Research Article

A study on adverse drug reactions to first line antitubercular drugs in DOTS therapy

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ABSTRACT

Background: Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis,* is the second leading infectious cause of death in the world. The objective was to study the demographic details of the tuberculosis patients experiencing adverse drug reactions (ADRs) and to identify the frequency of adverse drug reactions.

Materials and Methods: : It was a prospective observational study conducted in pulmonology department of Institute of Chest Disease, Govt. Medical College, Kozhikode, Kerala, India. All the TB patients admitted at the directly observed treatment, short course (DOTS) Center at Medical College Hospital were enrolled and were monitored for ADRs. The causality and severity of the reactions were determined using Naranjo algorithm and Hartwig questionnaire, respectively.

Results: A total of 511 tuberculosis patients who were on DOTS therapy were enrolled for the study. Out of 511 patients, 93 patients (18.20%) developed adverse drug reactions. The higher numbers of ADRs were observed in males (68.81%) and the remaining (31.18%) was observed in female. Diabetes mellitus (41.02%) was the most common comorbidity. Most of the ADR occurred in the intensive phase (85.71%) of treatment. It was observed that pulmonary TB (55.18%) was more common than extra pulmonary TB. Majority of adverse drug reactions were gastrointestinal (GI) problems (38.09%). The most serious ADR was hepatitis. Isoniazid was the major drug which caused 34.40% of adverse drug reactions.

Conclusion: About 17.02% people developed different type of ADRs during the study period. As a pharmacist we have the liability to support the patients during the period of antitubercular treatment. These ADR may steer the patient to make a judgment for stopping the medications and finally the occurrence of drug resistance and an amplified healthcare cost. If a proper educational system is implemented, most of the patients may report their ADR and thereby we can improve the patient adherence and therapeutic outcome.

Key words: Tuberculosis, adverse drug reactions, isoniazid, rifampicin, ethambutol, pyrazinamide.

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INTRODUCTION

Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis*, is the second leading infectious cause of death in the world. The World Health Organization (WHO) declared TB as a global health emergency in 1996.[1] It is a major public health problem in India. India accounts for one-fifth of the global TB incident cases and topping the list among high burden countries.[2] It is estimated that annually around 330,000 Indians die due to TB.[3] As per WHO estimate, 9 million people globally develop active TB and 1.7 million die of it annually. In India, it is estimated that nearly 2 million people develop active disease every year and about 0.5 million die from it.[4]

Tuberculosis is the most rampant communicable disease in the developing countries.

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The world adopts Directly Observed Treatment Short course (DOTS) for TB control thought the national TB control programs in different countries and is making good progress.[5] Antitubercular treatment (ATT) exhibit greater level of efficacy with a satisfactory degree of toxicity; however combination treatment may produce severe adverse events.[6] There may be considerable morbidity, even mortality, particularly with drug-induced hepatitis. These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations.[7] Alternative agents may have greater problems with toxicity, and are often less effective, so that treatment must be prolonged. Adverse drug reactions lead to decrease in patient compliance and adherence.[8] So close monitoring of adverse drug reactions and its effective management is needed. Pharmacovigilance activities can help in obtaining real information of safety and effectiveness of medicine when they are being used in the population.[9]

This study aims to explore and observe adverse drug reactions of first line antitubercular drugs in DOTS therapy. Good patient adherence to the treatment regimen is the foundation stone to effective antitubercular therapy. Noncompliance is cited as the major problem to the control of the tuberculosis at the level of public health and finally which escort to the drug resistance in case of TB.[10]

MATERIALS AND METHODS

Study setting

A prospective observational study was conducted in Institute of chest disease, Govt. Medical College, Kozhikode, India. The study was carried out in the Pulmonology department of Institute of Chest Disease, Kozhikode. Ethical Committee approval was obtained from the Institutional Ethics Committee (IEC) of the same Institute.

Patients and data collection

All the TB patients diagnosed with active TB from July 2013 to November 2013 were enrolled for the study as per the study criteria by taking their informed consent and were monitored for adverse drug reactions till January2014. (DOTS therapy is a 6 month course. Hence the patients enrolled in July 2013, completed their treatment in December 2013 or January 2014. Remaining patients completed their intensive phase of therapy). These patients routinely received combination of four anti-TB drugs (isoniazid, rifampicin, pyrazinamide and ethambutol).

