Antitubercular Drug Induced Hepatotoxicity: A Review

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Abstract: Hepatotoxicity is an emerging medical problem. It has multiple etiological factors but most common reason is chronic treatment with certain drugs during the cure of numerous life threatening diseases. Antitubercular drugs are the leading cause of injury or damage to liver. So this is a challenging task to prevent the drug induced hepatotoxicity during tuberculosis treatment. Generally it results into interruption of treatment and cause re-emergence of this disease. This review article highlights the different mechanisms of anti-tubercular drug induced hepatotoxicity, its incidence and clinical management.

Key words: Mycobacterium tuberculosis, Anti-tubercular drugs, Drug induced hepatotoxicity, Isoniazid, Rifampicin, Pyrazinamide, Hepatotoxins

1. INTRODUCTION

Tuberculosis (TB) remains a huge public concern worldwide. About one third of the world's population is infected and almost three million people per year are killed by this disease. *Mycobacterium tuberculosis* is one of the causes of infection that leads to tuberculosis, thus results in mortality and morbidity. TB is a curable disease that is properly treated with anti-TB drugs. Anti-TB treatment is the reason for the most frequent adverse effects that are hepatotoxic, skin reactions, gastrointestinal, neurological disorders. The first line treatment currently recommended for TB is a regimen of Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA), and Ethambutol (EMB) for two months, followed by INH, RMP and EMB for four months [1, 2]. One of the most frequent and serious adverse effects of anti-TB medication is hepatotoxicity and by compromising treatment regimens it may reduce treatment effectiveness. The quadruple therapy drugs: INZ, RMP & PZA are mainly metabolised by liver, thus are potentially hepatotoxic [3].

Incidence, Burden and Epidemiology

Hepatotoxicity occurs both during treatment of tuberculosis and primary prophylaxis (preventive therapy). Thus it is dependent on the drug host interactions, drug disease and dynamics of drugs. A study showed that an adult has an incidence rate of 2.6% for liver toxicity after co-administration of INH and RMP. But 1.1% alone with RMP and with INH alone about 1.6%. The incidence of anti-TB drugs induced hepatotoxicity during treatment has been reported between 2% and 28% [4, 5].

Mechanism of action for anti-TB hepatotoxicity

Isoniazid

Hepatotoxicity Induced by Isoniazid (INH) is a significant clinical problem and the current mechanistic hypothesis involves metabolic idiosyncrasy, which is the bioactivation of acetylhydrazine that involve cytotoxicity. Acetylhyadrazine is a metabolite of INH. The metabolic pathway involve isoniazid is metabolised byN-acetyl transferase 2 (NAT-2) into

acetyl isoniazid (AcINH) .Acetyl isoniazid is metabolised into non-toxic diacetyl hydrazine and monoacetyl hydrazine. Monoacetyl hydrazine is further converted into toxic products by cytochrome P_{450}. Mainly CYP2E1 and P_{450}2E1 are involved in anti-TB drugs hepatotoxicity. More hepatotoxins are produced by CYP2E1 C1/C1 genotype that leads to CYP2E1 activity further Isoniazid has an inhibiting effect on CYP1A2,2A6, 2C19, 3A4 activity. Enzyme induction or inhibition by INH may induce toxicity [5, 6].

