Antimycobacterial Drugs

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Antimycobacterial Drugs

Treatment of tuberculosis has become difficult in recent years, because of:

1. **Development of multidrug-resistant mycobacteria (to at least isoniazid and rifampin), which results from:**
   a) **Noncompliance with medication**
   b) **Incorrect drug selection**
   c) **Ineffective serum concentration**
2. **The acquired immunodeficiency syndrome (AIDS): increased incidence of TB to 170 times more than the general population.**

Antimycobacterial Drugs

1. **First-line drugs:** **Isoniazid, Rifampin, Ethambutol, Pyrazinamide.**
2. **Second-line drugs:** **Ethionamide, Aminosalicylic acid, Cycloserine, Capreomycin, Amikacin, Kanamycin, Streptomycin, Ciprofloxacin, levofloxacin, Linezolid, Clofazimine, Rifabutin & Rifapentine.**

Antimycobacterial Drugs

- **Isoniazid and rifampin are the most active drugs and will cure >95% of cases caused by susceptible strains.**
- **An initial intensive phase of treatment is recommended in the first 2 months due to the prevalence of resistant strains.**
- **Therapy is usually initiated with a four-drug regimen of either isoniazid, rifampin, pyrazinamide and ethambutol OR isoniazid, pyrazinamide, rifapentine, and moxifloxacin until susceptibility of the clinical isolate has been determined.**

Antimycobacterial Drugs

- **In susceptible isolates, the continuation phase consists of an additional 4 months with isoniazid and rifampin OR an additional 2 months of rifapentine, moxifloxacin, and isoniazid.**
- **Neither ethambutol nor other drugs adds substantially to the overall activity of the regimen and can’t reduce treatment duration, but the fourth drug is included in the traditional regimen in case the isolate proves to be resistant to isoniazid, rifampin, or both.**
- **Addition of pyrazinamide will shorten duration of therapy from 9 to 6 months.**

Recommended Duration of Therapy of TB

Regimen	Months
Isoniazid + Rifampin + Pyrazinamide	6
Isoniazid + Rifampin	9
Rifampin + Ethambutol + Pyrazinamide	6
Isoniazid + Pyrazinamide + Rifapentine + Moxifloxacin	4
Rifampin + Ethambutol	12
Isoniazid + Ethambutol	18

Antimycobacterial Drugs

Combination therapy is required to overcome the development of resistance, a notorious property of mycobacteria, and to cover for the various populations of tubercle bacilli:

1. **Intracellular mycobacteria (macrophages): isoniazid, rifampin, pyrazinamide.**
2. **Extracellular mycobacteria (cavities): isoniazid, streptomycin, ethambutol, fluoroquinolones.**
3. **Resting mycobacteria (caseating granulomas): pyrazinamide (isoniazid & rifampin may also be effective).**

Isoniazid

- The most active drug for treatment of TB.
- Structurally similar to pyridoxine (vitamin B_6).
- Bactericidal for actively growing tubercle bacilli.
- It penetrates into macrophages and is active against both intra- and extracellular mycobacteria.
- It is a prodrug, that is activated by the mycobacterial catalase-peroxidase system.

Mechanism of Action:

- Inhibition of synthesis of mycolic acids, synthesis which are essential components of mycobacterial cell wall.

Isoniazid

Mechanism of Resistance:

- Mutation in the gene involved in mycolic acid synthesis resulting in reduced affinity for isoniazid.

Pharmacokinetics:

- Readily absorbed from GIT
- Peak concentration decreases when given with a fatty meal
- Al^{3+} interferes with its absorption
- Diffuses readily into all body fluids and tissues including CNS and penetrates caseous material.

Isoniazid

- **Metabolized by N-acetyltransferase:**
  a. (RA vs SA)
  b. Plasma concentration in RA is 1/3rd – ½ of that in SA
  c. t½ < 1 hour in RA and < 3 hours in SA
  d. If the drug is given daily, there are no therapeutic consequences in RA, but if given once per week, or in the presence of malabsorption, the concentration may be subtherapeutic.
- **No dose adjustment is needed in renal failure, but dose adjustment should be directed by plasma concentration for patients with severe hepatic insufficiency.**

Isoniazid

Adverse Effects:

The incidence and severity are related to dose and duration of treatment.

