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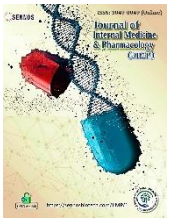

Review Article

Etiology, Risk Factors, and Future Perspectives on Hepatotoxicity Induced by Anti-Tuberculosis Medications

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ARTICLEINFO

ABSTRACT

Anti-tuberculosis drugs are one of the most common causes of idiosyncratic hepatotoxicity worldwide. Mostly first-line drug therapy of tuberculosis is the reason for hepatotoxicity. isoniazid-induced toxicity is more severe than hepatotoxicity, other factors are also cause of liver toxicity including age, gender, alcohol intake, etc are also responsible for hepatotoxicity. the liver is the main organ for maintaining the internal body environment and idiosyncratic drug toxicity result in death or transplant, therefore prevention method and good treatment for hepatotoxicity is necessary. Considering the hepatoxicity due to antituberculosis drugs are a major cause of liver failure this review throw light on the various anti-tuberculosis drug that produces toxicity, management of hepatotoxicity, and future directions.

Keywords: Tuberculosis, Hepatotoxicity, Isoniazid, Anti-tuberculosis

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1. Introduction

Tuberculosis is the common infectious disorder in the world, with an estimated one-third of the world's population infected with bacilli which are the reason for tuberculosis, mycobacterium Infection with TB is becoming more common. based on the WHO report, 9.2 million new tuberculosis cases were stated in 2006, up to 9.1 million in 2005 and 8.3 million in 2000. Each year, roughly 1.6 million people die from this disease[1]. Treatment for TB should include a combined drug therapy which continued for a minimum of six months to prevent the disease and avoid the expansion of drug resistance, which is a rising problem because of the long period of treatment and the usage of several drugs, unpleasant effects are an essential therapeutic consideration in TB affected patient[2]. Hepatotoxicity, skin-related problem, gastrointestinal irritation are adverse effects of antituberculosis medication. ATDH (Antituberculosis Drug-Induced Hepatotoxicity) outcomes in significant mortalities and morbidity, as well as a decrease in therapeutic effectiveness[3]. Although asymptomatic transaminase increases are typical with antituberculosis medication, liver toxicity can be harmful if not detected early and therapy is not completed in a manner. The most severe adverse effect of antituberculosis medicine is liver impairment. rifampicin, isoniazid, and pyrazinamide are the first-line antitubercular medicines, are all potentially hepatotoxic. The reason for acute liver failure is drug-induced liver damage[4]. As a result, DILI (Drug-Induced Liver Injury) has a significant impact on healthcare, impacting patient morbidity and mortality rates. This review focused on antituberculosis drug hepatotoxicity, other risk factors, prevention methods for drug reaction, treatment, and future directions for hepatotoxicity.

2. Mechanisam of Antiburculosis drug in hepatotoxicity

Medication used for tuberculosis treatment is the cause of idiosyncratic hepatotoxicity over the world[5]. The rate of drug-induced toxicity varies greatly depending on the cohort's characteristics, treatment regimens utilized, hepatotoxicity thresholds used, and monitoring and reporting techniques[6]. The antituberculosis drug including isoniazid, rifampicin, pyrazinamide, and ethambutol are the most common hepatotoxic drug discussed in the below section.

2.1 Isoniazid

Isoniazid (INH) has always been the therapeutic option for chronic tuberculosis treatment. Even though the symptoms induced with liver injury due to isoniazid include malaise, vomiting, nausea, and idiosyncratic toxicity[7].

The acetylation by the liver enzyme N-acetyltransferase-2 (NAT-2) is a much more prevalent metabolic process for isoniazid breakdown. acetyl isoniazid is produced by acetylating isoniazid, which is then hydrolyzed to make acetyl hydrazine and isonicotinic acid. diacetyl hydrazine is formed by acetylating acetyl hydrazine. INH is hydrolyzed rapidly into isonicotinic acid and hydrazine in a small proportion of cases, and this pathway is more relevant in slow acetylators than fast acetylators[8]. The previous research has focused on the notion that acetyl hydrazine is a dangerous isoniazid metabolite and

