Chapter-9

Antitubercular Agents

Mrs. Pooja Chauhan
Assistant Professor
Rajiv Gandhi Institute of Pharmacy
Faculty of Pharmaceutical Science & Technology
AKS University Satna, MP-India

ABSTRACT

Antitubercular agents are medications used to treat tuberculosis (TB), a serious infectious disease caused by Mycobacterium tuberculosis. These agents are categorized into first-line and second-line drugs based on their efficacy, toxicity, and role in TB treatment regimens. First-line antitubercular drugs, such as isoniazid, rifampin, pyrazinamide, and ethambutol, are the cornerstone of TB therapy due to their high potency and relative safety. These drugs are usually administered in combination to prevent the development of drug resistance and to effectively eradicate the bacteria. Treatment typically lasts for at least six months, with an initial intensive phase followed by a continuation phase. Second-line drugs, including fluoroquinolones and injectable agents like amikacin, are used when the first-line drugs are ineffective due to resistance or intolerance. The prolonged duration and complexity of TB treatment can lead to challenges with patient adherence, which is critical for preventing the spread of resistant TB strains. Advances in TB research aim to shorten treatment duration, improve drug efficacy, and reduce side effects. Additionally, public health strategies, including Directly Observed Therapy (DOT), are implemented to ensure compliance and successful treatment outcomes.

Introduction to Antitubercular Agents

Antitubercular agents are medications specifically used to treat tuberculosis (TB), an infectious disease caused by the bacterium Mycobacterium tuberculosis. TB primarily affects the lungs but can also impact other parts of the body, such as the kidneys, spine, and brain. The disease is a major global health issue, and effective treatment requires a combination of drugs to ensure the complete eradication of the bacteria and to prevent the development of drug-resistant TB strains. Antitubercular agents are divided into first-line and second-line drugs based on their effectiveness, toxicity, and role in treatment regimens.

Classification of Antitubercular Agents

1. **First-Line Antitubercular Drugs:** First-line drugs are the most effective and least toxic options for treating TB. They form the core of standard treatment regimens.
    - **Isoniazid (INH):** A bactericidal drug that inhibits mycolic acid synthesis, crucial for the bacterial cell wall. Example: Isoniazid.
    - **Rifampin (RIF):** A bactericidal antibiotic that inhibits bacterial RNA synthesis by binding to RNA polymerase. Example: Rifampin.

- **Pyrazinamide (PZA):** A bactericidal drug effective in acidic environments, such as within the macrophages where M. tuberculosis resides. Example: Pyrazinamide.
- **Ethambutol (EMB):** A bacteriostatic drug that inhibits cell wall synthesis by obstructing arabinosyl transferases. Example: Ethambutol.
- **Streptomycin:** An aminoglycoside antibiotic used in certain cases, particularly in severe TB infections. Example: Streptomycin.

2. **Second-Line Antitubercular Drugs:** Second-line drugs are used when first-line drugs are ineffective due to drug resistance or intolerance. They are generally more toxic and less effective than first-line drugs.
   - **Fluoroquinolones**
     - **Levofloxacin:** Example: Levofloxacin.
     - **Moxifloxacin:** Example: Moxifloxacin.
   - **Injectable Agents:**
     - **Amikacin:** Example: Amikacin.
     - **Capreomycin:** Example: Capreomycin.
   - **Other Second-Line Drugs**
     - **Ethionamide:** Example: Ethionamide.
     - **Cycloserine:** Example: Cycloserine.
     - **Para-aminosalicylic acid (PAS):** Example: PAS.
     - **Bedaquiline:** Example: Bedaquiline, used for multi-drug-resistant TB (MDR-TB).
     - **Delamanid:** Example: Delamanid, another option for MDR-TB.

3. ***Newer and Repurposed Drugs:*** Newer drugs and repurposed drugs are being developed and tested to improve TB treatment outcomes, especially for drug-resistant TB.
   - **Bedaquiline:** Used for multi-drug-resistant TB (MDR-TB).
   - **Delamanid:** Also used for MDR-TB.
   - **Linezolid:** Originally an antibiotic for Gram-positive bacteria, now repurposed for drug-resistant TB.

Examples of Treatment Regimens

Standard TB Treatment Regimen

- **Intensive Phase (2 months):** Isoniazid, Rifampin, Pyrazinamide, Ethambutol.
- **Continuation Phase (4-7 months):** Isoniazid, Rifampin.

MDR-TB Treatment Regimen

- **Customized based on resistance patterns:** May include second-line drugs such as fluoroquinolones (Levofloxacin, Moxifloxacin), injectable agents (Amikacin, Capreomycin), and newer drugs (Bedaquiline, Delamanid).

Isoniazid (INH)

1. **Mechanism of Action:** Isoniazid primarily inhibits the synthesis of mycolic acids, a key component of the mycobacterial cell wall. This disruption weakens the cell wall's structural integrity, making it more susceptible to damage and lysis by the immune system.

