e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

Review article

# A REVIEW ON USE OF FIRST LINE ANTI TUBERCULOSIS DRUGS IN SPECIAL SITUATION AND THEIR CLINICAL COMPLICATIONS

**Geervani PG[1]*, Raja Nandini K[2], Vaishnavi M[3], Chaitanya Srinivas B[4]**

[1*2,3] Pharm.D Interns, [4]Pharm D, SVIMS Hospital, Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati - 517506, Andhra Pradesh, India.

**ABSTRACT**

Anti-Tubercular drugs are the class of drugs used to treat Tuberculosis. The main aim of tuberculosis treatment is treat to the patient and reduce the transmission of Mycobacterium tuberculosis in healthy individuals. Tuberculosis treatment cause possible adverse drug reactions in the patient .In this we briefly review the mechanism of action, adverse drug reactions, Drug-Drug and Drug-food interactions and their use in specific individual.

**Key Words:-** Tuberculosis, Isoniazid, Mycobacterium, Clinical complications.

**Access this article online**

Home page: http://ijptjournal.com/

DOI: http://dx.doi.org/10.21276/ijpt.2020.11.2.3

Quick Response code

**Received:**12.01.20 **Revised**:02.02.20 **Accepted**:22.02.20

**Corresponding Author**

**PG Geervani**

Pharm D students, Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati - 517506, Andhra Pradesh, India.

**Email:-** geervanipg@gmail.com

## INTRODUCTION

Tuberculosis is an airborne disease that usually effects the lungs and cause severe cough, fever, and chest pain It is caused by mycobacterium tuberculosis and it was announced by Robert Koch in 1882.and it is a major global health burden. Drug interactions are common cause of adverse drug reactions, resulting undesirable or unexpected effects. and these adverse drug reaction is common in elderly patients because of usage of several drugs (Gallelli L *et al*., 2002 & Gallelli L.*et al*.,2003 & Gallelli L *et al*., 2007 & Gallelli L.*et al*.,2010).

Adverse reactions to antituberculosis drugs are related to various factors such as dose, time at which the medication is administered, patient age, nutritional status, together with the presence of Pre-existing diseases or dysfunctions, such as alcoholism, impaired liver function, impaired kidney function, and HIV coinfection (Pai MP, Momary KM *et al*.,2006).

At present first line treatment for tuberculosis is a regimen of Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA), and Ethambutol for 2 months, followed by 4 months of INH and PMP and/EMP (Blumberg HM *et al*.,2003).

In this review article, we describe the principal characteristics of each of the drugs that constitute its mechanisms of action, interaction and possible adverse drug effects (Conde MB *et al*.,2007).

## ISONIAZID

Isoniazid is one of the most commonly used drugs in the treatment of tuberculosis

### Mechanism of action

It inhibits the formation of mycolic acids of the bacterial cell wall, resulting DNA damage and, leads to death of the bacteria (Zhang Y *et al*.,2005& Slayden RA, Barry CE 3rd *et al*.,2000).

### Metabolization and excretion

Isoniazid is metabolized in the liver through N-acetyltransferase enzyme and excreted mostly by the kidney (70-96%) and little proportion is excreted through faeces. The half-life of isoniazid is approximately 1 h (range: 0.5-1.6 h) and in cases of liver and kidney disease

patients the half-life of isoniazid can be even more (Srivastava A *et al*.,2010).

**Adverse effects**

Isoniazid, rarely cause adverse reaction when used in isolation for tuber-culosis prophylaxis (at a dose of 10 mg • $kg^{-1}$ • $day^{-1}$, up to 300 mg),in individuals without liver disease or kidney failure (Blumberg HM *et al*.,2003). This is the dose that is presently recommended in brazil that isoniazid is used in combination with other drugs for tuberculosis treatment (Conde MB *et al*.,2007).

**Minor adverse effects**

Nausea, vomiting, and epigastric pain occurs when the isoniazid is administered at initiation of the treatment and it can be prevented by taking the drug after 2 hr of meal and by using medications such as metoclopramide, ranitidine or omeprazole can relieve the symptoms

**Major adverse effects**

• Psychosis, convulsive seizures, mental confusion, and coma (Thwaites G *et al*.,2009 & Tai WP, Yue H, Hu PJ *et al*.,2008).
• Haematological alterations or vasculitis (Silva Jr JB *et al*.,2004).
• Peripheral neuropathy (Blumberg HM *et al*.,2003 &. Nisar M *et al*.,1990).

**Use during pregnancy**

Isoniazid is C category drug .and it is considered safe during pregnancy. However, there is a risk of developing hepatitis in the postpartum period. Neonates born to mothers who have been under the treatment with isoniazid are at risk of developing convulsive seizures (Blumberg HM *et al*.,2003 & Nardiello S *et al*.,2002).

