TAJ June 2009; Volume 22 Number 1

ISSN 1019-8555
The Journal of
Teachers Association
RMC, Rajshahi

Original Article

The Changes in Levels of Serum Alanine Aminotransferase (ALT) During Anti Tubercular Treatment With 4FDC (Fixed Drug Combination)

I Mahmood[1], M Khalilur Rahman[2], M M Rahman Khan[2], M M Hoque Chowdhury[2], M Moazzam Hossain[3], Asif Iqbal[4]

Abstract

Tuberculosis (TB) is emerging as a major public health problem in Bangladesh, which now has the fifth highest burden of TB cases globally. Treatment of TB hampered with poor patient compliance and intolerance at least partly due to the adverse drug reactions, one of which is hepatotoxicity. Serum alanine aminotransferase level is an important indicator of such condition and impacts upon the continuation of anti tubercular treatment. A prospective randomized case study was conducted among 62 patients diagnosed as pulmonary tuberculosis receiving category I anti-TB drug treatment regimen in the DOTS (Direct observation therapy short-course) providing centers at Pabna district under DOTS during the period of July 2004 to July 2006. Category I comprised of four drugs (Rifampicin, Isoniazid, Ethambutol, Pyrazinamide) combination patients treated for initial 2 months, serum alanine aminotransferase levels were estimated at the first and fourth week of the treatment. Serum billirubin, HBsAg, Anti-HCV was also done to exclude some other liver diseases. 14(22.58%) patients were found to have no significant change, 34(54.84%) patients had their levels in the upper limits, 13(20.97%) patients had their levels in-between the upper limit and twice of the upper limit, while only 1(1.6%) patient crossed the level twice the upper limit.

TAJ 2009; 22(1): 106-110

Introduction

Tuberculosis (TB) is one of the most prevalent human infections and causes more deaths worldwide than any other infectious disease. Estimates show that approximately one third of the global population is infected with *Mycobacterium tuberculosis* and that 8 million new cases of TB occur each year, leading to nearly 3 million deaths annually. The World Health Organization (WHO) reports that TB is almost exclusively a disease of the developing world. 98% of TB-related deaths and 95% of TB cases occur in these countries. Bangladesh is one of the top five high burden countries in the world where TB is the second killer infectious disease next to diarrhea and about 0.6 million people are estimated to suffer from TB. Anecdotal evidence suggests that most Bangladeshi communities consider TB a greater threat than HIV/AIDS. NTP estimates that:

- There are 3,00,000 new cases annually; 1,37,000 are infectious, smear-positive cases;

[1] Associate Professor, Department of Medicine, Rajshahi Medical College, Rajshahi.
[2] Assistant Professor, Department of Medicine, Rajshahi Medical College, Rajshahi.
[3] Associate Professor, Department of Dermatology, Rajshahi Medical College, Rajshahi
[4] Indoor Medical Officer, Department of Medicine, Rajshahi Medical College, Rajshahi.

- The annual incidence of TB is 99 per 1,00,000 population for smear-positive cases and 221 per 1,00,000 for all forms;
- TB causes 70,000 deaths per year;
- The case detection rate is 41% (NTP, 2003);
- The cure rate of detected cases under DOTS is 84% (with 3,00,000 new cases annually, those cured comprise only 3.2% of all new cases);
- Incidence is believed to be higher in densely populated urban areas with poor living conditions eg. overcrowding;
- The female: male ratio is 2:5 among new smear-positive cases registered for treatment.

Despite the availability of effective chemotherapy TB is still a major health problem in most countries. The poor out-come was attributed to poor patient compliance, to primary multidrug resistance and to interruption partly due to adverse drug reaction (WHO, 1997). The most important step to ensure treatment is the patients' adherence to treatment are introduction of Direct Observation Treatment- Short course (DOTS) and use of fixed dose combination, as recommended by WHO. Despite the efficacy of anti-TB agents, hepatotoxicity from first-line drugs—isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA)—may result in drug(s) discontinuation, de novo liver disease, or exacerbation of pre-existing ones. Therefore, the aims of this study were to determine the incidence and pattern of anti-TB-DIH in patients with active pulmonary and extra-pulmonary T.B. Levels of serum alanine aminotransferase have been selected as the indicator for drug induced hepatotoxicity.

Material and Methods

A prospective randomized case study was carried out on 62 diagnosed pulmonary TB patients at the author's private practice chamber and receiving drugs from DOTS providing centers at Pabna districts during the period of July 2004 to July 2006. Inclusion criteria were pulmonary tuberculosis patients diagnosed as primary (category I). Cases of either sex with age above 14 years and patients who were under DOTS. Before attributing hepatotoxicity to anti-TB drugs, other causes of liver diseases were excluded by estimating: HBsAg, anti HCV, Alkaline phosphatase and abdominal ultrasound to asses for liver abscesses, focal lesions, or biliary obstruction. Serum alanine aminotransferase levels were recorded during initiation and after 4 weeks of treatment. Informed consent was taken.

