ORIGINAL ARTICLE J. Med. Sci. (Peshawar, Print) January 2010, Vol. 18, No.1: 45-48

ASSESSMENT OF RISK FACTORS FOR ANTI TUBERCULOUS DRUG INDUCED HEPATOTOXICITY

Shafaq Naz[1], Jamal-ud-din-Marwat[2], Muhammad Arshad[1], Aftab Ahmed[1], Hashim Riaz Khan[2], Zahid Ullah[2]

[1]Department of Medicine, Naseer Teaching Hospital, Peshawar - Pakistan
[2]Department of Medicine, Khyber Teaching Hospital, Peshawar - Pakistan

ABSTRACT

Objectives: To assess the risk factors in adults for hepatotoxicity caused by different antituberculous (TB) drugs.

Material and Methods: This observational descriptive study was conducted in Medical ward and Out Patient Department of Naseer Teaching Hospital, Peshawar and Khyber Teaching Hospital, Peshawar from August 2007 to June 2008. Fifty diagnosed patients of TB receiving first line anti TB drugs with normal pretreatment liver functions were monitored clinically and biochemically. Their data was collected on proforma. Amongst those who developed hepatotoxicity, the frequency of common risk factors was calculated.

Results: Five patients (10%) developed hepatotoxicity, observed mostly (80%) within 2 weeks of initiation of treatment. Among those who developed hepatotoxicity, majority were female of young age (< 35 years) and had sputum smear positive (30%) for acid fast bacilli. Nutritional status, assessed by BMI (kg/m^2) and serum albumin levels were other predisposing risk factors. Most patients were anemic with low hemoglobin levels.

Conclusion: Anti tuberculosis drug induced hepatitis is significantly more frequent in patients with hepatotoxicity risk factors. Early recognition and revision of dose administration needs to be proposed at least for these risk groups.

Keywords: Anti Tuberculous, drugs, Hepatotoxicity, Risk.

INTRODUCTION

Pakistan is the 7th most tuberculosis affected country in the world, a burden it shares with other countries in the region[1]. As per World Health Organization (WHO) estimates, more than 300,000 new cases of tuberculosis develop in Pakistan every year, three quarters of which are concentrated in the productive age group[2]. Despite the availability of effective chemotherapy, TB is still a major health problem in our country. The poor out comes are attributed to poor patient compliance, multi drug resistance and interruption partly due to adverse drug reactions. Among the adverse drug reactions, hepatotoxicity is a well known complication of chemotherapy[3,4]. The risk is enhanced when combination of drugs are used[5]. Two patterns of liver injury can be observed in patients receiving anti-TB drugs. The first pattern is characterized by an increase in serum transaminase activity that occurs soon (usually within first 15 days) after initiation of treatment. This pattern is likely to be caused by rifampicin or isoniazid. The prognosis is good in most cases. The second pattern is characterized by an increase in serum transaminase activity that occurs late (usually more than 1 month) after initiation of treatment, it has been suggested that this pattern is related to pyrazinamide hepatotoxicity. The prognosis of this type of hepatitis is generally poor[6,7].

A number of factors including old age, female sex, malnutrition, alcoholism, preexisting liver disease, hypoalbuminemia, advanced tuberculosis and inappropriate use of drugs, are found to predispose patients towards these adverse reaction of anti-TB drugs which can cause significant morbidity and compromise treatment regimen as well as prolong duration of illness. In order to reduce the morbidity and mortality associated with anti-TB drug induced hepatitis early identification of patients at increased risk and modification in their treatment regimen is important.

This study was conducted with the aim to assess frequency and relationship of fore mentioned risk factors with anti-TB drug induced hepatitis.

MATERIAL AND METHODS

This observational study was conducted in Medical Ward and OPD of Naseer Teaching Hospital and Khyber Teaching Hospital, Peshawar, from August 2007 to June 2008. Total of 50 patients with diagnosed pulmonary and/or extra pulmonary TB started on first line anti-TB drugs were subjects of this study. Drugs were given according to body weight. Among the 50

Address for Correspondence:
Dr. Shafaq Naz
House # G-19,
Old Jamrud Road,
University Town, Peshawar, Pakistan
Contact No. 091-5854804

patients, 40 (80%) patients were having pulmonary TB and 10 (20%) had extra pulmonary TB including 6 patients of tuberculous pleural effusion, 1 of TB lymphadenitis, 2 of abdominal TB and 1 patient diagnosed as having TB meningitis. There were 36 (72%) female patients and 14 (28%) male patients with age ranging from 16-60 years.

Criteria for induction were: Patients with normal pretreatment LFT's, having no evidence of liver disease clinically or biochemically, and not using any hepatotoxic drugs. Patients for re treatment of TB were not included in the study.

After taking a thorough history and performing clinical examination, data of all the patients was recorded. The variables of study were:

1. Duration of treatment after which Drug Induced Hepatitis (DIH) developed.
2. Predisposing risk factors e.g. age, sex, infectivity status, nutritional status and habits.

