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Risk Factors for Anti Tuberculous Drugs Induced Hepatitis: A Prospective Survey from a Chest Clinic in a General Hospital

A R M Fauzi, MRCP*, A Shah, MBBS*, M Y Rathor, MD*, S Satwi, MMed**

*Department of Internal Medicine, Kulliyah of Medicine, P.O. Box 141, 25710 Kuantan, Pahang, Malaysia, **Department of Medicine, Hospital Tengku Ampuan Afzan, Kuantan, 25150 Pahang

Summary

A prospective survey on 14 consecutive cases with tuberculous drug induced hepatitis was done at our chest clinic in a state general hospital over a period of 15 months. There were 30 controls chosen randomly from the chest clinic register. The cases had lower mean body mass index (P<0.008), serum albumin (P<0.005) and higher serum globulin (P<0.04). Serum liver transaminases and total bilirubin rose significantly during the acute episode of drug induced hepatitis. Among the risk factors studied, only chronic hepatitis B carrier status was found to be more prevalent among the cases. There was one death (7.1%) over the whole study period.

Key Words: Prospective survey, Tuberculosis drug, Hepatotoxicity, Risk factors

Introduction

Pulmonary tuberculosis (TB) represents an important worldwide health problem. It has been reported by the World Health Organization that one person in the world becomes infected every second, and that one third of the entire population of the world is now infected [1]. The World Health Organization also estimates that in the next decade, 300 million more people will be infected, 90 million people will develop the disease, and 30 million people will die from it[1].

The National Tuberculosis Control Programme in Malaysia was introduced in 1961[2]. This has led to a significant reduction in mortality such that diseases caused by mycobacterium tuberculosis (MTB) are no longer one of the 10 major causes of death [3]. In terms of treatment, short course chemotherapy containing rifampicin and isoniazid in combination has proved to be highly effective in eradicating diseases but not without the side effects of drug induced hepatitis. The exact mechanism of drug induced hepatitis is still unclear. The reported of incidence of hepatotoxic reactions during anti tuberculosis treatment varies with studies in Asia reporting higher risk of hepatitis (11.5%) than the West (4.28%) [5].

The reasons for the higher incidence of hepatitis in developing countries are unclear but prevalent viral hepatitis has been suggested as a potential cause [6]. Several other risk factors have also been suggested such as advanced age [7], sex [8], poor nutritional status [9], liver disease [10], inappropriate use of drugs, chronic infections, hepatitis B virus (HBV) carrier status [11], acetylator status[12] and high alcohol intake[8]. We report the findings of a prospective survey to study the roles of some of these factors in the development of anti tuberculosis drug induced hepatitis among our patients receiving short course anti-tuberculous chemotherapy at our chest

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Corresponding Author: A R M Fauzi, Department of Internal Medicine, Kulliyah of Medicine, P.O. Box 141, 52710 Kuantan, Pahang, Malaysia

clinic in Hospital Tengku Ampuan Afzan (HTAA), Kuantan, Pahang.

Materials and Methods

We conducted a prospective survey between January 2000 and March 2001 on consecutive TB cases that had developed icteric hepatitis whilst taking anti tuberculosis treatment. All the patients were registered at the chest clinic of HTAA and were admitted for hepatitis.

Diagnosis of drug-induced hepatitis was made based on the presence of all the following criteria:

1. Clinical features of icteric hepatitis (anorexia, nausea and jaundice).
2. Elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) above 200U/l (five times the upper limit of normal value) at the time of admission.
3. Serum total bilirubin of more than 34.2 micromol/l.
4. Absence of serological evidence of an acute infection with hepatitis A, B or C. IgM anti-hepatitis A virus (HAV) antibody for acute hepatitis A infection was done using enzyme linked immunosorbent assay at a local private laboratory (BP Lab). Hepatitis B surface antigen (HbsAg) and anti-hepatitis C virus (HCV) antibody for hepatitis B and C respectively were done at HTAA. A patient known to be positive for HbsAg for at least 6 months was regarded a HBV carrier. Otherwise IgM anti-hepatitis B core antigen (IgM anti-HBc) was requested to distinguish an acute infection (positive IgM anti-HBc) from a chronic one. Any patient who had positive anti HCV antibody test was excluded from the study.