cause of INH induce hepatotoxicity. Hydrazine metabolism is mostly achieved through oxidation. nitrogen and diamide are potential mediators in hydrazine reactions. nitrogen centered radical's forms during hydrazine metabolism are implicated in hepatoxicity. Isoniazid toxicity is not linked to free oxygen radicals. Individuals have a genetically based rate of acetylation, and persons can be classed as slow or quick acetylators[9]. Acetylators' activity can be evaluated using either physiological or genetic variation methods. according to a preliminary study, fast acetylators are more liable to produce ATDH. Slow acetylators had a much more than a two-fold risk of acquiring ATDH as compared to speedy acetylators. The lack of data on isoniazid densities that contain heavy metals responses, isoniazid dosage can be tailored based on acetylator position: a reduced dose in slow acetylators to decline the chance of ATDH, and a higher dose in rapid acetylators to raise early bactericidal effect and thus diminish the chances of therapeutic failure[2]. Genomic research has linked ATDH to cytochrome P450 2E1 (CYP2E1). Superior CYP2E1 activity has been connected to the CYP2E1 c1/c1 genotype, which might lead to higher hepatotoxic activity. INH and hydrazine both increase CYP2E1 activity in rats, according to research. Isoniazid inhibits the adenosine deaminase enzyme. Oxidative stress is caused by a mismatch between oxidants and antioxidants, which promotes the oxidants[10]. Several non-enzymatic antioxidants and enzymatic processes are involved in the detoxifying of reactive oxygen species. Glutathione concentrations significantly reduced in rats following isoniazid or hydrazine treatment, suggesting that oxidative stress is involved in is hepatotoxicity[11].

N-acetylcysteine a sulfhydryl-containing molecule that can transform oxidized glutathione to glutathione has been shown to defend the body in rats administered isoniazid and rifampicin. Additionally, ATDH-positive Patients usually had reduced glutathione plasma levels and oxidative indicators, presumably due to antituberculosis medication-induced oxidative stress. Furthermore, the reason for the identified glutathione depletion is undetermined, but it could be a consequence rather than an explanation of toxicity caused by a broad disruption of transitional metabolites[5]. The observation that generated glutathione reduction has no effect on isoniazid-induced toxicity in vitro indicates that glutathione is not directly engaged in isoniazid-induced mortality. Figure 1 depicts the mechanism by which isoniazid causes hepatotoxicity [7].

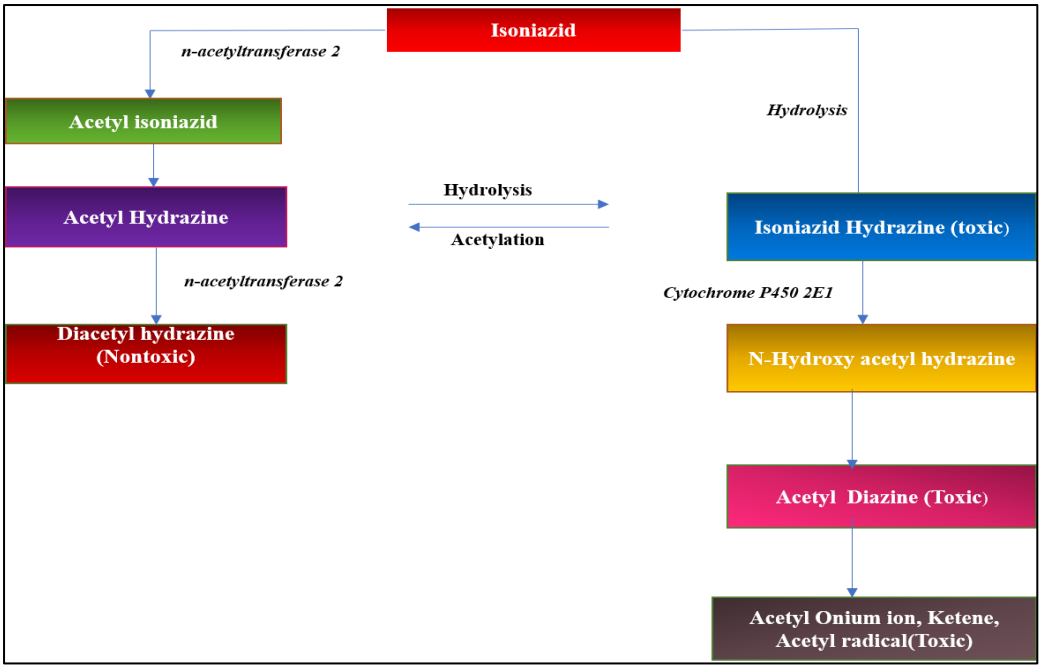

Figure1: Pathways involved in the metabolism of isoniazid

2.3 Pyrazinamide

Pyrazinamide is a nicotinic acid analog. Whenever Pyrazinoic acid is deamidated, Pyrazinoic acid is produced. This is then converted to 5-hydroxy Pyrazinoic acid by metabolic enzymes. metabolites are eliminated by the kidney. Pyrazinamide has a much-prolonged half-life than rifampicin and isoniazid, and it's even prolonged when combined therapy with another xanthine oxidase inhibitor as allopurinol. Pyrazinamide toxicity is dosage-dependent, with higher doses of 30–40 mg/kg being allied with a higher frequency of hepatotoxicity than current regimen doses (25–35 mg/kg)[12].

