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First Line Anti-Tuberculosis Medication: Current and Ongoing Clinical Management

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Abstract

Tuberculosis disease can be healed with early diagnosis and correct treatment. The intentions of tuberculosis treatments are to suppress relapse of tuberculosis, to inhibit death from active tuberculosis or its late effects, to de-escalate transmission of tuberculosis to others, to suppress the advancement of acquired medication resistance, to heal the patient from tuberculosis. Medication treatment is the solely effective. Rifampin binds strongly to the β-subunit of bacterial deoxyribonucleic acid dependent ribonucleic acid polymerase and thereby inhibits ribonucleic acid synthesis and blocking ribonucleic acid transcription. Adverse drug reactions of pyrazinamide are hepatotoxicity is the major concern in 15% of pyrazinamide recipients. It also can inhibit excretion of urates, resulting in hyperuricemia (acute gouty arthritis). The toxicity of pyrazinamide is both dose dependent with a higher dose at 40–50 mg/kg being associated with a greater frequency of hepatotoxicity than the doses used in current regimens (25–35 mg/kg). Pyrazinamide inhibited cytochrome P450 activity and nicotinic acid derivative levels were altered in association with free radical species mediated hepatotoxicity.

Keywords: Anti-Tuberculosis; First Line; Medication

Introduction

Tuberculosis remains a considerable public health challenge globally despite the fact that the causative organism has been known for greater than 100 years, and highly effective medications and vaccines have been applicable for decades. Further people who had TB disease can be cured with early diagnosis and correct treatment. Despite this, it has been persisted as a leading cause of death from a single infectious agent ranking on top of HIV/AIDS for the past five years. Globally there were estimated 10.4 million new TB cases, and 600,000 new cases with resistance to rifampicin, 490,000 had MDR-TB cases and 1.7 million people died from TB [1]. The intentions of TB treatments are: (1) To obviate relapse of TB (2) To obviate death from active TB or its late effects (3) To de-escalate transmission of TB to others (4) To obviate the advancement of acquired medication resistance (5) To heal the patient from TB. Medication treatment is

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the solely effective [2]. Treatment method for TB and the WHO has programmed a standardized DOTS/cease TB program, to ameliorate TB suppression and control [3]. First-Line anti-tuberculosis drugs (new 2016) are Isoniazid (INH); Rifampin (RIF); Rifapentine (RPT); Rifabutin (RFB); Ethambutol (EMB); Pyrazinamide (PZA). Details of those first line anti-tb medications discussed below;

Rifampicin: Rifampicin is a semisynthetic macrocyclic antibiotic generated from *Streptomyces mediterranei*. It is a consummate lipid-soluble molecule that is bactericidal for both intracellular and extracellular microorganisms. Rifampin is a potent inducer of hepatic cytochrome P450 enzymes escalates metabolism of multiplex medications. Rifampin has wide-spectrum activity and active against G+ cocci (involving drug-resistant S. aureus) [4]. Deacetyl rifampicin is more polar than the parent compound, and microbiologically active. This metabolite accounts for the majority of the antibacterial activity in the bile. Rifampicin is metabolized by liver and undergoes enterohepatic re-circulation.

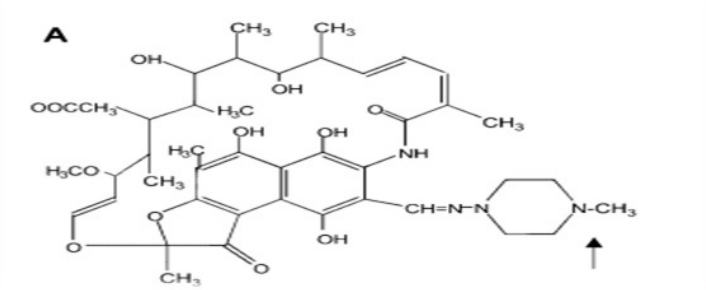

Figure 1: Chemical structure of rifampicin

Rifampicin resistance: The resistance of rifampicin occurs: 1 in 10^7 to 10^8 tubercle bacilli DNA-dependent RNA polymerase alteration. Mutations of rifampicin minimized the binding of the drug to the polymerase. This medicine should not be used alone since resistance develops very fast.