2. **Absorption and Bioavailability:** INH is well-absorbed from the gastrointestinal tract after oral administration. Its bioavailability is high, ranging from 60% to 100%. It achieves therapeutic levels in blood and tissues, including the lungs where TB infection occurs.

3. **Metabolism:** INH is metabolized in the liver by the enzyme N-acetyltransferase (NAT). Genetic variations in NAT can affect the rate of metabolism, leading to slow or fast acetylators. Slow acetylators are at an increased risk of INH toxicity.

4. **Excretion:** Metabolized INH and its acetyl derivatives are primarily excreted in the urine. The rate of excretion can vary based on NAT acetylator status.

5. **Drug Interactions:** INH can interact with other medications, including certain antiretroviral drugs, so it's important to be aware of potential drug interactions when treating patients with both TB and HIV.

Rifampin (RIF)

1. **Mechanism of Action:** Rifampin inhibits RNA synthesis by binding to the bacterial RNA polymerase, thereby preventing transcription of RNA from DNA. This disruption interferes with the production of vital bacterial proteins.

2. **Absorption and Bioavailability:** Rifampin is well-absorbed from the gastrointestinal tract, and its oral bioavailability is around 95%. It distributes well in various tissues, including the lungs and cerebrospinal fluid, making it effective against TB in different body compartments.

3. **Metabolism:** Rifampin is extensively metabolized in the liver, primarily through the cytochrome P450 enzyme system. It induces its own metabolism and can also induce the metabolism of other drugs, which may lead to decreased drug levels of co-administered medications.

4. **Excretion:** Metabolized rifampin is excreted in bile, and some reabsorption occurs in the small intestine. Only a small fraction of the drug is excreted in the urine.

5. **Drug Interactions:** Rifampin is known for its potent induction of cytochrome P450 enzymes, which can accelerate the metabolism of numerous drugs. This can lead to significant drug interactions, especially when co-administered with other medications. Clinicians need to be vigilant when prescribing rifampin alongside other drugs.

Ethambutol (EMB)

1. **Mechanism of Action:** Ethambutol disrupts the synthesis of the mycobacterial cell wall by inhibiting the formation of arabinogalactan, an essential component of the cell wall. It targets the enzyme arabinosyl transferase.

2. **Absorption and Bioavailability:** Ethambutol is well-absorbed from the gastrointestinal tract after oral administration, and its bioavailability is approximately 80%.

3. **Distribution:** Ethambutol distributes throughout various body tissues, including the lungs, where TB infection is prevalent.

4. **Metabolism:** Ethambutol is not significantly metabolized in the body.

5. **Excretion:** Ethambutol is primarily excreted unchanged in the urine, making it suitable for patients with impaired liver function.

6. **Adverse Effects:** Ethambutol can cause ocular toxicity, primarily affecting the optic nerve. Patients on EMB should be monitored for changes in vision, particularly color vision, and regular eye examinations are recommended to detect and prevent optic neuropathy.

Pyrazinamide (PZA)

1. **Mechanism of Action:** The exact mechanism of action of Pyrazinamide is not fully understood, but it is believed to disrupt the synthesis of mycolic acids in the mycobacterial cell wall and create an acidic environment within the bacterial cell, which impairs its function.

2. **Absorption and Bioavailability:** Pyrazinamide is rapidly and well-absorbed from the gastrointestinal tract. It achieves high concentrations in the tissues, including the lungs, where TB infection occurs.

3. **Distribution:** Pyrazinamide has good penetration into various body tissues, making it effective against intracellular mycobacteria.

4. **Metabolism:** Pyrazinamide is extensively metabolized in the liver, primarily by amidase enzymes, to its active form, pyrazinoic acid. The active metabolite is excreted in the urine.

5. **Excretion:** Both the parent drug and its metabolites are excreted in the urine, mainly in their conjugated forms.

6. **Adverse Effects:** Pyrazinamide can cause hepatotoxicity, and liver function should be monitored during treatment. It may also lead to hyperuricemia and gout in some patients.

Amikacin

1. **Mechanism of Action:** Amikacin is an aminoglycoside antibiotic that inhibits protein synthesis in the bacterial cell by binding to the 30S ribosomal subunit. This binding

disrupts the translation process, leading to faulty protein production and bacterial cell death.

2. **Administration:** Amikacin is typically administered intravenously (IV) or intramuscularly (IM). In the context of TB treatment, it is generally used as part of a combination regimen for multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).

3. **Absorption and Distribution:** After IV or IM administration, amikacin is rapidly absorbed and distributed widely throughout the body, including the lungs, where TB infection occurs.

4. **Metabolism and Excretion**: Amikacin is excreted unchanged by the kidneys. Its elimination depends on renal function, and dose adjustments are necessary in patients with impaired kidney function.

5. **Adverse Effects:** Amikacin can cause nephrotoxicity (kidney damage) and ototoxicity (hearing loss and vestibular dysfunction). Monitoring kidney function and hearing is crucial during treatment.

