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Original Research

Evaluation of anti-tuberculosis induced adverse reactions in hospitalized patients

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ABSTRACT*

Background: Tuberculosis has been one of the common diseases of human communities. Besides of disease-related complications, there are serious adverse reactions due to Anti-tuberculosis (Anti-TB) drug therapy.

Objectives: To assess the rate of Adverse Drug Reactions (ADRs) induced by Anti-TB drugs in the infectious disease department for a period of one year. To detect serious and preventable recognized ADRs.

Methods: All patients admitted to the infectious disease department at Imam tertiary teaching hospital in Iran who received Anti-TB drugs from July 2001 to July 2002 entered the study. These patients were monitored for ADRs during hospital stay. The ADRs were then classified based on patients and reactions factors. The causality and severity of the reactions were determined using Naranjo algorithm and Hartwig questionnaire, respectively.

Results: During the study period, 83 patients received Anti-TB drugs; of them 44 developed at least one ADR. Total number of 81 ADRs was detected in this study. ADRs were recognized as the major cause of hospital admission in 11 (13.3%) patients. The most frequent system-organ class affected by ADRs was Liver and biliary system (37%). Hepatitis was observed in 21 (25.3%) patients leading to death in two patients.

Conclusion: Anti-TB drugs could cause significant adverse effects both in quantity and severity leading to hospitalization, prolonged hospital stay and even death. More attention is needed to prevent these reactions.

Keywords: Tuberculosis. Inpatients. Adverse Drug Reaction Reporting Systems. Drug Toxicity. Iran.

RESUMEN

Antecedentes: La tuberculosis ha sido una de las enfermedades comunes de la humanidad. Además de las complicaciones relacionadas con la enfermedad, existen efectos adversos graves debidos al tratamiento antituberculoso (Anti-TB).

Objetivos: Evaluar la tasa de reacciones adversas a medicamentos (RAM) inducidas por medicamentos Anti-TB en el departamento de enfermedades infecciosas durante el periodo de un año. Detectar las RAM reconocidas como graves y prevenibles.

Métodos: Entraron en el estudio todos los pacientes admitidos que recibían medicamentos Anti-TB en el departamento de infecciosos del Hospital Universitario terciario Iman en Irán entre julio 2001 y julio 2002. Se monitorizaron las RAM de estos pacientes durante su estancia hospitalaria. Se clasificaron las RAM en función de los factores de los pacientes y de las reacciones. Se determinaron la causalidad y la gravedad de las reacciones adversas utilizando el algoritmo de Naranjo y el cuestionario de Hartwig, respectivamente.

Resultados: Durante el periodo de estudio, 83 pacientes recibieron medicamentos Anti-TB; de ellos, 44 desarrollaron al menos una RAM. El número total de RAM detectadas en este estudio fue de 81. Las RAM se reconocieron como la causa principal de ingreso hospitalario en 11 (13,3%) pacientes. El órgano-sistema más frecuentemente afectado fue el hígado y el sistema biliar (37%). Se observó hepatitis en 21 (25,3%) de los pacientes, y condujo a la muerte en dos casos.

Conclusión: Los medicamentos Anti-TB podrían causar significativos efectos adversos tanto en cantidad como en gravedad, conduciendo a hospitalización, prolongación de la estancia e incluso la muerte. Se necesita prestar más atención para prevenir estas reacciones.

Palabras clave: Tuberculosis. Pacientes hospitalizados. Sistemas de comunicación de reacciones adversas. Toxicidad de medicamentos. Irán.

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(English)

INTRODUCTION

Tuberculosis has been one of the common diseases in human communities during the past 40 years. It has been reported by World Health Organization (WHO) that one third of the world's population is infected with Mycobacterium tuberculosis resulting in 8.4 million new tuberculosis cases in 1999.[1] This high incidence of infection has caused a large number of morbidity and mortality which is partly due to serious adverse reactions induced by Anti-TB drugs.[2,3]

The frequency and nature of Anti-TB induced ADRs have been the matter of concern in many communities. One of the serious ADRs detected in these studies is hepatotoxicity. There are differences in reported rate of hepatotoxicity induced by Anti-TB drugs in different studies.[4-6] This reaction could be affected by the genotype of patients receiving these drugs e.g. rapid-acetylator patients are more susceptible for isoniazid induced hepatotoxicity. Studies show that the risk of hepatotoxicity in patients from India is higher than those reported in West (11.5% versus 4.3%).[7] Regarding the difference reported between Asian and Western people in developing Anti-TB induced hepatotoxicity, it is necessary to detect the rate of Anti-TB induced ADRs with emphasize on hepatotoxic reactions in Iranian patients, since it could be helpful to revise the therapeutic protocols.