Mechanism of action: Exact MOA unknown, although its target appears to be the mycobacterial fatty acid synthetase involved in mycolic acid biosynthesis. Nuclear eukaryotic RNA polymerases are unaffected. Large concentrations can obviate RNA synthesis in mammalian mitochondria, viral DNA-dependent RNA polymerases, and reverse transcriptase. It can kill organisms that are poorly accessible to multiple distinctive antibiotics, such as intracellular organisms and those sequestered in abscesses and lung cavities [5]. Uses: For treatment of leprosy, adjunctive therapy for infections of ventriculoperitoneal shunts with staphylococcus aureus, other G+ infections, prophylaxis for meningitis caused by highly penicillin-resistant strains of pneumococci, empiric treatment of TB [6]**. Adverse drug reactions:** GI **(**anorexia, diarrhoea or pseudomembranous colitis, dysphagia (most common)); skin rash pruritis, skin reactions, arthralgias, myalgias (fairly common), ataxia, hepatic (escalate accumulation of bilirubin in blood plasma levels, hepatitis), thrombocytopenia, shock like syndrome with hepatic involvement, thrombophlebitis, others: De-escalated thyroid, adrenal, vitamin D, abnormalities of liver function, influenza like symptoms, menstrual irregularities, extravasation following local irritation and inflammation, headache etc. Intermittent administration of rifampin (particularly high doses) is consociated with a flu-like syndrome, thrombocytopenia, haemolytic anaemia, and renal failure. It has been seldom consociated with medication-induced lupus [7, 8]**. Use during pregnancy:** Rifampin is a category C drug. Either inquests in animals have displayed adverse effects on the foetus (teratogenic or embryocidal, or other) and there are no restrained inquests in women or inquests in women and animals are not avail. Drugs should be accustomed only if the implicit advantage maintains the implicit peril to the fetus or the survey in animal model displayed slight pitfall to the pregnant animal, but there is no confirmation in fetal peril of human survey in pregnant women. As a precaution, neonates born to mothers who have been under treatment with isoniazid should be given vitamin K, in order to avoid postpartum hemorrhage [9]**. Use during breastfeeding:** If given for breastfeeding mothers it perhaps causes the skin of infant yellow, so the infant perhaps observed for color change of skin to yellow [10]**. Use in patients with liver failure:** Liver failure can impair rifampin clearance, escalating the serum levels of the medication. Nevertheless, owing to the indispensable

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function that rifampin plays in tuberculosis treatment regimens; the medication is ordinarily involved, with the proviso that the patients be closely monitored through often clinical evaluations and laboratory tests [11]. **Use in patients with kidney failure:** Because rifampin is metabolized in the liver, the medication can be used at full doses in patients with kidney failure [12]. **Contraindications:** Drug-induced hepatitis or solemn hepatic infirmity, hypersensitivity of rifamycin product, jaundice [13]. **Drug-drug interactions:** Antacids containing $Al_2(OH)_3$ detain the absorption of rifampin. A high number of interactions can happen between rifampin and distinctive medications. The medication is a potent inducer of the CYP450 system, involving the CYP3A and CYP2C subfamilies, which account for greater than 80% of the CYP450 isoenzymes. Consequently, rifampin can escalate the metabolism of oodles medications that are partially or completely metabolized by CYP450 when these medications are administered coincidently with rifampin. Furthermore, rifampin induces CYP450 enzyme subfamilies such as CYP1A2, 2C9, 2C19, 3A4 will escalate the metabolic clearance of multiple medications enclosing warfarin, corticosteroids, estrogens (involving oral contraceptives), antiarrhythmics, theophylline, anticonvulsants, ketoconazole, cyclosporine, and others [14]. **Toxicity:** If rifampicin is taken over dose, it causes; several toxicities such as hepatic toxicity, renal toxicity, haematological disorders and convulsions.

Rifapentine

Rifapentine is a cyclopentyl-substituted semisynthetic rifamycin that was first synthesized in 1965 by the Italian company that developed rifampin. Rifapentine has high anti-mycobacterial activity and a long elimination half-life of 15 hours that makes it an attractive candidate for treatment-shortening regimens. The drug is metabolized mostly by the liver and is excreted predominantly (70%) in feces. The drug is metabolized by hydrolysis and deacetylation to 25-O-desacetylrifapentine, which is microbiologically active, contributing 38% of the drug's overall activity [9].

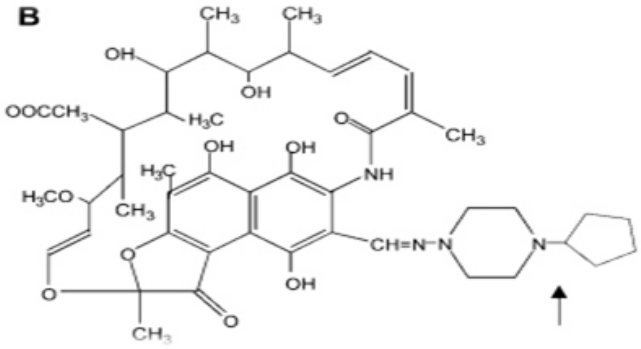

Figure 2: Chemical structures of rifapentine. A methyl group in rifampicin showed in figure 1 is substituted for a cyclopentyl group to yield rifapentine (the arrows on two drugs which are rifampicin (A) and rifapentine (B) chemical structure show the points of difference).

