PC
Pharmacology Concepts
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Anti Tubercular & Anti Leprosy Drugs

Website

Videos

Pharmacology 3

ANTI-TUBERCULAR DRUGS

Tuberculosis (TB) is a chronic granulomatous Disease (CGD), that infacted with "Mycobact. tuberculosis"

WHO, 2014 – 9.6 M TB cases globally, 2.2 M cases-India

RNTCP was launched in 1997, & treatment guidelines was revised 2016.

TB infection is highly prevalance in HIV patients (MAC – Mycobact. avium complex, infection among this patients)

Biology of Tuberculosis :-

It is a Aerobic Bacteria, first discovered in 1882 by "Robert Koch"

Growth of TB bacteria within patient depends on cond^n

(a) Rapid Growing with high bacillary load – as in the wall of cavity lesion where → ↑ O_2 & P^H - Neutral
H >> R, E, S

(b) Slow Growing :- locate inside the macrophages & Inflamed site where P^H is low (Acidic P^H)
Z >> H, R, E

(c) Spurters - Within the caseous material where O_2 is low & P^H - Neutral "R"

d) Dormant → Inactivated for prolong time
– bedaquiline

Therapeutic Goal

(A) Kill dividing bacilli → Early Bactericidal → H & R
(B) Kill Persisting bacilli – Prevent Relapse – R
(C) Prevent Emergency of Resistance – E

Drug Classificat^n & MOA

(A) First line Drug

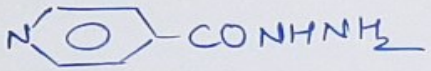
Isoniazid (INH) – H → ↓ mycolic ā Synthesis
Rifampicin – R → ↓ RNA Polymerase
Pyrazinamide – Z → ↓ mycolic ā Synthesis
Ethambutol – E → ↓ Arbinoglacton & mycolic ā
Streptomycin – S → ↓ protein Synthesis

B) Second line of Drugs –

Fluoroquinolones → ↓ DNA Gyrase Enz
P-amino salicylate → ↓ DHFR
Ethionamide, Prothionamide → ↓ mycolic ā
Cycloserine → ↓ bac. cell wall Synthesis
Kanamycin, Amikasin – ↓ protein Synthesis
Terizidone – ↓ bac. cell wall Synthesis
Rifabutin → ↓ RNA polymerase

ISONIAZID (INH)

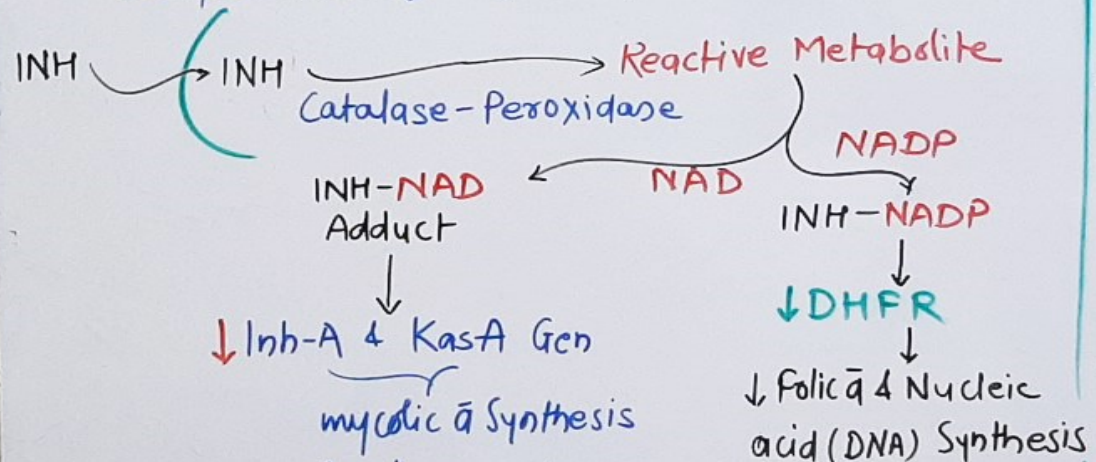
→ Isonicotinic acid hydrazide



Bacteriocidal - Rapid growing cells are killed rapidly but quiescent one are only inhibited

Kill both intracellular & Extracellular both

MOA → ↓ Synthesis of mycolic acid (fatty ā), major components of Mycobact. Cell wall



If INH is used alone → ↑ chance of Resistance

Resistance :- ① by mutatn of CAT-peroxidase (kat G gene)

② by mutation of Inh-A & Kas-A gene

③ Development of Efflux system

P'Kinetic :- Completely absorbed orally & penetrate to all body tissues. Metabolised by N-Acetylation by NAT-2. Acetylated products are excreted by Urine

