Journal of Research in Medical and Dental Sciences
Volume 5, Issue 1, Page No: 6-12

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Comparison of adverse drug reactions of antitubercular drugs in category 1 tuberculosis patients between daily and intermittent regimen and its impact on outcome

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DOI: 10.5455/jrmds.2017512

ABSTRACT

Aim of the present study was to compare the ADRs in patients taking antitubercular treatment under RNTCP regimen between intermittent treatment & daily therapy and to know the impact of ADRs on outcome of treatment in patients. 100 patients having pulmonary tuberculosis were included in the study who were taking the treatment of tuberculosis as per criteria, guidelines and various regimens of RNTCP. They were observed in DOTS group (group 1, intermittent) and in the group receiving treatment on OPD basis (group 2, daily treatment) for various ADRs and relevant findings were recorded during each clinical visit of the patients. The impact of ADRs on outcome of treatment was seen in the form of cured, relapsed, treatment failure, defaulted and alteration in therapy. 39 patients developed 1 or more ADRs out of 100 patients. The incidence of ADRs was more in group 2 (27, 54%) as compared to group 1(12, 24%) (p<0.01). Out of patients in group 1with ADRs & without ADRs , cure occurred in 25% & 81.57%, defaulters were 33.33% & 2.63%, failure of treatment occurred in 8.33% & 2.63%, relapse occurred in 8.33% & 13.15%, alteration of therapy required in 25% & 0% respectively (p<0.05). Out of patients in group 2 with ADRs & without ADRs , cure occurred in 55.55% & 91.3%, defaulters were 22.22% & 4.34%, failure of treatment occurred in 3.7% & 0%, relapse occurred in 11.11% & 4.34%, alteration of therapy required in 7.4% & 0% respectively (p<0.05). ADRs in daily treatment group (group 2) are significantly more as compared to intermittent group (group 1). Patients without ADRs have significantly better outcome as compared to patients with ADRs in both the groups

Key words: Pulmonary tuberculosis, daily, intermittent, adverse drug reaction, impact, outcome

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Received: 17/10/2016
Accepted: 12/02/2017

INTRODUCTION

The necessity use of multidrug regimens in Tuberculosis (TB) has been associated with increased incidence of adverse drug reactions (ADRs) of anti-tuberculosis drugs, these may be mild as well as fatal [1]. Various ADRs can occur such as hepatotoxicity, gastrointestinal (GI) disorders, allergic reactions, arthralgia, neurological disorders, and so on [2,3]. Studies suggest that more than 5% of the patients on anti-tubercular drugs (ATD) develop ADRs [4,5]. None of the anti-TB drugs is without adverse reactions. ADRs can be a potential factor leading to treatment non adherence [6]. Rarely, ADRs may be life threatening. The occurrence risk factors morbidity and mortality of adverse events from INH, particularly hepatotoxicity have been well defined [7,8]. Adverse reactions to rifampicin (R), pyrazinamide(PZA) and ethambutol (EMB) have also been clearly documented [9].

Therefore, despite the availability of effective chemotherapy, TB is still a major health problem in most countries this can be attributed to poor patient compliance, to primary multidrug resistance and to interruption partly due to ADRs [10]. This further causes development of resistant strains requiring second line therapy of drugs with higher cost and more serious ADRs. ADRs also contribute to excessive healthcare cost through increased patient morbidity and mortality which is of great concern to the general population, the pharmaceutical industry, the regulatory authorities and the medical profession [11].

ADRs are most important factor in deciding the use of drugs in human beings, their impact may also influence the final outcome of treatment . The present study, therefore, has been designed to compare the number and severity of ADRs between daily observed therapy at DOTS center and treatment on daily regimen (OPD treatment) the impact of ADRs on outcome of treatment in term of cure, treatment failure, default and death will also be observed and compared.

MATERIALS AND METHODS

In this observational descriptive longitudinal study, all registered patients who were taking the treatment of tuberculosis as per criteria, guidelines and various regimens of RNTCP were observed in DOTS group (intermittent) and in the group receiving treatment on OPD basis (daily treatment) for various ADRs and relevant findings were recorded during each clinical visit of the patients and their responses were documented. Findings were analyzed statistically to know the profile of ADRs and their impact, if any, on outcome of treatment of tuberculosis in both the groups. The present study was carried out at the department of Pharmacology, department of Pulmonary Medicine and the Microscopy cum DOTS center of SRMSIMS, Bareilly, Uttar Pradesh. The associated hospital is a 950 bedded tertiary level teaching hospital. Patients attending the Out Patient Department (OPD) of Pulmonary Medicine and those referred to Microscopy cum DOTS center were the source of study material.

