CHEMOTHERAPY

ANTI-MYCOBACTERIAL DRUGS

Dr Sindwa Kanyimba
Lecturer, Pharmacology

ANTI-MYCOBACTERIAL DRUGS

INTRODUCTION:

Anti-mycobacterial drugs are used in the treatment of mycobacterial infections

Mycobacteria are slow growing intracellular bacilli. In humans they cause tuberculosis (Mycobacterium tuberculosis), leprosy (Mycobacterium leprae) and atypical mycobacterial infections (caused by species of mycobacteria other than M. tuberculosis and M. leprae)

Mycobacteria differ in their structure and lifestyle from Gram-positive and Gram-negative bacteria, and are largely treated with different anti-microbial agents

ANTI-MYCOBACTERIAL DRUGS

LEARNING OBJECTIVES:

1. Describe the relevant pharmacology (mechanisms of actions, clinical indications, anti-microbial resistance, adverse effects, drug interactions, precautions and contraindications) of drugs used in the treatment of mycobacterial infections
2. Explain the rationale for prolonged therapy and combination therapy in the treatment of mycobacterial infections

DRUGS USED IN THE TREATMENT OF TUBERCULOSIS

TREATMENT OF TUBERCULOSIS (TB)

The aim of treatment in TB is to kill the dividing bacilli and to destroy the persisters in order to prevent relapse and ensure complete cure. This requires prolonged therapy.

Treatment of TB involves combination therapy:

- To delay the development of resistance
- To reduce toxicity
- To shorten the course of treatment

FIRST-LINE ANTI-TUBERCULOSIS DRUGS

1. Isoniazid
2. Rifampicin
3. Pyrazinamide
4. Ethambutol

ISONIAZID (INH, H)

- Structural analogue of pyridoxine
- MOA: Inhibits the synthesis of mycolic acids (by inhibiting the enzyme enoyl-acyl carrier protein reductase) which are important components of the mycobacterial cell wall (mycolic acids are unique to mycobacteria)
- Tuberculocidal for rapidly multiplying bacilli and tuberculostatic for resting bacilli
- Effective against both intracellular and extracellular organisms

ISONIAZID …. CONT'D

- It is the most active drug for the treatment of tuberculosis
- Active against mycobacterium tuberculosis only
- Administered in combination with other anti-TB drugs for treatment of TB
- For prophylaxis, INH is used alone

ISONIAZID …. CONT'D

Pharmacokinetics

- Completely absorbed orally and penetrates all tissues
- Metabolized by acetylation and the metabolite is excreted via the biliary tract. Metabolism of INH is genetically determined - patients can be fast or slow acetylators depending on genetic inheritance.

Drug interactions

Inhibits cytochrome P450 thereby reducing metabolism of some drugs (e.g. phenytoin)

ISONIAZID: ADVERSE EFFECTS

- Peripheral neuritis - due to interference with utilisation (inhibits pyridoxal kinase) and increased excretion of pyridoxine. More common in slow acetylators. Can be prevented by giving prophylactic pyridoxine.
- Hepatitis (due to the metabolite acetylisoniazid [acetylhydrazine]). More common in fast acetylators.
- Other adverse effects: psychosis, anorexia, GI discomfort, fever, allergic reactions and haemolysis in patients with G-6-P-D deficiency

RIFAMPICIN (R)

MOA: Inhibits DNA-dependent RNA polymerase thus inhibits RNA synthesis

Bactericidal to M.tuberculosis, M.leprae and atypical mycobacteria. Also inhibits most gram positive and gram negative bacteria.

Acts on both intra- and extracellular organisms

Resistance develops rapidly when the drug is used alone (due to reduced affinity for the drug by the RNA polymerase)

RIFAMPICIN: PARMACOKINETICS

- Well absorbed orally and penetrates all tissues
- Induces cytochrome P450 enzymes (hence accelerates metabolism of many drugs)

RIFAMPICIN: ADVERSE EFFECTS

- Hepatotoxicity
- GI disturbances: epigastric distress, nausea, vomiting, abdominal cramps, diarrhoea
- Flu-like syndrome (more common with intermittent dosing)
- CNS: headache, drowsiness, dizziness, ataxia, confusion, peripheral neuropathy
- Hypersensitivity reactions
- Stains sweat, tears, saliva and urine an orange red colour