To the best of our knowledge this is the first study for assessing Anti-TB induced ADRs in Iranian patients.

METHODS

This descriptive study was conducted in an infectious disease department of a 1200 bed teaching hospital, from July 2001 to July 2002. All patients diagnosed with pulmonary TB entered the study. These patients routinely received combination of four anti-TB drugs (Isoniazid, Rifampin, Pyrazinamide and Ethambutol). Hepatitis was defined as increased liver enzymes more than five times the base line accompanied with clinical symptoms including jaundice, nausea, vomiting, abdominal pain and anorexia. Patients with chronic hepatic illnesses such as cirrhosis, chronic hepatitis and acute viral hepatitis were excluded from the study. Patients' demographics, disease history, drug history and final diagnosis were recorded. All the patients who received anti-TB drugs were monitored for adverse drug reactions. The ADR definition used in this study is that of the WHO "Any noxious or unintended response to a drug, which occurs at doses normally used in human for the prophylaxis, diagnosis or treatment of disease or for the modification of physiological function".[8]

Detection and Monitoring was done by interviewing patients, reviewing laboratory tests and medical charts. Consulting with physicians about the patients' clinical problems and recorded ADRs was done routinely. A yellow card, the Form used for ADR reporting to national Pharmacovigilance Center, was filled for each ADR detected in the study.

To asses the probability, severity and preventability of the reactions, Naranjo algorithm[9], Hartwig questionnaire[10] and Shumock questionnaire[11] were used respectively.

RESULTS

During the study period 83 patients were diagnosed with positive TB. These patients were put on routine treatment protocol. Of these patients, 44 (53%) developed at least one adverse drug reaction. Total number of 81 adverse reactions detected in this study. The 44 patients with ADR consisted of 23 females and 21 males.

Occurrence of adverse reactions led to prolongation in hospital stay for 26 (59%) patients. The rate of adverse reactions was various in different age groups. It does appear that with Anti-TB drugs used in this study the rate of ADRs increases with increased age (Table 1)

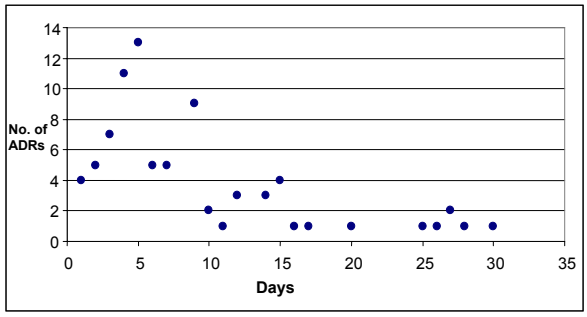

Figure 1. Number of ADRs occurred in different days of Anti-TB therapy

Table 1. Anti-TB induced adverse reactions in different age groups.

Age group	*Patients*	*Patients with ADR*
0-10 years	0	0
11-20 years	9	6
21-30 years	19	8
31-40 years	21	8
41-50 years	13	8
51-60 years	7	3
> 60 years	15	12
	83	44

The most frequent system-organ classes affected by ADRs were Liver and biliary system (37%) and gastrointestinal system (21%) (Table 2). The most serious adverse reaction was hepatitis (25.9%), leading to death in two patients (Table 3). In this study, 30 (36.1%) patients have shown the raise in liver transaminases. However only 3 patients developed increased enzymes level less than 3 times of the base line. Furthermore these patients didn't show any clinical or biochemical evidence of hepatotoxicity. Increasing in plasma uric acid was observed in 3 patients (3.7%) due to Pyrazinamid. These reactions occurred in average 26.7 days after the beginning of treatment and followed by arthritis. After discontinuing of Pyrazinamid, the level of uric

acid returned to normal range (2.1-8.5 mg/dl) in 10 days. Isoniazid caused reactions such as constipation (17.3%) and peripheral neuropathy (6.2%), while Rifampin was the major cause of headache (8.7%), rash and pruritus (4.9%) and diarrhoea (3.7%).

Table 2. Frequency of system-organ classes involved in ADRs induced by Anti-TB drugs.

