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Original Research Article

Impact of adverse drug reaction of first line anti - tuberculous drugs on treatment outcome of tuberculosis under revised national tuberculosis control programme

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ABSTRACT

Background: Tuberculosis (TB), an infectious disease caused by Mycobacterium tuberculosis, is the major health care burden responsible for morbidity and mortality. The objective was to study the profile of adverse drug reactions (ADRs) and its outcome.
Methods: It was a prospective observational study conducted in one of the RNTCP centre of Ahmedabad district. All TB patients visiting and taking short course of directly observed treatment (DOTS) were enrolled and monitored for ADRs. All the ADRs spontaneously reported or identified by the researcher were recorded and analyzed.
Results: Total 974 patients screened during the study period 72 (7.79%) developed ADRs. Significantly higher occurrence of ADRs were in age group of 31- 40 years ($p<0.01$). Out of these 72 patients, 49 (68%) were having pulmonary TB. No statistically significant association was found between gender of patient, site of TB and occurrence of ADRs ($p>0.05$). Occurrence of ADRs was significantly more ($p<0.05$) in patients of category I TB (31, 43%). Out of the 49 (68%) pulmonary tuberculosis patients who developed ADR, 32 patients (44%) were sputum positive showing significant association ($p<0.05$). Gastro-intestinal side effects were most common ADRs followed by giddiness and headache. Nine patients required complete stoppage of offending agent, while 2 patients require treatment interruption and most of the patients (61) were managed with supportive medication without removing anti tubercular drug from their treatment regimen. Out of these 72 patients, majority (56) declared cured at the end of treatment.
Conclusions: ADRs are major factor limiting completion of drug therapy under RNTCP and occurrence of drug resistance which requires attention of all health care professionals.

Keywords: Adverse drug reactions, Ethambutol, Isoniazid, Pyrazinamide, Rifampicin, Tuberculosis

INTRODUCTION

Tuberculosis is the primary worldwide cause of death due to infectious disease. Each year an estimated eight million new cases and two million deaths occur due to TB worldwide.[1] TB is one of the foremost public health problems in India, causing a significant burden of morbidity and mortality.[2] India is the highest TB burden country accounting for one-fifth of the global incidence in 2007 alone, more than 6.48 million TB suspects have been examined, and more than 1.47 million patients have been initiated on treatment.[3]

Revised national tuberculosis control programme (RNTCP) has successfully changed the scenario of TB management in India. Chemotherapy, when used in the best possible way, guarantees virtually cent percent success in the treatment of pulmonary tuberculosis and

other measures are rarely, if at all, needed, further, it plays a vital role in the community control of the disease by rendering infectious patients non-infectious and thus reducing the pool of infections.

The National treatment regimens for TB patients recommend the use of the five first lines anti TB drugs Isoniazid (INH), Rifampicin (R), Ethambutol (E), Pyrazinamide (P) and Streptomycin (S).[2] It is necessary to use multidrug regimen for prolong period of time to achieve complete cure in TB patients. Multidrug regimens have been associated with increased incidence of side effects. These side effects may vary from mild skin rash to allergic anaphylactic shock or mild gastrointestinal upset to hepatic toxicity. They could be mild or fatal. A severe side effect against one of the primary antituberculosis (anti-TB) drugs, which leads to the discontinuation of that drug, has several complications including an increased morbidity and mortality. At the same time, use of alternative agents may result in greater problems of toxicity and compliance. As a result, the risk of treatment failure and relapses are higher.[4-7] Therefore, it is necessary to be vigilant about any adverse effects (ADRs) occurring with the use of anti-TB drugs. Awareness of the risk groups may decrease the cost as well as the incidence of serious drug-related adverse effects.

This study was aimed to determine the current incidence of side effects, pattern of various ADRs associated with use of anti-tubercular drugs.

METHODS

This was a prospective observational single centre study to study profile of ADRs with antitubercular drugs. All patients who were treated for TB at the tuberculosis unit (RNTCP unit) of Bahrampura and Meghaninagar area, Ahmedabad, Gujarat, India between 2007 and 2008 were identified. The study was approved by the institutional ethics committee and all patients' written informed consent was taken before enrolling them for the study.

Diagnosis of TB was confirmed per RNTCP guidelines and treatment regimens were prescribed according to it. Patients with TB were seen at least monthly by the investigator 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 thereafter if symptoms arose. Patients were encouraged to return at any time if new symptoms or problems arose during therapy. If drug-induced hepatitis was suspected or observed then INH, RIF, and PZA were stopped, and if a rash or drug fever occurred then all anti-TB agents were stopped. Once the side effect improved, drugs were restarted, one by one. When the responsible drug was not known, the timing and order of rechallenge were at the discretion of the treating physician. From patients' medical and nursing records, information was recorded regarding age, sex, symptoms, co-morbid conditions, other medications, site of disease, potential risk factors for active TB, results of acid-fast bacillus smear, cultures, drug sensitivity results, dose plus duration of all anti-TB drugs prescribed, and patients' weight. All the ADRs spontaneously reported or identified by the researcher were recorded and analyzed. Records of patients who developed side effects were reviewed in detail for risk factors for side effects, specific investigations such as hepatitis serology or ultrasonic examinations, as well as consequences including hospitalizations, additional visits to clinic by patients, or at patients' homes by nurses.

