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Incidence of Hepatotoxicity Due to Antitubercular Medicine and Assessment of Risk Factors, Zahedan, Iran

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In order to evaluate the incidence of antituberculosis drug-induced hepatotoxicity among tuberculosis patients, a retrospective study was conducted in Zahedan, Southeast of Iran, where, tuberculosis is endemic. A total of seven hundreds tuberculous patients who, were treated with antituberculous drugs, during 5 years in Boo-Ali Hospital in Zahedan, were evaluated. Of the 700 patients, 60 cases had hepatotoxicity. The mean duration of treatment before the onset of hepatotoxicity was 31.07 $\pm$ 30.30 days. The rate of hepatotoxicity increased with increasing age and there were trends toward increased rates in women (Relative risk = 1.38; 95% Confidence interval [CI = 0.8-2.3]; p = 0.2). The frequency of the hepatitis between two groups of the Iranian and Afghanian patients was equal (Relative risk = 0.98; (95% Confidence interval [CI = 0.51-1.88]; p>0.05). The incidence of hepatotoxicity within this area has increased during the past decade, rising by 4.2% from 1995-1999 to 2000-2005. A finding of an 8.5% incidence of hepatotoxicity is considerably high. On the basis of these findings, the antituberculosis drugs most likely responsible for the occurrence of hepatitis during therapy for active tuberculosis in female gender and older patients Temporary withdrawal of the offending drug can completely cure antituberculous drug- induced hepatotoxicity.

Key words: Hepatotoxicity, antituberculosis drugs, Zahedan, Iran

INTRODUCTION

Antitubercular drugs cause derangement of hepatic function that is revealed by clinical examination and abnormal liver function test results. A major adverse reaction to the first-line antituberculosis drugs, which results in discontinuation of these drugs is, hepatitis which also has been shown in different studies. There may be considerable morbidity, even mortality, particularly with drug-induced hepatitis^[1,2]. These events may incur substantial additional costs because of added outpatient visits, tests and even more serious hospitalizations^[3,4]. Iran, especially Southeast of Iran is an endemic area for tuberculosis (TB). The annual incidence rate for all kinds of tuberculosis disease and smear positive pulmonary tuberculosis is 71 and 40 in 100,000 population, respectively^[5]. Despite the availability of effective chemotherapeutic agents that exist to treat this illness, hepatotoxicity from first-line drugs such as Isoniazid (INH), Rifampicin (RIF) and Pyrazinamide (PZA) is common and may limit their use. Alcohol use, increasing age, female gender, the presence of chronic liver diseases and immigrants from countries with a high incidence of TB (Asia, Iran) have been observed to have an increased incidence of the risk of developing anti-TB drug induced hepatotoxicity (DIH)^[6-8]. The occurrence, risk factors, morbidity and mortality of adverse events from anti-TB drugs, particularly hepatotoxicity, have been well defined, although causality of each drug may be less certain because they are seldom used alone^[2,8-10]. The different incidence rates of antitubercular drug-induced hepatitis have been reported by several studies in Iran and other countries^[2,7,9,10].

We conducted a retrospective study to investigate the incidence of anti-TB drug hepatotoxicity and risk factors in tuberculosis patients in Zahedan.

MATERIALS AND METHODS

All patients who were treated for active TB at the Boo-Ali Hospital (Zahedan, Iran) between Jan 2000 and Jan 2005 were identified. Active TB was considered as confirmed if *Mycobacterium tuberculosis* was isolated from mycobacterium culture or if they had two positive sputum smears on laboratory results, or pathology was positive in a patient who, was suspected has tuberculosis. Active TB was considered clinically diagnosed if patients were considered improved by their treating after completion of a full course of multidrugs treatment for tuberculosis. Patients with tuberculosis who were treated by anti-tubercular drugs, were visited at least monthly by the nurse and treating physician. At the time

of these visits, patients were questioned specifically regarding occurrence of common side effects to TB drugs. Liver transaminases were checked routinely in all patients after 1 month of therapy and then monthly for six months and thereafter if symptoms arouse. Patients were encouraged to return at any time if new symptoms or problems arose during therapy. Hepatitis was defined as liver transaminases levels more than 3 times higher than the upper limit of normal level in the presence of symptoms such as anorexia, nausea, vomiting or abdominal pain, or transaminases more than five times the upper limit of normal without symptoms. Episodes of hepatitis were considered drug-induced if transaminases were normal before the onset of therapy, increased during therapy and returned to normal after discontinuation of the drugs. At this time, the drugs (INH, RIF and PZA) were stopped and streptomycin and ethambutol were started. Once the side effect improved, drugs were started, gradually one by one. All patients, were evaluated for hepatitis B and C because the two infections are endemic in this area. From patients, medical and nursing records, information was extracted regarding age, sex, country of origin, alcohol use and history of liver disease. Then statistical analysis system (SSPS) was used for all statistical analysis.