Site of Reactions	Frequency	%
Liver and biliary system disorders	30	37
Gastro-intestinal system disorders	17	21
Central and peripheral nervous system disorders	12	14.9
Metabolic and nutritional disorders	7	8.6
Skin and appendages disorders	4	4.9
Urinary system disorders	4	4.9
Musculo-skeletal system disorders	3	3.7
Platelet, bleeding and clotting disorders	2	2.5
Vision disorders	2	2.5
Total	81	100.0

Table 3. Type of detected ADRs induced by Anti-TB drugs.

Reaction	Frequency	%
Hepatitis	21	25.9
Constipation	14	17.3
Increased Liver Transaminases	9	11.2
Hyperglycemia	7	8.7
Headache	7	8.7
Peripheral Neuropathy	5	6.2
Dysuria	4	4.9
Rash	4	4.9
Diarrhea	3	3.7
Increased Uric Acid	3	3.7
Vision abnormality	2	2.4
Prolonged PT	2	2.4
Total	81	100.0

The only adverse reaction suspected to be induced by Ethambutol was vision abnormality such as blurred vision and burning eyes observed in two patients (2.4%).

The main action taken in patients with detected ADR was discontinuation of drug regimen (34.5%). This action mainly was taken when hepatotoxicity and/or hyperuricemia were detected. In 21% of patients with detected ADR, Anti-TB drug regimen was continued with symptomatic therapy. In 7.4% of the cases a decrease in Anti-TB drug regimen was performed. There was no specific treatment for alleviating the adverse reactions in 33.4% of cases. These reactions mainly were those which didn't cause a serious problem for patients, such as headache or constipation.

The outcome of 71.6% of adverse reactions in this study was definite improvement. Anti-TB drugs were discontinued after observing adverse reaction in 34.5% of patients. In 21% of reactions symptomatic treatment was performed.

The causality assessment of ADRs revealed that 7 (8.6) cases were detected as certain, 35 (43.2%) as possible and 39 (48.2%) as probable reactions (Table 4).

Table 4. Causality of ADRs induced by Anti-TB drugs according to Naranjo algorithm

	Percent	Frequency
Probable	48.2	39
Possible	43.2	35
Certain	8.6	7
	100.0	81

Evaluation of the severity of ADRs indicated that most of the ADRs detected had severity in level 1 (38.2%) and 4a (34.5%). (Table 5)

Table 5. Severity of ADRs induced by Anti-TB drugs

Severity	Number	Percent
Level 1	31	38.2
Level 2	2	2.5
Level 3	13	16.2
Level 4a	28	34.5
Level 4b	4	4.9
Level 5	1	1.9
Level 6	0	0.0
Level 7	2	2.5

No adverse effect of anti-TB drugs were detected in the first 24 hours of drug therapy. The majority of adverse reactions (71.6%) were detected in the first 10 days of drug therapy (Figure 1). The frequency of adverse reactions in days 10-20 of drug therapy decreased to 19%. In days 21-30 the rate of ADRs detected was 21.4%. The adverse reactions that caused hospitalization mainly occurred on days 21-30 of drug usage.

DISCUSSION

Among 83 patients entered the study, 44 (53%) patients showed at least one adverse reaction. This relatively high percentage of occurring adverse reactions indicates that there is a need for more evaluation of susceptibility of Iranian patients for developing Anti-TB induced ADRs. Daphne Yee et al. conducted a study to estimate the incidence and risk factors of major side effects from first-line anti-TB drugs.[12] They evaluated 430 patients treated with Anti-TB drugs between 1990 and 1999. The results of the study showed that the incidence of all major adverse effects was 1.48 per 100 person-months of exposure (95% confidence interval [95% CI], 1.31 to 1.61) for Pyrazinamide, compared with 0.49 (95% CI, 0.42 to 0.55) for isoniazid, 0.43 (95% CI, 0.37 to 0.49) for Rifampin, and 0.07 (95% CI, 0.04 to 0.10) for Ethambutol. The occurrence of any major side effect in that study was associated with female sex (adjusted hazard ratio, 2.5; 95% CI, 1.3 to 4.7), age over 60 years (adjusted hazard ratio, 2.9; 95% CI, 1.3 to 6.3), birthplace in Asia (adjusted hazard ratio, 2.5; 95% CI, 1.3 to 5.0), and human immunodeficiency virus–positive status (adjusted hazard ratio, 3.8; 95% CI, 1.05 to 13.4). Among these risk factors age over 60 years and birth place in Asia may be considered as interactive factors in inducing high rate of ADRs in our study. The results of this study as well as previous reports show that with increase of age, the frequency of ADRs will be increased.