Detection and monitoring of adverse drug reaction was done by interviewing patients, consulting with physicians about the patients' clinical problems, reviewing laboratory test and medical records. Patients with chronic hepatic illnesses such as cirrhosis, chronic hepatitis and acute viral hepatitis were excluded from the study (because this will interfere with adverse drug reaction) Both category 1and category 2 patients are included in this study. Patients with multidrug resistant TB (MDR TB), pregnant and lactating people and children below 10 years were also excluded from the study.

Statistical analysis

Data was analyzed using SPSS version 16.0. Demographic details of the patients were analyzed by using descriptive statistics. A p value < 0.05 was used as statistically significant. Categorical variables such as patient's gender, age, type of tuberculosis, drug causing ADR, type of ADR, causality and severity expressed in frequencies and percentage.

RESULTS

Demographic details

A total of 511 patients received antitubercular drugs during the study period. Out of 511 patients 93 patients (18.19%) developed 105 adverse drug reactions. Among 93 patients,

four of them developed more than two adverse drug reactions. Among 511 patients, 102 patients completed their treatment. Out of 102 treatment completed patients, there were 19 adverse drug reactions Remaining patients completed their intensive phase of therapy. Most of the ADR occurred in the intensive phase (85.71%) of treatment, because intensive phase of therapy included more number of drugs compared to continuous phase of therapy.

Out of 105 ADRs, most of them occurred within a week of treatment. One ADR occurred on the first day of the treatment. Nineteen ADRs were seen in treatment completed patients. Among 93 patients with ADRs, 70 patients (75.26%) were from category 1 and 23 patients (24.73%) were from category 2. Among 93 patients with ADRs, majority of patients (20%) were in the age group of 50-70 years. The mean age was found to be 44.92 (± 17.22 years).

Out of 93 patients with ADR, 63 were males and 29 were females. More numbers of ADRs were observed in males (68.81%). Out of 93 patients, 28 patients (30.10%) had 39 co-morbid conditions. Diabetes, HIV, hypertension and asthma co-infections were detected in 16 (41.02%), 2 (5.12%), 13 (33.33%), 18 (20.51%) patients respectively. Diabetes was the most common comorbidity. At the habitual history 21 (22.80%) were smokers and 17 (18.22%) of them had the history of alcohol consumption. The most common ADR developed in alcoholics was hepatitis. 12 (12.90%) patients who developed adverse drug reactions had a previous history of allergic reaction to certain medicines and food.

Type of tuberculosis

Among 511 patients, 282 cases were pulmonary tuberculosis and 229 cases were extrapulmonary tuberculosis. 58 patients with pulmonary tuberculosis and 35 patients with extra pulmonary tuberculosis developed different types of ADRs due to ATT. From this it was observed that pulmonary tuberculosis is more common than extra pulmonary tuberculosis and patient with pulmonary tuberculosis had the more chance of developing adverse drug reaction. Occurrence of adverse drug reactions in pulmonary tuberculosis patients was 20.56% and extrapulmonary tuberculosis was 15.28%. Among pulmonary tuberculosis patients, patients with sputum positive (54%) developed more number of adverse drug reactions.

Specific drug causing ADRs

39.78% patients developed adverse drug reaction due to ATT. Isoniazid was the main drug causing the adverse drug reaction (35.48%). (Most of the patients developed gastrointestinal (GI) upset during the treatment period. We couldn't distinguish the drug that can cause GI upset, and it is also considered as adverse drug reaction due to ATT (Table 1).

Reported Adverse Drug Reactions

Table 1: Drugs involved in the ADR

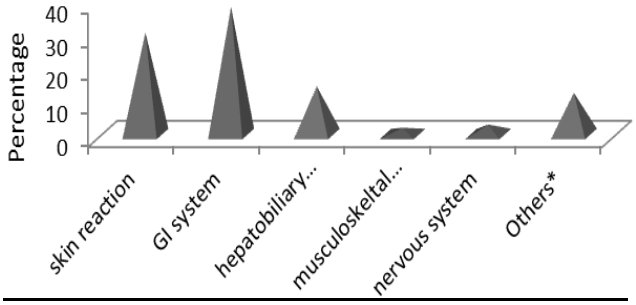
Name of the drug	Number of patients	Percentage
Isoniazid	33	35.48
Rifampicin	13	13.97
Ethambutol	1	1.07
Pyrazinamide	5	5.38
Isoniazid + rifampicin	4	4.30
ATT(Antitubercular treatment)	37	39.78

93 patients experienced a total number of 105 adverse drug reactions, skin reactions being the major. Hepatitis was the serious adverse drug reaction in our study because patients who developed with hepatitis needed prolonged hospital stay (Figure 1).