Fast Acetylatn : 30-40% Indian - $t_{\frac{1}{2}}$ = 1 hour

Slow Acetylatn : 60-70% Indian - $t_{\frac{1}{2}}$ = 3 hours

Peripheral Nuritis is common in Slow Acetylator

Acetyl hydrazide —CyP2E1→ minor Metabolite → Hepatotoxic Effects

ADR :- → Neurological Disturbance - due to interfere with productn of active co-Enz pyridoxal phosphate from pyridoxine, ∆ it increased urine excretn — Pyridoxine

10mg/day - prophylactic dose

100mg/day - For treatment

→ Hepatitis - ↑ older & Alcoholic patients

DRUG INTERACTION -

① INH - Metabolic Enz Inhibitor → ↓ metabolism of Phenytoin, Diazepam, warfarin, theophylline etc

② $Al(OH)_3$ - ↓ absorptn of INH

③ Rifampicin - Enz inducer - Counteract the inhibitory effect of INH

4) PAS - ↓ metabolism of INH

RIFAMPICIN

Semisynthetic derv. of Rifamycin-B, which is obtained from Streptomyces mediterranei

MOA – Rifampin binds with β subunit of mycobac. DNA-dependent RNA polymerase (encoded by rpoB gene) & blocking the polymerizing functn
↳ ↓ Mycobac. RNA Synthesis

Bacterial Actn – Bacteriocidal to Mycobac. & other g(+) & g(-) bac. like Staph. aureus, N. meningitis H. influenzae, E. Coli, Klebsiella, Proteus etc

Anti-TB actn – R = INH > Others Z, E, S
R – acts mainly on "Spurters" – TB bacilli
R also acts on M. lepraе (highly sensetive)
R kills both Extra & Intracellular bacilli

Resistance – "Resistance due to mutation on rpoB gene"
– No cross resistance, with other anti TB drugs

P'kinetics – Oral BA = 70 %, *Foods ↓ the Absorptn
– It is widly distributed in the body, It penetrates intracellular, enters tubercular cavity, caseous masses & placenta.
It also crosses meninges, & largly pump out from CNS by P-glycoprotein
→ Metabolised in liver & active deacetylated product is mainly excreted by bile
→ R. & deacetylated R undergoes to enterohepatic circulatn
→ $t_{1/2}$ = 2-5 h

Uses ① Tuberculosis (R dose – 150 to 600 mg)
Fixed dose comb → INH 150 mg + R 300 mg
→ INH 50 mg + R 120 mg + Z 300 mg
Alone – R – 600 mg/day – Adult – before meal
R – 10 mg/day – children
for TB, Rifampin never used alone due to ↑chance of Resistance
② Leprosy
③ Prophylaxis of Meningococcal & Influenzae
③ 2nd choice – Diphtheroids & Legionella infectn
④ 1st line – "brucellosis" – R + Doxycycline

ADR:– "Hepatitis", Flu like Symptoms,
→ Cutaneous – Flushing, pruritis, rash, redness
→ Abdominal Cramp, nausea, Diarrhoea,
→ Urin & Excretn – Orange-red

Drug Interactn –
Rifampicin – CyP Enzyme inducer – ↑ metabolism of its own & others warfarin, contraceptives, corticosteroids, sulfonylurea, HIV protease inhibitor, theophylline etc

ANTI-TB DRUGS

PYRAZINAMIDE (Z)

↳ chemically similar to INH, was developed in 1952

MOA :- Pyrazinamide —(Mycobac. Pyrazinamidase, PncA gene)→ Pyrazinoic ā

Pyrazinoic ā → ↓ Mycolic acid

Pyrazinoic ā → disrupt Myc. Cell mem. Δ transport system

Action :- # More active in acidic media, Δ more lethal to intracellular bacilli

It is highly effective during first 2 months of therapy, by adding 'Z', duration Δ Relapse (↓)

Resistance :- Due to mutatⁿ on Pnc A gene

P'kinetics - Oral active, widely distributed in tissue Δ Fluids including CSF (useful in Meningeal TB), Metabolised by Liver Δ exc. through Urine, $t_{\frac{1}{2}}$ = 6-10h

ADR - # Hepatotoxicity, more common in western contries

Hyperuricaemia ⇝ Gout can occurs

ETHAMBUTOL (E)

highly active against Fast multiplying TB., also active against MAC Δ other Mycobac.

