REVIEW ARTICLE

Journal of Army Medical College Chattogram
Volume 3 Issue 1 June 2020; 33-37

Antitubercular Drug-Induced Hepatotoxicity : A Comprehensive Review

Saifun Nahar Faiz[1] Mahmudul Haque[2] S M Kamrul Hoque[3]*

ABSTRACT

Background: Hepatotoxicity is one of the most frequent and serious adverse effects of Antitubercular therapy (ATT) in the whole world including Bangladesh. It may reduce treatment effectiveness by compromising treatment regimens. Our aim is to motivate the physician so that they can identify Antitubercular drug induced hepatotoxicity and manage the problem accordingly.

Materials and methods: We reviewed several literatures in the major medical databases with the subject search terms "Antitubercular drug induced hepatotoxicity" .We then performed a systematic review.

Results: After reviewing the papers we found old age and female sex are more prone to develop hepatotoxicity. Moreover malnutrition, HIV, Hepatitis B, Hepatitis C are also risk factors for developing Antitubercular drug induced hepatotoxicity. It is also found that hepatotoxicity by anti TB therapy is more in developing countries due to high incidence rate of tuberculosis and lack of awareness. About 7% -34% patient developed hepatotoxicity in different study. This paper describes the mechanism of hepatotoxicity, risk factors, and treatment modalities of the hepatotoxicity associated with antitubercular therapy.

Conclusion: Early recognition of risk factors with close follow-up of patients and subjecting them to repeated liver function tests will significantly reduce morbidity and mortality. It will also improve the compliance of the patients receiving antitubercular therapy.

Key words: Hepatotoxicity; Antitubercular drugs; Isoniazid; Rifampicin; Pyrazinamide; Anti TB -DIH.

Introduction

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. The disease has become rare in high income countries, but is still a major public health problem in low income countries like Bangladesh. The challenge in the treatment of tuberculosis lies in the necessity of long duration of the treatment, multiple drug administration and toxicities related to them. One of the important complications associated with Anti-Tubercular Therapy (ATT) is hepatotoxicity. Liver is the most susceptible organ to toxicity from foreign agents. The majority of drug metabolism process is found to be associated with this organ.

People in all age groups are affected by TB, but the highest burden is among adult men, who accounted for 56% of all cases, compared with 32% of cases in adult women and 12% in children[1].

1. Associate Professor of Biochemistry
Army Medical College Chattogram, Chattogram.
2. Professor of Biochemistry
Chittagong Medical College, Chattogram.
3. Post Graduate Students of Internal Medicine (Thesis Part)
Chittagong Medical College, Chattogram.

*Correspondence: **Dr. Saifun Nahar Faiz**
Cell: +88 01978 01 00 81
Email: dr.snahar35cmc@yahoo.com

Submitted on : 15th January 2021
Accepted on : 10th February 2021

Some medicines when taken in overdoses and sometimes even when introduced within therapeutic ranges, may cause hepatotoxicity. Hepatotoxic drugsinclude -Antitubercular Drugs (Rifampicin, Isoniazid, Pyrazinamide) Non Steroidal Anti-Inflammatory Drugs (Acetaminophen, Nimesulide, Diclofenac, Ibuprofen, Sulindac) Anti-Retroviral Drugs, Anti-Hyperlipidemic Drugs, Anaesthetic Agents, Anti-Rheumatic Drugs, Anti-Epileptic Drugs (AED) Anti-Depressants, Anti-Hypertensive Drugs, Neuroleptic Drugs or Anti-Psychotic Drugs, Acetylcholinesterase Inhibitors, Drugs of Abuse etc. Few other drugs also reported to cause hepatotoxicity are Glucocorticoids, Antibiotics (Amoxicillin, Ciprofloxacin, Erythromycin) Oral contraceptives and antifungal drugs (Fluconazole, itraconazole)[2,3].