Rifapentine resistance: The incidence of rifapentine-resistant organisms associated with spontaneous mutations in an otherwise susceptible population of Mycobacterium tuberculosis strains is □1 in 10^7 –10^8 bacilli. Resistance develops quickly when exposed to a single drug. **Mechanism of action:** Like other rifamycins, rifapentine inhibits bacterial DNA-dependent RNA polymerase. Rifamycins are unique among drugs that work by this mechanism, because the inhibition of RNA polymerase will occur even when enzyme exposure to the drug is very brief in otherwise metabolically dormant organisms [4]. **Drug-drug interactions:** Isoniazid may interact with foods containing tyramine/histamine (such as cheese, red wine, certain types of fish). This interaction may cause increased blood pressure, flushing of the skin, headache, dizziness, or fast/pounding heartbeat. Individuals who wish to avoid pregnancy should know that rifapentine (like other rifamycins) decreases the effectiveness of hormonal contraceptives. These individuals should consider using a different, or additional, form of contraception when taking rifapentine-based TPT. Rifapentine induces cytochrome P450 enzymes and can also accelerate the metabolism of certain drugs, such as birth control pills and antiretroviral drugs, methadone, warfarin, b-blockers, benzodiazepines, and oral anticoagulants [3]. **Adverse drug reaction:** Rifamycins can occasionally cause drug-induced hepatitis and have rarely been associated with severe thrombocytopenia.

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In clinical trials, rates of adverse reactions were similar for rifampin and rifapentine, with increased aminotransferase activity seen in □5% of all patients. Rifapentine, like other rifamycins, may produce an orange-red discoloration of body fluids (urine, tears, sputum, saliva, feces, and CSF). Contact lenses and dentures can become permanently stained [7]. **Use during pregnancy:** Pregnancy increases the risk of TB infection progressing to active TB disease. Rifapentine is currently not recommended for use in individuals who are pregnant. This is due to a lack of data on the safety of giving rifapentine during pregnancy. If a woman becomes pregnant while receiving rifapentine, we recommend that the regimen be changed to rifampin-isoniazid [9].

Isoniazid (INH) Isoniazid is one of the consummate indispensable medications in the treatment of TB. The structure of isoniazid is simple. It comprises a pyridine ring and a hydrazine group. Notwithstanding isoniazid has a bactericidal effect on hastily growing bacilli, it has a limited outcome on slow-growing (ordinarily intracellular) and intermittently growing (ordinarily extracellular) bacilli [15].

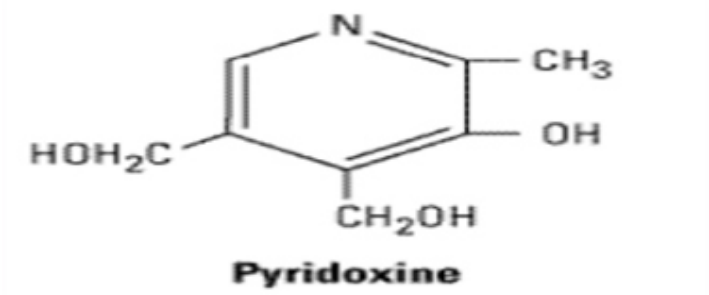

Figure 3: Chemical structure of pyridoxine and isoniazid.

INH is metabolized by liver and INH is acetylated to acetyl INH by N-acetyltransferase. The key enzymes in the metabolic pathway, N-acetyltransferase 2 (NAT2) and microsomal enzyme cytochrome P4502E1 determine the risk of hepatotoxicity. As illustrated in Figure 1, N-acetyltransferase 2 is responsible for metabolism of isoniazid to acetyl isoniazid, which in turn is hydrolyzed to acetyl hydrazine [8].

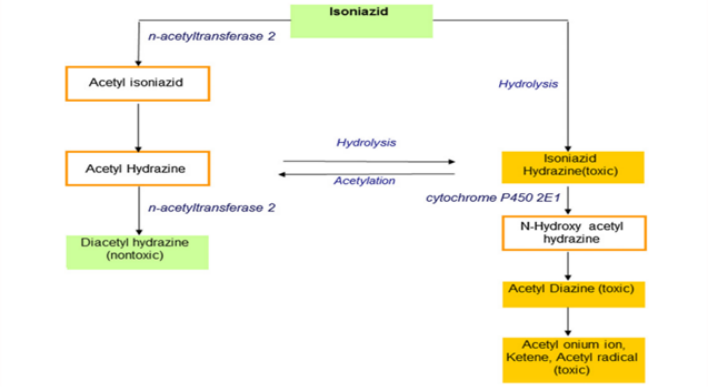

Figure 4: Pathways involved in the metabolism of isoniazid.

