Antituberculosis Drugs

A) 1st line drugs: Isoniazide, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin are efficacious and have acceptable degree of toxicity.

Principles of antituberculosis therapy:

- combination therapy of at least three drugs must be used to:

-Kill large number of rapidly multiplying bacilli: INH is bacteriocidal against replicating bacteria

- Treat persisters (semidormant intracellular bacilli) that metabolise slowly or intermittently and can cause relapse): Rifampicin and Pyrazinamide are most efficacious.

-Prevent the emergence of drug resistant mutants: rifampicin, INH and ethambutol achieve this.

- NOTE :-INH, rifampicin, ethambutol and pyrazinamide are given orally .

Isoniazid (isonicotinic acid hydrazide) (INH)

Mechanism of action: It is selectively effective to mycobacterium tuberculosis because it prevents synthesis of mycolic acids (a component that is unique to mycobacterial cell walls). It is effective against both intracellular (within macrophages) and extracellular bacilli.

PKs:It is Well absorbed from the GIT .Food and aluminum –containing antacids reduce absorption. It is distribute into all body tissues, tubercular cavities, CSF and meninges ,hence it is also effective for treatment of tuberculous meningitis. It is metabolized in liver by acetylation and the rate of the reaction is genetically bimodally distributed. The persons are either ‘‘slow’’ or ‘‘fast’’ acetylators . Acetylation status does not affect response to drug when INH is taken daily but biweekly regimens are less effective in fast acetylators and peripheral neuropathy-side effect is more common in slow acetylators.

Side effects:

1-Peripheral neuropathy: paresthesia and numbness of the finger tips; due to pyridoxine (vitamin B6) deficiency, because INH is a structural analog of pyridoxine and increases its renal excretion. Neuropathy is more common in slow acetylators, malnourished, elderly, liver diseases and alcoholics. Pyridoxine

supplement prevents neuropathy without interfering with the therapeutic effect of INH.
2-liver damage (due to its metabolite acetylhydrazine) ranges from loss of appetite, nausea, vomiting, jaundice, right upper quadrant pain, elevation of liver enzymes to fatal hepatitis.

- ❖ Liver function tests should be monitored monthly.

3- mental disturbance, optic neuritis and convulsions.
4- INH inhibits metabolism of phenytoin carbamazepin and ethosuximide, increasing their blood level and toxicity.

2-Rifampicin (Rifampin):
Mechanism of action: inhibits bacterial RNA synthesis. It is particularly effective against semidormant intracellular mycobacteria.
It also has activity against M. *leopori* , Staphylococcus*, Niesseria meningitides, H.influenza and Legionella* species.

Pharmacokinetics: It is well absorbed orally.It distributes widely in body fluids and tissues. Since the substance itself is red, its distribution is the reason for the orange-red color of the saliva, tears and sweat. It is excreted in urine and faeces. The red color of urine can be used as a marker for whether or not the drug has been effectively absorbed and to detect non-compliance.

It penetrates well into CSF when meninges are inflamed. The half life is shortened on repeated dosing because it is an enzyme inducer and increase its own metabolism.

Uses:
1-treatment of tuberculosis 2- serious Staphylococcus *aureus* infections such as osteomyelitis and endocarditis 3-brucellosis 4-leprosy
5-elimination of nasal carriers of meningococci, because it can distribute to nasal secretions.
6-prophylaxis in contacts of patients with *Haemophilus influenza* type b.

Side effects: 1- hepatitis, jaundice 2-thrombocytopenia 3- pruritus and rash
4- if administered less often than twice weekly it causes immunological reactions characterized by Flu-like symptoms (chills, fever, and muscle pain), acute haemolytic anemia, thrombocytopenia and acute renal failure
5 –harmless red discoloration of urine, sweat and tears
6-It induces C P450 enzymes which increases the elimination of many other drugs as warfarin , oral contraceptives, sulfonylureas, and phenytoin; dose of these drugs need to be increased to avoid treatment failure.

3-Pyrazinamide:

- is a derivative of nicotinamide.

- is included in combination therapy of tuberculosis because it can kill persisters (dormant) intracellular mycobacteria that may cause relapse.It is taken by macrophages and diffuses into mycobacteria where it is converted to pyrazinoic acid- the active form of the drug- by mycobacterial pyrazinamidase.

-Pyrazinamide is only used in the first two months of treatment and it losses effectiveness after that because the enzyme pyrazinamidase is only effective at acidic PH which is available inside phagolysosomes in macrophages, that present in huge amount only during the early stages of the disease.

-It can cross into CSF so it is also useful in tuberculous meningitis.

Side effects: hyperuricemia and joint pain, hepatitis, jaundice, urticaria

4-Ethambutol:

-is bacteriostatic, usually given in combination therapy with other antituberculosis drugs to delay or prevent the emergence of resistant bacilli.
-can cross the inflamed meninges and is useful in tuberculous meningitis.
-is excreted unchanged by the kidneys, the dose should be reduced in renal impairment.

Side effects: Optic neuritis resulting in loss of visual acuity and red-green color blindness hence it is contraindicated in children aged 6 years and below as they are too young to notice deterioration in their visual acuity so may end with blindness.
Periodic test of vision must be done throughout the treatment period.

5- Streptomycin is an aminoglycoside, administerd by IM injection.

Treatmaent regimen of tuberculosis:

1- UNSUPERVISED REGIMEN: drugs are taken by the patient himself daily. The drugs are INH and rifampicin for 6 months, plus pyrazinamide for the first 2 months.

2- DOTs (directly observed treatment short course). Drugs are given under supervision of a health provider, to improve compliance: Thrice weekly INH and rifampicin for 6 months, plus pyrazinamide for the first 2 months.

- With both regimen , ethambutol or streptomycin must be added if there is a possibility of drug resistant organism or if the patient is severly ill with extensive active lesions

- The initial 2 months three drugs treatment phase aim to reduce number of bacilli as rapidly as possible and render the sputum non-infectious. The use of rifampicin and INH for 4 additional months aims to eliminate the remaining intracellular bacteria and prevent relapse.

Chemoprophylaxis for tuberculosis

For symptom- free persons in contact with disease, who develop a positive tuberculin test.

- INH twice weekly for 9 months
- Rifampicin daily for 4 months

B)2nd line drugs: are either less effective or more toxic than the first line drugs and they are used when there is intolerance or resistance to 1st line drugs.

Ex.kanamycin, amikacin, ethionamide, Ciprofloxacin, levofloxacin clarithromycin, rifabutin,capreomycin and rifapentine