ANTI-TB DRUGS – ISONIAZID

- Inhibits the synthesis of mycolic acid – imp. constituent of cell wall.
- Small water soluble mol. → passively diffuse in cell.

2 – POINTS

- effective against both intracellular & EC – M. bacteria
- Bacteriostatic = For resting organism
- Bactericidal = rapidly multiplying

MOA:

INH (pro-drug) —KatG (catalase peroxidase)→ INH (active) —form covalent complex→ ⊖ InhA, ⊖ KasA → ⊖ mycolic acid synthesis

- enzyme acyl carrier protein = InhA
- β-keto acyl-ACP synthase = KasA

Spectrum

- M. Tuberculosis (specific)
- M. kansasii (at high conc.)
- most Non-Tuber myco. are resistant.

Resistance – chromosomal mutation

- mutation/deletion of Kat-G (most common).
- acyl carrier protein mut.
- over-expression of target enzy InhA

Cross resist occur b/w INH & Ethionamide

KINETICS

Absorption

- Rapid oral.
- abs ↓ = food esp. High-fat meal
- or histamine-containing food.

Distribution

- all Body cells & caseous material
- Serum conc = CSF conc.

Metabolism

N-acetylation & Hydrolysis

- Fast acetylator = 90 min $t_{1/2}$
- Slow acetyl. = 3–4 hr $t_{1/2}$ → excrete more parent comp.

Excretion

- Kidney (GFR + secretion as metabolite predomin.)

ADR

(can't detoxify metabolites completely ⇒ ↑ level = Toxicity in blood)

Hepatitis

- esp. in pts:
  - age > 35 yr
  - co-adm rifampin
  - alcohol drinker

Body

- peripheral neuropathy → manifested as paraesthesia of hand & feet (burning/pricking sensation)
- Due to pyridoxine deficiency.
- AVOIDED BY: Vit-B6 20–50 mg/day

★ CNS-ADRs

- convulsion in pt. prone to seizure
- ★ Hypersensitivity
  - ↳ Rash
  - ↳ Fever.

DI

- Inhibi. of metab of
  - carbamazep.
  - Phenytoin

Use serum conc ⇩ ↑ adrs – e.g. nystagmus & ataxia

- Acetaminophen

vision condition in which eye make repetitive uncontrolled movement

group of structu. similar Macrocyclic antibio — **Rifamycins** (rifampin, rifabutin, rifapentine)

*Rifampin:

- Broader spectrum than INH
- can be use as adju. in various infec
- Never given as monotherapy → as it can induce/↑se resistance

MOA

- Block RNA transcription ⇩ by interacting ē β-subunit of Mycobac. DNA-depen. RNA polymerase ⇩ [responsible for copying DNA seq. into RNA seq.]

Do watch lecture on Pharmaco-study youtube

Spectum

Bactericidal
- Intra
- Extracellu Myco.
  - M.tb. TB & Non-Tubercu. mycobac. e.g M. kansasii, M. avium complex (MAC)

- against many g+ve & g-ve
- use- prophylic — for indivi exp. sec. to meningitis — caused by H. influenza or meningococci
- Active against M. Leprae

Resistance: mutation = RNA polymer affinity ↓se.

KINETICS

Absorpt.
- Adequate after oral.

Distrib.
- All body fluid
- CSF conc = 10-20% of blood conc.

Metabo.
- Enterohepatic recycling
- Inducer of CYP450
- Unrelated to CYP450 effect, also undergoes self or autoinduction leading to ↓ $t_{1/2}$

Elimination: primarily through bile into feces, urine [in small amount]

⚠ = urine, feces & other secretion have an ORANG-RED color.
- Tears may stain soft contact lenses - orange red.

* ADRS: - generally well-tolerated

- N/V/ Rash
- Hepatitis — rare: precaution as in case of INH

⇨ When DOSED INTERMITTENTLY, esp ē dose ≥ 1.2g
- Flu-like symp
- fever, Chills, myalgia ⇩ extending to acute renal failure, Hemolytic anemic & shock

• DI:

- Inducer of phase I CYP450 & ph-II enzy ⇩ ↓se $t_{1/2}$ of many drugs ↑ clearance

So ⇩ either
- give higher dose of co-adm drugs
- replace it by rifabutin
- or replace that drug ē less affected one

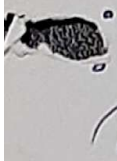
Bacteriostatic ← **ETHAMBUTOL** → speci. for mycobac.

MOA: Inhibit arabinosyl transferase – an enzy. imp. for mycobac. cell wall synthesis

Usage: use in comb. ē pyraz, INH, & rifampin pending culture & susceptibility data.

- If the isolate is determined to be susp. to INH, rifam & pyra. then ethamb. must be DISCONTINUED.

KINECTICS :- — Well-distri throughout — CSF dis is minimal
- Excreted via kid. (parent & metabo.).