Causality assessment (naranjo scale)

As per Naranjo's scale, majority of the reactions were probable (68.57%), followed by possible (20%). There were no definite reactions

Figure 1: System wise distribution of ADRs



* Others - visual problem, hearing problem and fever

Severity scale (using Modified Hartwing & Siegel Scale)

Out of 105 adverse drug reactions, 33(68.57%) were moderate, 72(31.42%) were mild reactions and there were no severe reactions reported as per Hartwig & Siegel's scale.

DISCUSSION

A total of 511 tuberculosis patients who were on DOTS therapy were enrolled for the study. Out of 511 patients, 93 patients developed 105 ADR (18.20%).Among 93 patients, four of them developed more than two adverse drug reactions. Tak D K [11] et al conducted a study on " Safety evaluation of antitubercular therapy under revised national tuberculosis control programme in India"in which the incidence of ADR was found to be 17.02%.

Among 105 reported adverse drug reactions, the highest numbers of ADRs were observed in males (68.81%) and the remaining (31.18%) was observed in female. A study conducted by Sainul Abideen P et al reveals [9] that the pervasiveness of TB is more in males than in the females in the ratio of 7:3. Also the National Tuberculosis Program (NTP) summarized as the ratio of occurrence of TB between male &female were 5:2.[11] Most of the literature says that the female gender is the one of the predisposing factors for ADRs.[12] But in the present study, males developed more ADRs, and it could be because more numbers of males were included in the study.

Majority of adverse drug reaction was GI problem (38.09%), followed by skin reaction (30.48%), then hepatotoxicity (14.28%). The most frequent organ system affected by ADR was GI system. Most of the gastritis occurred within the first week of therapy. The most serious ADR was hepatitis. Only 3 patients developed increased enzyme level (ALT) greater than 3 times of the base line. Increasing plasma uric acid was observed in 2 patients (1.90%), due to pyrazinamide. They experienced severe joint pain. After discontinuing pyrazinamide, uric acid returned to normal range (2.1-8.5 mg/dl) in 10 days.

The only ADR suspected to be induced by ethambutol was vision abnormality such as blurred vision and burning eyes observed in only one patient. One patient each developed hearing problem (0.95%) & visual problem (0.95%). Isoniazid is the major drug which caused 35.48% of adverse drug reactions. Major side effect of the ATT was skin rash, GI problem, hepatitis and fever. A study conducted by Sainul Abideen P et al [9] reveals that, GI system, liver and biliary system is the most frequent organ system affected by ADRs. Multiple drug therapy was noticed to be a major predisposing factor for developing GI problem. Itching was developed by majority of patients. The drugs, which are responsible for itching and rash may be, pyrazinamide, rifampicin, and isoniazid. The drug which is responsible for the joint pain (1.90%) may be pyrazinamide and peripheral neuropathy was by isoniazid.

Causality assessment using standard method is probably the best way to establish the causal relationship between a drug and its effect. The Naranjo algorithm is used widely in the causality assessment of ADRs. It is based on the score calculated on the basis of points assigned to each of the ten questions that comprises the table. As per Naranjo's scale majority of the reactions were probable (68.57%), followed by possible (20%). There were no definite reactions. Gholami etal[6] also supported the same findings that the probable reaction was the more.

In order to take appropriate initiatives towards the management of ADRs, it is necessary to assess the severity of the ADRs. The Hartwig's scale is widely used for this purpose. Out of 105 adverse drug reactions, 68.57% were moderate and 31.42% were mild reactions. A study by Gholami etal[6]shows similar result in which most of the adverse drug reaction are of moderate severity. A study by Tad D K [11] also supported this result.

About 18.20 % of patients suffered diverse types of ADRs due to ATT in the pulmonology department during the study. Hence implementation good patient care oriented program is need of the hour at our hospital. Pharmacist have the liability to support the patients during the period of ATT. The side effects may steer the patient to make a judgment for stopping the medications and finally the occurrence of drug resistance and an amplified healthcare cost. In addition, a proper educational system may promote more ADR reporting by patients. These strategies may improve the patient adherence to treatment and therapeutic outcome.

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