Tuberculosis (TB) remains a huge health burden worldwide. The currently recommended first-line treatment for TB is a regimen of Isoniazid (INH) Rifampicin (RMP) Pyrazinamide (PZA) and Ethambutol (EMB) for 2 months, followed by 4 months of INH and RMP and/or EMB, which are more or less hepatotoxic[4,5].

This article attempts to provide a comprehensive review of diagnosis and probable management strategies for this global problem of ATT-induced hepatotoxicity. Regular liver function tests and follow up by the primary care providers might be helpful to minimize the morbidity and mortality.

Search Strategy

Available studies and abstracts were identified through data PubMed and Medline data bases (From 2001-2020) and Cochrane data bases. Key search topic were "Antitubercular

Journal of Army Medical College Chattogram
Volume 3 Issue 1 June 2020; 33-37

Drug Induced Hepatotozicity : A Comprehensive Rev iew" and relevant articles.

The reference list of review article were also searched. The search term were following key words used in verious combination : Hepatotoxicity; Antitubercular drugs; Isonizaid; Rifampicia; Pyrazinamide; Anti TB-DH.

Discussion

Tuberculosis continues to remain a significant infectious disease across the developing world. Globally, an estimated 10 million people fell ill with TB in 2019 AD, a number that has been declining very slowly in recent years. There were an estimated 1.2 million TB deaths among HIV-negative people in 2019 AD (a reduction from 1.7 million death occurred in 2000 AD) and an additional 2,08,000 deaths among HIV-positive people (a reduction from 6,78,000 in 2000 AD). Men (Aged≥15 years) accounted for 56% of the people who developed TB in 2019 AD; women accounted for 32% and children (Aged<15years) for 12%. It exacts a significant socioeconomic burden on the individual and society. According to the Global Tuberculosis Report 2019 AD, 47,000 people die of TB in Bangladesh every year. The estimated incidence rate is 221 per 100,000 people[1-5].

The overall incidence of antitubercular drug induced hepatotoxicity (Anti-TB DIH) in the population is unknown and is probably unrecognized. Toxicity is dependent on the dynamics of drugs, drug- disease and drug-host interactions. Among the first-line drugs (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol), the first three have the potential for hepatotoxicity with Pyrazinamide being the most hepatotoxic followed by isoniazid and rifampicin[6]. Rifampicin combined with Pyrazinamide (PZA) is more hepatotoxic than with Isoniazid (INH)[7,8]. About 7% -34% patient developed hepatotoxicity in different study. However, when hepatotoxicity occurs following the use of 4-drug combination regimen, it is impossible to quantify the contribution of each drug in the development of Drug Induced Hepatotoxicity (DIH)[9-11].

1. Definition of Hepatotoxicity

In the absence of symptoms, elevation of transaminases up to 5 times the Upper Limit of Normal (ULN) and in the presence of symptoms up to three times the ULN or twice the ULN of bilirubin constitutes DIH, provided competing causes such as acute viral hepatitis, autoimmune hepatitis and other liver diseases are ruled out[4,12].

2. Antitubercular Therapy Induced Hepatotoxicity: (Mechanism)[5,12,13].

Isoniazid (INH) is metabolized toacetylisoniazid via hepatic enzyme N-acetyl Transferase 2 (NAT2) and is followed by hydrolysis to acetyl hydrazine. Further, acetyl hydrazine is oxidized by Cytochrome P450 2E1(CYP2E1)to form hepatotoxic intermediates, which destroy hepatocyte resulting in liver injury.

Hepatotoxicity by Rifampicin (RIF) can take place when taken concurrently with other anti-TB drugs. RIF is an effective inducer of CYP2E1 isoenzyme and plays a key role to increase INH induced toxicity, most probably by increasing the formation of its toxic metabolite hydrazine.

Pyrazinamide (PZA) is only used in combination with other drugs such as INH and RIF inthe treatment of TB. PZA is metabolized to Pyrazinoic Acid (PA) by the enzyme liver microsomal amidase and further oxidized to 5-Hydroxy Pyrazinoic Acid (5-OH-PA) by xanthine oxidase. These two reactive metabolites of PZA are considered to have hepatotoxic effect.