Results

A total number of 78 patients were included of which 62 completed the study. 16 patients dropped out. Among the patients completed the study, 51 (82.26%) were male and 11 (17.74%) were female. The age range of male and female patients was 14-67 years.

All of 51 (100%) male patients and out of 11 female patients 9 (81.81%), yielding a total number of 60(96.77%) were in undernutritional group and lived in low socio-economic condition. In habitual status 42 (82.35%) of males were smoker, while none of female had that habit. 30 (58.82%) of male and 9 (81.81%) female patients making a total number of 39 (62.90%) were habituated with betel nuts. None of them consumed alcohol. Out of the treated patients 47(75.80%) experienced some unwanted effects (Table I). 14(22.58%) patients were found to have no significant change in their levels of serum alanine aminotransferase, 34(54.84%) patients had their levels in or near the upper limit, 13(20.97%) patients had their levels in-between the upper limit and twice of the upper limit, while only 1(1.6%) patient crossed the level twice the upper limit. The upper limit normal of serum alanine aminotransferase was 42U/L in this study.

Table- 1: Unwanted effects of anti- TB drugs

Symptoms	n = 62
Nausea	43 (69.35%)
Vomiting	4 (6.45%)
Anorexia	32 (51.61%)
Abdominal pain	3(4.84%)
Joint pain	0
Joint swelling	0
Muscle weakness	0
Visual disturbances	0
Rash	0
Vestibular disturbances	0
Peripheral neuropathy	0
Jaundice	1

Table- 2: Changes in levels of serum alanine aminotransferase (sex distribution)

Sex	change in the levels of serum alanine aminotransferase			
	No significant change	In or near the upper limit	In-between the upper and 2x upper limit	Above 2x upper limit
Male n=51	12(23.53%)	27(52.94%)	11(21.57%)	1(1.96%)
Female n=11	2(18.18%)	7(63.64%)	2(18.18%)	----------

Table- 3: Changes in levels of serum alanine aminotransferase (age distribution)

Change in the levels of serum alanine aminotransferase	14-25 years N14-25=4 (6.45%)	25-35 years N25-35=13 (20.97%)	35-45 years N35-45=21 (33.87%)	45-55 years N45-55=19 (30.65%)	55+ years N55=5 (8.65%)	Total N=62
No significant change	_	4(30.08%)	5(23.81%)	4(21.05%)	1(20%)	14(22.58%)
In or near the upper limit	2(50%)	5(38.46%)	13(69.90%)	13(68.42%)	1(20%)	34(54.84%)
In-between the upper and 2x upper limit	2(50%)	3(23.08%)	3(14.29%)	2(10.53%)	3(60%)	13(20.97%)
Above 2x upper limit	_	1(7.69%)	_	_	_	1(1.6%)

Table- 4: Changes in levels of serum alanine aminotransferase (personal habit)

Personal habits	N= 62	Change in the levels of serum alanine aminotransferase			
		No significant change	In or near the upper limit	In-between the upper and 2x upper limit	Above 2x upper limit
Non smoker Non betel nut chewer	6(9.68%)	2(23.53%)	3(33.33%)	1(16.67%)	_
Exclusive smoker	17(27.42%)	4(23.53%)	9(52.94%)	4(23.53%)	_
Both smoker and betel nut chewer	25(40.32%)	3(12%)	17(68%)	5(20%)	_
Exclusive betel nut chewer	14(22.58%)	5(35.71%)	5(35.71%)	3(21.43%)	1(7.14%)

Discussion

In 1998 the global TB program of WHO[1] established Global TB Research initiative to support related research. Research has been done by NGOs on Health System and Service Research that include studies on DOTS by community health workers[2], on microscopic diagnosis[3] and drug resistance surveillance [5]. However, TB is not life threatening if appropriate diagnosis (screening and case detection) and treatment are provided on time.

The WHO-recommended strategy of directly observed treatment, DOTS, has proven successful in many parts of the world and is considered cost-effective. Nevertheless, DOTS is still not used widely: Less than 15% of TB patients worldwide have been treated through DOTS. Furthermore, over the past decade, poly-, multi-drug-resistant forms of TB have become a significant threat to TB control. With increased use, misuse, and defaulting use, the number of multi-drug-resistant TB cases has risen dramatically and alarmingly. Compliance with anti-TB medication is essential to effective management. Two strategies to ensure compliance are DOTS and fixed dose combination (FDC). Compliance is affected by the adverse effects of drugs. Our study fully applied on DOTS strategy. Generally these drugs are well tolerated[4], may be associated with unwanted effects of different origin. Adverse drug reactions had been extensively studied and reviewed [5 6 7 8]