2.4 Rifampicin

The main process of rifampicin is deacetylation, which results in desacetylrifampicin, and hydrolysis, which results in 3-formyl rifampicin. In initial treatment, rifampicin might cause hepatocellular dysfunction, which solves without the need to stop taking the medicine. Rifampicin-induced hepatotoxicity has an uncertain and unpredictable mechanism. Rifampicin increases the metabolism of several other drugs by inducing the cytochrome-P450 system in the liver and intestine[13].

2.5 Ethambutol

The FDA has approved ethambutol as a bacteriostatic antibiotic for the treatment of mycobacterial infections. The adverse effects of ethambutol are visual difficulties and liver toxicity. Although liver damage has been recorded in ethambutol patients, they all had hypersensitivity reactions, therefore the drug's hepatotoxic effects aren't a serious worry. Hepatotoxic consequences as a report of treatment. The interval between starting antituberculosis treatment and experiencing hepatotoxic symptoms vary, but liver impairment commonly begins within weeks to months of

starting treatment. in patients with latent tuberculosis who are receiving isoniazid monotherapy, about two-thirds of the hepatotoxic effects occur within three months of starting therapy and 80% occur within the first 6 months of therapy. hepatotoxic effects can occur early or late in the course of combination therapy, according to limited data. Although the data from existing research are inconsistent, the duration of the onset of liver failure may have prognostic consequences. even in patients with liver failure, raised aminotransferase levels that occur within the first two weeks of therapy are usually associated with a good prognosis, whereas hepatic injury effects that appear weeks or more after therapy initiation appear to be related to a poor prognosis[14].

3. Host Related factors

Although various risk variables have indeed been linked to hepatic injury, there are significant differences in research design, batch size, and case criteria, making it difficult to make firm conclusions[15].

3.1 Age

Some studies propose that hepatotoxicity affects people over 35 years old at a rate of 22 to 33 percent, compared to 8 to 17 percent in those under 35 years old. Severe hepatoxicity was identified in a pediatric patient below age 5 years due to pyrazinamide use. Also, some studies revealed that isoniazid produces more hepatotoxicity in pediatric and above 35-year age patients[2].

3.2 Gender

Liver injury is 4 times as common in females than in males as an effect of anti-TB treatment. Women's CYP3A expression is higher, rendering them more susceptible to liver injury. A greater prevalence of INH hepatic injury was seen in women who are pregnant in the 3rd month and the first 3 months following birth[16].

3.3 Alcohol Intake

By stimulating catalysts, alcohol causes liver problems. Alcohol has been established in several studies to extend the liver injury caused by anti-TB medications. This risk has been observed even in patients who received rifampicin as a preventive therapy[17].

3.4 Malnutrition

The harmful significances of antituberculosis drug therapy are more common in malnourished people than in well-nourished people. changes in drug metabolism and detoxification in malnourished individuals, as well as the use of set adult doses rather than correct dose estimations based on the patient's weight. In malnourished individuals, a dose of the antituberculosis drug should be avoided since they may result in higher than necessary levels of these drugs.

3.5 HIV Infection

Based on different studies antituberculosis drugs have been linked to a fourfold increase in toxic effects in HIV patients. This rise is unrelated to drug-drug interactions with HIV drugs used in extremely active antiretroviral treatment. As a result, HIV infection can have an impact on medication metabolism. In persons with HIV, however, adverse effects associated with the Two-month rifampicin and pyrazinamide combination are minimized associated with those without HIV. This

attenuation shows that some of the antituberculosis therapy's hepatotoxic effects have an immunological origin[18].

4. Management of hepatotoxic effects

Many guidelines have been established to manage hepatotoxic effects produce due to antituberculosis.

4.1 Prevention

The two most significant measures for preventing hepatotoxicity due to antituberculosis therapy are selecting the proper beginning medication regimen to depend on the patient's underlying liver status and monitoring liver function during treatment, mainly in patients with hepatotoxic risk factors[19]. certain high-risk patients require a valuation of the danger of tuberculosis vs the risk of hepatotoxic consequences of antituberculosis therapy so that healthcare providers might adopt a low-toxicity regimen or postpone or discontinue treatment[6]. Pregnant women, chronic alcoholics, patients with latent tuberculosis and other risk issues, and those with pre-existing liver disease and a threefold increase in aminotransferase levels or severe diseases such as hypoalbuminemia, coagulopathy, or hepatic encephalopathy are all included in this group[12].