Among the investigations all the patients had LFT's (Serum bilirubin, alanine amino transferase, and alkaline phosphatase, serum albumin), hemoglobin level, viral profile (HBS Ag, anti HCV Ab), abdominal ultrasound and sputum for AFB.

Table 1: Risk Factors for Hepatotoxicity

Risk Factors and No. of patients	Cases of hepatotoxicity
Sex	
Female (n=36)	4(11.11%)
Male (n=14)	1(7.14%)
Age	
16-35 yrs (n=35)	4(11.42%)
36-60 yrs -=15	1(6.66%)
Sputum infectivity	
Sputum AFB +ive (n=10)	3(30%)
Sputum AFB –ive (n=30)	2(6.6%)
Alcohol Intake	
Yes (n=1)	0(0%)
No (n=49)	5(10.20%)
Albumin level	
> 3.5 gm/dl (n=21)	1(4.76%)
< 3.5 gm/dl (n=29)	4(13.79%)
Hemoglobin level	
7-10 gm/dl (n=36)	4(11.11%)
> 10 gm/dl (n=14)	1(7.14%)
BMI (Kg/m2)	
< 20 (n=30)	4(13.33%)
> 20 (n=20)	1(5%)

Patients were advised to report if symptoms suggestive of hepototoxicity like nausea, vomiting and anorexia occur or if clinically jaundice appears. In patients who developed hepototoxicity, medications were stopped immediately and serum transferases were measured twice weekly until symptoms resolved and transferases came to near normal values[8].

CRITERIA FOR DRUG INDUCED HEPATITIS[4]:

Normalization of liver enzymes level and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti-TB drugs, and presence of at least one of the following criteria:

- A rise of five or greater than five times the normal level of ALT and / or AST.
- A rise in the level of serum total bilirubim over 1.5 mg/dl.
- Any increase in ALT and / or AST above pretreatment levels together with anorexia, nausea, vomiting and jaundice.

Treatment regimen for all adults consisted of 2 months intensive phase of isoniazed (INH), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E). The continuation phase was given for six months and drugs included were isoniazid (INH), and Rifampicin (R). The dosages of drugs were: INH 5mg/kg/day, Rifampicin10 mg/kg/day, Pyrazinamide 20-25 mg/kg/day, ethambutol 15 mg/kg/day.

RESULTS

During the one year study period 5 (10%) patients developed hepatotoxicity detected clinically and confirmed biochemically. Majority of affected 4 (80%) patients developed hepatotoxicity during early days of treatment (within 2 weeks) and only 1 patient (20%) had drug induced hepatitis (DIH) after 4 weeks.

Regarding symptoms, all the affected patients had gastrointestinal manifestations of nausea, vomiting anorexia, abdominal discomfort and yellow discoloration of sclera. The SGPT levels of 3 (60%) patients were more than 5 times the upper limit.

Female sex was more affected i.e. 4 out of 36 (11.11%) as compared to males 1 out of 14, (7.14%). Patients of younger age group (up to 35 years) developed DIH more 4 out of 35 (11.42%) as compared to elderly 1 out of 15, (6.66%). Three (30%) patients with DIH had positive sputum for AFB. BMI (kg/m^2) of 13.33% patients was less than 20 with low serum albumin levels (13.79%). Those patients who developed hepatotoxicity had hemoglobin levels less than 10 gm/dl (11.11%).

Regarding habitual status, 10 males were smoker while none of the females had the habit, one male patient was alcoholic. Details of risk factors along with their frequency counts are shown in Table 1.

DISCUSSION

Tuberculosis has caused more deaths than any other infectious disease and 95% of these deaths are in the developing world[9]. It is the fourth major cause of death in Pakistan[10]. Early diagnosis and effective treatment is the best way of controlling TB but despite the availability of treatment regimen, it remains a problem in those patients who can not tolerate the drugs because of its side effects. One of the commonest side effects is hepatotoxicity.

Identification of patients at increased risk of hepatotoxicity is important because it can cause significant morbidity and mortality and requires modification of treatment regimen.

Frequency of hepatotoxicity with anti-TB drugs has been assessed in this study in relation to age, sex, sputum infectivity, nutritional status and duration of chemotherapy.

In our study, 5 (10%) patients developed hepatotoxicity. Similar results have been seen by other observers[11,12,13]. The incidence of hepatotoxicity is higher in developing countries when compared with western studies[14]. Multiple factors like genotyping of patients, nutritional and infectivity status and ethnic factors are said to be responsible for the differences[15,16]. Combination of drugs used for treatment of TB is also associated with increased risk as compared to INH monotherapy for prophylaxis of tuberculosis[5].

The study showed that hepatotoxicity is more common in females and this matches other studies conducted[7,13,17,18]. This increased incidence in females is mainly due to differences in pharmacokinetics and slow acetylator status[19]. Regarding age, study showed increased incidence in young reproductive age group strengthening previous studies[7,13] . Three of patients with hepatotoxicity had sputum positive for AFB[7]. This increased incidence is due to the products of tubercle bacilli liberated in the liver after their destruction by anti-TB drugs[20].