A. Allergic (or immunologic) reactions:

1. Occasional fever and skin rash.

2. Drug induced lupus syndrome.

B. Direct toxicity:

1. Isoniazid-induced hepatitis: major toxic effect, requires cessation of therapy, fatal, occurs in 1-3% of patients.

Isoniazid

- **Clinically, hepatitis manifests as loss of appetite, nausea, vomiting, jaundice and right upper quadrant pain.**
- **Histologically, hepatocellular necrosis.**
- **The drug should be discontinued promptly and not reused again.**
- **The risk of hepatitis increases with age, alcohol use, pregnancy and the postpartum period.**
- **Transient elevation of serum aminotransferases in 10-20% of patients, usually asymptomatic and does not require cessation of therapy (??).**

Isoniazid

2. Peripheral neuropathy:

- **Occurs in ~ 10-20% of patients, especially at high doses (>300 mg/day).**
- **More likely in SAs, malnutrition, alcoholism, diabetes, AIDS & uremia.**
- **Due to relative pyridoxine deficiency because of reduced formation of pyridoxal phosphate, and increased excretion.**
- **Can be prevented by coadministration of vitamin B_6 (10 mg/day).**

Isoniazid

3. CNS toxicity:

- **Less common**
- **Memory loss, psychosis, seizures**
- **Also can be prevented by vitamin B_6**
- **Others: Tinnitus, GIT irritation, pyridoxine deficiency anemia and hemolysis in G6PD deficiency.**

Drug Interactions:

It reduces the metabolism of phenytoin, carbamazepine, benzodiazepines, primidone, warfarin and others.

Rifampin

Mechanism of Action:

- It inhibits bacterial DNA-dependent RNA polymerase.
- Bactericidal for both intra- & extracellular mycobacteria.
- It does not affect human RNA polymerase.

Mechanism of Resistance:

Alteration (mutation) of the RNA polymerase resulting in reduced affinity for rifampin.

Rifampin

Antibacterial activity:

1. ***Mycobacterium tuberculosis***
2. ***Mycobacterium leprae***
3. **Gram positive bacteria: *Staphylococcus aureus***
4. **Gram negative bacteria: *E. coli, Proteus, Klebsiella, Brucella***
5. ***Neisseria meningitidis***
6. ***Haemophilus influenzae***
7. ***Chlamydia***

Rifampin

Pharmacokinetics:

- Well absorbed after oral administration.
- Absorption is delayed by co-administration of aminosalicylic acid.
- It is eliminated in bile and undergoes enterohepatic cycling & is excreted as deacylated metabolites in feces.
- It readily penetrates most tissues and phagocytic cells and into abscesses and lung cavities.
- It is highly plasma protein bound.

Rifampin

- **Adequate CSF concentrations are only achieved in the presence of meningeal inflammation.**
- **Dosage adjustment in renal and hepatic insufficiency is not necessary.**
- **It induces several drug metabolizing enzymes, and thus, the metabolism of several drugs: digitoxin, quinidine, propranolol, verapamil, cyclosporine, warfarin, theophylline, sulphonylureas, oral contraceptives, steroids, narcotics, zidovudine, protease inhibitors, ketoconazole, ….**

Rifampin

Therapeutic Uses:

1. **Mycobacterial infections: TB & Leprosy, and some atypical mycobacterial infections.**
2. **Alternative to isoniazid prophylaxis for patients who are unable to take it (close contacts of an active TB case).**
3. **Prophylaxis against meningitis due to *Neisseria meningitidis* and *Haemophilus influenzae* in persons in contact with active cases.**
4. **Elimination of meningococcal carrier state.**

Rifampin

6. Eradication of staphylococcal carrier state.
7. In combination with other agents, it is used for serious staphylococcal infections, such as osteomyelitis and prosthetic valve endocarditis.
8. In combination with ceftriaxone or vancomycin for highly penicillin-resistant strains of pneumococci.
9. Brucellosis.

Rifampin

Adverse Reactions:

1. It imparts a harmless orange color to urine, sweat, tears, contact lenses, sputum, and other secretions.
2. Allergic reactions: rash, thrombocytopenia & interstitial nephritis.
3. Cholestatic jaundice and occasionally hepatitis.
4. Commonly, light chain proteinuria.
5. Superinfections.
6. Elevation of hepatic enzymes.

Rifampin

7. It potentiates isoniazid hepatotoxicity, probably by increasing enzyme activity responsible for conversion of monoacetylhydrazine into a hepatotoxic intermediate.
8. If it is administered less often than twice weekly, it can produce a flu-like syndrome characterized by fever, chills, myalgia,..
9. Anemia, thrombocytopenia.
10. Acute renal tubular necrosis.
11. GIT irritation.

Pyrazinamide

Mechanisms of action:

- It is a prodrug that should be converted into its active form, pyrazinoic acid (POA), by bacterial pyrazinamidase.
- Pyrazinoic acid accumulates within the bacterial cell and disrupts multiple cellular processes, primarily the bacterial cell membrane.
- It interferes with membrane potential and transport functions, leading to a disruption in the energy production and nutrient uptake of the bacterium.
- This interference weakens the cell and contributes to its eventual death.

Pyrazinamide

- It disrupts mycobacterial cell wall synthesis by inhibition of fatty acid synthase which reduces the synthesis of fatty acids which are crucial components of the mycobacterial cell wall.
- The accumulation of POA in the bacterial cell lowers the intracellular pH, creating an acidic environment that is detrimental to bacterial survival.
- POA has been found to interfere with the bacterial stress response also.