All adverse events, even if it feels minor for the patients were also recorded. Hepatitis was defined as liver transaminases more than three times higher than the upper limit of normal 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 therapy, increased during therapy, and returned to normal after discontinuation of the responsible drug.

A drug was defined as responsible for the side effect if symptoms and signs resolved after withdrawal, and recurred after re-challenge with that drug. Attribution was also made if a major side effect resolved with discontinuation of the drug, even without re-challenge. If a side effect resolved after discontinuation of two or more drugs, which were not reintroduced, then for the calculation of incidence, each event was divided equally between all possible causative drugs.

Statistical analysis: data were presented as actual frequencies and percentages. Chi square test was used to analyze the association between risk factors and TB and p value less than 0.05 was considered significant.

RESULTS

Out of 974 patients screened during the study period 72 (7.79%) had some or other adverse drug effects. The age of the patients screened in the study ranges from less than 20 to 75 years. Maximum number of patients was in their 3rd (21, 29%) and 4th (24, 33%) decade of life. Significantly higher occurrence of ADRs was found in age group of 31-40 years ($p<0.01$). Age and gender wise distribution is shown in table 1. Occurrence of ADRs was more in male patients (45, 63%) as compared to females (27, 37%). Out of 72 patients developed ADRs, 49 (68%) were having pulmonary TB and rest 23 (32%) had extrapulmonary TB. No statistically significant association was found between gender of patient, site of TB and occurrence of ADRs ($p>0.05$). Occurrence of ADRs was significantly more ($p<0.05$) in patients suffering from category I TB (31, 43%) as compared to category II and III as shown in Table 1.

Table 1: Demographic and baseline parameters of patients having TB and its association with occurrence of ADRs (n=974).

Parameter	No. of patients with ADRs (%)	No. of patients without ADRs (%)	P value
Age in years			0.001
≤20	05 (7)	102 (11.30)	
21-30	21 (29)	106 (11.75)	
31-40	24 (33)	346 (38.35)	
41-50	14 (20)	187 (20.73)	
51-60	4 (5)	90 (9.97)	
>60	4 (5)	71 (7.87)	
Total	72 (7.39)	902 (92.60)	
Gender			0.19
Male	45 (63)	630 (69.84)	
Female	27 (37)	272 (30.15)	
Total	72 (7.39)	902 (92.60)	
Site of TB			0.17
Pulmonary TB	49 (68%)	540 (59.86%)	
Extra pulmonary TB	23 (32%)	362 (40.13%)	
Total	72 (7.39%)	902 (92.60%)	
Category of TB			0.006
CAT I	31 (43%)	270 (29.93%)	
CAT II	28 (39%)	410 (45.45%)	
CAT III	13 (18%)	222 (24.61%)	
Total	72 (7.39%)	902 (92.60%)	
Sputum positivity for the TB for pulmonary TB only			0.001
Sputum positive	32 (65.30%)	225 (41.66%)	
Sputum negative	17 (34.70%)	315 (58.33%)	
Total	49 (8.3%)	540 (91.68%)	

Out of the 49 (68%) pulmonary tuberculosis patients who developed adverse drug reaction, 32 patients (44%) were sputum positive pulmonary tuberculosis and remaining 24% patient were sputum negative pulmonary tuberculosis showing significant association with ADRs ($p<0.05$). Different manifestations of ADRs are shown in Table 2. Out of 72 patients, gastro-intestinal upset was the prime complaint noticed in majority (49) patients, followed by giddiness and headache in 37 of the patients.

Table 2: Different manifestations of ADRs (n=72).

Adverse effects	No. of patients
Hearing difficulty	2
Nausea, vomiting and loss of appetite	49
Giddiness, headache	37
Joint pain	17
Burning pain in limb	09
Hypersensitivity reaction	09
Itching	15
Generalized swelling	05
Bleeding	01
Others	08

The prevalence rate was also calculated for different ADRs as shown in Table 3. Prevalence of gastritis and jaundice was found to be highest, which was around 1.64% and 1.74% respectively in this study. Skin hypersensitivity reaction due to anti-tubercular drug was also common adverse drug reaction encountered which was around 1.43%.

Table 3: Prevalence rates of ADRs: (n=72).