Capreomycin

1. **Mechanism of Action:** Capreomycin is a cyclic peptide antibiotic that disrupts protein synthesis by binding to the 70S ribosomal subunit in bacteria. This binding inhibits the translocation step in protein synthesis, leading to the accumulation of nonfunctional proteins and bacterial cell death.

2. **Administration:** Capreomycin is typically administered by intramuscular (IM) injection. It is used as a second-line drug for the treatment of MDR-TB and XDR-TB.

3. **Absorption and Distribution:** After IM injection, capreomycin is absorbed and distributed in various body tissues, including the lungs.

4. **Metabolism and Excretion:** Capreomycin is primarily excreted unchanged in the urine. Dose adjustments are necessary for patients with impaired kidney function.

5. **Adverse Effects:** Capreomycin can cause ototoxicity, nephrotoxicity, and neuromuscular blockade. Regular monitoring of kidney function and hearing is essential, and neuromuscular blockade may require the administration of calcium and/or neostigmine to reverse its effects.

Levofloxacin

1. **Mechanism of Action:** Levofloxacin is a fluoroquinolone antibiotic that interferes with bacterial DNA replication and repair by inhibiting DNA gyrase and topoisomerase IV. This disruption leads to the inhibition of bacterial growth and cell division.

2. **Administration:** Levofloxacin is usually administered orally. It is used as part of combination therapy for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).

3. **Absorption and Distribution:** Levofloxacin is well-absorbed from the gastrointestinal tract, and it achieves good distribution throughout the body, including the lungs where TB infection occurs.

4. **Metabolism and Excretion**: Levofloxacin is primarily excreted unchanged in the urine. Dose adjustments may be required for individuals with impaired renal function.

5. **Adverse Effects:** Levofloxacin can cause various side effects, including gastrointestinal symptoms, central nervous system effects, and, in rare cases, tendon rupture. Patients receiving levofloxacin should be monitored for any adverse reactions, and they should be educated about the potential risks of tendon damage.

Ethionamide

1. **Mechanism of Action:** Ethionamide disrupts mycobacterial cell wall synthesis by inhibiting the enzyme InhA, which is involved in the synthesis of mycolic acids. This disruption weakens the bacterial cell wall, making it more susceptible to damage and lysis.

2. **Administration:** Ethionamide is administered orally. It is used as part of multidrug regimens for the treatment of drug-resistant TB.

3. **Absorption and Distribution:** Ethionamide is well-absorbed from the gastrointestinal tract, and it distributes throughout various body tissues.

4. **Metabolism and Excretion:** Ethionamide is metabolized in the liver. One of its metabolites, the active form of the drug, is excreted in the urine.

5. **Adverse Effects:** Ethionamide can cause gastrointestinal side effects, including nausea, vomiting, and anorexia. Additionally, it may lead to hepatotoxicity and neurotoxicity. Patients should be closely monitored for these adverse effects, and liver function tests should be conducted regularly.

Streptomycin

1. **Mechanism of Action:** Streptomycin is an aminoglycoside antibiotic that disrupts bacterial protein synthesis by binding to the 30S ribosomal subunit, causing misreading of the genetic code and preventing the correct assembly of proteins in the bacterial cell.

2. **Administration:** Streptomycin is typically administered by intramuscular (IM) injection. It is used in combination with other drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB).

3. **Absorption and Distribution:** After IM injection, streptomycin is absorbed and distributed in various body tissues, including the lungs, where TB infection occurs.

4. **Metabolism and Excretion:** Streptomycin is primarily excreted unchanged in the urine. Dose adjustments are necessary for patients with impaired kidney function.

5. **Adverse Effects:** Streptomycin can cause nephrotoxicity (kidney damage), ototoxicity (hearing loss and vestibular dysfunction), and neuromuscular blockade. Regular monitoring of kidney function and hearing is essential, and neuromuscular blockade may require the administration of calcium and/or neostigmine to reverse its effects.

Bedaquiline

1. **Mechanism of Action:** Bedaquiline is a diarylquinoline antibiotic that inhibits ATP synthase, a key enzyme in mycobacterial energy metabolism. This disruption impairs the production of ATP, leading to bacterial cell death.

2. **Administration:** Bedaquiline is administered orally. It is used in the treatment of multidrug-resistant tuberculosis (MDR-TB) when other treatment options are limited.

3. **Absorption and Distribution:** Bedaquiline is well-absorbed from the gastrointestinal tract, and it achieves good distribution in various body tissues, including the lungs.

4. **Metabolism and Excretion:** Bedaquiline is primarily metabolized in the liver, primarily by cytochrome P450 enzymes, and is excreted in the feces. It has a long half-life, which allows for less frequent dosing.

5. **Adverse Effects:** Bedaquiline can cause QT interval prolongation on electrocardiograms, which may increase the risk of arrhythmias. Monitoring of cardiac function and regular ECG assessments are necessary during treatment. Additionally, it may lead to hepatotoxicity, arthralgia, and mild nausea.