At Risk
- ē high dose

ADR
- ← Optic neuritis → may cause
  - Diminish visual acuity (ability to recognize the shapes & details of the things you see).
  - loss of ability to discrimin. b/w green & red.
- ↓ uric acid excretion [caution in gout pt.]

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less effective – **Second-LINE** – More toxic

Streptomycin
- first AG → For TB
- effective against extracellular infec.
- In case of resistance, Kana & amikacin may be used

P-aminosalicylic acid (PAS) (incorporate into DHPS & DHFR ↓ Inhibit DHFR activity; ↓ like sulfonamide)
- previously used in 18 month treat. regimen ē INH & strep
- Largely replace by ethambutol
- Now imp. only for MDR-TB
  - Hepatotoxic
  - GI intole.
  - Hypothyroidism

Capreomycin
- Parenx parenter. adm. polypeptide ↓ inhibit protein syn.
- For MDR-TB
- NO → Toxicity

→ FQ
- Levo & moxi
- For MDR-TB.

→ macrolide
- Azi & clari.
- Azi prefer due to less DI

Cycloserine
- CNS adrs
- Orally effective – Bacteriostatic
- Disrupt D-alanine incorpor. into cell wall
- Distribute: Body + CSF
- Accumu. ē renal insuffi
- CNS disturbances (lethargy, diff. concentrating, anxiety, suicide thoughts) & seizures.

ETHIONAMIDE – Static
- Isoniazid struc. analog
- Disrupt mycolic acid syn.
- Cross-resis ē isonia.
- Distrib – Body + CSF
- Meta. by liver
- N/V/Hepatotoxic.
- Hypothyroidism, gyne comastia
- alopecia - impotency & CNS ADR.

Bedaquiline
- TB-TP ↑ (QTc) – CPD.
- ATP-synthase inhibi.
- ⊖ ATP → cell die due to lack of energy.
- Oral agent
- QTc ↑
- CI ē rifampin as it is CYP3A4 substrate & rifam is inducer

Other Rifampins

Rifabutin

→ preffered for TB ē HIV, receiving Protease inhibitors or several non-nucleoside reverse transcriptase inhibits (NNRTIs)

→ less potent inducer of (approx ~ 40%) CYP-450 = ↓ DI

→ ADR = similar = can also cause
- Uveitis (form of eye inflam) (affect middle layers called uvea).
- skin Hyperpigment.
- Neutropenia (low neutrophil level)

Rifapentin

- -pentin > Activity than rifampin
- Long $t_{1/2}$
- For LTBI ⇒ use in combi. ē INH once/week
- For selective HIV -ve pt ē minimal pulm. TB

Rifampin – DIs:

H → HIV protease inhib.
M → Methadone
P → prednisolon
O → oral-contia.
P → propranolol
Q → Quinidine
V → varicona-zole
W → warfarin

* PYRAZINAMIDE :- Synthetic and orally effective, use in comb.

MOA

pyrazinamide —(Pyrazimidase / (Hydrolysis))→ pyrazinoic acid (active form) → interfere ē Fatty acid synthetase FAS-I ⇓ ↓ new Fatty acid synthesis

Required for growth & replication.

- Some resistant strain lack pyrazimidase enzyme
- PYZ is active against T.B bacilli in acidic lesion & macrophages

KINETICS

Distribute Trough out + CSF

ADR
- rash
- joint ache
- Liver toxicity
- uric acid retention

- Most of clinical benefit from PZM is seen early in treatm. so this drug is usually discontin. after 2 months of a 6-month regimen.

DRUGS FOR LEPROSY

Dapsone & rifampin, adding clofazimine in multibacillary cases → effective in treatment

*-DAPSONE:- structurally related to sulfonamide,

- **MOA:** inhibit DHPS in folate synthesis
  Bacteriostatic — for M. leprae.

Other use: pneumonia caused by pneumocystis jirovecii in immunocomp. pts

Kinectics

- Well-absorb from GIT
- distrib. throughout esp in skin
- parent drug → Hepatic acetylation
- BOTH parent & metab. → excre. in urine

ADR:
- Hemolysis (esp in G6PD deficiency).
- methemoglobinemia: (RBCs contain methemoglobin at higher level than 1%.)
- peripheral neuropathy

*-CLOFAZIMINE: It is a phenazine dye.

MOA

Binding to DNA

Its redox properties may lead to generation of → Cytotoxic oxy. radical → Toxic to bacteria

- Bactericidal to M. leprae
- useful against M.TB & NTM

KINECTICS

- after oral absorp. → accumulate in tissues
- Doesn't enter CNS
- ADRs → pink to brownish-black discoloration of skin [pt. should be informed]
- Eosinophilic & other form of enteritis, sometime requi surgery.

- Has anti-inflam & anti-immune activi. — Thus erythema nodosum leprosum (immune-medial. complic. of leprosy; skin inflam reddish, painful, tender lumps) may not develop.