Adverse drug reactions	Prevalence rate of ADRs (%)
Gastritis	16 (1.64%)
Jaundice	17 (1.74%)
Ototoxicity	2 (0.20%)
Skin hypersensitivity reaction	14 (1.43%)
Peri neuropathy	6 (0.61%)
Gout	6 (0.61%)
INH induced dermatitis	2 (0.20%)
Injection *Streptomycin* induced giddiness	7 (0.71%)
Thrombocytopenia	1 (0.10%)
INH induced psychosis	1 (0.10%)

Out of the 72 patients who developed adverse drug reactions, only 9 patients required complete stoppage of that offending agent, while 2 patients require interruption of treatment in whom, all the drug where started one by one in order of ethambutol, rifampicin, pyrizinamide, and

isoniazid, and most of the patients (61) were managed with supportive medication without removing anti tubercular drug from their treatment regimen.

Outcome of patients having adverse drug effects are shown in Table 4. Out of these 72 patients, majority (56) declared cured at the end of treatment, while only 03 patients were declared as failure on treatment. In this study 07 patients were defaulted during treatment because of adverse drug reaction or because of poor compliance towards anti-tubercular treatment, while 6 patients have died during the treatment.

Table 4: Treatment outcome of the patients of ADRs.

Outcome	No. of patients
Cured	56
Treatment not completed	00
Default	07
Death	06
Failure	03
Transfer out	00
Total	72

DISCUSSION

Tuberculosis is the most rampant communicable disease in the developing countries and imposes a major burden on health care system. After implementation of revised national tuberculosis control programme (RNCP), the cure of tuberculosis has been possible. One of the common reasons responsible for noncompliance to RNTCP guidelines are development of ADRs. Therefore, it becomes important to study the profile of ADRs and its outcome. The results of this study indicate that intolerance of anti-TB standard therapy due to the side effects of anti-TB drugs is still a serious problem in the patients with tuberculosis. In our study, we found that the current incidence of side effects was 7.79%, in a total of 72 patients. Although the major severe side effects were gastric side effects, hepatotoxicity, ototoxicity, hyperuricemia and neuropsychiatric manifestations, the incidence of side effects was almost comparable to the other studies (range 5.1–23%).[8-10]

On analyzing specific ADRs due to Isoniazid, it was found that only 6 (0.61%) of 974 patients had developed peripheral neuropathy with standard intermittent dose of 300mg which is comparable to other studies and literature.[11] The other common finding in above both studies were also development of rash which was around 2% compare to present study which is 1.43%.

The development of Jaundice among the patients on intermittent isoniazid therapy was found to be 0.3-2.3% comparable with the other study which showed the incidence of jaundice to be around 1.74%.[11,12] The present study shows that in the main toxic reaction to Rifampicin are Nausea, vomiting (1.64%), Jaundice (1.74%) and Rash (1.02%). Another study (13) had reported the incidence of Nausea and vomiting as 1.5%, which was also comparable to the present study. Present study has shown only single case of bleeding- rifampicin induced thrombocytopenia the incidence is about (0.10%) which cannot be comparable with other study. It is apparent from this study that a small percentage of cases with this type of adverse drug reaction can be re-started again with Rifampicin in mild toxicity like nausea, and vomiting.

Present study shows that main toxic manifestations to pyrizinamide are gastro-intestinal upset, Jaundice, and joint pain and sometime allergic reaction. The most striking feature is development of Jaundice among the study group which is around 1.74% which is comparable with the other study.[14,15] Only small group of patient had developed skin-hypersensitivity reaction due to the pyrizinamide which can be managed by symptomatic treatment. It is clearly seen from the present study that ethambutol is the safest drug among five first line anti-tubercular drug, because none of the patient from the study group developed a single adverse drug reaction.

In the present study, it is apparent that vertigo and skin hypersensitivity rash is commonest adverse drug reactions with injection streptomycin. Incidence of vertigo (giddiness) in present study is around 0.71% which is lower than other studies and literature.[16,17] This can be explained by the fact that the dose of inj. streptomycin used by other researchers was 1gm which is quite high, compare to the present study. 1.43% patients developed skin rashes in the study group, which is lesser than reported literature.[15]

Occurrence of ADRs was significantly associated with age of the patient, category of TB, and sputum positivity in this study which was also supported by other studies and literature.[6,15,18] Highlighting finding of this study is that it has identified the rate of occurrence, type of ADRs and its outcome in patients taking DOTS therapy under RNTCP. Major limitation of the study is that it was a single centre study on few patients. Larger studies directed towards specific population are required before generalizing findings of this study to whole community.

CONCLUSION

Management of active tuberculosis includes the initiation and the completion of anti-TB therapy, and also the interference of side effects related to anti-TB drugs. In conclusion, it must be kept in mind that severe side effects with anti-TB drugs are common especially among patients of pulmonary tuberculosis and they should be followed up by closer monitoring for the side effects related to anti-TB drugs.

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