**Use during breastfeeding**

Isoniazid is able to exist with breastfeeding; the infant should be recommended to monitored for jaundice.

**Use in patients with liver failure**

Isoniazid cause hepatotoxicity and it has more evidences, so the patients should be closely monitored in case of liver disease (Blumberg HM *et al*.,2003 &Sun HY *et al*.,2009).

**Use in patients with kidney failure**

Isoniazid doses adjustment of isoniazid is not required in case of kidney failure and haemodialysis patient (Blumberg HM *et al*.,2003 & Vikrant SI *et al*.,2005).

**Interactions**

**Foods**

It should be taken with empty stomach and it should not be taken with foods rich in tyramine and histamine such as cheese, fish, alcohol, etc. The symptoms of these interactions include palpitation, sweating, flushing of the face, chills, headache, diarrhoea, erythema, and pruritus.

**Antacids**

Antacids such as Rantac and aluminium compound should be taken 1 hr after isoniazid administration because it increase gastric PH and delays isoniazid absorption.

**Other drugs**

It should not be taken with drugs such as 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 (Blumberg HM *et al*.,2003 &.Pai MP *et al*.,2006 Self TH *et al*.,1999).

**RIFAMPICIN**

Rifampicin is the most important drug which is used in treatment of tuberculosis.it is given at about 0.05-0.50 µg/mL (Zhang Y *et al*.,2005).

**Mechanism of action**

Rifampicin inhibits DNA dependent RNA polymerase enzyme resulting blocking of RNA synthesis and causing death of the cell (Ramaswamy S, Musser JM *et al*.,1998).

**Metabolization and excretion**

Most of the dug is metabolised in liver by microsomal enzyme that is about 85%.and the drug is excreted through biliary tract at about (60-65%) and small portion of the drug is excreted in urine), and the half-life of rifampicin is reduced from 3-5 h to 2-3 h.

**Adverse effects** (Blumberg HM *et al*.,2003):

**Minor adverse effects**

• Gastrointestinal reactions: Nausea, anorexia, and abdominal pain
• Orange coloured tears, sweat, and urine
• Skin reaction
• Flulike syndrome.
• Fatigue, dizziness, headache, dyspnoea, and ataxia can also occur in patients treated with rifampicin.

**Major adverse effects**

• Exanthema
• Hepatotoxicity
• Immunological reactions

**Use during pregnancy**

It belongs to C category drug and do not have any teratogenic effect which can be used during pregnancy (Blumberg HM *et al*.,2003 & Zhang Y *et al*.,2005).

**Use during breastfeeding**

Rifampicin is compatible with breast feeding, the infant should be monitored for jaundice.

**Use in patients with liver failure**

In liver failure patient the rifampicin clearance get reduced and serum drug concentration get increased.so,the the patient who is taking rifampicin is closely monitored through frequ'ent laboratory tests and clinical evaluation (Blumberg HM *et al*.,2003).

**Use in patients with kidney failure**

As rifampicin is metabolized in the liver, the kidney failure patient can take the drug even at full doses (Blumberg HM *et al*.,2003).

**Interactions**

**Foods**

As food decreases absorption of rifampicin, it should be taken at empty stomach (Pai MP *et al*.,2006).

**Antacid**

Antacid such as aluminium hydroxide delays the absorption of rifampicin (Pai MP *et al*.,2006).

**PYRAZINAMIDE**

Pyrazinamide is a nicotinic acid derivative and its molecular structure is similar to isoniazid (Zhang Y, Yew WW *et al*.,2001 & Somoskovi A et.al 2001).

**Mechanism of action**

Pyrazinamid enters in mycobacterium tuberculosis and impairs mycolic acid biosynthesis in bacillus .results in impairment of bacteria

**Metabolization and excretion**

About 70% of drug is metabolised in liver and 3% excreted in urine its half-life is 9-10h but can be as long as 26h in patients with kidney failure if the dosed are not adjusted (Blumberg HM *et al*.,2003).

**Adverse effects**

**Minor adverse effects**

Nausea, vomiting, and anorexia, Hyperuricemia and arthralgia in non-gouty individuals Exanthema and pruritus, Dermatitis (Blumberg HM *et al*.,2003).

**Major adverse effects**

Severe exanthema and pruritus, Hepatotoxicity.

**Use during pregnancy**

Pyrazinamide belongs to C category drug and according to WHO it is safe it has no risk to use pyrazinamide during pregnanc (Rakotoson JL et.al.,2009).

**Use during breastfeeding**

Pyrazinamide is compatible with breastfeeding, so, the infant should be monitored for jaundice (Blumberg HM *et al*.,2003).

**Use in patients with liver failure**

It is a hepatotoxicity drug. The liver patient who is taking these drug should be closely Monitored (Blumberg HM *et al*.,2003 & Silva Jr JB *et al*.,2004).