INH resistance: Rapid resistance if used alone (10%) so combination therapy is required for active TB. Resistance is due to mutations/deletion in KatG gene which is required for activation of INH providing protection of the bacterial cells. Cross-resistance between isoniazid and other anti-tuberculosis agents (except ethionamide) does not occur. **Mechanism of actions**: bactericidal, it obviates DNA synthesis of mycolic acids, which are constituents of mycobacterial cell wall and kill rapidly the multiplying organism. It is the consummate active medication for the treatment of TB. A prodrug, which means it, necessitates activation by enzyme (mycobacterial catalase-peroxidase KatG) [16]. **Adverse drug reactions:** Peripheral neuropathy: Tingling and numbness, coincident pyridoxine administration with INH obviates consummate of these complications and predisposing conditions diabetes, uremia, malnutrition, HIV infection**.** Distinctive side effects: agranulocytosis anemia (hemolytic anemia, or aplastic anemia), progressive liver affliction, otic neuritis, hepatic dysfunction, seizures, psychosis, lupus-like syndrome, hypertension, tachycardia, palpitation, depression, encephalopathy, memory impairment, slurred speech, hyperglycemia, metabolic acidosis, gynecomastia [17]. **Use during pregnancy:** Isoniazid is a category C drug. Isoniazid use during pregnancy is considered safe, although, there is a pitfall of advancing hepatitis in the postpartum period. The WHO recommends that all pregnant women receiving isoniazid also take pyridoxine (25-50 mg/day). Neonates born to mothers who have been under treatment with isoniazid are at peril of advancing convulsive seizures [18].

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Use during breastfeeding: If given for breastfeeding mothers it perhaps causes the skin of infant yellow, so the infant perhaps observed for color change of skin to yellow [19]. **Use in patients with liver failure:** Isoniazid is a hepatotoxic drug, the outcome of which becomes further evident in individuals with liver disease, in alcoholic individuals, and in individuals over 50 years of age. In such patients, the $t1/_2$ of isoniazid is longer, and the serum levels of the medication are higher. These patients should be closely monitored and should undergo clinical examination and laboratory tests further often than is necessary for patients without liver malady [20]. **Use in patients with kidney failure:** Adjustments to the doses of isoniazid are not necessitated in patients with kidney failure or in those on hemodialysis [21]. **Contraindications:** hypersensitivity of INH, acute liver disease, past history of hepatic damage [22]. **Drug-drug interactions:** Medications that escalate the gastric pH delay the absorption of isoniazid. Antacids containing AL_2 $(OH)_3$ or ranitidine should be administered 1 h after the administration of INH. Isoniazid is an inhibitor of the cytochrome P450 (CYP450) system families CYP2C9, CYP2C19, and CYP2E1, but its effect on the CYP3A family is minimal. This inhibitory consequence of isoniazid can escalate the plasma concentrations of some medications to toxic levels. The plasma concentrations of anticonvulsants, such as phenytoin and carbamazepine, can escalate when these medications are used in combination with isoniazid. The identical happens with the benzodiazepines that are metabolized by oxidation (e.g., diazepam and triazolam), as well as with theophylline, valproic acid, disulfiram, acetaminophen, and oral anticoagulants. The combination of isoniazid and levodopa can cause hypertension, palpitation, and flushing of the face. MAOI inhibitor (weak); histamines; P-450 inhibitor (CYP2C19, CYP3A4): May increase the risk of toxicity of certain drugs such as anticonvulsants (e.g., phenytoin, carbamazepine) and some benzodiazepines (e.g., diazepam, triazolam) [23]. **Toxicity:** If isoniazid is taken over dose, it causes recurrent seizures, profound metabolic acidosis, coma and even death.

Pyrazinamide: Synthetic pyrazine analog of nicotinamide**.** It is stable, slightly soluble in H_2O, and completely affordable is active against tubercle bacilli in the acidic environment of lysosomes, as well as, in macrophages**.** Medication is taken up by macrophages and exerts its activity against intracellular organisms residing within acidic environment**.** Synthetic prodrug; converts to form pyrazinoic acid (POA); bactericidal; accumulates in bacteria, causing lethal membrane damage [24]**.** Pyrazinamide is a nicotinic acid derivative. It is deamidated to pyrazinoic acid. This is further oxidized by xanthine oxidase to 5-hydroxy pyrazinoic acid. Pyrazinamide is metabolized by liver and it undergoes extensive metabolism.