Ethambutol (ETH) and Streptomycin are also used as anti-TB therapy. The mechanism of liver injury due to ETH is still unclear. It has been found to be associated with minor, transient and asymptomatic elevations inserum aminotransferase levels. Streptomycin (STR) has no known hepatotoxicity.

3. Risk Factors:[6,7,8,9,14, 15]

Age: Patients more than 35 years are noticed to be associated with increased risk of anti-TB-DIH .

Gender: Many studies have implicated female gender to be at increased risk for anti-TB-DIH. In another report of Mahmood et al. a higher incidence of anti-TB-DIH in female than males (26.3% vs. 19.7%).

Diabetes: After reviewing several articles it is found that diabetic patients are more prone to develop DIH.

Malnutrition: Malnutrition also contributes to increased incidence of DIH, which is more in South-East Asian regions Measures of malnutrition such as skin fold thickness, body mass index, and mid-arm circumference did not significantly predict DIH. Malnutrition measured in terms of hypoalbuminemia (Serum albumin levels <3.5 g/dl) predicted twofold higher incidence of DIH.

Site and Stage of TB: It is found that abdominal TB has increased risk of DIH. This may be due to subclinical liver involvement. Severity of TB also was an independent predictor of DIH. Higher the severity of TB infection, higher the incidence of DIH.

Genetic Factors: A study showed that slow acetylators had increased risk of hepatotoxicity than rapid acetylators. Furthermore, slow acetylators had more severe hepatotoxicity in comparison with rapid acetylators. This basis can be explained by the fact that slow acetylators convert the toxic intermediate monoacetyl hydrazine to diacetyl hydrazine slowly. Furthermore, several studies indicate that Rifampicin, a well known human PXR agonist and P450 inducer, can potentiate Isoniazid induced hepatotoxicity in man, especially in slow acetylators[15]. Other factors like enzymes, Human Leukocyte Antigens (HLA) have shown significant association in the development of hepatotoxicity.

Journal of Army Medical College Chattogram
Volume 3 Issue 1 June 2020; 33-37

Table I : Risk of AT -DIH.

Risk factors		Risk of AT -DIH
Physiologic	Age	Increased age is associated with increased risk of AT-DIH
	Gender	Females have increased risk of AT-DIH
Pathologic	Liver disease Nutrition	HCV infection Malnutrition (Serum Albumin <3.5gm/dl)
TB site and stage	Abdominal TB And Severe TB infection	Increased Risk
Associated condition-	Hepatitis B, C HIV	Increased Risk
Genetic factors	Slow acetylators	Increased Risk

Table II : Hepatotoxic potential of first line ATT drugs.

Hepatotoxic potential	Drugs
High	INH, Rifampicin, , Pyrazinamide
Less	Streptomycin, Ethambutol

4. Management of Antitubercular Drug Induced Hepatotoxicity: [8,9,19].

All hepatotoxic first line drugs of ATT should be discontinued at the first sign of symptomatic hepatitis. It is observed that in mild hepatotoxicity clinical and biochemical improvement occurs just after withdrawal of responsible drug. In severe cases presenting with acute liver failure should be managed with N-acetyl Cysteine (NAC) which is non toxic. First line ATT is re-introduced sequentially to prevent rapid dissemination of TB.

Rechallenge of Anti-TB Therapy:

American Thoracic Society[10-12].

i) After returning of serum Alanine-aminotransferase (ALT) level to less than two times the Upper Limit of Normal (ULN) Rifampicin may be restarted with or without Ethambutol.

ii) After 3 to 7 days, Isoniazid may be reintroduced, subsequently rechecking ALT.

iii) If symptoms recur or ALT increases, the last drug added should be stopped.

iv) For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with Rifampicin and Isoniazid, rechallenge with Pyrazinamide may be hazardous. In this circumstance, Pyrazinamide may be permanently discontinued, with treatment extended to 9 months.

