation:
  - Slow and Fast Acetylators

Isoniazid(INH)

- **Adverse Reactions:**

Hepatitis: in about 1% especially in the fast acetylators

nausea vomiting

- **Anorexia, N,V, jaundice, pain, death.**
- **Depends on age, alcohol use, and pregnancy**

Neuropathy:10-20%

TB patients usually have malnutrition (because they're probably from poor nations)

- **More in slow acetylators, malnutrition, alcoholism, DM, AIDS, uremia.**
- **Due to pyridoxine deficiency.** The treatment is by supplemental pyridoxine doses

Neurotoxicity: Memory loss, Psychosis, Seizures.

Neuropathy is different from Neurotoxicity,
Neuropathy: peripheral
Neurotoxicity: Central

Hematologic Tinnitus GI irritation Drug interactions

Hematologic, Tinnitus, GIT, Interactions

Rifampin

derived from

- ***Stretomyces miditerranei.***
- **Gram+ve and –ve** (effective against Gram+ and Gram-), so it's a wide spectrum antibiotic
- **Mycobacteria, enterococci and chlamydia.** TB
- **Binds to the beta subunit of bacterial DNA-dependant RNA polymerase and therefore inhibits RNA synthesis.**

Rifampin

- Bactericidal
- Well absorbed, highly bound to proteins.
- Widely distributed.
- Hepatic metabolism and exhibits enterohepatic recirculation.

Uses of Rifampin

- TB
- Leprosy الجذام
- Meningococcal Carrier State
- Prophylaxis in *H.influenzae.*
- Serious Staph osteomyelitis and valve endocarditis.
- Was *loosely used in the treatment of Staph infections.*

Toxicity of Rifampin

- Imparts harmless orange color to secretions(tears, urine, sweat).
- Nephritis
- Rashes
- Hepatitis
- Flu-like syndrome
- Liver Enzyme Inducer, so can lower serum levels of many drugs

Streptomycin

- First aminoglycoside antibiotic, 1943.
  it was the primary drug → then shifted to second line drugs
- Primary---Second-line------ Primary anti-tuberculus agent.
  nowadays, it's a primary anti-tuberculus agent
  Used for:
- Plague, Tuleremia, Brucellosis.
- Endocarditis.

Toxic:

Allergy: Fever, Rashes

Pain, after i.m. injection.

Vestibular toxicity---- Irreversible.

The most important toxicities are:
- Hearing loss
- Renal failure
even if the drug was stopped, the hearing won't be restored :(

Antituberculous Agents

Secondary or Second Line Drugs:

- Ethionamide
- Capreomycin
- Cycloserine
- Para-Amino-Salicylic Acid (PAS)
- Amikacin
- Flouroquinolones
- Linezolid
- Rifabutin
- Rifapentine

Indications for Secondary or Second Line Drugs

- 1. Resistance to first –line drugs.
- 2. Failure of clinical response to conventional therapy.
- 3. Occurrence of serious treatment-limiting adverse drug reactions.
- 4. When expert guidance is available to deal with the toxic effects to second line drugs.

(they have so many serious side effects)

Secondary or Second Line Drugs

Ethionamide:

Related to Isoniazid

Blocks mycolic acid synthesis

Oral, Good distribution

Poorly tolerated:

- Severe GIT irritation
- Neurotoxic
- Hepatotoxic

Secondary or Second Line Drugs

antibiotic

Capreomycin:

Peptide protein synthesis inhibitor

Injectable

Nephrotoxic, ototoxic

Local pain and sterile abscesses may occur.

Secondary or Second Line Drugs

Cycloserine:

Inhibits cell wall synthesis.

Peripheral neuropathy and CNS toxicity including depression and psychotic reactions.

Secondary or Second Line Drugs

Para-Amino-Salicylic Acid (PAS):

Folate synthesis antagonist Causes folic acid deficiency

Well absorbed

Dose 8-12 gm/day, *Too large !!!*

Widely distributed, except CNS

Excreted in urine.

GI toxicity

Hypersensitivity reactions

Crystalluria

Secondary or Second Line Drugs

- **Amikacin:**

Another aminoglycoside antibiotic.

Used for

Multidrug-resistant strains

Atypical mycobacteria

Secondary or Second Line Drugs

- **Flouroquinolones:**

Examples: Ciprofloxacin and Moxifloxacin

Are an important addition

Resistance develops rapidly if used alone.

This is a general rule in all TB drugs

Secondary or Second Line Drugs

Linezolid:

Multidrug-resistant strains.

Bone marrow suppression

Irreversible peripheral and optic neuropathy.

Drug of last resort الملاذ الأخير

Secondary or Second Line Drugs

Rifabutin
Rifapentine

Related to Rifampin.

Inhibit bacterial RNA polymerase.

Both, like Rifampin, are inducers for CYP P450 enzymes. But Rifabutin is less potent inducer.

Rifabutin is indicated in place of Rifampin in the treatment of TB in HIV-infected patients receiving protease inhibitor or nonnucleoside reverse transcriptase inhibitor (e.g. efavirenz)

We use Rifabutin to reduce the breakdown of the antiviral drug

Drug-Resistant TB (3)

Mono-resistant	Resistant to any one TB treatment drug
Poly-resistant	Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)
Multidrug resistant (MDR TB)	Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs
Extensively drug resistant (XDR TB)	Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin, kanamycin, or capreomycin)

Isoniazid and rifampin are active

Resistant to the 2 main drugs (isoniazid and rifampin)

Resistant to isoniazid, rifampin and others...

- Annually, 9 million cases are recorded.
- 5% of these are multi drug-resistant tuberculosis.
- Forty-nine percent of those with XDR-TB died compared to 19 percent of patients with ordinary MDR-TB,

IT CAN TAKE

resistant TB take 2 years for treatment.
No resistant -> 6-9 months are enough for treatment

WE NEED BETTER TREATMENT NOW