In our study the major cause of admission was adverse drug reactions in 13.6% of patients. In

similar study conducted in Iranian population hospitalized in general ward, ADR has been reported as the cause of admission for 8% of patients.[13] In another study conducted for detecting Anti-Infectives induced adverse reactions in Iranian hospitalized patients, the total rate of hospitalization because of an ADR was estimated as 2.2%.[14] These results suggest that Anti-TB drugs may cause more serious ADRs resulting in hospitalization comparing with other drug classes used in infectious and general wards which were subject of two other studies.

Hepatitis was observed in 21 patients (25.9%), leading to death of 2 patients. It has been estimated that 10%-20% of INH recipients develop elevated liver enzymes.[15] However, In case of mild, subclinical hepatic damage, the reaction do not progress to overt hepatitis and recover completely despite of continuing INH therapy. In contrast, if clinical symptoms occur, severe hepatocellular toxicity could be happened which is associated with a higher fatality rate than that of patients whose INH was discontinued immediately. The exact mechanisms responsible for INH hepatotoxicity are still unclear. Slow or fast acetylation of INH in the liver has been the matter of controversy as a probable mechanism for INH hepatotoxicity. Previously, it was believed that rapid acetylators might be at a greater risk for INH hepatitis than slow acetylators. Monoacetylhydrazine, the hepatotoxic metabolite of Isoniazid, is formed more rapidly in fast acetylators comparing with slow acetylators. In contrast, rapid acetylators also would eliminate this compound at a faster rate, and this should equalize the risk of toxicity between slow and fast acetylators. One study demonstrated a different incidence of hepatitis between Asian males and females. Because both groups were fast acetylators, this study suggested that hepatitis is probably caused by factors other than acetylators' phenotype. Thus it does appear that acetylators' status alone does not explain the development of INH hepatitis. However, the results of this study suggest that more studies are needed to evaluate the risk of increased rate of INH induced hepatitis among Asian people.

Some evidence initially suggested that concurrent use of INH and Rifampin might lead to a greater incidence of hepatotoxicity. It is believed that Rifampin can induce the metabolism of INH to hepatotoxins. A meta-analysis conducted by Steele et al. looking at the incidence of hepatitis in all studies between 1966 and 1989 using regimens contained INH without Rifampin, Rifampin without INH and regimens containing both drugs, revealed that the incidence of clinical hepatitis was greater in regimens containing both INH and Rifampin (2.7%) versus regimens of INH alone (1.6%). The authors suggested that this effect was additive, not synergistic, therefore the use of the two drugs together, is not contraindicated. However, caution should be used in high-risk groups such as the elderly, alcoholics, those taking additional hepatotoxic agents, and those with pre-existing liver disease. If transaminase serum levels rise by using Anti-TB drugs, normal serum levels usually will be achieved after three to six weeks from the beginning of therapy. On time diagnosis of liver toxicity caused by Anti-TB drugs will reduce the rate of mortality of patients. The death rate due to liver damage will be about 50% if the drug is continued after increasing transaminase enzymes up to 3 times of base line. But with on time discontinuation of drug regimen, this rate could be decreased to 10 %.[16]

Increase serum level of transaminases mainly is due to Isoniazid. In the other hand Rifampin usually causes cholestasis, which leads to raise alkaline-phosphatase and bilirubin. Liver toxicities can be the major side effect of all three main anti-TB drugs, Isoniazid, Rifampin and Pyrazinamid.

Generally, in order to decrease the risk of liver damage of these drugs the following points can be helpful:

- Recording liver enzymes baseline levels before prescribing the Anti-TB drugs
- Monitoring the transaminase serum levels in patients over 20 years of age. This monitoring should be performed twice a week in the first two weeks and once a week in the next two months.
- Discontinuing the drug regimen immediately after raising the enzymes 3 times of the baseline.
- Avoiding concurrent use of Anti-TB drugs with CYTP450 inducers.
- Avoiding concurrent use of Anti-TB drugs with other hepatotoxic medications.

CONCLUSION

In conclusion, Anti-TB drugs could cause significant adverse effects both in quantity and severity. These reactions may lead to hospitalization, prolonged hospital stay and even death. Asian People may develop more frequently severe adverse reactions, such as hepatitis, induced by this class of medicines. This result suggests that the protocol of Anti-TB therapy for Asian population may need some revision to prevent fatal hepatotoxicity. To confirm this hypothesis many more studies with larger population is needed.

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