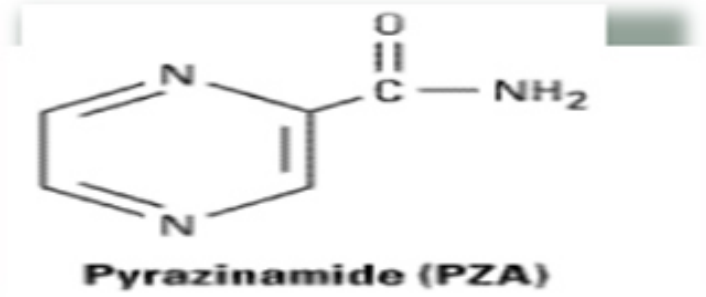

Figure 5: Chemical structure of Pyrazinamide

Pyrazinamide resistance: Mutation in the gene (pncA) that encodes pyrazinamidase is responsible for drug resistance. Resistance develops fairly readily, but there is no cross resistance with INH or other anti-mycobacterial drugs. **Mechanism of Action:** Transformed to pyrazinoic acid in susceptible strains of mycobacterium which lessens the PH of the environment; it act by inhibition of mycolic acid synthesis by interacting with gene of fatty acid synthesis [25]**. Adverse drug reaction:** Hepatotoxicity (hepatomegaly and jaundice)**,** GI: anorexia, vomiting and nausea**,** non-gouty poly-arthralgia, hyperuricemia, abnormal liver function test, rash, photosensitive, dermatitis, fulminant hepatitis, malaise, fever**.** In patients with pyrazinamide-induced hepatitis, the drug should be temporarily discontinued or even replaced [26]**. Use during pregnancy:** Pyrazinamide is a category C drug. The WHO considers it safe to use pyrazinamide during pregnancy [27]. **Use during breastfeeding:** If given for breastfeeding mothers it perhaps causes the skin of infant yellow, so the infant

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perhaps observed for color change of skin to yellow [28]. **Use in patients with liver failure:** Pyrazinamide is a hepatotoxic medication, the outcome of which is more apparent in individuals with liver disease. These patients should be closely monitored and should undergo clinical examination and laboratory tests further often than is necessary for patients without liver disease [29]. **Use in patients with kidney failure:** The metabolites of pyrazinamide are eliminated by the kidney and can accumulate in patients with kidney failure, which necessitates that the dose of the medication be de-escalated. The peril of advancing pyrazinamide-induced hyperuricemia also accelerates in patients with kidney failure. The daily dose should be downgraded to half when creatinine clearance is lower than 10 mL/min. Patients with creatinine clearance lesser than 30 mL/min or those on hemodialysis should be bestowed pyrazinamide at a dose of 25-35 mg/kg, three times a week [30]. **Drug-drug interactions:** Antacids do not interfere with the absorption of pyrazinamide. Probenecid, rifampin, isoniazid, and ethionamide can potentiate the toxic effects of pyrazinamide. The combination of pyrazinamide and zidovudine can de-escalate the outcome of pyrazinamide. Pyrazinamide antagonizes the effects of probenecid and de-escalates the serum concentration of cyclosporine. Pyrazinamide can escalate the serum concentrations of uric acid, and it might be necessary to adjust the doses of allopurinol and colchicine in patients under gout treatment [31]. **Toxicity:** If pyrazinamide is taken over dose, it causes hepatic dysfunction, gastrointestinal upset and skin rashes.

Ethambutol: Ethambutol was synthesized in 1961 and has been used in the treatment of tuberculosis since 1966. It acts on intracellular and extracellular bacilli, substantially on hastily growing bacilli. The MIC of ethambutol for M. tuberculosis is 1-5 µg/mL. At the usual doses, ethambutol has a bacteriostatic effect [32]. Ethambutol is mainly oxidized by an aldehyde dehydrogenase to an aldehyde metabolite, followed by conversion to the dicarboxylic acid 2, 2-(ethylinediimino) di-butyric acid.