Hepatotoxicity is the most common cause of iatrogenic disease in anti-TB treatment. Anti-TB drugs can induce various degrees of hepatotoxicity, from a transitory asymptomatic rise in transaminases (which in extreme cases may lead to interruption of TB treatment) to acute liver failure (ALF) (when hepatic encephalopathy occurs and prothrombin time is <50%, usually leading to the need for liver transplantation or even to death). The frequency of hepatotoxicity in different countries varies from 1% to 10%. Hepatotoxicity due to isoniazid is most common, as isoniazid has been used for TB treatment (both latent and active TB) since 1952.[9] However, pyrazinamide is the most hepatotoxic among essential anti-TB drugs, in particular at doses >30

mg / kg /day. Rifampicin has a low hepatotoxicity. However, due to its enzyme inducer effect it may increase the toxicity of isoniazid when the two drugs are combined.[6] Mild hepatotoxicity (a rise in transaminases of three to five times the normal level) does not require any modification in treatment, only more frequent visits and laboratory tests are needed. In cases of moderate hepatotoxicity (a rise in transaminases level between five and 10 times the normal) chemotherapy should be stopped as soon as possible, controlling for the risk of ALF should be started and patients should be hospitalized if necessary. However, the risk of ALF is low.

The present prospective study was undertaken to demonstrate extent of elevation of level of alanine aminotransferase, a vital marker of drug induced hepatotoxicity (DIH) during anti-tuberculosis drug treatment regimens under DOTS. In our study the predominance of male patients may be due to the chance of contact with T.B. patients and habit of smoking . Most of the subjects are from low socioeconomic class. It supports malnutrition to be a risk factor for tuberculosis. The elevation of enzyme level does not show any significant correlation with age or sex. As predisposing risk factors for adverse effects age, sex, nutritional status, socioeconomic condition and habit were observed. Smoking and betel nut chewing seem to have association with increased risk of hepatic enzyme elevation. Serum glucose was estimated before the treatment initiation with the aim to assess hyperglycemia as predisposing risk factor for TB or adverse drug events involving hepatic or renal dysfunction. It was found to be normal in all the cases. Most of the TB patients completed treatment without any significant adverse effects, however data[9] showed that side effects occur in 57.8% patients, while it was observed 75.80% of patients experienced some sort of unwanted effects. Unwanted effects were minor in nature, only 1.6% exhibited major adverse effects e.g. hepatitis in our study, while Shakya et al.[10] reported an 8% incidence of hepatotoxicity. Serious adverse effects require documented change in therapy or hospitalization. If minor adverse effects developed patients should continue with reduced doses and receive symptomatic treatment, if major side effects develop the offending drug should be stopped (WHO, 2003). The withdrawal of treatment due to major adverse effect e.g. hepatitis in 1.8 to 6.0% patients [11 12].

It is very uncommon to have adverse reactions to a single anti-TB drug, but such reaction with more than one is very small[12], while adverse reactions to multiple drugs were reported [13 14]. In our observation, major side effects as hepatitis developed in 2.94%, that was similar to the report (Dutt et al., 1983)[4]

During the initial phase of 4-drug combination treatment regimen side effects were reported in 22.4% of patients [5 23].

In our study 98.4% patients exhibited increase of ALT that was not in agreement with other reports [15 16]. Fattinger et al. (1997) [17]reported eight times increase of ALT, while we observed more than 2 times increase in one patient. Incidence of hepatitis was reported in 7.7% with combination of use of rifampicin and pyrazinamide [16], compared to drug used alone viz. with pyrazinamide 15%, with isoniazid 7%, with rifampicin 1.5% and hepatitis was suggested due to pyrazinamide rather than isoniazid or rifampicin [18]. Isoniazid and pyrazinamide combination administration was associated with an increased mortality in patients with hepatitis. Hepatotoxic potential of rifampicin or pyrazinamide is far less in the doses used in the modern day short-course regimen. We did not observe such results in our study.

Risk factors for anti-TB drugs-induced hepatitis had been studied [10 19 20 21]. Case control studies were undertaken to assess the risk factors for hepatotoxicity with variable like age, sex, BMI, acetylator status, extent of disease, protein, alcohol intake . In our study hepatotoxicity developed in younger males who were given PZA that also is observed . As predisposing risk factors there is no suggestive finding in our observation related to age and habit, however it was observed that TB is more common in male; in poor nutritional and low socio-economic status. In our study some of the markers of acute hepatitis could not be assessed due to lack of resources.

Conclusions

Anti-TB-DIH is not uncommon, can be fatal, and is significantly more frequent in patients with pre-

existing liver disease, malnourished patients, and those with hypoalbuminemia. Also, extensive or open pulmonary TB may have a role in predisposing patient to hepatotoxicity. In our study the 4 FDC regimen was found to be well tolerated. Still close follow-up, early recognition, and the immediate withdrawal of the causative agent are essential to prevent progression and allow the liver to heal. This topic is of higher importance in the developing countries where both TB and liver diseases are endemic.