RESULTS AND DISCUSSION

Of the 700 (389 female and 311 male) patients treated for active tuberculosis, 60 cases (38 female, 22 male) had drug induced hepatitis (Table 1 and 2). Of these, all had normal pretreatment liver transaminases, none had a history of alcohol or drug use, but 3 cases were HBsAg positive without history of clinical hepatitis. In recent group HBsAg and HCV were negative but HBc-Ab was positive. In one patient HBsAg and anti-HCV and PCR (polymerase Chain Reaction) for HCV were positive. Forty two cases were more than 55 years old. For the remaining 640 patients, completion of a full course of treatment was documented in their hospital and TB center records. Statistical analysis showed the mean duration

Table 1: Number of patients under study according to sex and age

	Age					
Sex	0-34	35-44	45-55	55-64	>65	Total
Females	74	73	98	61	83	389
Male	44	64	31	57	115	311

Table 2: Frequency of drug induced hepatotoxicity according to age and sex

Age (years)	0-34	35-44	45-54	55-64	>65	Total
Male (No.)	0	1	4	11	6	22
Female (No.)	1	4	8	15	10	38
Total	1	5	12	26	16	60

(Relative risk = 1.38; 95% confidence interval [CI = 0.8-2.3]; p = 0.2)

Table 3: Number of patients under study and patients with DIH according race and age

Race	Age				
	0-34	35-44	45-54	55-64	>65
Iranian patients with DIH/total Iranian patients	1/81	4/123	10/100	23/98	12/183
Afghanian patients with DIH/total Afghanian patients	0/37	1/14	2/29	3/20	4/15
Total patients with DIH/total patients	1/118	5/137	12/129	26/118	16/198

(Relative risk = 0.98; 95% confidence interval [CI = 0.51-1.88] $p > 0.05$)

of treatment before the onset of hepatotoxicity was 31.07 ± 30.30 days. The rate of hepatotoxicity increased with increasing age (70% of cases with DIH had an age more than 55) and there were trends toward increased rates in women (relative risk = 1.38; 95% confidence interval [CI = 0.8-2.3]; $p = 0.2$) (Table 2). Ten cases of the patients with drug-induced hepatitis were Afghanian patients. The frequency of the hepatitis was equally among Iranian patients and Afghanian patients (relative risk = 0.98; 95% confidence interval [CI = 0.51-1.88] $p > 0.05$) (Table 3).

With utilization of multidrug regimens for the treatment of TB such as the combination of INH, RIF and PZA have been associated with an increased incidence of DIH when compared with INH monotherapy used for TB prophylaxis^[10]. In this study, among 700 patients treated for active TB, 60 cases (8.5%) had hepatitis, therefore the incidence of hepatotoxicity was high and was associated with multiple factors such as; female gender, older age. An advantage of the study was the inclusion of all patients with a wide spectrum of disease severity and comorbid illnesses which were treated at a single center by a small group of physicians who provided a reasonably standardized approach to identification and management of side effects. In other study in Zahedan in 1999 by Alavi *et al.*^[7] incidence of hepatitis due to anti-TB drugs was 3.7% and it was associated with male gender and older age. In this study among DIH patients, the frequency of female gender was higher (63.3%) and 70% of the patients with hepatitis were more than 55 years old. But in Alavi study, among the drug-induced hepatitis patients, frequency of male gender was higher (54.4%) and 68% of patients with hepatitis had an age of more than 50. Mortality in Alavi's study was 9.1% but in present study only one patients (1.6%) was expired at 5 month of treatment due to massive hemoptysis. Other studies have been done in Iran and other countries^[10-13]. In one study in Nepal, in 2004, incidence of hepatotoxicity was 8% and female gender was at high risk ($p = 0.219$, OR = 4.2) but hepatotoxicity was found more in younger patients (Less than 50 year) (6% vs 2%; $p = 0.368$; OR = 2.75). In Copenhagen study^[13] and Canada study^[14] as this study hepatitis was higher in older patients and female

