

# **Antitubercular Drug**

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# Introduction

- Tuberculosis - most important communicable disease in the world.
- Mycobacteria are intrinsically resistant to most antibiotics
  - Grows more slowly than other bacteria – antibiotics active against **rapidly growing cells**
  - **lipid-rich mycobacterial cell wall** is impermeable to many agents
  - It grows inside macrophage – poorly penetrated by drugs
  - Excellent ability to develop resistance – Multiple Drug Resistant (MDR)

# Introduction

- Combinations of two or more drugs
  - to overcome these obstacles
  - to prevent emergence of resistance during the course of therapy
- The response of mycobacterial infections to chemotherapy is slow - treatment must be administered for months to years, depending on which drugs are used

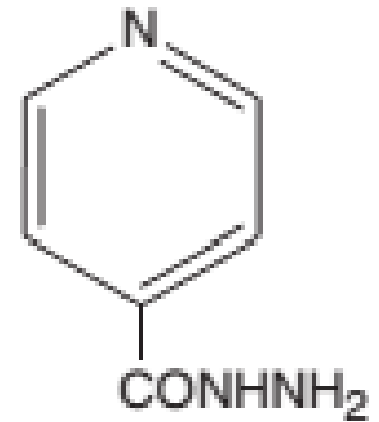
# Classification

- According to clinical utility the anti TB drugs can be divided into 2 groups
  - **First Line** : high antitubercular efficacy as well as low toxicity – routinely used
    - Isoniazid (H) , Rifampin (R), Pyrazinamide (Z), Ethambutol (E), Streptomycin (S) - HRZES
  - **Second Line** : low antitubercular efficacy or high toxicity
    - Paraminosalicylic Acid, Cycloserine, Kanamycin, Amikacin, Ciprofloxacin, Ofloxacin, Clarithromycin, Azithromycin

**First Line Drug**

# ISONIAZID

- Isonicotinic acid hydrazide
- Most active drug for the treatment of tuberculosis
- freely soluble in water
- bactericidal for actively growing tubercle bacilli
- less effective against atypical mycobacterial species
- penetrates into macrophages and is active against both extracellular and intracellular organisms



Isoniazid

# Mechanism of Action & Basis of Resistance

- inhibits synthesis of mycolic acids - essential components of mycobacterial cell walls
- Highly selective for mycobacterium
- Resistance
  - Its prodrug – activated by enzyme catalase-peroxidase
  - Mutation causes inhibition of this enzyme
  - No cross resistance occurs with other antitubercular drug
  - Always given in combination

# Pharmacokinetics

- readily absorbed from the gastrointestinal tract - diffuses readily into all body fluids and tissues.
- acetylation by liver *N*-acetyltransferase, is genetically determined
- half-lives :1 hour(fast acetylators) and 3 hours (slow acetylators)
- Excreted, mainly in the urine - need not be adjusted in renal failure
- Contraindicated - severe preexisting hepatic insufficiency



# Clinical Uses

- Typical dosage of isoniazid is 5 mg/kg/d – 10 mg/kg/d (sever infection) or 15 mg/kg dose – twice weekly
- **Adult dose** : 300 mg oral dose O.D.
- Pyridoxine, 25–50 mg/d - predisposing to **neuropathy**, an adverse effect of isoniazid
- Can also be given parenterally in the same dosage
- **Latent tuberculosis** : 300 mg/d (5 mg/kg/d) or 900 mg twice weekly for 9 months

# Adverse Reactions

- Depends on dosage and duration of administration
- **Immunologic Reactions**
  - Fever and skin rashes are occasionally seen.
  - Drug-induced **systemic lupus erythematosus** has been reported.
- **Direct Toxicity**
  - Clinical hepatitis with loss of appetite, nausea, vomiting, jaundice – promptly discontinued
  - The risk of hepatitis is greater in individuals
    - Alcohol dependence
    - Possibly during pregnancy and the postpartum period

# Adverse Reactions : Direct

- Peripheral neuropathy is observed in 10–20% - occur in slow acetylators and patients with predisposing conditions
  - malnutrition,
  - alcoholism,
  - diabetes,
  - AIDS, and uremia
- Relative pyridoxine deficiency - promotes excretion of pyridoxine
- readily reversed by administration of pyridoxine in a dosage as low as 10 mg/d
- Central nervous system toxicity : less common, includes memory loss, psychosis, and seizures.