Drug regimens used on the patients were as follows: (Streptomycin:S, Isoniazid:H, Rifampicin:R, Pyrazinamide:Z and Ethambutol:E)

1. 2SHRZE/4RH2
2. 2SHRZ/4SRH2
3. 2HRZE/4RH2
4. 2HRZ/4RH2

Dosages of the drugs were calculated in relation to the weight of the patients as follows:

1. Streptomycin: 15mg/kg
2. Rifampicin: 10mg/kg
3. Isoniazid: 5mg/kg
4. Ethambutol: 20mg/kg
5. Pyrazinamide: 25mg/kg

Details of patients' demographics were taken from the case notes or during the interview. Treatment regimens, doses, duration, alcohol intake, chronic Hepatitis B carrier status, previous anti HCV antibody test, HIV status and severity of chest radiograph (CXR) were also noted. Significant alcohol intake was defined as consumption of more than 6 units of alcohol daily for more than six months. The CXR severity was classified using the following criteria:

1. Minimal disease.
Slight lesions without demonstrable cavitation confined to a small part of one or both lungs. The total extent of the lesions shall not exceed the equivalent of the volume of the lung tissue which lies above the second costochondral junction or the spine of the fourth or the body of the fifth thoracic vertebrae on one side regardless of distribution.

2. Moderately advanced disease.
One or both lungs may be involved but the extent of the lesions shall not exceed the following limits:

i. Slight disseminated lesions, which may extend through not more than the volume of one lung or the equivalent in both lungs
ii. Dense confluent lesions which may extend through not more than the equivalent of one third the volume of one lung and
iii. Total diameter of cavities is less than 4cms

3. Advanced disease is a lesion more extensive than in moderately advanced disease. All the CXRs were assessed and graded by the first author. The duration of treatment in days before the development of drug induced hepatitis was also noted. During admission, all the TB drugs were stopped and serial liver function tests (LFTS) were done. Once normalization was noted, chemotherapy was recommenced with S and E and drug challenge was done sequentially with R, H and Z. The offending drug if proven would then be gradually introduced to the regime starting at the lowest dose and gradually increasing to the dose calculated according to the patient's weight. Failing this, an alternative regime was used excluding the offending drug. There were two patients who required an alternative regimen (HZE) as reintroduction of rifampicin caused recurrence of hepatitis.

A total of 30 patients from the chest clinic register agreed to be controls. They had all been treated with anti tuberculous chemotherapy during the study period without hepatotoxicity and had also agreed to answer the preset questionnaires and agreed to blood taking.

Cases and controls were compared using t test and Chi Square test for continous and categorical variables respectively. Corrrelation was done using Pearson correlation test and multiple regression analysis was used to identify the factors that were significant in the severity of hepatitis.

Results

There were 14 patients who developed anti tuberculous drug induced hepatitis over the 15 months study period. The cases and controls were compared (Table I) in terms of age, male to female ratio and body mass index (BMI) calculated from height (in metres) and weight (in kilogram). The mean age was higher among the cases but this was not significant. The male to female ratio and mean BMI were lower in cases but only the latter was significant (P<0.008). Base line liver function tests revealed lower mean serum albumin (P<0.005) and higher mean serum globulin (P<0.04) among cases compared to controls (Table II). Both cases and controls used similar treatment regimen (Table III). The latency period between the start of treatment and development of hepatitis varied from 28 days to 77 days with mean of 53 (13.7) days.

During the acute episode of drug induced hepatitis, serum total bilirubin, ALT and AST rose significantly but serum albumin was somewhat reduced (Table IV). Serum globulin remained unchanged. All cases in the study were jaundiced and were admitted for observation. One patient developed severe hepatic failure and died despite stopping all anti tuberculosis drugs. All other patients were successfully treated conservatively and recommenced on similar drug regimes except in two patients who required HZE. Among the risk factors studied (Table V) we found that HBsAg was more prevalent among the cases. The other risk factors were not significantly different between the two groups.

