ANTITUBERCULOSIS DRUGS

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Learning objectives

By the end of this lecture, you should be able to:

1. List the causative agents for tuberculosis (TB) and atypical tuberculosis
2. Define MDR TB
3. Classify ant-tuberculosis drugs
4. Explain the mechanism of action of some anti-TB drugs including their mechanism of action , side effects and drug interaction
5. Explain the rationale of corticosteroids use in the management of TB
6. Describe drugs that are used to treat atypical tuberculosis

ANTITUBERCULOSIS DRUGS

- These are drugs that are used in the treatment of T.B, a chronic disease caused by mycobacterium tuberculosis and atypical mycobacterium.

- The Cure of T.B is possible if one adheres strictly to the prescribed regimen.

Classification of Antituberculosis Drugs

Two types of classification are as follows :

- First line and second line Drugs
- Tuberculocidal and Tuberculostatic

Causative agents

- Mycobacterium tuberculosis (M. tuberculosis)
- Mycobacterium bovis (M. bovis)
- Mycobacterium africanum (M. africanum)
- Mycobacterium microti
- Mycobacterium canettii

First line Drugs

Isoniazide, pyrazinamide, Ethambutol ,Rifampicin

Second line Drugs

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Group	Medicine
A	Levofloxacin, Moxifloxacin, Linezolid , bedaquiline
B	Cycloserine or Terizidone , clofaZimine
C	Ethambutol , amikacin streptomycin, Prothionamide, Ethionamide ,Pyrazinamide , Meropenam, delamanid , Imipenem – cilastantin and para aminosalicylic acid

Tuberculocidal Drugs

Isoniazide, Refampicin, streptomycin, Amikacin, Kanamycin, Quinolones, Pyrazinamide,linezolide

Tuberculostatic Drugs

Ethambutol, cycloserine, ethionamide , clarythromycin, azithromycine, PAS.

The main obstacles in the effective treatment of T.B are:

- Patients non compliance to treatment
- Infection being chronic
- Metabolically hypoactive intracellular organisms
- Tendency to develop resistance

Questions

1. Which one of the following anti-TB drugs are first line?

a. Cycloserin
b. Isoniazide
c. Kanamycin
d. Streptomycin

2. Tuberculostatics drugs include:

a. Rifampicin
b. Ethambutal
c. Pyrazinamide
d. Cycloserine

N.B . Multe Drug Resistance (MDR) is defined as when there is drug resistant to isoniazide and refampicin. In MDR second line drugs and some first line drugs retaining sensitivity are used

Review of some objectives 1,2 and 3

Are we now able to?

1. List the causative agents for mycobacterium tuberculosis (TB)
2. Define MDR TB
3. Classify ant-tuberculosis drugs

Isoniazide

- It is a bacteriocidal drug and kills extra cellular and intra cellular organism. It is bacteriostatic to non proliferating bacilli and bacteriocidal to fast proliferating bacilli.

Mechanism of Action

- Inhibit the biosynthesis of mycolic acid the vital component of mycobacterial cell wall leading to cell death.

Pharmacokenetics

- **Absorption**. It is rapidly and completely absorbed. Food and anti acid interfere with its absorption.

- **Distribution.** It is well distributed through out the body. It is able to cross the blood brain barrier and producing concentrate similar to those found in serum.

- **Excretion** : Excreted through the kidney

- **Metabolism**. Metabolized by the liver by the process of acetylation into isonicotinic and monoacetylhydrazine

ADVERSE EFFECTS

- Fever, rash, hepatitis, peripheral neuropathy
- Rarely causes granulocytosis, eosinophilia, thrombocytopenia, convulsions and anaemia.
- Psychosis

Drug interaction.

- It inhibits the metabolism of some drugs, especially that of phenytoin

Refamycins

Refampicin, Refabutin

- Bacteriocidal antituberculosis drugs.
- In addition to activity against mycobacteria and typical mycobacteria Rifampicin has also activity against various gram + v and – v bacteria.

Mechanism of Action

Inhibits DNA dependant RNA polymerase leading to inhibition of RNA synthesis

Pharmacokenetics

- **Absorption** : Readily absorped from the GIT.
- **Distribution** : Well distributed through out the body and penetration through the non inflamed meninges is poor but able to attain therapeutic concertration. It impart orange colour to body fluidas like saliva, urine sputum and tears.
- **Excretion** : Partly excreted in the urine (30%) and the rest is metabolized by the liver.
- **Metabolism** : 70% of the Drug is metabolized by the liver and hepatic metabolites have some antibacterial activity.