Study Population:
All registered patients of category 1 TB who were treated as per current guidelines and various regimens of RNTCP under DOTS strategy (group 1) and on OPD basis (group 2) were enrolled in the study after proper informed consent.

Study period: All patients registered for treatment in Microscopy cum DOTS center of Hospital of SRMSIMS during period of study i.e. from 01/09/2014 to 31/05/2015.

Inclusion Criteria:
Patients between the ages of 15 and 80 years with Tuberculosis, who were taking treatment under DOTS in category 1 of RNTCP regimens and category 1 of tuberculosis patients attending OPD of pulmonary medicine. Diagnosis of Tuberculosis was established on the basis of clinical history and examination, sputum examination and X-ray chest and other relevant investigations.

Exclusion Criteria:

1. Category 2 (previously treated) cases including MDR case and XDR cases.
2. Previously existing severe disease.
3. History of recurrent psychotic disorders, alcohol or drug abuse within the previous year.
4. Current cardiac, renal or hepatic dysfunction.
5. Pregnant and lactating women were also excluded from study.

Estimation of sample size (n) of a health survey is based on simple random sampling method for which central information is required. Assuming 5% significance level & 80% power of the study, sample size came out to be 100. Patients were clinically evaluated and examined for their response at every month. Patients were advised to visit any time if they develop any untoward-reaction or severe problems during treatment.

Methodology
1. All recruited patients were given the treatment of tuberculosis as per criteria, guidelines of category 1(DOTS) of RNTCP.
2. Baseline investigations of patients viz liver function tests, renal function tests, serum uric acid were done for each patient. Patients with normal values were included in the study. These were repeated at follow up visits
3. All such patients were observed for various adverse drug reactions and relevant findings were recorded under various headings in predefined format
4. During each clinical visit patients were questioned regarding adverse drug reactions and their response was documented in clinical patient record.
5. The presence of symptoms suggestive of adverse drug reactions and as well as their severity like grade1,2, 3 was determined and documented.
6. Primary variables were organ related adverse effects e.g. symptoms and function test. Secondary variables predisposing risk factors were age and sex.
7.At the end of study observations were compiled and analyzed to know the impact of ADRs if any, on the outcome of treatment in both the treatment groups. For this, patients who experienced adverse drug reaction were grouped separately and compared with patient who did not experience

adverse drug reactions by using appropriate statistical tests.
8. The impact of ADRs on outcome of treatment was seen in the form of- cured, relapsed treatment failure, defaulted, required alteration in therapy.

Statistical Methods:-
Proportions were expressed as percentages and for continuous variables ranges were used with means and standard deviations. Accordingly Chi-square-test and 'Z' test were used to compare categorical data.

Treatment Category and Drug Regimens
All category 1 Tubercular patients treated on OPD basis were given 4 drugs HRZE daily for 2 months in intensive phase and 2 drugs HR daily in continuation phase for 4 months. Patients treated in DOTS regimen were given 4 drugs HRZE on alternate days for 2 months in intensive phase and 2 drugs HR on alternate days in continuation phase for 4 months. HIV coinfection &its risk is ruled out. The patients who were sputum positive at the end of 2 months therapy, continuation phase extended to 7 months. The adverse drug reactions can be graded according to CTCAE version 4[12].

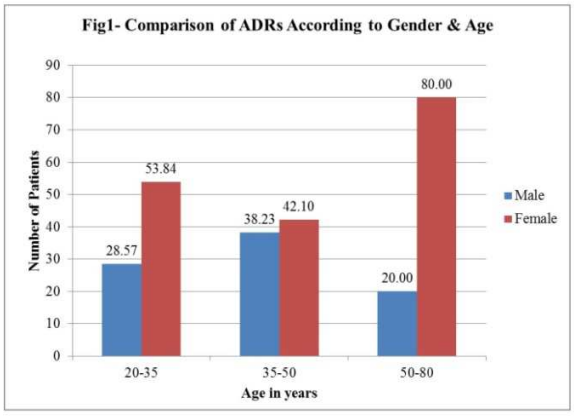
To know the impact of ADRs over the outcome of DOTS therapy in RNTCP various outcome were observed under the following headings:
(i) **Cured:** Initially sputum smears positive patients who had completed treatment and had negative sputum smears, on two occasions, one of which was at the end to treatment.
(ii) **Relapse**: Sputum smear positive patient who has completed treatment with negative smears at the end of the intensive phase but positive at the end of treatment.
(iii) **Treatment failure**:
Any TB patient who is smear positive at 5 months or more after starting treatment.
(i.v) **Defaulter:**
A patient who has not taken anti-TB drugs for 2 months or more, consecutively after starting treatment, possibly due to adverse drug reactions or other reasons.