# RIFAMPIN

- Semisynthetic derivative of rifamycin -produced by *Streptomyces mediterranei*
- Active in vitro against gram-positive and gram-negative cocci, some enteric bacteria, mycobacteria, and chlamydiae.
- Resistant mutants - approximately 1 in  $10^6$  organisms
- Rapidly selected out if rifampin is used as a single drug – must be used in combination
- no cross-resistance to other classes of antimicrobial drugs

# Mechanism of Action & Resistance

- Binds to the bacterial DNA-dependent RNA polymerase - inhibits RNA synthesis
- Bactericidal for mycobacteria
- Readily penetrates most tissues and penetrates into phagocytic cells
- Can kill organisms that are poorly accessible to many other drugs
  - Intracellular organisms
  - sequestered in abscesses and lung cavities
- **Resistance:** mutations result in reduced binding of rifampin to RNA polymerase

# Pharmacokinetics

- Well absorbed after oral administration and excreted mainly through the **liver into bile**
- **Enterohepatic recirculation** - bulk excreted as a **deacylated metabolite** in feces and a small amount excreted in the urine
- Dosage adjustment for renal or hepatic insufficiency is not necessary.
- Distributed widely in body fluids and tissues.
- Relatively highly protein bound

# Clinical Uses

- 10 mg/kg/d O.D. for 6 months in combination with isoniazid or other **antituberculous** drugs to patient.
- Some **atypical mycobacterial infections** and in **leprosy**
- 600 mg twice daily for 2 days can eliminate **meningococcal carriage**
- 20 mg/kg/d for 4 days - prophylaxis in contacts of children with ***Haemophilus influenzae* type b disease**
- Serious staphylococcal infections - **osteomyelitis and prosthetic valve endocarditis**

# Adverse Reactions

- harmless **orange color** to urine, sweat, and tears
- Occasional adverse effects include
  - rashes, thrombocytopenia, and nephritis
  - cholestatic jaundice and occasionally hepatitis
  - light-chain proteinuria
  - flu-like syndrome characterized by fever, chills, myalgias, anemia, and thrombocytopenia



# Adverse Reactions

- Induces most cytochrome P450 isoform - elimination of numerous other drugs
  - Methadone,
  - Anticoagulants,
  - Cyclosporine,
  - Some anticonvulsants,
  - Protease inhibitors,
  - some nonnucleoside reverse transcriptase inhibitors
  - contraceptives,
  - And a host of others

# ETHAMBUTOL

- Synthetic, water-soluble, heat-stable compound - dispensed as the dihydrochloride salt
- Bacteriostatic
- Additionally it slows the rate of sputum conversion
- Development of resistance
- Given in the combination with RHZ

# Mechanism of action

- Inhibits mycobacterial **arabinosyl transferases** - an essential component of the mycobacterial cell wall.
- Resistance – due to alteration in target gene
- No cross resistance with other drug
- Reesistance to ethambutol emerges rapidly when the drug is used alone - combination with other antituberculous drugs

# Pharmacokinetics

- well absorbed from the gut
- 20% of the drug is excreted in feces and 50% in urine in unchanged form
- crosses the blood-brain barrier only when the meninges are inflamed
- Temporarily stored in RBC
- $T_{1/2}$  - 4 hrs
- Caution taken for renal failure patient

# Clinical Use

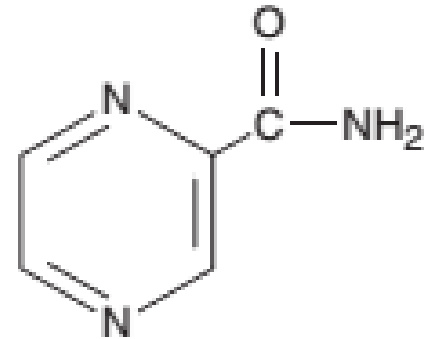
- Ethambutol hydrochloride - 15–25 mg/kg/d  
O.D
- higher dose is recommended for treatment of tuberculous meningitis
- 50 mg/kg when a twice-weekly dosing schedule

# Adverse Reactions

- **Retrobulbar neuritis** - 25 mg/kg/d continued for several months.
  - loss of visual acuity and red-green color blindness.
  - 15 mg/kg/d or less, visual disturbances are very rare
- **Contraindicated** in children too young to permit assessment of visual acuity and red green color discrimination