MOA :- It inhibit arbinosyl transferase (encoded by embAB gene) that involve in arbinoglacton Synthesis thereby interfering with mycolic ā incorporatⁿ in mycobac. cell wall

Resistance - Mutation on embAB gene, No Cross Resistance

P'kinetics - Oral active (3/4 abs), Widely distributed, ½ E metabolised in liver & Exc. through urine (GF, TS) Some portⁿ exc. by faeces, $t_{\frac{1}{2}}$ - 4h

ADR - # Loss of visual activity, colour vision (Ocular toxicity)

Field defects due to retrobulbar neurities

Treatment Regimen

① Daily dose of 1st line drug (WHO, 2010 - guidelines)

INH -	5 mg/kg	E -	15 mg/kg
R -	10 mg/kg	S -	15 mg/kg
Z -	25 mg/kg		

② For New & Preveously treated Pat. (RNTCP 2016 guideline)

NEW -	2 HRZE	4 HRE	total 6 months
Prev. treated -	2HRZES + 1 HRZE	5 HRE	total 8 months

LEPROSY PATHOPHYSIOLOGY - HANSEN'S DISEASE

Leprosy, caused by "Mycobacterium leprae"
It is infective dis. that cause sever, disfiguring skin sores & nerve damage in the arms & legs
It has been considered incurable since ages & bears a social stigma. Now availability of drugs it is curable but deformities may not reversed

TYPES:→ Based on Ridley-Jopling system, There are six categories (based on severty of symptoms)

1. **Intermediate** :- A few flat lesions that sometimes heal by themselves & may progress to more severe
2. **Tuberculoid** :- some large lesions, nerve damage, can be heal itself & may progressive (TT)
3. **Borderline Tuberculoid** :- lessions are similar to tuberculoid but smaller & numerous; less nerve enlargment; persist; revert to tuberculoid or advance to another form (BT)
4. **Mid Borderline leprosy**:- Redish plaques, moderate numbness, swollen lymph glands, may regress, persist, or progress to other forms. (BB)
5. **Borderline lapromatous**:- several types of lesions, persist, regress or progressive. (BL)
6. **Lapromatous leprosy**- Many lesions with bacteria, hair loss, nerve involvement, limb weakness, disfigurements, doesn't regress (LL)

SYMPTOMS :- It is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract

Skin lesions - light & dark patches - External Sign
Progress → Permanent damage to Skin, Nerve Limbs, Eyes
Secondary Infection → Tissue loss, shortened and deformed toes & Fingers.

CLINICAL SIGN & FETURES

Hypopigmented / Erythromatous Skin Patches
Thickened Peripheral Nerve
Acid fast bacilli detected on skin smear or biopsy material

TRANSMISSION :- # Skin, # Nasal mucosa (Resp. Tract)

INCUBATION PERIODS:- Variable (Weeks to Years)

minimum → few weeks
maximum → 30 Years
Avg. → 3 - 10 years

RISK FACTORS:- # Inadaquate Bedding
Contaminated water & Foods
Insufficient Diet
Immunocompromised diseases (AIDS, TB)

TARGET CELL → Schwan Cells & Macrophages

LAPROSY / HANSEN'S DISEASE

↳ Mycobacterium leprae, M. lepromatosis
↳ Tissue ⇒ Skin & Nerves
↳ G.H. Armaur Hansen - discovered M. leprae, 1873

PATHOGENESIS :-

1. Schwan Cells → Major Target area

"M. leprae" (PGL-1) → Laminin-2 binding proteins (ML-targeted receptor on SCs)

Neuregulin Receptor (+) → Erk ½, Erb B2

Peripheral Nerve damage → Demyelination → Disability due to loss of Axonal Conduct^{n}

2. Macrophages (Monocyte derived macrophages)

M. leprae (+) → Complement Receptor on macrophages CR1(CD35), CR2(CD11b/CD18), CR4(CD11c/CD18) (+) → Protein kinase

Inflammatory & Immune Laprosy Reaction

Type I (RR) Reversible Reaction
↳ Borderline Tuberculoid (BT)
↳ Borderline Lapromatous (BL)

Type II (ENL) Erythema Nodosum Leprosum
↳ Borderline Lapromatous (BL)
↳ Lapromatous leprosy (LL)

Type I (RR) → Delayed type Hypersensitivity React^{n}
→ CD4+ Lymphocyte INFγ, TNF-β → Inflammatory React^{n} - Skin, Nerv

Edema, Erythema, neuritis, sensory & motor loss, etc

Type II (ENL) → TNFα, IL-1, INFγ, C-reactive protein
↓
Inflammatory Response
↓
Appearance of tendor, Erythromatous, nodules on Skin, Systemic Symptoms — Fever, Enlarged lymph node, Edema, weight loss, anorexia

TREATMENT = MDT by NLEP (1982)

	MBL	PBL
Rifampin	600 mg/month, supervised	600 mg/month, Supervised
Dapsone	100 mg/day, Self	100 mg/day, Self
Clofazimine	300 mg/month, Supervised + 50 mg/day, Self	
Duration	12 months	6 months

CHILD — Rifampin - 10 mg/kg/month
Dapsone - 2 mg/kg/day
Clofazimine - 1 mg/kg/day + 6 mg/kg/month

CLOFAZIMINE (Clo) - PHARMACOLOGY

↳ It is a dye with laprostatic & antiinflammatory properties.