4.2 Treatment

Although some authors advocate for the use of steroids to treat the hepatotoxic effects of the antituberculosis drug, no formal recommendations currently support this practice. steroids may be beneficial in individuals who have significant hepatotoxic effects that do not resolve spontaneously following the withdrawal of the causal drug, particularly if substantial hypersensitivity symptoms are present[10].

4.2.2 Second-line treatment

Hepatotoxic symptoms or multidrug resistance emerge during first-line therapies, second-line therapies including cycloserine, capreomycin, streptomycin, and the quinolone agents gatifloxacin, ofloxacin, moxifloxacin, and levofloxacin can be administered. Streptomycin is an antibiotic that works by attaching to a component of the bacterial ribosome and inhibiting protein synthesis. because this medicine is not metabolized and is thus removed unchanged through the kidneys, it is deemed safe for use in individuals who suffer from liver disease. Streptomycin produces a less toxic effect and is excreted through the kidney. Quinolones are frequently used in tuberculosis treatment are show better results in tuberculosis patients with less toxicity effect only 5-10% of side effects occur in patients during therapy[20]. On the other side aminoglycoside kanamycin, amikacin is also the better choice for tuberculosis treatment. According to some studies, second-line therapy is a good option for tuberculosis treatment.

4.2.3 New regimens and medications

Novel regimens and drugs are being developed to increase treatment efficacy, decrease therapy time, and reduce the side effects and the formation of drug-resistant mycobacteria strains. Antituberculosis drugs, such as pyrroles, nitroimidazoles, and pyrroles are being researched to regulate the best dose and period of treatment[21]. Quinolones, such as moxifloxacin, are now being studied to see if they help shorten the interval of treatment regimens. In a single treatment,

moxifloxacin is used as an alternative to isoniazid for the initial two months, followed by a two-month continuation period with moxifloxacin[10]. Because it does not include isoniazid and is shorter in length than conventional medication, this treatment is related to fewer hepatotoxic effects than normal therapy. However, because studies examining the regimen's care and efficiency are continuing, it should not be used in clinical practice just yet. Because the major issue with all quinolone-based regimens is their high expense, the true challenge is to discover less-priced alternatives[22].

5. Future guidelines

Research into hereditary polymorphisms in enzymes involved in TB biotransformation, prospective hepatoprotective medications, and the mechanism of ATDH is desirable. The creation of solid pharmacologic foundations for more reasonable use of already accessible drugs can help to lessen the prospect of TB-treated adverse effects. Very little research has explored the impact of genetic variants of drug-metabolizing enzymes on ATDH risk. In health risk evaluation with large sample sizes and communities, the comparative relevance of these polymorphisms to certain other risk factors should be examined. Despite the lack of data in the sector, ATDH prevention through genetic research may one day be achievable. Changing medication dosages to avoid ATDH while maintaining treatment effectiveness in subjects with elevated genotypes should indeed be investigated. It's critical to look at the link among risk genotype, pharmaceutical concentrations, and hepatic injury risk. Its NAT2 genotype, for instance, can be used to separate the population into two groups: some who take low doses of isoniazid as well as those who take high doses. In rats, both N-acetylcysteine and silymarin had hepatoprotective effects on ATDH. More research is needed into the anti-tuberculosis characteristics of such drugs in people, and also possible interactions with anti-tuberculosis treatments.

The prolonged TB treatment time is the most challenging problem to conquer. Antituberculosis drugs with improved bactericidal activity will minimize healing time and, as a result, improve adherence and efficacy. It will be necessary to test new, lower hepatotoxic regimens for safety and tolerance. Fluoroquinolones like moxifloxacin and levofloxacin, which have lower toxicity rates, are being prioritized in the expansion of new antibiotic combinations. even though their potential utility has been known for years, these drugs are today underutilized, most likely due to bacteriological, toxicological, or economic reasons. Liver injury can be a reason for medication management in advanced TB facilities (TDM). The plasma concentrations of antituberculosis medicines are assessed in TDM during treatment. Although most antitubercular drugs have no link between blood concentrations and toxicity, pyrazinamide dose is linked to hepatotoxicity. TDM's goal is to detect abnormally high or low amounts of antitubercular medicines in the bloodstream and take appropriate action. TDM can discover and resolve drug-drug interaction before the first patient's prescription fails, symptoms, or dies, which is especially essential in Hospital patients on antiretroviral drugs. One of the most pressing future issues is the development and implementation of effective and safe TB/HIV co-infection therapy regimens. Efforts should be done to design regimens that are less harmful in HIV-positive individuals to improve TB cure rates. Liver

injury is a typical side effect of TB/HIV treatment, but other symptoms such as skin reactions and gastrointestinal disorders should be examined as well.

Conflict of Interest

The authors declare no competing interests.

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Data Availability

The authors confirm that the data supporting the findings of this study are available within the article

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