**Use in patients with kidney failure**

The dose of the drug should be reduced in kidney failure patient as there is more risk in them. when creatinine clearance is lower than 10mL/min the dose should be reduced to half and the patient with creatinine clearance lower than 30mL/min or to patient with haemodialysis should be given pyrazinamide at a dose of 25-35 mg/kg three times a week (Blumberg HM *et al*.,2003).

**Interactions**

**Foods**

The drug can be taken at a meal time as food is having little impact on absorption of pyrazinamide

**Antacids**

Absorption of pyrazinamide doesn't interfere with antacids.

**Other drugs**

The drugs such as Probenecid, rifampicin, and ethionamide can affect the toxic effects of pyrazinamide Pyrazinamide when taken with zidovudine can reduce the effect of pyrazinamide. In gout patient the doses of allopurinol and colchicine should be adjusted as pyrazinamide increases the serum concentration of uric acid (Blumberg HM *et al*.,2003 & Yew WW *et al* 2002 &Conde MB *et al*.,2007).

**ETHAMBUTOL**

**Mechanisms of action**

Ethambutol inhibits the arabinosyltransferase and interfere with arabinogalactan the principal polysaccharide of bacterial cell wall resulting death of the cell (Zhang Y *et al*., 2005.&.Somoskovi A *et al*.,2001).

**Metabolization and excretion**

It is metabolised in liver and the serum half-life of ethambutol is 3-4h, and it can be as long as in patients 10 hr in patients with severe kidney failure. About 50-

80% of drug is excreted in urine and 20% is excreted in faeces (Blumberg HM *et al*.,2003).

**Adverse effects** (Blumberg HM *et al*.,2003.&. Chan RY *et al* 2006):
Retrobulbar neuritis, blurred vision, In rare cases ethambutol causes Retrobulbar neuritis, Peripheral neuritis.

**OTHER EFFECTS**

Symptoms (nausea, vomiting, abdominal pain, and hepatotoxicity), haematological symptoms (eosinophilia, neutropenia, and thrombocytopenia), cardiovascular symptoms (myocarditis and pericarditis), neurological symptoms (headache, dizziness, and mental confusion), hyperuricemia/gout (due to a reduction in the excretion of uric acid by the kidney), hypersensitivity (skin rash, arthralgia, and fever), and (occasionally) pulmonary infiltrates (Blumberg HM *et al*.,2003).

**Use during pregnancy**

Ethambutol is a B category and according to WHO it is considered as safe drug during pregnancy and and can use during breast feeding (Blumberg HM *et al*.,2003).

**Use in patients with liver failure**

Full dose of ethambutal can be used in liver failure patient dose adjustment is not necessary for the liver failure patient who are taking Ethambutal (Blumberg HM *et al*.,2003).

**Use in patients with kidney failure**

In kidney failure patient if the creatinine clearance is 30-50mL/min use the drug at intervals between doses usually every 36h.and if the creatinine clearance is about 15-20mg/kg the dose and the patient is on haemodialysis the doses should be administered three times a week (Blumberg HM *et al*.,2003 & Malone R *et al*.,1999).

**Interactions**

**Antacids**

Antacids such as aluminium hydroxide can reduce the concentration at about 28% of ethambutol
Foods have less effect on the bioavailability of ethambutol.

**Other drugs**

Ethionamide can worsen the toxic effects of ethambutol (Migliori GB *et al*., 2009).

**CONCLUSION**

Patients with tuberculosis treatment attains so many adverse drug reaction so it's the responsibility of clinical pharmacist to to check the dose , adverse drug reactions and also their food interaction and monitor them by evaluating lab reports and should give the drug and its dose according to their individual case by applying their pharmacological knowledge.

**REFERENCES**

Blumberg HM, Burman WJ,Chaisson RE,Daley CL,Et kind SC,Friedman LN,Fujjiwara p,Gr Zemska M,Hopewell Pc Isemen MD,*et al* center for disease control and prevention/Infectious diseases society of America:Treatment of Tuberculosis: *AnJespire crit care med*. 167, 2003,1472_1477.

Chan RY, Kwok AK. Ocular toxicity of ethambutol. *Hong Kong Med J*. 12(1), 2006, 56-60.

Conde MB, Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcin Pde T, *et al*. III Brazilian Thoracic Association Guidelines on tuberculosis. *J Bras Pneumol*. 35(10),2009,1018-48.

Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis*. 9(12),2009,737-46.

Engelhard D, Stutman HR, Marks MI. Interaction of ketoconazole with rifampin and isoniazid. N Engl J Med. 311(26),1984,1681-3.

Forget EJ, Menzies D. Adverse reactions to first line antituberculosis drugs. *Expert Opin Drug Saf.* 5(2),2006,231-49.