(v**) Alteration in therapy:**

6. Change in regimens due to adverse drug reaction
7. Hospitalization due to adverse drug reaction
8. Required specific treatment for adverse drug reaction.
9. Suspension of one or more drug of multidrug therapy.

RESULTS

Total no of 39 patients developed 1 or more ADRs out of 100 patients. The incidence of ADRs was more in group 2 as compared to group 1. 61 patients did not develop ADRs. Group wise difference in incidence of ADRs was found to be highly significant. ($p<0.01$). Overall incidence of ADRs was higher in females (51.42%) compared to males (32.30%). Both males and females in group 2 developed more ADRs as compared to group 1. Difference in incidence of ADRs in males and females in group 1 was found to be statistically significant ($p<0.05$) while the difference in group 2 was not found to be significant ($p>0.05$). Higher incidence of ADRs was present in the patients who belonged to the age group of 35-50 years This was followed by age groups 50-80 and 20-35 respectively. Difference in age of patients who developed ADRs had no significant relationship ($p>0.05$)(fig1)



It is clear that in group1, maximum side effects were from gastrointestinal system followed by generalized weakness rest of other side effects, joint pains, tingling & numbness, hepatotoxicity & allergic skin reactions form equal proportion. (table 1) In group 2, maximum side effects were from gastrointestinal system followed by generalized weakness, joint pains, tingling & numbness, hepatotoxicity, allergic skin reactions& ocular side effects.(table 1) There was no significant difference ($p>0.05$) in ADRs between group 1 and group2.

Table 1: Comparison of ADRs between Group 1 & Group 2

Types of ADRs	Group 1	%	Group 2	%	Z value (p value)
Gastrointestinal	12	27.27	20	30.76	0.39(>0.05)
Joint pains	06	13.63	6	9.23	0.02(>0.05)
Generalized weakness	08	18.18	12	18.46	0.03(>0.05)
Tingling & numbness	06	13.63	8	12.30	0.2 (>0.05)
Hepatitis	06	13.63	10	15.38	0.38(>0.05)
Allergic skin reactions	06	13.63	8	12.30	0.2 (>0.05)
Ocular side effects	0	0	1	1.53	0.82(>0.05)
Total	44	100	65	100	2.98(<0.05)

Table 2- Comparison of Severity Wise Distribution of ADRs Between Group 1 &2

Severity of ADRs	Patients developed ADR				Z value	P value
	Group 1 (n)	%	Group 2 (n)	%		
Grade 1	07	14	19	38	2.7	<0.05
Grade 2	05	10	06	12	1.04	>0.05
Grade 3	00	00	02	04	1.4	>0.05
Total	12	24	27	54		<0.01

There is significant difference b/w grade 1 ADRs of group 1& group 2 (P<0.05) but is insignificant in case of grade 2 & 3 ADRs (P>0.05). Over all statistically significant difference was found between group1 & group2 (P<0.01)

Table 3: Outcome of Group 1 Therapy in Relation to Presence and Absence of ADRs

Outcome of treatment	Patients with ADRs		Patients without ADRs		Total	Z & (p) value
	No.	%	No.	%		
Cured	3	25%	31	81.57	34	5.8363 (<0.05)
Relapse	1	8.33	05	13.15	6	3.2828 (<0.05)
Failure	1	8.33	1	2.63	2	3.8361 (<0.05)
Default	4	33.33	1	2.63	5	4.3051 (<0.05)
Alteration in therapy	3	25	0	0.00	3	3.6204 (<0.05)
Total	12	100.00	38	100.00	50	

Out of patients with ADRs, 25% were cured while this is 81.57% in patients without ADRs (p<0.05). Percentage of patients who defaulted was 33.33% in patients with ADRs but this is 2.63% in case of patients without ADRs (p<0.05), failure percentage was more in patients with ADRs (p<0.05). Percentage of patients who relapsed was more in patients without ADRs as compared to patientswith ADRs (p<0.05). 3 patientsrequired alteration of therapy among patients with ADRs while none required modification of treatment in patients without ADRs (p<0.05)