# PYRAZINAMIDE

- Relative of nicotinamide
- Stable and slightly soluble in water but week drug
- Inactive at neutral pH, but at pH 5.5 it inhibits tubercle bacilli
- Taken up by macrophages and exerts its activity
- Highly effective during the first 2 month of therapy



Pyrazinamide (PZA)

# Mechanism of Action

- Pyrazinamide is converted to pyrazinoic acid (active form) - by mycobacterial pyrazinamidase.
- Disrupts mycobacterial cell membrane metabolism and transport functions
- Resistance
  - impaired uptake of pyrazinamide
  - mutations of enzyme causing conversion of pyrazinamide to its active form



# Pharmacokinetics

- well absorbed from the gastrointestinal tract
- widely distributed in body tissues, including inflamed meninges
- half-life is 8–11 hours
- Metabolized by the liver
- Metabolites are renally
- no cross-resistance

# Clinical Use

- Used as front line drug for tuberculosis with rifampin and isoniazid
- **Normal Dose:** 40–50 mg/kg thrice weekly or twice-weekly treatment regimens for 6 months
- **Hemodialysis patients & creatinine clearance less than 30 mL/min :** 25–35 mg/kg three times weekly (not daily)

# Adverse Effect

- **Hepatotoxicity** (in 1–5% of patients) – less common in Indian population
- Nausea, vomiting, drug fever, and hyperuricemia.
  - occurs uniformly – drug therapy should be not stopped
- Contraindicated in liver disease patient

# Streptomycin

- Part of aminoglycosides antibiotic
- First clinically useful antitubercular drug, but less effective than INH or rifampin
- Acts only on extracellular bacilli – poor penetration into cells
- Doesn't cross the BBB, but penetrates tubercular cavities

# Mechanism of action

- Irreversible inhibitors of protein synthesis,
- Bactericidal
- Inside the cell, aminoglycosides bind to specific 30S-subunit ribosomal proteins and inhibits protein synthesis
- **Resistance**
  - Inactivation by adenylylation, acetylation, or phosphorylation
  - impaired entry into the cell
  - receptor protein on the 30S ribosomal subunit - deleted or altered as a result of a mutation

# Pharmacokinetics

- absorbed very poorly from the intact gastrointestinal tract
- intramuscular injection or usually administered intravenously as a 30- to 60-minute infusion
- Normal half-life - 2–3 hours, but in renal failure patient it reduces to 24-48 hrs

# Clinical Use

- Treatment of infections resistant to other drugs
- Adults: 20–40 mg/kg/d daily for several weeks
  - Followed by 1–1.5 g two or three times weekly for several months
- Other drugs are always given in **combination** to prevent emergence of resistance
- Nontuberculosis species of mycobacteria other than *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii* are **resistant**
- Dose is reduced to half in hemodialysis patient

# Adverse Reactions

- Ototoxic and nephrotoxic
- Vertigo and hearing loss - common adverse effects and may be permanent
- Dose-related, and the risk is increased in the elderly
- Therapy should be limited - no more than 6 months whenever possible



# **Second Line Drugs**

# Second Line Drugs

- This drugs are considered only when
  - resistance to first-line agents
  - failure of clinical response to conventional therapy;
  - Serious treatment-limiting adverse drug reactions
- Expert guidance to deal with the toxic effects is required
- **Ex: Paraminosalicylic Acid, Cycloserine, Kanamycin, Amikacin, Ciprofloxacin, Ofloxacin, Clarithromycin, Azithromycin**

# Para-aminosalicylic Acid

- structural analogue of *p*aminobenzoic acid (PABA)
- **highly specific** for *M. tuberculosis* - not effective against other mycobacterium species
- Combined with isoniazid - **an alternative substrate** and **block hepatic acetylation of isoniazid**- increasing free isoniazid levels.
- limited to the treatment of **MDR tuberculosis**
- **Discouraged its use** : primary resistance, poor compliance due to GI intolerance, and lupus like reactions

# Ethionamide

- Chemically related to isoniazid
- Blocks the synthesis of mycolic acids
- Poorly water soluble and available only in oral form.
- Dosage of 15 mg/kg/d - initial dose of 250 mg once daily, which is increased in 250-mg increments to the recommended dosage
- Intense gastric irritation and neurologic symptoms as well as hepatotoxic