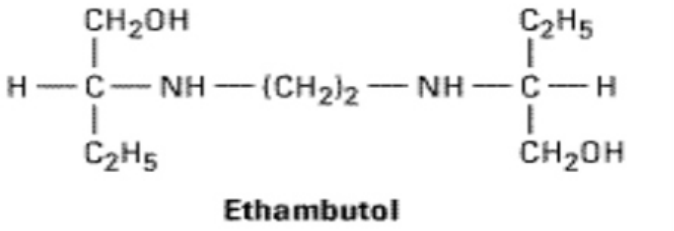

Figure 6: Chemical structure of ethambutol

Ethambutol resistance: Ethambutol drug resistance relates to point mutations in the gene (EmbB) that encodes the arabinosyl transferases that are involved in mycobacterial cell wall synthesis. **Mechanisms of action:** Ethambutol interferes with the biosynthesis of arabinogalactan, the general polysaccharide on the mycobacterial cell wall. Ethambutol obviates the arabinosyl transferase enzyme encoded by the embB gene, which mediates the polymerization of arabinose into arabinogalactan. In vitro resistance to ethambutol develops slowly and is likely owing to mutations in the embB gene [33]. **Adverse drug reactions**: Optic neuritis: most common and serious dose related, blurred vision, central scotoma, red-green color blindness, hyperuricemia: rare, peripheral neuritis: rare, green-red colour blindness, retinal hemorrhage, GI disturbances (abdominal pain, nausea, anorexia), rash, dizziness, hallucinations, jaundice, pulmonary infiltrates [34]. **Use during pregnancy:** Ethambutol is a category B1 medication. Ethambutol crosses the placental barrier, and the plasma concentration of ethambutol in the fetus can be as great as 30% of the plasma concentration of the medication in the mother. The WHO considers it safe to use ethambutol during pregnancy [35]. **Use during breastfeeding:** Ethambutol concentrations in breast milk are identical to the plasma concentrations of the medication. The American Academy of Paediatrics considers ethambutol to be amicable with breastfeeding [36]. **Use in patients with liver failure:** Ethambutol can be used at full doses in patients with liver failure. It is not necessary to adjust the dose of the medication in such patients [37]. **Use in patients with kidney failure:** Ethambutol and its metabolites can accumulate in patients with kidney failure.

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Patients with a creatinine clearance of 30-50 mL/min should use the medicine at longer intervals between doses, usually every 36 h. In patients on hemodialysis or in those in whom creatinine clearance is lesser than 30 mL/min, a dose of 15-20 mg/kg should be administered three times a week. Ethambutol is removed by peritoneal dialysis and, to a lower degree, by hemodialysis [38]. **Contraindications:** hypersensitivity to the products, optic neuritis, lactation [39]. **Drug-drug interactions:** Antacids (AL_2 (OH) $_3$) can downgrade the maximum concentration and absorption of ethambutol by as much as 28%. The drugs should consequently be administered at longer intervals. Ethionamide can exacerbate the toxic effects of ethambutol. Coincident administration of ethambutol with other antitubercular medications has synergistic effects [40]. **Toxicity:** If ethambutol taken over dose, it causes optic neuropathy.

Conclusion

Tuberculosis (TB) remains a major public health problem globally. Mycobacterial infections are the most difficult of all bacterial infections to cure. It is currently accepted that any anti-TB treatment should include at least four drugs that are likely to be effective of which at least two are essential or core drugs and two are companion drugs. Isoniazid is the most active drug for the treatment of tuberculosis. It is bactericidal against actively growing M. tuberculosis bacteriostatic against non-replicating organisms. Isoniazid is active against susceptible bacteria only when they are undergoing cell division. Pyrazinamide is taken up by macrophages and exerts its activity against intracellular organisms residing within acidic environment. Adverse drug reaction of pyrazinamide is hepatitis (greater risk in alcoholics & pregnancy and is a contraindication to further use of the drug); peripheral neuropathy due to a relative pyridoxine deficiency (more likely in slow acetylators, malnutrition, alcoholism, diabetes, AIDS). INH promotes excretion of pyridoxine which minimized by administration of pyridoxine CNS toxicity (memory loss, psychosis, and seizures) May respond to pyridoxine.

Abbreviations

AL_2 (OH) $_3$: Aluminium oxide; TB: Tuberculosis; CYP450: Cytochrome P450; DOTS: Directly observed treatment, the short-course; INH: Isoniazid; PZA: Pyrazinamide.

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Data Sources: Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Lance, EMBASE, Science direct, Scopus database, Scielo and Cochrane database. Search terms included: about first line anti-tuberculosis medication

Availability of data and materials

The data-sets generated during the current study are available with correspondent author.

Conflict of interest

The author has no financial or proprietary interest in any of material discussed in this article.

References

1. Bereda G, Bereda G. Prevalence of, and Factors Influencing First Line Antiretroviral Treatment Failure among Adult HIV Patients at Antiretroviral Treatment Clinic of Mettu Karl Referral Hospital, South Western, Ethiopia: A Prospective Cross-Sectional Study, 2021. Int J Virol AIDS. 2021; 8:075.