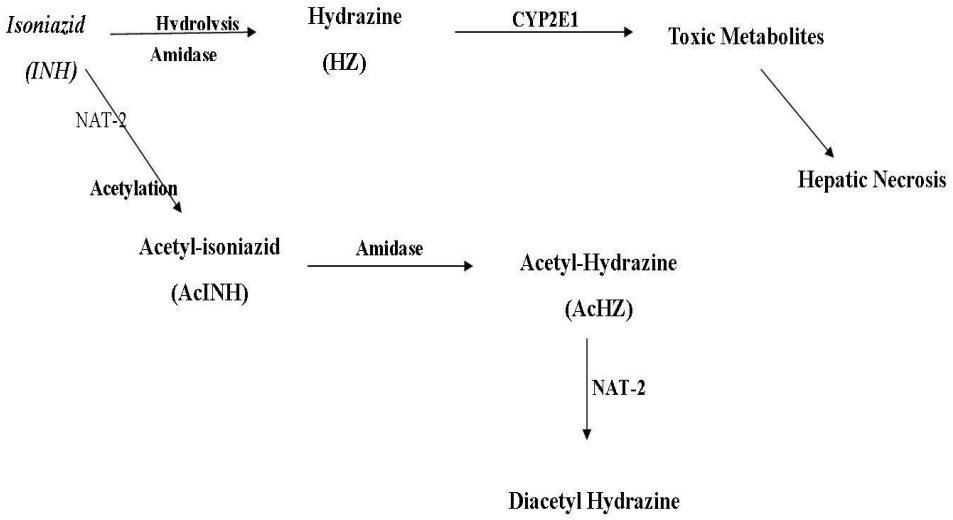

FIG.1 The metabolic pathway of Isoniazid

Rifampicin

The pathway of rifampicin involves formation of desacetylrifampicin from desacetylation and produces a 3- formyl rifampicin by a separate hydrolysis. In the early treatment, it induces hepatocellular dysfunction. Cytochrome p_{450} enzyme induction is caused by rifampicin. From acetyl hydrazine, it causes an increase in toxic metabolites production [7]. Further Isoniazid is metabolised by rifampicin to hepatotoxic isonicotinic acid and hydrazine.Combination of INH and rifampicin leads to higher incidence of liver necrosis.

Pyrazinamide

Liver enzyme microsomal amidase metabolised pyrazinamide to pyrazinoic acid (PA) and later oxidised by xanthine oxidase to 5-Hydroxy pyrazinoic acid (5-OH-PA).These

metabolites of PZA are known to possess hepatotoxic potential. The excretion of metabolites take place through kidneys. The half-life of pyrazinamide is longer as compared to isoniazid and rifampicin, In case of liver disease and concomitant administration of other drugs such as allopurinols that inhibit xanthine oxidase, the half-life of PZA is gets prolonged. The other minor metabolic pathway of PZA consists of PA and glycine forming PA. PA is associated with hepatotoxicity and hyperuricemia also [6, 8, 9].

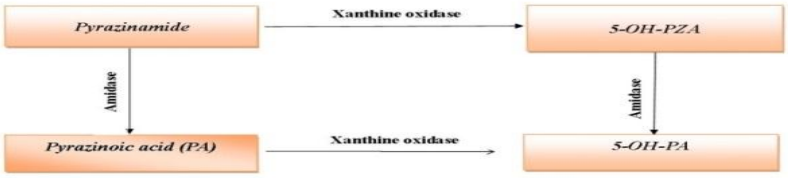

FIG.2: The metabolic pathway of pyrazinamide.

Management of Hepatotoxicity [9]

Risk stratification

Hepatotoxicity monitoring or pre-treatment evaluation with liver tests is recommended in the following groups: patients who consume alcohol, those on concomitant hepatotoxic drugs, those with chronic hepatitis B or C, HIV, have elevated baseline transaminase levels [10].

Management issue

In some cases, anti-TB treatment causes fatal drug induced liver injury. A controversial issue raises that during the course of anti-TB whether and when liver tests should be monitored. Base line measurements of liver enzyme are recommended by The American Thoracic society. According to this, patients with normal baseline levels, routine laboratory monitoring is not necessary to be considered in most cases; exceptions are patients with known risk factors. Acute liver failure may results due to continuation of a drug that is responsible for hepatotoxic adverse effects. So in most cases, to prevent the occurrence of acute liver failure discontinue the use of drugs. For early discontinuation of anti-TB drugs, the only reliable policy is that during the anti-TB treatment frequently liver monitoring is required. However, in liver with tuberculosis usually in the form of microgranulomata occasionally leads to abnormal baseline liver function tests and this will laterally be treated with anti- tubercular drugs. Mostly drugs with-in the initial 2 months of therapy cause hepatitis. So to prevent this closer monitoring should be done at weekly or biweekly intervals [8,11-17]. The American Thoracic Society proposed the following recommendations:

1. Determine serum transaminase level regularly. It should be performed twice weekly for the first 2 weeks of treatment; then weekly during the rest of first 2 months.
2. When level of serum transaminase is elevated, but less than 3 times the upper limit of normal may continue the treatment.
3. When the level of serum transaminase is elevated more than 3 times the upper limit of normal, then the therapy of rifampicin should be stopped.