Table 4: Outcome of Group 2 Therapy in Relation to Presence and Absence ADRs

Outcome of treatment	Patients with ADRs		Patients without ADRs		Total	Z & (p) value
	No.	%	No.	%		
Cured	15	55.55	21	91.30	36	4.9527 (<0.05)
Relapse	03	11.11	01	4.34	4	3.2581 (<0.05)
Failure	01	3.70	0	0.00	1	3.8527 (<0.05)
Default	06	22.22	1	4.34	7	4.1820(<0.05)
Alteration in therapy	02	7.40	0	0.00	2	3.3816(<0.05)
Total	27	100.00	23	100.00	50	

Out of patients with ADRs, 55.5% were cured while this is 91.30% in patients without ADRs (p<0.05). Percentage of patients who defaulted was 22.22% in patients with ADRs but this is 4.34% in case of patients without ADRs(p<0.05), there was no failure in patients without ADRs but only one failure case was found in patients with ADRs. Percentage of patients who relapsed was more in patients without ADRs ac compared to patients with ADRs (p<0.05). 2 patients required alteration of therapy among patients with ADRs while none required modification of treatment in patients without ADRs (p<0.05).

Statistically significant difference was found in total number of ADRs in group 1 and group2, Table 2depicts, total 24% of patients developed ADRs in group 1while it was 54% in group 2. There was significant difference b/w grade 1 ADRs of group 1 & group 2 (P<0.05) but is insignificant in case of grade 2 ADRs (P>0.05). Over all statistically significant difference was found between group1 & group2 (P<0.01)

Regarding outcome of treatment, more no of patients were cured in group 2, defaulters were also high in group 2 as compared to group 1. On the other hand, number of relapse patients, treatment failure patients & patients requiring change in therapy were more in group 1. (p>0.05) (fig2)

The table 3 shows that number of patients cured were more in patients without ADRs as compared to patients with ADRs in group 1 (p<0.05). Percentage of patients who defaulted was more in patients with ADRs as compared to patients without ADRs (p<0.05), failure percentage was more in patients with ADRs (p<0.05). Percentage of patients who relapsed was more in patients without ADRs as compared to patients with ADRs (p<0.05). 3 patients required alteration of therapy among patients with ADRs while none required modification of treatment in patients without ADRs (p<0.05)

Table**4** shows number of patients cured were more in patients without ADRs as compared to patients with ADRs in group 2 (p<0.05). Percentage of patients who defaulted was more in patients with ADRs as compared to patients without ADRs (p<0.05), no failure case in patients without ADRs but only one failure case was found in patients with ADRs (p<0.05). Percentage of patients who relapsed was more in patients with ADRs as compared to patients without ADRs (p<0.05). 2 patients required alteration of therapy among patients with ADRs while none required modification of treatment in patients without ADRs (p<0.05).

Maximum cure rate (85.29%) was seen in 20 – 35 year age group followed by 64.15% in the 35-50 year age group that in turn followed by 53.84% in the 50-80 years age group .In the age group 35-50 years 13.2% patients relapsed. No patient of treatment failure was found in the 20-35 age group .In 35-50 years it was found in 2 patient and in 50-80 years it was found in 1 patient .2 patients defaulted in age group 20-35 years,7 in 35-50 years ,3 in 50-80 years. 3 patients required alteration in therapy in the age group 35-50 years and 1 patient each in 20-35 years and 50-80 years .

DISCUSSION

Considering long term treatment compliance antitubercular medication is essential for effective management. Two strategies to ensure compliance are DOTS & fixed dose combination (FDC). Worldwide there are very few studies which have compared the daily regimen with the intermittent regimen & most of the studies were done in HIV positive patients. Our study focused the comparison between two groups (DOTS or Intermittent & Daily or OPD basis) in non HIV patients.