RIFAMPICIN: CLINICAL INDICATIONS

- Tuberculosis, leprosy and atypical mycobacterial infections
- Prophylaxis of Haemophilus influenzae
- Treatment of resistant staphylococcal infections
- Brucellosis
- Eradication of carrier state of N. meningitidis, H. influenzae and S. aureus

RIFAMPICIN ANALOGUES: RIFABUTIN

- More active against atypical mycobacteria than rifampicin
- Less cytochrome P450 induction than rifampicin
- Can be used in place of rifampicin in patients receiving drugs that are substrates for cytochrome P450 (e.g. protease inhibitors)
- Can be used for multi-drug resistance tuberculosis (MDR-TB)

RIFAMPICIN ANALOGUES: RIFAPENTINE

- Its pharmacodynamics is similar to rifampicin but has a longer half-life
- Used once weekly in TB treatment after sputum cultures convert to negative (during the continuation phase of TB therapy)

PYRAZINAMIDE (PZ, Z)

- An analogue of nicotinamide
- MOA: Inhibits mycolic acid synthesis
- Active only against Mycobacterium tuberculosis
- Tuberculocidal for rapidly multiplying bacilli and tuberculostatic for resting bacilli
- Active against intracellular bacilli. Inactive at neutral pH, thus does not affect extracellular bacilli. Inhibits the bacilli in the phagosomes of macrophages where the pH is 5.

PYRAZINAMIDE …. CONT'D

- Well absorbed orally and penetrates all tissues
- Metabolised in the liver and the metabolites are excreted by the kidneys (the metabolites are toxic and can accumulate in renal impairment)
- Adverse effects: Hepatotoxicity, hyper-uricaemia with precipitation of gout (reduces excretion of uric acid), arthralgia, anorexia, vomiting and rashes

ETHAMBUTOL (E)

- MOA: Inhibits the incorporation of mycolic acids into the mycobacterial cell wall (inhibits arabinosyl transferases involved in this process)
- Acts on fast multiplying bacilli
- Also effective against atypical mycobacteria
- Well absorbed orally
- 50% of ethambutol is excreted in urine unchanged. It accumulates in renal failure and the dose should be reduced by half if creatinine clearance is less than 10mL/min.

ETHAMBUTOL: ADVERSE EFFECTS

- Causes reversible optic (retrobulbar) neuritis resulting in reduced visual acuity and inability to differentiate red from green
- Avoid in children because it is not easy to reliably test for visual acuity in them
- Other adverse effects: Nausea, anorexia, headache, fever, allergic reactions and gout precipitation (decreases excretion of uric acid)

SECOND LINE ANTI-TUBERCULOSIS DRUGS

Include ethionamide, streptomycin, amikacin, kanamycin, capreomycin, cycloserine, flouroquinolones, bedaquiline, delaminid, linezolid, clofazimine and rifabutin

The second line drugs usually considered only in the following cases:

- Resistance to first-line drugs
- Failure of clinical response to conventional therapy
- Serious treatment-limiting adverse drug reactions with the first-line drugs

ETHIONAMIDE

- An analogue of isoniazid, and acts by inhibiting synthesis of mycolic acid
- Does not exhibit cross-resistance with INH
- Effective against both intra- and extracellular organisms
- Also effective in atypical mycobacteria
- Poorly tolerated
- Adverse effects: Anorexia, nausea, metallic taste, hepatitis, skin rashes, peripheral neuritis (prevent with prophylactic pyridoxine)

CYCLOSERINE

- An analogue of d-alanine
- Inhibits cell wall synthesis
- Given orally
- Also effective against some gram positive organisms
- Adverse effects: Headache, depression, psychosis, tremors and seizures
- Should be given with pyridoxine to reduce neurotoxicity

STREPTOMYCIN, AMIKACIN, KANAMYCIN AND CAPREOMYCIN

- Streptomycin, amikacin and kanamycin are aminoglycosides, while capreomycin is a peptide antibiotic
- MOA: Inhibit 30s ribosomal subunit thereby inhibit protein synthesis
- Given parenterally
- Are ototoxic and nephrotoxic
- Amikacin is also effective against atypical mycobacteria