MOA - ① Interfere with the template funct^n of DNA
② Alteration of membrane function & transport System
③ Disruption of mitochondrial Electron Transport Chain

It's clinical response is slower than Dapsone
Resistance develops in 1-3 year
It is a component of Multi drug therapy (Dapsone + Rifampin + Clofazimine) of leprosy, due to antiinflammatory property to ↓ Lepra Reaction

P'kinetic :- Orall active (40-70% absorbed)

It accumulated in macrophages & get deposited as needle shaped crystal in subcutaneous Fats.
t1/2 = 70 days

ADR - # Redish-black discolouration of skin
discolouration of hair
Dryness of skin, itching, Photoxicity occurs
Conjuctival pigmentation
GI disturbance - Nausea, Anorexia, abdominal pain, weight loss, loos stool, etc

Contraindication - # Early Pregnancy
Liver & kidney patient

Rifampin -

Laprocidal Action
It prevents development of resistance of Dapsone
aprox 99.9% M. leprae are killed with 3-7 day of 600 mg/day dose
Clinical efficacy is rapid, It subsides nasal symptoms & Lapromatous leprosy with in 2-3 weeks

MOA - DNA polymerase inhibitor

C.I. → Contraindicated in hepatic & Renal dysfunct^n and during Type II (Erythema nodosum lepro-sum ; ENL) & Type I (Reversible Reaction). because it releases large quantity of mycobac. Antigen by inducing rapid bacilli killing

MDT	MBL-	PBL
Rifampin -	600 mg/month	600 mg/month Supervised
Dapsone -	100 mg/day, self	100 mg/day, self
Clofazimine -	300 mg/month + 50 mg/day	
	12 months	6 months

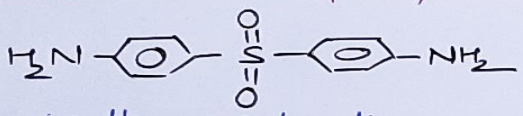
Child -

Rifampin -	10 mg/kg/month
Dapsone -	2 mg/kg/day
Clofazimine -	1 mg/kg/day + 6 mg/kg/month

ANTI LEPROTIC DRUGS :- DAPSONE

Drugs :- 1. Sulfone → Dapsone
2. Phenazine → Clofazimine → ✗ DNA, membrane, ETC
3. Anti-TB drugs → Rifampin, Ethionamide
4. Antibiotics → Fluoroquinolones, Minocycline, clarithromycin

DAPSONE - Diamino Diphenyl Sulfone (DDS)



chemically relate to Sulfonamide

This is the most active, commonly used member of its class. Other Sulfones have become obsolete

MOA - Inhibit DHFS (Synthase) Enzyme & ↓ Folic ā

PABA Antagonist, PABA —✗→ DHFA

Highly sensetive to M. leprae DHFS, thus for other bacteria, required high concentration, & may lead to toxic action, hence not used for other.

Dapsone is also active to protozoal infection along with pyrimethamine, Alternate to Sulfonamide-pyrimethamine for "P. falciparum" & "Toxoplasma gondi" & also in some Fungi (Pneumocystis jirovecii)

It also shows antiinflammatory activity

At low conc. it shows Laprostatic Action

It is drug of choice for - Dermatitis herpetiformis

Resistance - # ↓ affinity to DHFS enzyme.

Primary Resistance - Untreated Patient, that infected from "Resist Mycobacteria" from other patients

Secondary Resistance - during monotherapy

MDT recommended for ↓ incidence of Resistance

PKinetic - Complete absorbed after oral administrat^n,
↳ Widely distributed, 70% Protein Binding
↳ Metabolized by Acetylation, Glucuronide & Sulfate conjugation. Metabolite are excreted in bile & reabsorbed from intestine. Mostly Exc. through Urin
↳ The drug is cummulative due to tissue retention & Enterohepatic Circulation

ADR : - # Haemolytic Anaemia (↑ in G6PD deficient)
Gastric Intolerance - Anorexia, Nausea
Methaemoglobinaemia, headach, fever Mental
Cutaneous React^n - itching, allergy, phototoxicity
Sulfone (DDS) Syndrome - (4-6 weeks after administration)
↳ Fever, Malaise, lymph node enlargement, Anaemia, Jaundice, etc

Contra-Indication -
Anaemia Patients (Hb < 7 g%)
G-6PD deficient Patients
Allergic patients