We performed a multiple regression test to see if the level of serum urea and creatinine (during acute hepatitis), pretreatment albumin and globulin were significant in the severity of hepatitis (by the level of AST). Using enter and remove method, none of the factors above was significantly linked to the severity of hepatitis. There was also no difference in the level of elevated serum transaminases between males and females in the cases. There was a single (7.1%) mortality due to fulminant hepatitis within the period of study.

Table I: Age, male/female ratio and body mass index of the cases and controls

	Cases (n=14)	Controls (n=30)	P value
Mean age (SD)	47 (14.1)	41.9 (13.5)	NS
M/F ratio	2.5:1	2.7:1	NS
Mean BMI (SD)	22.6 (2.1)	24.2 (1.5)	0.008
Ethnic group			
Malay	11	24	NS
Chinese	3	5	NS
Indian	0	1	NS

BMI= body mass index, M/F= male/female, SD=standard deviation.

Table II: Mean (SD) of liver function tests results pre anti-tuberculous chemotherapy

	Cases (n=14)	Controls (n=30)	P value
Total bilirubin (g/L)	7.6 (3.4)	7.6 (2.6)	NS
ALT (U/L)	21.5 (8.4)	17.7 (5.7)	NS
AST (U/L)	19.7 (7.1)	17.3 (6.2)	NS
Albumin (g/L)	33.0 (5.9)	35.8 (2.9)	P<0.005
Globulin (g/L)	38.6 (5.8)	33.8 (4.5)	P<0.04

Total bilirubin= total serum bilirubin, ALT=alanine transferase, AST=aspartate transferase, Alk Phosphatase=alkaline phosphatase, Albumin= serum albumin, Globulin=serum globulin.

Table III: Drug regimens used in cases and controls

Regimen*	Cases (n=14)	Controls (n=30)	P value
2HRZE/4R2H2	11	18	NS
2SHRZ/4R2H2	1	9	NS
2HRZ/4R2H2	0	3	NS
2SHRZE/4R2H2	2	0	NS

* See text for details of drug regimens.

Table IV: Liver function test results* among cases during admission for hepatotoxicity

	Cases (n=14)
Total bilirubin (g/L)	62.1 (17.4)
ALT (U/L)	291.6 (21.6)
AST (U/L)	280.1 (16.5)
Albumin (g/L)	30.4 (6.2)
Globulin (g/L)	38.8 (6.3)

*all results are expressed as mean (SD)

Table V: Potential risk factors in cases and controls.

	Cases (n=14)	Controls (n=30)	P value
High alcohol intake*	2	2	NS
HBV carrier*	4	1	0.014
HIV+ve	3	1	NS
Severe CXR lesions*	4	8	NS

*see main text for further explanation.
HIV+ve=positive HIV test

Discussion

The development of anti tuberculosis drug induced hepatitis is of great significance because it necessitates cessation of therapy. Occasionally different regimen may have to be initiated if the patients are intolerant of the drugs. Steele et al reported in a meta-analysis[13] that isoniazid and rifampicin given together produce hepatotoxicity more often than when isonizid is given alone. Wide variations in the incidence of hepatotoxic reactions have been reported[4,5]. The relatively high incidence of hepatotoxicty in developing countries have been attributed to various factors such as old age, higher alcohol intake, malnutrition, intestinal parasitism, past history of jaundice, chronic liver disease, indiscriminate use of drugs and viral hepatitis[14]. There is no consensus as to which of these factors are involved either singly or in combination in causing hepatitis. We need to identify the group with risk factors as close monitoring can be done to avoid severe drug induced hepatitis.

Previous studies[7] have shown that older age was significantly more frequent in the group that developed hepatitis. Our study demonstrated a similar trend in that the mean age was higher in the cases compared to controls but the difference was not significant. We attributed this to our small sample size. Some studies[8] have also shown female preponderance in the hepatitis group and similarly this trend was noticeable in our study.

Poor nutritional status has been found to be one of the risk factors for hepatotoxicity[9]. Our study has shown that both BMI ($P<0.05$) and serum albumin ($P<0.005$) were lower in cases compared to controls but these

values were not sufficiently low to be labelled as malnutrition.