4. When serum transaminase level returns to normal after that pyrazinamide should not be reintroduced but isoniazid can be reintroduced but at lower daily dose [3].

Clinical management for hepatotoxicity induced by anti-tubercular drugs

1. **N-acetylcysteine-** A study showed the protective effect of N-acetylcysteine (NAC) that was conducted over new 60 TB patients with age of 60 years or more. Patients were divided into two groups. In group I, only anti-TB drugs were given and in group II anti-TB drugs along with NAC .Thus regimen were followed upon 2 weeks. After appearance of clinical symptoms of hepatotoxicity, liver enzymes and bilirubin were measured [18].
2. **Silymarin-** Concomitant administration of silymarin with anti-TB drugs reversed abnormal conditions. By histological observations silymarin changed the alterations revealed by anti-TB drugs like increased level of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), elevated lipid peroxidation and intracellular calcium [19].

Alternative interventions for drug induced hepatotoxicity

1. **Ginger:** A study showed ginger has various health benefits and hepatoprotective effects. Further preclinical studies suggested the protective action against different xenobiotic compounds includes alcohol, fungicides, tetracyclines, acetaminophen, heavy metal mediated through free radical scavenging, cytoprotective and antioxidant and also further modulating the detoxifying enzymes levels [20].
2. ***Mirabilis jalapa*:** A study carried out by Jyothi et al., reported that the Mirabilis jalapa leaves has protective effect against anti-tubercular drugs induced hepatotoxicity. Also reported to have antioxidant potential [21].
3. ***Selaginella corymbosa*:** The protective potential of Selaginella corymbosa leaves extract has reported by a study carried out by V Patil et al., (2015) .They reported a significant reversal of histological and biochemical modifications which was produced by chloroquines and isoniazid in rats by using this extract as treatment .
4. **Honey:** Chandane et al., [22] (2013) carried out a study that showed the protective potential of honey against hepatotoxicity in albino rats induced by anti-tubercular drugs. Honey depicts its effects by lipid peroxidation inhibition and elevation of antioxidant defense mechanism.
5. **Kaemferol:** A study showed the protective effect of kaemferol against isoniazid and rifampicin used as Antitubercular drugs .Further this study was aim to screen for CYP2E1 inhibitors in vitro. In addition to this, it revealed the investigation of inhibitors of CYP2E1 which was found to be about 83 known compounds mainly from herbal medicines and food. Hepatotoxicity was assessed by using single point method and dose of INH/RIF was 50/100mg/kg^{-1} day. Further examination was done by histopathology, melondialdehyde assay and involves AST.ALT measurements. Thus kaemferol inhibited CYP2E1 activity in mice and decrease the values of AST and ALT by its administration. Significantly,it reduced the depletion of hepatic glutathione and prevented the increase in MDA formation in mice [23].
6. **Liv.100:** The Hepatoprotective effect of liv.100 of about 400mg/kg was assessed simultaneously on antitubercular drugs (INH, RMP AND PZA) which induced lipid peroxidation in liver of rats .Further results showed that in rats administered antitubercular drugs leads to increase in their serum levels and a significant decrease in the levels of marker enzymes in the liver and also a fall in activities of Na^+K^+ATPase ,Ca^{2+}ATPase ,Mg^{2+}ATPase ,glutathione content, activities of antioxidant enzymes. Thus, liv.100 provides protective effect by reducing lipid peroxidation and restoring the antioxidant defense system against hepatotoxicity induced by antitubercular drugs [24].
7. ***Azadirachta indica*:** The Hepatoprotective activity of AI was assessed by two phases. In first phase antitubercular drugs along with AI aqueous leaf extract. In secondphase effect

of AI aqueous leaf extract is given to established hepatotoxicity rats for 20 days [25]. Further examination of liver includes biochemical and histological parameters. Results showed the prevented changes in serum levels of AST, ALT, bilirubin, protein and alkaline phosphate. Ultimately prevents the hepatotoxic damage induced by antitubercular drugs in albino rats.