Side Effects.

Hepatotoxic, discolouration of body fluids, rash, hypersensitivity

Drug Interactions

Increases metabolism of warfarin, Integrase inhibitors, Protease Inhibitors ,eastrogen and progestogens containing contraceptives

N.B : Rifabutin is a less potent inducer of cytochrome P3A than rifampin.

Ethambutol

It is a bacteriostatic antituberculosis drug, it is effective to almost all the strains of mycobacteria

Mechanism of Action

The precise mechanism of action is not known but it is shown to inhibit incorporation of myolic acid, into mycobacterial cell wall.

Pharmacokenetics

It is well absorbed from the GI, food and antiacid do not interfere with its absorption.

Distribution

It is well distributed through out the body reaches the **CSF** when the meninges are inflamed.

Excretion

A major part **(70%)** of the administered dose is excreted unchanged via the kidneys.

Metabolism. A small portion is metabolized by the liver.

Side Effects

Retrobulber neuritis, renal toxicity, fever, rash.
Retrobulbar neuritis leads to diminished visual acuity.

Contra – Indication

Children, Severe renal failure

Pyrazinamide

It is a derivative of nicotinic acid just as isoniazide. Its Mechanism of action is not known

Pharmacokenetics

- **Absorption** : It is well absorbed from the GIT.
- **Distribution** : well distributed throughout the tissue .It reaches the CSF when the meninges are inflamed therefore suitable for tuberculosis meningitis.
- **Excretion** : The metabolites of it are excreted via the kidney and it competes with uric acid for tubular secretion leading to increased uric acid stores in the body.
- **Metabolism.** It is metabolized by the liver

Side Effects

Hepatotoxicity (most common side effects) nausea and vomiting.

Gout(joint pains)

Questions

1. Which one of the following ant-TB drugs are hepatotoxic?

a. Ethambutol
b. Pyrazinamide
c. Isoniazide
d. Streptomycin
e. Rifampicine

2. Which one of the following anti-TB drug can induce Gout ?

a. Ethambutol
b. Cycloserine
c. Isoniazide
d. Pyrazinamide

3. Which one of the following ant-TB can cause psychosis?

a. Isoniazide
b. Rifampicine
c. Ethambutol
d. Pyrazinamide

Second line Drugs

Kanamycin and Amikacin

- They are aminoglycosides used in the management of resistant tuberculosis and other atypical mycobacterium tuberculosis.

- Mechanism of Action, Pharmacokenetics and side Effects refer to aminoglycosides.

Cycloserine

Mechanism of Action

- It is an analogue to amino acide – alanine. Therefore it inhibits the incorporation of D – alanine within the mycobacterium cell wall. It is bacteriostatic.

Pharmacokenetics

Absorption.

- It is well absorbed from the G1T, food and antacids do not interfere with its absorption.

Distribution

- It is well distributed and the plasma concentration is the same as that in the **CSF**.

- **Excretion and Metabolism**
- Half of the drug is metabolized in the liver and half of the drug is excreted unchanged via the kidneys.

Adverse Effects.

The main hindrance are CNS effects such as

- Headache
- tremors,
- Convulsions
- psychiatric symptoms
- visual disturbances
- vertigo

Ethionamide

It is a derivative of thionicotinic acid. It is active against both extra cellular and intracellular mycobacteria and atypical. It is extensively metabolized in the liver.

Side Effects.

- Mostly G1T
- Hepatotoxicity

Other Newer Anti – T.B Drugs in use includes

Quinolones.

- Ciprofloxacin
- Ofloxacin and levofloxacin

Macrolides.

- Clarythromycin – 4 times active than azithromycin against, atypical mycobacteria.
- Azithromycin. It has good tissue penetration than clarythromycin. Tissue concentration is twice as much as that is found in the plasma

Bedaquiline

Mechanism of action:- Inhibits the proton pump of mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in Mycobacterium tuberculosis.

- Bacterial death occurs as a result of bedaquiline.

Pharmacokinetics

Abosorption:

- Tmax, oral dose = 5 hours;
- Food increases the oral bioavailability.
- AUC increases proportionally up to the highest dose.

Distribution:
Vd, central compartment = 164 L
>99.9 bound to plasma proteins

Metabolism:
- Hepatically metabolized.
- The main enzyme involved is CYP3A4 which metabolizes bedaquiline into the N-monodesmethyl metabolite (M2).
- This metabolite is 4 to 6-times less active in terms of antimycobacterial potency

Elimination

- Primarily elimination in the feces.
- Renal clearance of unchanged drug is insignificant

Adverse effects

≥10% of patients, nausea, arthralgia, and headache.