High alcohol intake[8] was not found to be significantly different between the two groups although this has been shown to be a significant risk factor. We are not certain whether or not denial among our patients was in any way contributory to this finding. There was no significant difference between the severity of CXR and the regimens used in both the cases and the controls. Previous studies [13] have shown that isoniazid and rifampicin given together cause hepatotoxicity more frequently than isoniazid alone. The addition of pyrazinamide has not been shown to alter the rates of hepatotoxicity significantly[5].

Our study has also noted significant difference in the number of HB s Ag positive among cases compared to controls. Earlier studies have shown that HB s Ag positivity[11] was significantly associated with the hepatotoxicity, although there was no difference in the level of pretreatment liver transaminases between the two groups in our study. Pretreatment albumin however was lower among cases. There was a significant positive correlation between the level of serum urea and the level of serum transaminases during acute drug induced hepatitis. This was probably a reflection of the severity of nausea and vomiting in severe hepatitis. The patients as a consequence were deprived of adequate oral intake and this was reflected by higher serum urea and creatinine in severe hepatitis.

Our study has an obvious limitation in terms of numbers. Nevertheless the findings are consistent with the findings from previous studies. A bigger prospective study is required to validate these findings within the context of Malaysia. In conclusion, patients who developed tuberculosis drug induced hepatitis at our chest clinic were more likely to have lower BMI, lower pretreatment serum albumin and higher serum globulin. The number of chronic HBV carriers was also significantly higher. We also found that the higher the level of liver transaminases during an acute drug induced hepatitis the higher the level of serum urea and creatinine.

Conclusion

Our study findings demonstrate that EUGIE performed for appropriate indications yields more significant findings. Standard guidelines should be utilised to improve or maintain standards of endoscopic services in ensuring cost-benefit and quality assurance. Future research should address the issue of the outcome of patients with indications labelled inappropriate because endoscopies labelled inappropriate were found to be associated with occasional important endoscopic lesions.

References

1. World Health Organization. Tuberculosis. Fact sheet No. 104 (revised). Available at: http://www.who.int/inf-fs/en/fact. Accessed May 2002.
2. Inaugural bulletin of the Medical Advisory Committee of the Malaysian Association for the Prevention of Tuberculosis. Inaugural issue. Aug 1993.
3. Ministry of Health Annual Reports 1996.
4. Pathasarthy R, Raguphati Sarma G, Janardhanam B et al. Hepatic toxicity in south Indian patients during treatment of tuberculosis with short course regimens containing isoniazid and rifampicin and pyrazinamide. Tubercle 1986; 67: 99-108.
5. British Thoracic Society and Tuberculosis Association. Short course chemotherapy in pulmonary tuberculosis. Lancet 1975; I: 119-24.
6. Kumar A, Misra PK, Mehrotra R, Govil et al. Hepatotoxicity of rifampicin and isoniazid: is it all drug induced hepatitis? Am Rev Respir Dis 1991; 143: 1350-2.
7. Centre for Disease Control. National Consensus Conference on Tuberculosis. Preventive treatment of Tuberculosis. Chest 1985; 87(Suppl 2): 128-32.
8. Gronhagen RC, Hellstrom PE, Froseth B. Predisposing factors in hepatitis induced by isoniazid-rifampicin treatment of tuberculosis. Am Rev Respir Dis 1978; 118: 461-6.
9. Rugmini PS, Mehta S. Hepatotoxicty of isoniazid and rifampicin in children. Indian J Pediatr 1984; 21: 119-24.
10. Riska N. Hepatitis in isoniazid treated group and in a control group. Bull Int Union Tuberc 1976; 51: 203-6.
11. Wu JC, Lee SD, Yeh PF. Isoniazid, rifampicin induced hepatitis in hepatitis B carriers. Gastroenterology 1990: 98: 502-4.
12. Mitchell JR, Thorgiersson UP, Black M. Increased incidence of isoniazid hepatitis in rapid acetylators: possible relation to hydralazine metabolites. Clin Pharmacol Ther 1975: 18: 70-79.
13. Steele MA, Burk RF, Desprez RM. Hepatitis with isoniazid and rifampicin-a meta analysis. Chest 1971; 99: 465-71.
14. Gangadharan PRJ. Isoniazid, rifampicin and hepatotoxicity. Am Rev Respir Dis 1986; 133: 963-5.