2. Wallis RS, Hafner R. Advancing host-directed therapy for tuberculosis. Nature Reviews Immunology. 2015 Apr;15(4):255-63.

Journal of
Molecular Biology and Drug Design

Review Article Open Access

3. Probandari A, Lindholm L, Stenlund H, Utarini A, Hurtig AK. Missed opportunity for standardized diagnosis and treatment among adult tuberculosis patients in hospitals involved in public-private mix for directly observed treatment short-course strategy in Indonesia: a cross-sectional study. BMC Health Services Research. 2010 Dec;10(1):1-7.

4. Tompkins LM, Wallace AD. Mechanisms of cytochrome P450 induction. Journal of biochemical and molecular toxicology. 2007 Aug;21(4):176-81.

5. Julius C. *Non-canonical RNA capping by DNA-dependent RNA polymerases & screen for bacteriophage regulators of mycobacterium smegmatis transcription* (Doctoral dissertation, Newcastle University).

6. Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B, Hall SL, Chakravorty S, Cirillo DM, Tukvadze N, Bablishvili N. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. The Lancet Infectious Diseases. 2018 Jan 1;18(1):76-84.

7. Calix L, editor. Modell's Drugs in Current Use and New Drugs, 2006. Springer Publishing Company; 2006 Feb 8.

8. Cashy C, De Leon A, Anderson J, Boes T. Fusobacterium: A Rare Case of Septicemia in a Patient with Multiple Abscesses. Ohio Chapter/Air Force Chapters. 2020 Oct:26.

9. Kim JH, Nam WS, Kim SJ, Kwon OK, Seung EJ, Jo JJ, Shresha R, Lee TH, Jeon TW, Ki SH, Lee HS. Mechanism investigation of rifampicin-induced liver injury using comparative toxicoproteomics in mice. International journal of molecular sciences. 2017 Jul;18(7):1417.

10. Siddiqi N, Campbell A. Post-transplant Medication Challenges. InChallenges in Pediatric Kidney Transplantation 2021 (pp. 305-356). Springer, Cham.

11. Abulfathi AA, Decloedt EH, Svensson EM, Diacon AH, Donald P, Reuter H. Clinical pharmacokinetics and pharmacodynamics of rifampicin in human tuberculosis. Clinical pharmacokinetics. 2019 Sep;58(9):1103-29.

12. Vasakova M. Challenges of antituberculosis treatment in patients with difficult clinical conditions. The clinical respiratory journal. 2015 Apr;9(2):143-52.

13. Misra UK, Kalita J, Tripathi A, Mishra P. Oxidative stress and ER stress may contribute to drug-induced hepatitis in tuberculous meningitis. Journal of the neurological sciences. 2020 Jul 15; 414:116825.

14. Skelin M, Lucijanić T, Klarić DA, Rešić A, Bakula M, Liberati-Čizmek AM, Gharib H, Rahelić D. Factors affecting gastrointestinal absorption of levothyroxine: a review. Clinical therapeutics. 2017 Feb 1;39(2):378-403.

15. Villamizar-Mogotocoro AF, Vargas-Méndez LY, Kouznetsov VV. Pyridine and quinoline molecules as crucial protagonists in the never-stopping discovery of new agents against tuberculosis. European Journal of Pharmaceutical Sciences. 2020 Aug 1; 151:105374.

16. Dookie N, Rambaran S, Padayatchi N, Mahomed S, Naidoo K. Evolution of drug resistance in Mycobacterium tuberculosis: a review on the molecular determinants of resistance and implications for personalized care. Journal of Antimicrobial Chemotherapy. 2018 May 1;73(5):1138-51.

17. Drug-Resistant TB. Scale-Up Treatment Action Team. DR-TB Stat: Country Updates.

Journal of
Molecular Biology and Drug Design

Review Article Open Access

18. Brhane Y, Gabriel T, Adane T, Negash Y, Mulugeta H, Ayele M. Recent Developments and Novel Drug Delivery Strategies for the Treatment of Tuberculosis. International Journal of Pharmaceutical Sciences and Nanotechnology. 2019 May 31;12(3):4524-30.

19. Hill WC, Paruolo JB, Giovino AC. Prophylaxis for tuberculosis in pregnant women. Clinical obstetrics and gynecology. 2019 Dec 1;62(4):846-56.

20. Metushi I, Uetrecht J, Phillips E. Mechanism of isoniazid-induced hepatotoxicity: then and now. British journal of clinical pharmacology. 2016 Jun;81(6):1030-6.