No association has been found in relation to habits (alcoholism, smoking) however, it was found that poor nutritional status increases the risk of hepatotoxicity. Decreased glutathione stores and slower rate of liver metabolism are the possible causes of increased vulnerability among malnourished individuals[21].

Combination of drugs was given to the patient and it is difficult to presume which particular drug is hepatotoxic. Four of the affected patients developed hepatotoxicity within first 15 days Rifampacian induced hepatotoxicity is likely to be responsible for this hepatotoxicity. The formation of hydrazine, a key intermediate of INH metabolism and a potent acylating agent capable of causing liver necrosis is facilitated by RMP[7]. Only 1 patient developed hepatotoxicity late (after 4 weeks) which is probably pyrazinamide induced.

CONCLUSION

Hepatotoxicity is one of the most serious adverse effects of anti-TB drugs. Early detection, temporary withdrawal and revised dose administration is proposed, at least, for high risk groups. Malnourished female patients are particularly at risk and need to be closely monitored.

REFERENCES

1. Khan AA. The problem of Latent tuberculosis in Pakistan (editorial). Inf Dis J Pak 2007 Jan-March: 2.
2. Pakistan Chest Society Center Guidelines for diagnosis of tuberculosis. A National Clinical Guideline: Med Today 2005 Oct-Dec; 3(4).
3. Mahmood K, Hussain A, Jairamani KL, Talib A, Abbassi B, Salkeen S. Hepatotoxicity with Anti tuberculosis Drugs: The risk factors. Pak J Med Sci 2007 Jan-March; 23(1): 33-38.
4. Tanaogllu K. The management of anti-TB drug induced Hepatotxicity. The Int Union against tuberculosis and Lung disease. 2001; 5 (1): 65: 69.
5. Durand F, Bernuau J, Pessayre D, Samuel D, Deggott, Bismith H, et al. Deliterous influence of PZA on outcome of patient with fulminant or sub fulminant liver failure during anti-TB treatment including INH. Hepotology 1995; 21: 929-32.
6. Durand F, Jebrak G, Pessayre D, Fournier M, Bernuau J. Hepatotxicity of anti tubercular treatment. Rationale for monitoring liver status. Drug Saf 1996 Dec; 15 (6): 394-405.
7. Shakya R, Rao BS, Shrestha B. Evaluation of risk factors for Anti tuberculosis drug induced hepotatoxicity in Nepalese population. Kath Un J of Sci, Eng and Tech Feb 2006; II (1). 33-40.
8. Guidelines for the management of adverse drug effect of anti mycobacterium agents, 1998. Lawrence Flick Memorial tuberculosis clinic, Philadelphia TB Control Program.
9. Javaid A. Over view of tuberculosis problem in Pakistan. Pak-J-Chest-Med 1997 Nov; Special Supp: 23-33.
10. Bokhari SNH. Current concepts in the diagnosis of TB. Specialist 1999 Oct-Dec; 16 (1): 39-46.
11. Senaratne WV, Pinidiyapathirage MJ, Perera GA, Wickre masinghe AR. Anti tuberculosis drug induced hepatitis- a Sri Lankan experience. Ceylon Med J 2006 Mar; 5 (1): 9-14.

12. Mekonnen T, Abseno M, Meressa D, Fekde B. Prevalence and management outcomes of anti TB drugs induced hepotatoxicity. J Ethopia Med Pract 2002; 4 (1): 32-38.

13. Shakya R, Roa BS, Shrestha B. Incidence of hepotatoxicity due to anti tubercular Medicines and assessment of risk factors. Ann Pharmacother 2004; 38 (6): 1074-9.

14. Sharma SK, Balamurgan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immonogenetic risk factors for the development of hepotatoxicity during anti tubercular treatment. Am J Respir crit care Med 2002; 166: 916-19.

15. Kumar A, Mishra PK, Govil YC. Hepotatoxicity of RMP and INH. Is it all drug induced hepatitis? Am Rev Respir Dis 1991; 143: 1350-52.

16. Ungo JR, Jones DF, Askin D. Anti TB drugs related hepatotoxicity; the role of hepatitis C and human immodefeciency Virus. Am J Respir crit care Med 1998; 157: 1871-76.

17. Haq MU, Rasul S, Khan SU, Saeed S, Tahir TM. Anti tuberculosis drug induced hepatitis. Pak J chest Med Mar 2001; 7 (Supp): 41-45.

18. Teleman MD, Chee CB, Earnest A, Wang YT. Hepotatoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis Aug 2002; 6(8): 699-705.

19. Marwin W. Impacts of gender on drug responses. Drug topics 1998; 591-600.

20. Singh J, Garg PK, Tandon R. Hepotatoxicity due to anti TB therapy, clinical profile and reintroduction of the therapy J. Clin Gastroenterol 1996; 22: 211-14.

21. Pandle JN. Risk factors for hepotatoxicity from anti TB drugs. A case control study. Thorax 1996; 51: 1326-31.

The Journal of Medical Sciences, Peshawar is indexed with WHO IMEMR (World Health Organisation Index Medicus for Eastern Mediterranean Region) and can be accessed at the following URL.

http://www.who.int/EMRJorList/details.aspx?docn=4468