gender. In Casnadaian study Hepatitis was seen 2 fold in female gender^[10]. Almost in the most studies incidence of hepatotoxicity was higher in female patients than male patients. It has not found why, this incidence is higher in female gender but until recently, it was thought that age greater than 35 year was the main risk factor for development of drug-induced hepatitis in patients receiving antitubercular medicine^[6]. Infection with hepatitis B, C and HIV are risk factors for the development of DIH during TB therapy^[6,10]. In this study four cases had chronic infection with HBV and only one patient had hepatitis C. Statistical analysis was not done because of limited numbers. Chronic alcohol use is a known risk factor for the development of anti-TB drugs hepatitis. None of our patients who developed DIH were found to use alcohol. Our study did not show a link between anti-TB DIH and nationality. Eighty three percent of our patients with DIH, were from Iranian population. The incidence of DIH is higher in slow acetylator than fast acetylator. It has been observed that the risk of DIH is also higher in the presence of specific Major Histocompatibility Component (MHC) class II.^[14] It was reported that, Asian people and for example Iranian population are slow acetylator and the risk of drug-induced hepatotoxicity is higher in these groups^[10]. Afghanian patients are also from Asian population and in our study frequency of the DIH between two groups of Iranian and Afghanian patients was equal.

CONCLUSIONS

A finding of an 8.5% incidence of hepatotoxicity is considerably high and indicating a significant increase in the risk of anti-TB DIH in our patients during recent years. On the basis of these findings, the antituberculosis drugs most likely develop hepatitis in female gender and older patients during therapy for active tuberculosis. Usually temporary withdrawal of the offending agents can completely cure antituberculosis drug-induced hepatotoxicity if these patients routinely (every two week in the initial 2 months of therapy) be evaluated for liver function tests.

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REFERENCES

1. Kopanoff, D.E., D.E. Sinderand G.J. Caras, 1988. Isoniazid-related hepatitis. Am. Rev. Respir. Dis., 117: 991-1001.

2. Schaberg, T., K. Rebhan and H. Lode, 1995. Risk factors for side effect of isoniazid, rifampicin, Pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Hepatology*, 21: 929-932
3. Frank, A.I., N.J. Binkin and N.J. Sinder *et al.*, 1989. Isoniazid hepatitis among pregnant women and postpartum Hispanic patients. *Public Health Rep.*, 104: 151-155.
4. Durand, F., J. Bernuau and D. Pessayre *et al.*, 1995. Deleterious influence of Pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculosis treatment including isoniazid. *Hepatology*, 21: 929-932.
5. Aliand, M. and R. Alavi-Naini, 2003. Tuberculosis radiculomyelitis: Review and presentation of five patients. *Intl. J. Tuberc. Lung Dis.*, 7: 1186-1190.
6. Ungo, R., J.D. Jones and D. Ashkian, 1998. Antituberculosis drug-induced hepatotoxicity. *Am. J. Respir.*, 157: 1871-1876.
7. Alavi-Naini, R., H.R. Kouhpayeh and B. Sharifi *et al.*, 2000. Hepatotoxicity due to anti-tuberculosis drugs in Zahedan. Abstract of 16th National Congress of Tuberculosis, Zahedan, Iran, pp: 68.
8. Shama, S.K., A. Balamurugan and P.K. Saha *et al.*, 2002. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antitubercular treatment. *Am. J. Respir.*, 166: 907-908.
9. Nolan, C.M., S.V. Goldberg and S.E. Buskin, 1999. Hepatotoxicity associated with isoniazide preventative therapy: A 7-years survey from a public health tuberculosis clinic. *JAMA.*, 281: 1014-1018.
10. Yee, D., C. Valiquette and M. Pelletier *et al.*, 2003. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am. J. Respir.*, 167: 1472-1477.
11. Emami, Z. and K. Tayeri, 2003. Side effects of antituberculosis drugs in tuberculosis patients in Isfahan, Iran. Abstract of 17th National Congress of Tuberculosis, Isfahan, Iran, pp: 84.
12. Shakya, R, B.S. Rao and B. Sherstha, 2004. Incidence of hepatotoxicity due to anti Tubercular medicine and assessment of risk factors. *Ann. Pharmacother.*, 36: 1074-1079.
13. Dssing, M., J.T. Wilcke, D.S. Askgaard and B. Nybo, 1996. Liver injury during anti Tbuberculosis treatment. *Tuber Lung Dis.*, 77: 335-340.
14. Bakayev, V., 2004. Pharmacogenetics and infectious diseases. Abstract of 12th Iranian Congress on Infectious Diseases and Tropical Medicine, Tehran, Iran, pp: 24-31.