FLUOROQUINOLONES

- The fluoroquinolones that are used as second-line TB treatment are gatifloxacin, moxifloxacin, levofloxacin and ofloxacin
- Are active against Mycobacterium tuberculosis and atypical mycobacteria
- Useful in multi-drug resistance tuberculosis (MDR-TB) in combination with other drugs

BEDAQUILINE

- Bedaquiline inhibits adenosine 5′-triphosphate (ATP) synthase in mycobacteria thereby blocking the bacilli from making ATP
- It is active against both replicating and non-replicating bacilli
- Indication: MDR-TB in combination other medications for tuberculosis
- Given by mouth
- Adverse effects: Nausea, joint pains, headaches, chest pain, QT prolongation and liver dysfunction

DELAMINID

- MOA: Blocks the synthesis of mycolic acids thus destabilizing the bacterial cell wall
- Indication: MDR-TB in combination with other anti-tuberculosis drugs
- It is taken by mouth
- Adverse effects: Headache, dizziness, nausea and QT prolongation

LINEZOLID, CLOFAZIMINE AND RIFABUTIN

- Linezolid: Can be used in combination with other drugs to treat multi-drug resistant tuberculosis
- Clofazimine: Has shown activity against MDR-TB and is now recommended by WHO for use in combination with other drugs to treat MDR-TB as a medicine with "unclear efficacy"
- Rifabutin: An analogue of rifampicin that is effective in MDR-TB treatment in combination with other drugs

DRUGS USED IN THE TREATMENT OF ATYPICAL MYCOBACTERIAL INFECTIONS

DRUGS USED FOR MYCOBACTERIUM AVIUM COMPLEX (MAC)

- Drugs that are effective in MAC include: rifampicin, rifabutin, macrolides (clarithromycin and azithromycin), fluoroquinolones, ethambutol, clofazimine, amikacin and ethionamide
- The macrolides are highly effective and are the first choice drugs in MAC
- Rifabutin or a macrolide are used for prophylaxis

DRUGS USED IN THE TREATMENT OF LEPROSY

DAPSONE

- A sulfone related to sulfonamides
- Inhibits dihydropteroate synthetase, therefore inhibits synthesis of folic acid
- It is leprostatic
- Also used as a second-line drug in the treatment of pneumocystis pneumonia

DAPSONE: ADVERSE EFFECTS

Include:

- Anorexia, nausea, vomiting, hepatitis, agranulocytosis, and haemolysis in G-6-P-D deficiency
- Erythema nodosum leprosum: An inflammatory process that develops during dapsone therapy of lepromatous leprosy; suppressed by corticosteroids or thalidomide

CLOFAZIMINE

- A dye that has weak bactericidal actions against M. leprae
- Has anti-inflammatory properties which is useful in suppressing lepra reactions
- Adverse effects: Reddish-black discoloration of the skin, dryness of the skin, pruritus and photo-dermatitis

CLOFAZIMINE: MECHANISM OF ANTI-MYCOBACTERIAL ACTION

- Binds to the guanine bases of bacterial DNA, thereby blocking the template function of the DNA and inhibiting bacterial proliferation. It is selective for mycobacterial DNA.
- It also increases activity of bacterial phospholipase A_2, leading to release and accumulation of lysophospholipids which are toxic and inhibit bacterial proliferation

RIFAMPICIN

- Rapidly bactericidal to M. leprae and is highly effective – a single dose of 1500mg can kill 99% of the lepra bacilli
- It can be given once monthly
- Used in combination with dapsone

OTHER DRUGS USED IN LEPROSY TREATMENT

Fluoroquinolones: Ofloxacin is lepricidal and is used in multi-drug regimens along with rifampicin

Minocycline: Used in combination regimens to shorten the duration of treatment

Clarithromycin: Has bactericidal activity against M. leprae

Ethionamide: Bactericidal to M.leprae, but more toxic than dapsone. Used in multidrug regimen in patients who cannot tolerate clofazimine.

TREATMENT OF LEPROSY

WHO has recommended a combination of drugs in leprosy in order to:

- Eliminate persisters
- Prevent drug resistance
- Reduce the duration of therapy

END