21. Lin SY, Chiu YW, Lu PL, Hwang SJ, Chen TC, Hsieh MH, Chen YH. Three months of rifapentine and isoniazid for latent tuberculosis infection in hemodialysis patients: high rates of adverse events. Journal of Microbiology, Immunology and Infection. 2019 Feb 1;52(1):158-62.

22. Combrink M, du Preez I. Metabolomics describes previously unknown toxicity mechanisms of isoniazid and rifampicin. Toxicology letters. 2020 Apr 1; 322:104-10.

23. Bekker Z. *Cytochrome P450 and the immune response to prolonged administration of isoniazid, nevirapine and paracetamol in a rat model* (Doctoral dissertation, University of the Free State).

24. Dastidar DG, Ghosh D, Ghosh S, Chakrabarti G. Drug Delivery in Respiratory Diseases: Current Opportunities, Molecular and Cellular Mechanism, and Future Challenges. InTargeting Cellular Signalling Pathways in Lung Diseases 2021 (pp. 847-902). Springer, Singapore.

25. Njire M, Tan Y, Mugweru J, Wang C, Guo J, Yew W, Tan S, Zhang T. Pyrazinamide resistance in Mycobacterium tuberculosis: Review and update. Advances in medical sciences. 2016 Mar 1;61(1):63-71.

26. Tan W, Zhao K, Xiang J, Zhou X, Cao F, Song W, Liu Q, Zhang X, Li X, Tan Z. Pyrazinamide alleviates rifampin-induced steatohepatitis in mice by regulating the activities of cholesterol-activated 7α-hydroxylase and lipoprotein lipase. European Journal of Pharmaceutical Sciences. 2020 Aug 1; 151:105402.

27. Rohilla M, Joshi B, Jain V, Kalra J, Prasad GR. Multidrug-resistant tuberculosis during pregnancy: two case reports and review of the literature. Case reports in obstetrics and gynecology. 2016 Feb 24;2016.

28. Vasakova M. Challenges of antituberculosis treatment in patients with difficult clinical conditions. The clinical respiratory journal. 2015 Apr;9(2):143-52.

29. Lewis JH, Stine JG. prescribing medications in patients with cirrhosis–a practical guide. Alimentary pharmacology & therapeutics. 2013 Jun;37(12):1132-56.

30. Dhlamini L. *Drug-related toxicity of HIV patients on antiretroviral and tuberculosis therapy* (Doctoral dissertation).

31. Bekker A, Schaaf HS, Draper HR, van der Laan L, Murray S, Wiesner L, Donald PR, McIlleron HM, Hesseling AC. Pharmacokinetics of rifampin, isoniazid, pyrazinamide, and ethambutol in infants dosed according to revised WHO-recommended treatment guidelines. Antimicrobial agents and chemotherapy. 2016 Apr 1;60(4):2171-9.

32. Guzman JD, Montes-Rincón X, Ribón W. Research and development of new drugs against tuberculosis. InTuberculosis—current issues in diagnosis and management 2013 Mar 20. InTech, Rijeka.

33. Alderwick LJ, Harrison J, Lloyd GS, Birch HL. The mycobacterial cell wall—peptidoglycan and arabinogalactan. Cold Spring Harbor perspectives in medicine. 2015 Aug 1;5(8): a021113.

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34. Chamberlain PD, Sadaka A, Berry S, Lee AG. Ethambutol optic neuropathy. Current opinion in ophthalmology. 2017 Nov 1;28(6):545-51.

35. Dela AI, Tank ND, Singh AP, Piparva KG. Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: A four-year retrospective study. Lung India: Official Organ of Indian Chest Society. 2017 Nov;34(6):522.

36. Loveday M, Hlangu S, Furin J. Breastfeeding in women living with tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2020 Sep 1;24(9):880-91.

37. Milburn H, Ashman N, Davies P, Doffman S, Drobniewski F, Khoo S, Ormerod P, Ostermann M, Snelson C. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. Thorax. 2010 Jun 1;65(6):559-70.

38. Sadun AA, Wang MY. Ethambutol optic neuropathy: how we can prevent 100,000 new cases of blindness each year. Journal of Neuro-ophthalmology. 2008 Dec 1;28(4):265-8.

39. Dedun AR, Borisagar GB, Solanki RN. Impact of adverse drug reaction of first line anti-tuberculous drugs on treatment outcome of tuberculosis under revised national tuberculosis control programme. Int J Adv Med. 2017 May 23;4(3):645-9.

40. Srivastava AK. Pharmacology: A book of achieving knowledge for drugs. Educreation Publishing; 2017 Jul 5.