# Capreomycin

- **peptide protein synthesis** inhibitor antibiotic obtained from *Streptomyces capreolus*
- Daily injection of 15 mg/kg/d intramuscularly
- treatment of **drug-resistant tuberculosis**
- Strains of *M tuberculosis* that are **resistant to streptomycin or amikacin** - susceptible to capreomycin.
- Nephrotoxic and ototoxic - Tinnitus, deafness, and vestibular disturbances occur
- local pain, and sterile abscesses may occur

# Cycloserine

- inhibitor of cell wall synthesis
- 0.5–1 g/d in two divided oral doses
- Cleared renally - Dose is reduced to half in case of renal dysfunction
- peripheral neuropathy and central nervous system dysfunction, including depression and psychotic reactions.
- Pyridoxine, 150 mg/d given in addition to it

# Kanamycin & Amikacin

- Treatment of tuberculosis suspected or known to be caused by **streptomycin-resistant or multidrug-resistant strains**
- Kanamycin is more toxic comparatively – **absolute**
- Prevalence of **amikacin-resistant strains** is low (< 5%)
- Also active against atypical mycobacteria.
- 15 mg/kg intravenous infusion
- No cross-resistance between streptomycin and amikacin but it occurs with kanamycin
- used in combination with at least one and preferably two or three other drugs

# Fluoroquinolones

- In addition to their activity against many gram-positive and gram-negative bacteria inhibit strains of *M. tuberculosis*
- Also active against atypical mycobacteria
- Standard dosage
  - **Ciprofloxacin:** 750 mg orally twice a day
  - **Levofloxacin:** 500–750 mg once a day
  - **Moxifloxacin:** 400 mg once a day



# Revised National Tuberculosis Control Programme (RNTCP 1997) Guidelines- India

TB category	Type of TB	Initial phase	Continuation Phase	Total duration
I	New, untreated TB	2H <sub>3</sub> R <sub>3</sub> Z <sub>3</sub> E <sub>3</sub>	4H <sub>3</sub> R <sub>3</sub>	6
II	Smear positive failure, relapse and interrupted treatment cases	2H <sub>3</sub> R <sub>3</sub> Z <sub>3</sub> E <sub>3</sub> S <sub>3</sub> <sup>-</sup> 1H <sub>3</sub> R <sub>3</sub> Z <sub>3</sub> E <sub>3</sub>	5H <sub>3</sub> R <sub>3</sub> E <sub>3</sub>	8
III	Less severe form extra-pulmonary TB – smear negative	2H <sub>3</sub> R <sub>3</sub> Z <sub>3</sub>	4H <sub>3</sub> R <sub>3</sub>	6

**\* Numeral before a phase is duration in months**

**# Sub-script numbers – does per week**

**Followed Under DOTS - Directly Observed Treatment**

# Summary

Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥ 24

Drug	Typical Adult Dosage <sup>1</sup>
<b>First-line agents (in approximate order of preference)</b>	
Isoniazid	300 mg/d
Rifampin	600 mg/d
Pyrazinamide	25 mg/kg/d
Ethambutol	15–25 mg/kg/d
Streptomycin	15 mg/kg/d
<b>Second-line agents</b>	
Amikacin	15 mg/kg/d
Aminosalicylic acid	8–12 g/d
Capreomycin	15 mg/kg/d
Ciprofloxacin	1500 mg/d, divided
Clofazimine	200 mg/d
Cycloserine	500–1000 mg/d, divided
Ethionamide	500–750 mg/d
Levofloxacin	500 mg/d
Rifabutin	300 mg/d <sup>2</sup>
Rifapentine	600 mg once or twice weekly

# Summary

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
<b>ISONIAZID</b>	Inhibits synthesis of mycolic acids, an essential component of mycobacterial cell walls	Bactericidal activity against susceptible strains of <i>M tuberculosis</i>	First-line agent for tuberculosis • treatment of latent infection • less active against other mycobacteria	Oral, IV • hepatic clearance (half-life 1 h) • reduces levels of phenytoin • <i>Toxicity:</i> Hepatotoxic, peripheral neuropathy (give pyridoxine to prevent)
<b>RIFAMYCINS</b> <ul style="list-style-type: none"> <li>• Rifampin</li> </ul>	Inhibits DNA-dependent RNA polymerase, thereby blocking production of RNA	Bactericidal activity against susceptible bacteria and mycobacteria • resistance rapidly emerges when used as a single drug in the treatment of active infection	First-line agent for tuberculosis • atypical mycobacterial infections • eradication of meningococcal colonization, staphylococcal infections	Oral, IV • hepatic clearance (half-life 3.5 h) • potent cytochrome P450 inducer • turns body fluids orange color • <i>Toxicity:</i> Rash, nephritis, thrombocytopenia, cholestasis, flu-like syndrome with intermittent dosing
<ul style="list-style-type: none"> <li>• <i>Rifabutin:</i> Oral; similar to rifampin but less cytochrome P450 induction and fewer drug interactions</li> <li>• <i>Rifapentine:</i> Oral; long-acting analog of rifampin that may be given once weekly in the continuation phase of tuberculosis treatment</li> </ul>				

