Chapter III: CHEMOTHERAPY OF TUBERCULOSIS

Year III Pharm.D
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TUBERCULOSIS

Tuberculosis is a chronic granulomatous disease caused by

- *M. tuberculosis*
- *M. avium*
- *M. bovis*
- *M. murine*

**Incubation period:** 2-10 weeks

**Mode of transmission:**
1. Inhalation - Through droplets during sneezing
2. Ingestion – swallowing the own sputum
3. Innoculation – specimen handling
4. Intraplacental- from mother to foetus
**Symptoms:**

cough, fever,
Night sweating
loss of weight and appetite
Dyspnoea

In severe conditions

pulmonary hemorrhage
pulmonary insufficiency
pulmonary sepsis

**Diagnosis:**
1. microscopic examination of sputum (zeil nelson strain)
2. Radiography
3. Tuberculin skin test
Classification of anti tubercular drugs

1. First line antituberculosis drugs
   - Isoniazid (INH)
   - Rifampicin
   - Pyrazinamide
   - Ethambutol
   - Streptomycin

2. Second line antituberculosis drugs
   - Fluroquinolones
   - Capreomycin
   - Cycloserine
   - Para amino salicylic acid
   - Amikacin
   - Kanamycin

3. Newer agents
   - Linezolid
   - Rifabutin
   - Clarithromycin
   - Azithromycin
   - Ofloxacin
Isoniazid
- Potent anti tuberculosis agent
- Structurally resembles pyridoxine
- Effective against both extracellular and intra cellular tubercle bacilli

Pharmacokinetics
Absorption- orally
Distribution- rapidly in pleural , peritoneal, synovial fluid
Metabolism –liver by n-acetyl transferase to acetylisoniazid
rapid acetylators- plasma half life is 1hr
slow acetylators – plasma half life is 3 hrs

Mechanism of action

INH(prodrug)

\[ \downarrow \] catalase peroxidase

\[ \downarrow \] biologically active

\[ \downarrow \] inhibit the synthesis of mycolic acid
Resistance development
1. mutation in catalase peroxidase gene responsible for activation of INH
2. mutation in promoter gene inhA involved in mycolic acid synthesis

Adverse effects:
1. **Peripheral neuritis** (muscular weakness, numbness)
   - common in slow acetylators
   - INH induced excretion of pyridoxine
   - accumulation of INH inhibits pyridoxin kinase
2. **Hepatoyotoxicity**
   - common in fast acetylators
   - due to formation of toxic metabolites like acetyl isoniazid
   - acetyl hydrazine

Drug interactions:
Alluminium hydroxide – inhibits the absorption of INH
Alcohol – increases the risk of hepatitis
Phenytoin and carbamazepine – INH inhibits the metabolism
Preparations available
  Isonex 100mg tab
  Isonex forte 300mg tab
  Isokin 300mg tab

Rifampicin (rifampin, RMP)
  It is a semi synthetic derivative of macrocyclic antibiotic Rifamycin

Pharmacokinetics:
  - Absorption- oral administration
  - Excretion through liver
  - It is a potent enzyme inducer

Mechanism of action:
  inhibits bacterial DNA-dependent RNA polymerase

Resistance:
  Point mutation in rpoB gene the gene that is present in β-subunit of RNA polymerase

Adverse effects:
  - Hepatitis
  - Flu-like syndrome (fever, chill, myalgia, thrombocytopena)
  - Imparts red orange colour to urine
**Drug interactions:**
Oral contraceptives since it is an enzyme inducer it enhances the metabolism
Anticoagulants
Protease inhibitors

**Clinical uses:**
1. Treatment of leprosy along with dapsone
2. For prosthetic valve endocarditis
3. Treatment of brucellosis

**Preparations available:**
R-CIN-150mg 300mg 450mg 600mg cap
ZUCOX
RIMACTANE
Ethambutol:

it is a synthetic tuberculo static drug

**Mechanism of action:**

inhibits arabinosyl transferase enzyme to prevent polymerisation of arabinoglycans
Which are essential constituents foe mycobacterial cell wall

**Resistance development:**

Due to point mutation in emb B gene that encodes the arabinosyl transeferase

**Adverse effects:**

1. Retrobulbar neuritis impairing visual acuity and red green colour descrimination
2. Gouty arthritis

**Preparations available:**

COMBUTOL
MYCOBUTOL
Pyrazineamide (PZA)  
it is a pyrazine derivative of nicotinamide  

**Mechanism of action:**

1. PZA enters through passive diffusion
2. Bacterial pyrazineamidase enzyme
3. Pyrazinoic acid
4. Inhibits mycobacterial synthase-I enzyme
5. Inhibits mycolic acid synthesis
Resistance development:

mutation in gene pcnA gene that encodes pyrazineamidase enzyme

Adverse effects:

Hepatotoxicity
Hyperuricaemia

Preparations available:

P-ZIDE
PYZ INA
PZA_CIBA
Treatment of Tuberculosis

Key points in treatment of tuberculosis is
1. The therapy must contain two or more drugs to avoid development of resistance
2. The drug must be taken regularly
3. Drug therapy must continue for a sufficient duration

Reason for longer therapy
1. Grows slowly
2. Resistance development
3. Development of cell mediated immunity after 2-8 weeks of infection