Although Pyrazinamide can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from Pyrazinamide rechallenge.

British Thoracic Society:[13,19].

Once liver function is normal challenge dosages of the original drugs can be reintroduced sequentially in the order: Isoniazid, Rifampicin, Pyrazinamide with daily monitoring of the patient's clinical condition and liver function. Isoniazid should be introduced initially at 50 mg/day, increasing sequentially to 300 mg/day after 2–3 days if no reaction occurs, and then continued. After a further 2–3 days without reaction rifampicin at a dose of 75 mg/day can be added, increasing to 300 mg after 2–3 days, and then to 450 mg (50 kg) as appropriate for the patient's weight after a further 2–3 days without reaction, and then continued. Finally, Pyrazinamide is added at 250 mg/day, increasing to 1.0 g after 2–3 days and then to 1.5 g (50 kg). If there is no further reaction standard chemotherapy can be continued and any alternative drugs introduced temporarily can then be withdrawn.

If there is a recurrence of hepatotoxicity subsequent to the use of a first-line drug, then that particular drug responsible is stopped and therapy should be continued with the use of second-line agents in its place.

5. Risk of Co-infection for DIH[7,20-22].

Coinfection with HIV, hepatitis B, hepatitis Cmarkedly increasethe risk of hepatotoxicity. HIV alone and coinfection-with hepatitis C increases the risk of TB DIH 4 and 14fold respectively, in patients on antitubercular therapy.

6. Anti-TB-DIH in Children: [23-29,30].

In children anti-TB-DIH occurs less frequently than adults but not uncommon[30]. Use of pyrazinamide increases the risk of hepatotoxicity.

The patients need to follow them up more closely, to identify hepatotoxicity at the earliest possible time to design new drug regimen. Routine monitoring for hepatotoxicity in patients receiving ATT is important to prevent morbidity and mortality.

7. Monitoring:[31-35].

Therapeutic drug monitoring has been shown to improve clinical response. It is recommended that baseline Liver Function Tests (LFT) values are obtained prior to starting ATT therapy and they are monitored every 2 weeks for the first 2 months and monthly until regimen is over. This is essential for high-risk groups such as alcoholics, Hepatitis B carrier, Hepatitis C infected, HIV-infected, pregnant females and at extremes of age (<5 and >65).Regular clinical review of patients is helpful to monitor treatment adherence and effectiveness.

8. Prevention of DIH : [36-38,39,40].

Education of the patient and their family members about the risk of TB drugs should be emphasized. The primary

Journal of Army Medical College Chattogram
Volume 3 Issue 1 June 2020; 33-37

care providers should emphasize on the importance of immediate discontinuation of the drug immediately on development of symptoms in order to prevent progressive liver disease. Since old age is a risk factor, a recent study concluded that co-prescription with N-acetylcysteine (NAC) in patients above 60 years prevented DIH, when compared to those who did not receive NAC. Further studies are needed to confirm this finding.

Conclusion

After analyzing the articles on drug induced hepatotoxicity we found the incidence of anti-TB drug induced hepatotoxicity ranges from 7% -34%. At the same time full dose and course of ATT (Anti-TB therapy) is also necessary. So it is important for the clinician to follow up the patients regularly. They should counsel the patients about sign and symptoms of hepatotoxicity, so that they can report to the hospital as soon as they develop hepatotoxicity. This practice will decrease morbidity and mortality.

Disclosure

All the authors declared no competing interests.

References

1. WHO Report. Global Tuberculosis Control. Epidemiology, Stratetgy and Financing. Geneva: World Health Organization. 2019.

2. Pandit A, Sachdeva T and Bafna P. Drug-Induced Hepatotoxicity: A Review, Journal of AppliedPharmaceutical Science. 2012;02: (05)233-243.