References

1. WHO. Standardized treatment regimens. Treatment of tuberculosis. Guide lines for national programs, WHO/ TB. 2nd ed. 1997, pp 23-31.
2. Chowdhury AM. Chowdhury S. Islam MN, et al. Control of tuberculosis by community health workers in Bangladesh. Lancet. 1997; 350: 169-72.
3. Vandeun A. Portalels F. Limitation and requirement for quality control of sputum smear microscopy for AFB. Int J Tuberc Lung Dis. 1998; 2: 756-57.
4. Dutt AK. Moers D, Stead WW. Undesirable side-effect of isoniazid and rifampicin in largely twice-weekly short-course chemotherapy for tuberculosis. Am Rev Respir Dis. 1983; 128: 419-24.
5. Haque MA, Golam Nabi PD. Achievements of national TB control program. Bangladesh Med Res Counc Bull. 1999; 25: 71-82.
6. Mohan A, Sharma SK. Side effects of anti-tuberculosis drugs. Am J Respir Crit Care Med. 2004; 169: 882-83.
7. Resi D, Gangliotti C, Moro ML. Side effects of anti-tuber-culosis therapy. Am J Respir Crit Care Med. 2004; 169: 542.
8. Maddrey WC. Drug-induced hepatotoxicity. J Clin Gastro-enterol. 2005; 39: S83-89.
9. Ormerod LP, Horsfield N. Frequency and type of reactions to anti-tuberculosis drugs: observation in routine treat-ment. Tuberc Lung Dis. 1996; 77: 37-42.
10. Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from anti-tuberculosis drugs: a case-control study. Thorax. 1996; 51: 132-36.
11. Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to anti-tubercular medicines and assessment of risk factors. Ann Pharmacother. 2004; 38: 1074-79.
12. Girling DJ. The hepatictoxicity of antituberculosis regi-mens containing isoniazid, rifampicin and pyrazinamide. Tubercle. 1978; 59: 13-32.
13. Smith JM, Zirk MH. Toxic and allergic drug reaction during the treatment of tuberculosis. Tubercle. 1961; 42: 287.
14. Mathus KC, Jain VK, Gupta PP, Jain A. Multiple drug reaction during chemotherapy of tuberculosis. Indian Med Gazette. 1979; 8: 274.
15. Thamari JP, Gupta VK. Hypersensitivy of multiple drug in treatment of pulmonary tuberculosis. Indian J Tuberc. 1981; 28: 143.
16. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampicin and pyrazina-mide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. Int J Tuberc Lung Dis. 2002; 6: 995-1000.
17. Lee WM. Drug-induced hepatotoxicity. N Engl J Med. 2003; 349: 474-85.
18. Fattinger K, Braunschweig S et all, Liver injury under tuberculostatic treatment. Schweiz Rundsch Med Prax. 1997; 86: 626-29.
19. Schaberg T, Rebhan K, Lode H. Risk factors for side-effect of isoniazid, rifampicin and pyrazinamide in patients hos-pitalized for pulmonary tuberculosis. Eur Respir J. 1996; 9: 2026-30.
20. Fauzi AR, Shah A, Rathor MY, Satwi S, Risk factors for antituberculous drugs-induced hepatitis: a prospective survey from a chest clinic in a general hospital. Med J Malaysia. 2004; 59: 72-77.
21. Marti L, Del Olmo JA, Tosca J, et all, Clinical evaluation of drug induced hepatitis. Rev Esp Enferm Dig. 2005:97 258-65.
22. Tost JR, Vidal R, Cayla J, Diaz-cabanela D, Jimenez A, Broquetas JM. Study group for severe hepatotoxicity due to anti-tuberculosis Drugs. Int J Tuberc Lung Dis. 2005; 9: 534-40.
23. Okhawa K, Hasiguchi M, Ohno K, et al, Risk factors for anti tuberculosis Chemotherapy induced hepatptoxicity in Japanese pediatric patients. Clin Pharmacol Ther. 2002; 72:220-26.
24. Ohkawa K, Hashiguchi M, Ohno K, Kiuchi C, Takahashi S, Kondo S, Echizen H, Ogata H. Risk factors for anti-tuberculosis chemotherapy-induced hepatotoxicity in Japanese pediatric patients. Clin Pharmacol Ther. 2002; 72: 220-26.
24. Nahar et al Adverse effects of two anti-tubercular drugs Vol. 1, No. 2, Bangladesh Journal of Pharmacology December 2006 P 51- 56.

All correspondence to:
Iftekhar Mahmood
Associate Professor, Department of Medicine
Rajshahi Medical College, Rajshahi