8. ***Solanum xanthocarpum:*** Daily administration of Solanum x. for35 days in experimental animals .Next it significantly prevented increase in serum levels of hepatic enzyme which are induced by drugs. Furthermore it reduced the LPO in the liver tissue and restored activities of antioxidant enzymes and attenuated the hepatocellular necrosis and lead to reduction in inflammation [26].
9. ***Monotheca buxifolia:*** Administration of Monotheca buxifolia at dose of 150 and 300 mg/kg for 21 days provides protective effect by restoring serum levels which was elevated by isoniazid and rifampicin. Besides this, it restores histopathological changes in the liver [27].
10. ***Garlic extract:*** Protective potential of garlic was evaluated by co-administration with antituberculosis drugs. Its result showed the significantly higher values of AST, ALT, ALP with administration of Antitubercular drugs in 20 rats as compared to Antitubercular drugs given with garlic [28].

S.No	***Name of drug***	***Type of study***	***Reference***	***Inference***
1	Ginger	Preclinical	Mishra *et al.*, 2013	Protective action against different xenobiotics through free radical scavenging, cytoprotective and antioxidant
2	*Mirabilis jalapa*	preclinical	Haniadka *et al*., 2013	Antioxidant potential
3	*Selaginella corymbosa*	preclinical	V Patil *et al*., 2015	Significant reversal of histological and biochemical modifications
4	Honey	preclinical	Chandane et al., 2013	Lipid peroxidation inhibition and elevation of antioxidant defense mechanism
5	Kaemferol	preclinical	Shih Tung Yuan *et al*., 2013	Inhibition of CYP2E1 activity and decrease the AST ,ALT level and reduced the depletion of hepatic glutathione and prevent increase in MDA formation
6	Liv.100	preclinical	Saraswathy S.D. et al.,1998	Decrease activities of Na^+K^+ATPase,Ca^+ATPase ,Mg^+ATPase and reduce lipid peroxidation and restore antioxidant

				potential
7	*Azadirachta indica*	preclinical	Kale B.P. et al.,2003	Prevent changes in serum levels of AST,ALT, bilirubin, protein ,alkaline phosphate and reversed hepatotoxic damage
8	*Solanum xanthocarpum*	preclinical	Hussain et al.,2012	Prevent drug induced increase in serum levels of hepatic enzyme and restore antioxidant effect and attenuate the hepatocellular necrosis and reduced inflammation
9	*Nigella sativa oil*	preclinical	Jadhav Rakesh and Mateenuddin M. ,2013	Prevent rise in the enzyme levels of AST.ALT ,reduced serum bilirubin and reduction in scores at degeneration and necrosis
10	*Monothecabuxifolia*	preclinical	Ullah Irfan et al., 2016	Protection against histopathological changes and restored serum levels
11	Garlic	preclinical	A.Nasiru et al.,2012	Reduced oxidative stress and Hepatoprotective against xenobiotics
12	*Asteracantha longifolia*	preclinical	Shah et al.,2012	Liver protective and liver regeneration by decreasing biochemical, histological changes

CONCLUSION

Patients with TB disease are more prone to anti-TB drug induced hepatotoxicity. Moreover during treatment of this disease, two or more drugs are given simultaneously which may further cause certain complications during the long duration of treatment due to drug-drug interactions. Also if treatment is interrupted in between, it may cause reoccurrence or relapse of this disease. Therefore for the treatment of hepatotoxicity caused by anti-TB drugs, some natural or alternative options which are clinically proven should be used. Ginger, garlic and honey are the most commonly used natural drugs for liver damage and hepatotoxicity in wide variety of patients.

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