3. Progress and Challenges in TB control program. Daily Star. March 10, 2020.

4. Teleman MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. The International Journal of Tuberculosis and Lung Disease. 2002; 6: 699-705.

5. WHO- Global tuberculosis Report. 2020.

6. Shu CC, Lee CH, Lee MC, Wang JY, Yu CJ, Lee LN. Hepatotoxicity due to first-line anti-tuberculosis drugs: A five-year experience in a Taiwan medical centre. International Journal of Tuberculosis and Lung Disease. 2013; 17:934e9.

7. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG,Raviglione MC et al. The growing burden of tuberculosis: Globaltrends and interactions with the HIV epidemic. Archives of International Medicine. 2003;163:1009–1021.

8. Naqvi IH, Mahmood K, Talib A and Mahmood A. Anti-tuberculosis drug induced liver injury: An ignored fact, Assessment of Frequency, Patterns, Severity and Risk factors. Open journal of gastroenterology. 2015;5:173-184.

9. Forget EJ, Menzies D. Adverse reactions to first-lineanti-tuberculosis drugs. Expert Opin Drug Saf. 2006;5:231–249.

10. Tajiri K, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. World J Gastroenterol. 2008;14(44):6774-6785.

11. Faiz SN, Chowdhury N, Khan MAH, Parvin R. Evaluation of risk factors for hepatotoxicity in patients receiving antitubercular Four drugs Regimen in initial Two months. Official Journal of Chattogram Maa-O-Shishu Hospital Medical College. 2015;14(1):15-18.

12. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA,Nolan CM, et al. ATS (American Thoracic Society)Hepatotoxicity of Antituberculosis Therapy Subcommittee. Anofficial ATS statement: hepatotoxicity of antituberculosis therapy.Am J RespirCrit Care Med. 2006;174: 935–952.

13. Joint Tuberculosis Committee of the British Thoracic Society* Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Thorax. 1998;53:536–548.

14. Raviglione MC, O'Brien RJ. Tuberculosis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's principles of internal medicine. 18thedn. USA: McGraw-Hill Medical Publication Division. 2012;1340-1359.

15. Wang P, Pradhan K, Zhang X and Xiaochao Ma. Isoniazid metabolism and hepatotoxicity. ActaPharmaceuticaSinica B.2016;6(5): 384-392.

16. PeterD.Davies, Peter Barnes, Stephen B Gordon. Clinical Tuberculosis. 4th edn. London: Hodder Education Ltd. 2008: 8-12.

17. Mo P, Zhu Q, Teter C, Yang R, Deng L, Yan Y et al. Prevalence, drug induced hepatotoxicity, and mortality among patients multi-infected with HIV, tuberculosis, and hepatitis virus. International Journal of Infectious Disease. 2014;28: 95e100.

18. Mahmood K, Hossain A, Jairamani KL, Talib A, Abbasi BU, Salkeen S. Hepatotoxicity with anti-tuberculosis drugs: The risk factors. Pakistan Journal of Medical Sciences. 2007; 23(1): 56-59.

19. Nabi T, Rafiq N and Arifa Q. A prospective study of N-acetylcysteine treatment in drug induced fulminent hepatic failure. International Journal of Basic & Clinical Pharmacology. 2019;8(5):1000-1006.

20. Shakya R, Rao BS, Shrestha B. Evaluations of risk factors for anti-tuberculosis drug-induced hepatotoxicity in Nepalese population. Kathmandu University Journal of Science, Engineering and Technology. 2006; 2:

21. Kishore PV, Palatan S, Pandol R, Mishra P, Prabhu M, Shankar PR. Drug induced hepatitis with anti-tubercular chemotherapy: challenges & difficulties in treatment. Kathmandu University Medical Journal 2007; 5(2):18.

22. Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology. 2002;35(4):883-889.