Pyrazinamide

- **Resistance is due to a mutation that impairs conversion of the drug into its active form.**
- **Impairment of drug uptake by macrophages may also contribute to resistance.**

Pyrazinamide

Pharmacokinetics:

- **Well absorbed from GIT.**
- **It is taken up by macrophages and exerts its activity against mycobacteria residing within the acidic environment of lysosomes.**
- **Widely distributed in body tissues including inflamed meninges.**
- **Eliminated by hepatic metabolism and metabolites are excreted by glomerular filtration.**

Pyrazinamide

Adverse Reactions:

1. Hepatotoxicity: the major limiting adverse effect, dose-dependant, common (1-5% of patients).
2. Photosensitivity
3. Joint pain.
4. Hyperuricemia → acute gouty arthritis because of inhibition of uric acid excretion leading to arthritis.
5. GIT irritation: notorious nausea and vomiting .
6. Allergic reactions including drug fever.

Ethambutol

Mechanism of Action:

- Inhibition of the polymerization of arabinoglycan by arabinosyl transferase, an essential component of mycobacterial cell wall.
- It is bacteriostatic.

Mechanism of Resistance:

- Overexpression of the gene of an enzyme needed for formation of arabinoglycan.

Ethambutol

Pharmacokinetics:

- **Well absorbed orally.**
- **Crosses the blood-brain-barrier when the meninges are inflamed.**
- **Excreted 20% in feces and 50% in urine.**
- **Accumulates in renal failure**
- **The dose should be reduced by 50% when CL_{cr} < 10 mL/min, or administered 3 times weekly instead of daily.**

Ethambutol

Adverse Effects:

1. **Hypersensitivity reactions.**
2. **Retrobulbar neuritis: loss of vision, visual field defects and red-green color blindness.**

   a. most serious adverse reaction.

   b. the drug is contraindicated in children too young to permit vision assessment.

   c. dose-related, more likely at high doses (25 mg/kg/day) or if continued for several months.

Ethambutol

3. GIT irritation.
4. Peripheral neuritis.
5. Confusion, disorientation, headache.
6. Hyperuricemia → acute gouty arthritis.

Alternative, Second Line Drugs for TB

Indications:

1. **Resistance of drugs of first choice.**
2. **Failure of response to conventional therapy.**
3. **Treatment-limiting adverse drug reactions.**
4. **When expert guidance is available to deal with the adverse effects.**

Ethionamide

It is similar to isoniazid in mechanism of action, mechanism of resistance (with cross resistance between the two) and adverse effects but is bacteriostatic.

Adverse effects:

1. **Intense gastric irritation. The therapeutic dose is seldom tolerated by patients.**
2. **Peripheral neuropathy. Prevented by pyridoxine.**
3. **Convulsions.**
4. **Olfactory and visual disturbances.**
5. **Hepatotoxicity**

Capreomycin

- A peptide.
- Inhibits protein synthesis.
- Effective
- Used IM but produces significant local pain and may form sterile abscess at site of injection.
- Nephrotoxic
- Ototoxic to both auditory and vestibular divisions.

Cycloserine

- **Inhibits mycobacterial cell wall synthesis.**
- **It is a structural analog of D-alanine and it inhibits the incorporation of D-alanine into peptidoglycan.**
- **It also inhibits many gram positive and gram negative bacteria.**
- **It is widely distributed to tissues, including CNS.**
- **Eliminated by the kidney and the dose should be reduced by 50% if CL_{cr} <50 mL/min, or used 3 times weekly.**

Cycloserine

- **The most serious adverse effects are peripheral neuropathy and CNS dysfunction including, convulsions, depression and psychosis. Ameliorated by 150 mg/day pyridoxine.**
- **Needs therapeutic drug monitoring. Peak concentration of 20-40mg/L, 2-4 hours after the dose.**

Rifabutin

- Similar to rifampin (rifamycin derivative).
- Has similar activity and cross resistance
- Less potent inducer of drug metabolizing enzymes. Therefore, it is preferred over rifampin for TB in HIV infected patients who are receiving concomitant antiretroviral therapy (protease inhibitors or nucleoside reverse transcriptase inhibitors).
- **Rifapentine** is similar to rifampin.

Bedaquiline

- **Bedaquiline inhibits adenosine 5’-triphosphate (ATP) synthase in mycobacteria**
- **It has been associated with both hepatotoxicity and cardiac toxicity due to QTc prolongation and associated mortality.**

Pretomanid

- It requires selective activation in mycobacteria by reduction.
- It blocks mycolic acid synthesis and thus cell wall.
- It is metabolized by multiple pathways, in part by CYP3A4.
- It is excreted in both the urine and the feces.

Adverse effects:

- Neuropathy, headache, acne, anemia, gastrointestinal symptoms, elevated liver enzymes, rash, and hyperamylasemia.
- QT prolongation
- Others include pancreatitis, elevated creatine phosphokinase, electrolyte disturbances, and seizures.