# Summary

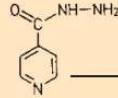
<b>PYRAZINAMIDE</b>	<p>Not fully understood          • pyrazinamide is converted to the active pyrazinoic acid under acidic conditions in macrophage lysosomes</p>	<p>Bacteriostatic activity against susceptible strains of <i>M tuberculosis</i> • may be bactericidal against actively dividing organisms</p>	<p>“Sterilizing” agent used during first 2 months of therapy • allows total duration of therapy to be shortened to 6 months</p>	<p>Oral • hepatic clearance (half-life 9 h), but metabolites are renally cleared so use doses 3 × weekly if creatinine clearance &lt; 30 mL/min • <i>Toxicity:</i> Hepatotoxic, hyperuricemia</p>
<b>ETHAMBUTOL</b>	<p>Inhibits mycobacterial arabinosyl transferases, which are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall</p>	<p>Bacteriostatic activity against susceptible mycobacteria</p>	<p>Given in four-drug initial combination therapy for tuberculosis until drug sensitivities are known • also used for atypical mycobacterial infections</p>	<p>Oral • mixed clearance (half-life 4 h) • dose must be reduced in renal failure • <i>Toxicity:</i> Retrobulbar neuritis</p>
<b>STREPTOMYCIN</b>	<p>Prevents bacterial protein synthesis by binding to the S12 ribosomal subunit (see also Chapter 45)</p>	<p>Bactericidal activity against susceptible mycobacteria</p>	<p>Used in tuberculosis when an injectable drug is needed or desirable and in treatment of drug-resistant strains</p>	<p>IM, IV • renal clearance (half-life 2.5 h) • administered daily initially, then 2 × week • <i>Toxicity:</i> Nephrotoxic, ototoxic</p>

# Combination therapy

Reduced risk of bacterial resistance

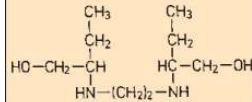
Reduction of dose and of risk of adverse reactions

## Isoniazid



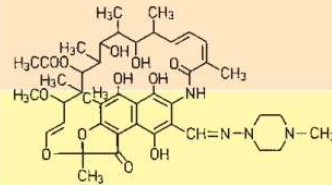
CNS damage and peripheral neuropathy (Vit. B<sub>6</sub>-administration)  
Liver damage

## Ethambutol



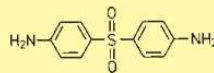
Optic nerve damage

## Rifampin



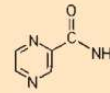
Liver damage and enzyme induction

## Dapsone



Hemolysis

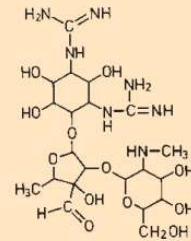
## Pyrazinamide



Liver damage

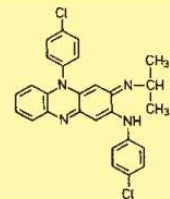
## Streptomycin

an aminoglycoside antibiotic



Vestibular and cochlear ototoxicity

## Clofazimine

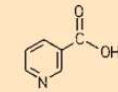


Skin discoloration

### Mycobacterium tuberculosis



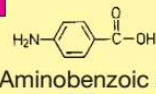
← Isonicotinic acid



Nicotinic acid

1

2



p-Aminobenzoic acid

Folate synthesis

### Mycobacterium leprae

# References

- **Basic & Clinical Pharmacology** Bertram G. Katzung Twelfth Edition
- Essential of medical pharmacology - K.D. Tripathi 6<sup>th</sup> edition
- Lippincott - Modern Pharmacology With Clinical Applications 6E
- Color Atlas Of Pharmacology, 2Nd Ed (Lüllmann, Thieme 2000)