Journal of Army Medical College Chattogram
Volume 3 Issue 1 June 2020; 33-37

23. Yuhua Li, QiangMeng, etal., Current trends in drug metabolism and pharmacokinetics. ActaPharmaceuticaSinica B. 2019;09(6)

24. National Guidelines and Operational Manual for Programmatic Management of Drug Resistant TB (PMDT) Second Edition.National Tuberculosis Control Programme. Directorate General of Health Services Dhaka, April, 2013.

25. Katzung BG. Basic and clinical pharmacology. 10thedn. Lange Medical Books /McGraw-Hill Medical Publishing Division. 2009; 1409-1413.

26. Huang YS, Chern HD, Su WJ, Wu JC, Chang SC, Chiang CH, Chang FY, Lee SD. Cytochrome P4502E1 genotype and the susceptibility toantituberculosis drug-induced hepatitis, Hepatology. 2003;37(4):924-930.

27. Hayes, J. D, Flanagan J.U,Jowsey. I.R. Glutathione-transferases, Annual Review of Pharmacology and Toxicology. 2005;45:51-88.

28. Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis. 2010;50(6):833-839.

29. Kaneko Y, Nagayama N, Kawabe Y, Shimada M Suzuki J, Kunogi M, et al. Drug-induced hepatotoxicity caused by anti-tuberculosis drugs in tuberculosis patients complicated with chronic hepatitis. Kekkaku. 2008;83(1):13-19.

30. Donald PR. Antituberculosis drug induced hepatotoxicity in Children.Paediatric Report.2011;16:3(2): e 16.

31. Nakajima A, Fukami T, Kobayashi Y . Humanarylacetamidedeacetylase is responsible fordeacetylation of rifamycins: Rifampicin, rifabutin and rifapentine, BiochemPharmacol. 2011;82(11):1747–1756.

32. Dodig S, Raos M, Zricic I. Hepatotoxicity of antituberculosis drugs in a mother and a child affected by pulmonary tuberculosis. A case report. BiochemiaMedica. 2008; 18 (1): 99.

33. Wen X, Wang JS, Neuvonen PJ. Isoniazid is a mechanism-based inhibitor of cytochrome P450 1A2, 2A6, 2C19 and 3A4 isoforms in human liver microsomes, Eur J ClinPharmacol. 2002;57(11):799-804.

34. Adam R, Karam V, Delvant V, O'Grady J Mirza D, Klempnaauer J, et al. evaluation of indications and results of liver transplantation in Europe. A report from the Europian Liver Transplant Registry (ELTR). Journal of Hepatology.2012; 57: 675- 688.

35. Stout JE, Engemann JJ, Cheng AC, Fortenberry, Hamilton CD. Safety of 2 months ofrifampin and pyrazinamide for treatment oflatent tuberculosis, American Journal of Respiratory and Critical Care Medicine. 2003;167(6):824-827.

36. Shih TU, Pai CH, Yang P, Wen LC, Wang NC, Hu OY. A novel mechanism underlies the hepatotoxicity of pyrazinamide. Journal of American Society for Microbiology. 2013;57 (4):1685-1690.

37. Sadaphal P, Astemborski J, Graham NM, Sheely L, Bonds M, Madison A. Isoniazid preventive therapy, hepatitis C virus infection, and hepatotoxicity among injection drug users infected with Mycobacterium tuberculosis. Clinical Infectious Disease. 2001;33:1687e91.

38. Faiz SN ,Haque M, Islam H.Evaluation of changes in Levels of Serum Alanine Aminotransferase (ALT) Serum bilirubin, Serum Total Protein and Serum Albumin in Patients Receiving Antitubercular four Drugs Regimen in initial two months. The Healer. 2014;17(2): 4-7.

39. Ramappa V, Aithal GP. Hepatotoxicity Related to Antituberculosis Drugs: Mechanisms and Management.Journal of Clinical and Experimental Hepatology. 2013; 3(1): 37–49.

40. Nunn P, Reid A, De Cock KM. Tuberculosis and HIV infection: the global setting. The Journal of Infectious Disease. 2007;196:S5–14.