Reason for multi drug therapy:
1. To delay emergence of resistance
2. Reduce toxicity
3. To reduce duration of course
Reasons for failure of multi drug therapy:

1. Incorrect prescription
2. Non-compliance
3. Resistance development
4. Poor health of patient – malnutrition
5. Associated diseases

WHO recommended the Directly Observed Therapy using Short course (DOTS)

- Anti tubercular drugs are given under the direct supervision of the Medical professional 3 days a week

WHO categorisation of patients and recommended dosage regimens as per Revised national tuberculosis programme of India (1997) are as follows
### Category and type of patients:

**Category –I**
- New (un treated) smear positive pulmonary TB
- New(un treated) smear negative pulmonary TB bur seriously ill
- New cases of seriously ill extrapulmonary TB

**Category-II**
Smear positive re treatment group due to
- tretment failure
- relapse/default

**Category-III**
New (untreated ) smear negative pulmonary TB but not seriously ill
Less severe cases of extrapulmonary TB
<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>Drug regimen</th>
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<tbody>
<tr>
<td><strong>Category-I</strong></td>
<td></td>
</tr>
<tr>
<td>Intensive phase (2 months)</td>
<td>INH+RMP+PZA+ET B</td>
</tr>
<tr>
<td>Continuation phase (4 months)</td>
<td>INH+RMP</td>
</tr>
<tr>
<td><strong>Category-II</strong></td>
<td></td>
</tr>
<tr>
<td>Intensive phase (2+1 months)</td>
<td>INH+RMP+PZA+ETB+SM (2 months)</td>
</tr>
<tr>
<td></td>
<td>INH+RMP+ETB+PZA (1 month)</td>
</tr>
<tr>
<td>Continuation phase (5 months)</td>
<td>INH+RMP+ETB</td>
</tr>
<tr>
<td><strong>Category-III</strong></td>
<td></td>
</tr>
<tr>
<td>Intensive phase (2 months)</td>
<td>INH+RMP+PZA</td>
</tr>
<tr>
<td>Continuation phase (4 months)</td>
<td>INH+RMP</td>
</tr>
</tbody>
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Leprosy:
it is an infectious chronic granulomatous disease which effects cooler body parts such as skin, mouth, eyes, respiratory tract, peripheral nerves, lymph nodes, Testis.

Causative organism: *M. leprae*

Incubation period:
2-20 years

Mode of transmission:
1. Direct contact with infected skin
2. Nasal secretion
3. Mucus membrane of mouth
4. Hair follicle
5. Foetal transmission
6. From milk to infants
7. Haematogenous transmission
**Symptoms:**

- Skin lesion
- Affected area loses sensation
- Peripheral neuropathy
- Dysfunction of eyelid closure
- Trauma and ulceration in the cornea leads to blindness

**Diagnostic methods:**

1. Sensory nerve examination
2. Biopsy of the affected area
3. Scrabbings from the affected area by using zeil nelson staining
Clasification of Drugs

Sulfones
  Dapsone
Phenazine derivatives
  Clofazamine
Anti tubercular drugs
  Rifampicin
Antibiotics
  a.fluroquinolones
    Ofloxacin,Sparfloxacin
  b.macrolides
    Clarithromycin
  c.tetracyclins
    Minocycline
**Dapsone**

it is closely related to sulphonamides

**Pharmacokinetics**

- Absorption - orally
- Distributed throughout the body fluids and tissues
- It tends to remain in skin, muscle, kidney and liver up to 3 weeks after the therapy is stopped
- Metabolised in liver by acetylation
- Excreted in bile
- Plasma half life is 1-2 days

**Mechanism of action**

- inhibits incorporation of PABA with folic acid

**Adverse effects:**

- Nonhaemolytic anemia
- Methaemoglobinemia in persons having G6PD deficiency
- Pruritis
- Reversible neuropathy
Lepra reactions:

During Dapsone therapy for lepromatous leprosy some reactive episodes may occur. These are known as lepra reactions.

Types

Type 1 lepra reactions
- These are delayed hypersensitivity reactions to *M. leprae* antigens
- It is characterised cutaneous ulceration,

Type 2 lepra reactions
- These are humoral antibody response to dead bacteria
WHO regimen for leprosy treatment

For multibacillary (lepromatous) leprosy

Dapsone -100mg daily
+ for 29 days
Clofazamine 50mg daily
followed by 300mg on 30th day
+ 
Rifampicin 600mg once a month for 24 months

For pausibacillary(tuberculoid)leprosy

Dapsone -100mg daily
+ 
Rifampicin -600mg once a month for 6 months
if dapsone is not tolerated
Clofazamine -50mg daily for 29 days followed by 300mg on 30th day
Alternative regimen for multibacillary leprosy

a. If Rifampicin is insuitable because of resistance or intolerance

Clofazamine -50mg daily +Ofloxacin 400mg daily +Minocyclin 100mg daily

For first 6 months, thereafter

Clofazamine 50 mg daily +Ofloxacin 400mg daily for 18 months

b. When Clofazamine cant be given because of unacceptable skin pigmentation

Dapsone 100mg daily +Ofloxacin 400mg daily

+ 

Rifampicin 600mg once a month for 24 months