Linezolid

Mechanism of Action:
Binds to bacterial 23S rRNA of the 50S subunit to prevent protein translation; also elicits nonselective MAO inhibition

Pharmacokinetics

Absorption
Rapid and extensive
Bioavailability: 100%
Peak plasma time: 1-2 hr

Distribution
Protein bound: 31%
Vd: 40-50 L

Metabolism
Hepatic via oxidation of the morpholine ring, resulting in 2 inactive metabolites (aminoethoxyacetic acid, hydroxyethyl glycine); does not involve CYP

Elimination
Half-life: 4-5 hr (adults); 1.5-3hr
Clearance: Nonrenal (65% of total clearance)
Excretion: Urine (80% of administered dose [30% unchanged, 50% metabolites]); feces (9% [metabolites])

Adverse Effects

Diarrhea(common)
Headache(common)
Nausea, Vomiting, Dizziness, Hypersensitivity, Vaginal moniliasis, Taste alteration, Oral moniliasis, Abnormal LFTs, Fungal infection, Localized abdominal pain,Tongue discoloration, Generalized abdominal pain

Clofazimine

Mechanism of Action

Exerts a slow bactericidal effect on Mycobacterium inhibits mycobacterial growth and binds preferentially to mycobacterial DNA; however, its precise mechanisms of action are unknown

Absorption
45-62% (PO): variable absorption rate in patients with leprosy
Serum concentration: 0.7-1 mcg/mL (100-300 mg/day)

Distribution
Highly lipophilic and tends to be deposited predominantly in fatty tissue and in cells of the reticuloendothelial system; taken up by macrophages throughout the body

Elimination
Half-life: 70 days (at steady state)
Excretion: Negligible in urine; small amount in feces and bile; small amount sputum, sebum, and sweat

Adverse Effects:
Rash and pruritus
Ocular: Conjunctival and corneal pigmentation due to crystal deposits, dryness, burning, itching, irritation
Discoloration of urine, feces, sputum, sweat
Increased blood glucose, Increased ESR

Class	Drug(s)	Mechanism of action
Diarylquinoline	Bedaquiline	Interferes with how bacterial cells make energy by targeting the proton pump adenosine triphosphate synthase.
Ethylenediamine	SQ109	Disrupts bacterial cell-wall construction by disturbing the assembly of mycolic acids, possibly by targeting the MmpL3 protein; in vitro activity has yet to be confirmed in humans.
Fluoroquinolone	Gatifloxacin, levofloxacin, moxifloxacin, ofloxacin	Disrupts bacterial replication by inhibiting the DNA gyrase enzyme, thus preventing bacterial DNA from unwinding and duplicating.
Nitroimidazole	Delamanid, PA-824, TBA354 (preclinical)	Destabilizes the bacterial cell membrane by blocking the synthesis of mycolic acids; poisons the bacterial cell by releasing nitric oxide when metabolized.
Oxazolidinone	AZD5847, linezolid, sutezolid, tedizolid (for MRSA)	Blocks protein synthesis (translation) by inhibiting the initiation step at the ribosome.
Rifamycin	Rifabutin, rifampicin, rifapentine	Blocks messenger RNA synthesis (transcription) by inhibiting the bacterial DNA-dependent RNA polymerase.
Riminophenazine	Clofazimine	Unclear, but it appears that the bacterium's ineffective attempts to metabolize drug lead to cycle (redox cycle), which generates toxic reactive oxygen species within the bacteria; may target the bacterium's outer membrane by inhibiting the bacterial respiratory chain and ion transporters.