Gallelli L, Colosimo M, Tolotta GA, Falcone D, Luberto L, Curto LS *et al* racecadotril compared with loperamide in elderly people with gastroenteritis living in nursing homes.*Eur J Clin Pharmacol*.662010,137–44.

Gallelli L, Ferreri G, Colosimo M, Pirritano D, Flocco MA, Pelaia G, *et al*, *et al*. Adverse drug reactions to bronchodilators observed in two pulmonary divisions of Catanzaro. *Pharmacol Res*.47, 2003, 493–9.

Gallelli L, Ferreri G, Colosimo M, Pirritano D, Guadagnino L, Pelaia G, *et al* Adverse drug reactions to antibiotics observed in two pulmonology divisions of Catanzaro. *Pharmacol Res*.13, 2002, 395–400.

Gallelli L,Colosimo M, Pirritano D, Ferraro M, De Fazio S, Marigliano NM, *et al*. *et al*.Adverse drug reactions induced by nonsteroidal anti-inflammatory drugs.*Clin Drug Investig*. 27,2007,115–22.

Malone R, Fish DN, Spiegel DM, Childs JM, Peloquin CA The effect of hemodialysis on isoniazid, rifampin, pyrazinamide, and ethambutol. *Am J Respir Crit Care Med.* 159(5 Pt 1),1999,1580-4.

Migliori GB, D'Arcy Richardson M, Sotgiu G, Lange C Multidrug-resistant and extensively drug-resistant tuberculosis in the West. Europe and United States: epidemiology, surveillance, and control. *Clin Chest Med*.30(4),2009,637-65.

Nardiello S, Pizzella T, Ariviello R. Risks of antibacterial agents in pregnancy *Infez Med*. 10(1),2002,8-15.

Nisar M, Watkin SW, Bucknall RC, Agnew RA, Exacerbation of isoniazid induced peripheral neuropathy by pyridoxine. *Thorax*. 45(5),1990,419-20.

Pai MP, Momary KM, Rodvold KA. Antibiotic drug interactions. *Med Clin North Am.* 90(6),2006,1223-55.

Rakotoson JL, Randriamanana D, Rakotomizao JR, Andrianasolo R, Rakotoarivelo R, Andrianarisoa AC, Severe systemic lupus erythematosus induced by isoniazid *Rev Pneumol Clin.* 65(6),2009,361-4.

Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in Mycobacterium tuberculosis: 1998 update. *Tuber Lung Dis*.79(1),1998,3- 29.

Self TH, Chrisman CR, Baciewicz AM, Bronze MS Isoniazid drug and food interactions. *Am J Med Sci*.317(5),1999,304-11.

Silva Jr JB. Tuberculose: Guia de vigilância epidemiológica. *J Bras Pneumol.* 30(Suppl 1),2004,S57-S86.

Slayden RA, Barry CE 3rd. The genetics and biochemistry of isoniazid resistance in mycobacterium tuberculosis. *Microbes Infect*. 2(6);2000:659-69.

Somoskovi A, Parsons LM, Salfinger M. The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in Mycobacterium tuberculosis. *Respir Res*. 2(3),2001,164-8.

Srivastava A, Maggs JL, Antoine DJ, Williams DP, Smith DA, Park BK, Role of reactive metabolites in drug-induced hepatotoxicity. Handb *Exp Pharmacol*. 196,2010,165-94.

Sun HY, Chen YJ, Gau CS, Chang SC, Luh KT. A prospective study of hepatitis during antituberculous treatment in Taiwanese patients and a review of the literature. *J Formos Med Assoc.* 108(2),2009,102-11.

Tai WP, Yue H, Hu PJ. Coma caused by isoniazid poisoning in a patient treated with pyridoxine and haemodialysis. *Adv Ther*. 25(10),2008,1085-8.

Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J, *et al* British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect*. 59(3),2009,167-87.

Vikrant S, Agarwal SK, Gupta S, Bhowmik D, Tiwari SC, Dash SC, *et al*. isoniazid chemoprophylaxis during renal replacement therapy. *Transpl Infect Dis.* 7(3-4),2005,99-108

Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. *Drug Saf*. 25(2),2002,111-33.

Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis. Int J Tuberc Lung Dis. 2009;13(11):1320-30.) Somoskovi A, Parsons LM, Salfinger M. The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in Mycobacterium tuberculosis. Respir Res. 2(3),2001,164-8.

Zhang Y. The magic bullets and tuberculosis drug targets. *Annu Rev Pharmacol Toxicol*. 45,2005,529-64.

**Cite this article:**
Geervani PG, Raja Nandini K, Vaishnavi M, Chaitanya Srinivas B. A Review on Use of First Line Anti Tuberculosis Drugs in Special Situation and Their Clinical Complications. *International Journal of Pharmacy & Therapeutics*, 11(2), 2020, 56-60. DOI: http://dx.doi.org/10.21276/ijpt.2020.11.2.3