Substance	Common adverse effects	Management
	Group I	
Ethambutol	Optic neuropathy	Inform the patient to report decreased vision immediately. Discontinue and refer to an ophthalmologist if vision deteriorates
Pyrazinamide	Hepatotoxicity, rash, gout	Discontinue drug if hepatotoxicity occurs. For Rash manage symptomatically, if extensive stop drug and consider reintroduction
	Group II	
Amikacin; Capreomycin; Kanamycin	Ototoxicity, nephrotoxicity	Monitor levels, hearing and renal function monthly. If problems occur consider reducing dose frequency to three times a week. Discontinue if problems persist, but balance risk of cure versus deafness.
	Group III	
Levofloxacin; Moxifloxacin	GI disturbances, tendinitis, insomnia	QT interval prolongation may be potentiated with other drugs
	Group IV	
Para-Aminosalicylic Acid	Nausea and vomiting, gastritis, hepatotoxicity, hypothyroidism	Give antiemetics. Hypothyroidism: levotiroxine
Protionamide/Etionamide	GI disturbances, depression, hepatotoxicity, hypothyroidism	GI disturbances: initiate a stepwise approach to manage nausea and vomiting. Start antiemetics.
Terizidone/Cycloserine	Neurotoxocity, peripheral neuropathy	Give high dose pyridoxine, up to 50 mg for every 250 mg of drug. If neuropathy progresses discontinue drug. Discontinue if psychosis develops. Seizures can be amanaged with anitconvulsants but drug may ned to be discontinued.
	Group V	
Amoxicillin/Clav. acid	Hypersensitivity, GI disturbances	For serious allergic reactions, stop all therapy pending, resolution of reaction.
Clofazimine	Skin discolouration, GI disturbances	-
Imipenem, Meropenem	Hypersensitivity, neurotoxocity	Monitor blood count
Linezolid	Neuropathy, anaemia	Monitor blood count, avoid prolonged use. Stop if peripheral neuropathy or hematological problems occur.
Isoniazid (high dose)	Peripheral neuropathy, hepatotoxicity	Give with pyridoxine

The Role of Coticosteroids in T.B

- I deally corticosteroids are contra- indicated in active. T.B However, they can be used in the following situation.
- 1.Millary T.B with respiratory Distress
- 2. To prevent development of adhesions in tuberculosis meningitis pericarditis and pleural effusion.
- 3.As a replacement therapy in tuberculosis include adrenocorticac insufficiency.
- 4.Endobronchol tuberculosis.

- Prednisolone in the dose of 1- 2mg/kg/day for a period of four to six weeks is recommended.

Drugs used in treatment of atypical mycobacterial infections

- Atypical mycobacterial infections, also known as non-tuberculous mycobacterial (NTM) infections, are caused by mycobacteria other than Mycobacterium tuberculosis
- Mycobacterium avium complex (MAC):
- Mycobacterium kansasii:
- Mycobacterium abscessus:
- Mycobacterium fortuitum
- Mycobacterium chelonae: Similar to M. fortuitum

Macrolides:

- Clarithromycin and Azithromycin are often used as first-line agents.
- They inhibit protein synthesis in mycobacteria, leading to bacterial death.
- Common side effects include gastrointestinal upset and QT interval prolongation.

Fluoroquinolones:

- Ciprofloxacin and Levofloxacin are frequently used.
- They disrupt DNA replication and repair in mycobacteria.
- Potential side effects include tendonitis, tendon rupture, and QT interval prolongation.

Ethambutol:

1. This drug is often included in multi-drug regimens to prevent resistance.
2. It inhibits the formation of the mycobacterial cell wall.
3. Ocular toxicity (optic neuritis) is a concern and requires regular eye examinations.

Amikacin and **Streptomycin**:

1. Aminoglycosides are reserved for severe or resistant NTM infections.
2. They disrupt protein synthesis in mycobacteria.
3. Close monitoring for nephrotoxicity and ototoxicity is essential.

Rifamycins:

- Rifampin and Rifabutin are used less frequently but may be considered.
- They inhibit RNA synthesis in mycobacteria.
- Drug interactions with rifamycins are common due to their enzyme-inducing properties.

Linezolid:

- An oxazolidinone antibiotic that can be used for drug-resistant NTM infections.
- It inhibits protein synthesis in mycobacteria.
- Potential side effects include bone marrow suppression and neuropathy.

Doxycycline and Minocycline:

- Tetracyclines can be used as part of a multidrug regimen.
- They inhibit protein synthesis in mycobacteria.
- Photosensitivity is a common side effect.

Sulfonamides:

- Sulfamethoxazole-Trimethoprim is sometimes used in combination with other drugs.
- They interfere with folate metabolism in mycobacteria.
- Potential side effects include skin rashes and bone marrow suppression.

Clofazimine:

- Used in the treatment of Mycobacterium avium complex (MAC) infections.
- Its mechanism of action is not entirely understood.
- Skin discoloration (reddish-brown) is a common side effect.

Bedaquiline:

- A newer drug used in multidrug-resistant cases.
- It targets the mycobacterial ATP synthase.
- Cardiac arrhythmias can occur, so close monitoring is essential.

Review of objective 3 and 4

4. Explain the mechanism of action of some anti-TB drugs including their mechanism of action , side effects and drug interaction

5. Explain the rationale of corticosteroids use in the management of TB

END OF LECTURE