In our study, males constitute the larger proportion that is 65% and females constitute 35%. This is in accordance with Sinha et al.,[13]; Mandal & Mandal [14]., who also found 76.47% males against 25.53% females and 3.3:1 ratio respectively. In the current study, overall incidence of ADRs was 39% ,this is in accordance with Anusha et al., [15] who showed 48% incidence of ADRs. A multicenter study conducted by Shakya et al.,[16], in five hospitals in Nepal identified that 15.87% of drug related complications were due to antitubercular drugs. Study from United Kingdom by Ormerod & Horsfield, [10] reported only 5.1% ADRs that required modification of treatment. In another study carried out in Nepalese population by Koju *et al*., [17], ADRs were reported by 80% of population. The difference in the results between the previous studies and the present study could have been due to differences in genetic, demographic and nutritional status in the different population groups.

The majority of ADRs reported in this study were categorized as 'possible' as per the Naronjo algorithm [18] signs & symptoms were enquired. No dechallenge or rechallenge was done to establish the causative agent, placebo effect was not studied, and no laboratory investigations were done to determine the concentration of drug in body fluids or tissue. Owing to the lack of all these parameters, none of the reported ADRs could be classified as definite to the suspected drugs.

In our study, females had a higher incidence of ADRs that is 45.71% as compared to males 35.35%.

This is in accordance with Ormerod & Horsfield, 1996. This may be because females are considered to be more at risk of ADRs due to their smaller body size and less body weight. Menstruation & pregnancy may also add to this. Study conducted by Anusha et al.,[15], male patients were more (68.6%).
Group wise frequency of ADRs was found numerically higher in group 2(27%, daily treatment) as compared to group 1(12%, intermittent), which was in accordance with a study where it was 61.76% & 50% in respectively while Mandal & Mandal, [14], did not find it statistically significant ,where it was 35% & 27.9% respectively. This may be due to daily exposure of patients to the drugs.

In our study, higher incidence of ADRs was present in the patients who belong to the age group of 50-80 years (46.15%) followed by 39.62% & 35.29% in the age groups of 35-50 years and 20-35 years respectively. This is in accordance with Pande et al,[19] who concluded that drug induced hepatitis was more frequent in older patients. On contrary to this, Sinha et al.,[13] reported highest incidence of ADRs in <20years of age group followed by 31-40 years age group.

The most common ADRs associated with the ATT drugs in our study were related to gastrointestinal system (30.76% in group 2 & 27.27 % in group 1) in the form of epigastric pain, burning, anorexia and vomiting . Dhingra et al., [4], also reported that out of total 8.37% patients who experienced ADRs, 53% had gastrointestinal reactions. Sinha et al.,[13]also concluded highest percentage of GI symptoms (53.52% & 30.67%) respectively.

Several studies have documented the hepatotoxic effect of ATT drugs. Frequency of hepatotoxicity we found was 13.63% in intermittent group & 15.38% in daily treatment group ($p>0.05$). Similar type of results were found in a study from Nepal, done by Shakya et al.,[16], reported 8% hepatotoxicity to ATT drugs. On the other hand, Dhingra et al., 2004 had reported only 1% hepatotoxicity in patients who were treated with DOTS.

Maximum cure rate that is 85.29% was observed in age group of 20-35 years followed by 64.15% in 35-50 years, 53.84% in 50-80 years of age group. In group 1 (intermittent) among patients with ADRs, 25% were cured while in patients without ADRs, 81.57% were cured. This difference was statistically significant ($p<0.05$). Likewise, patients who relapsed, defaulted, underwent alteration of therapy & who failed to response exhibited statistically significant difference between patients with ADRs & those without ADRs($p<0.05$). Same findings were noted for group 2 (daily treatment). This suggests that ADRs had produced negative impact on the outcome or efficiency of chemotherapy of tuberculosis. We could not find any other study that has compared the results like this. In present study, alteration of therapy required in 10% of patients including both the groups and the difference between the two was not statistically significant ($p>0.05$). Ormerod & Horsefield [10] had reported that modification was required in 5.1% of cases. The present study analyzed the pattern and nature of ADRs due to ATT in patients receiving intermittent & daily treatment of TB & its impact on outcome of treatment. Results have shown that ADRs can influence the outcome of treatment by antitubercular drugs.

CONCLUSION

ADRs in daily treatment group (group 2) are significantly more as compared to intermittent group (group 1). There is no significant difference between age of the patient and development of ADRs in both the groups. Gastrointestinal system was the most common affected organ system but there is no significant difference in frequency of ADRs between the two groups. Regarding severity of ADRs, there is significant difference in grade 1 ADRs between both the groups but not in grade 2 & 3.

Patients without ADRs have significantly better outcome as compared to patients with ADRs in both the groups except for number of relapse patients which is more in patients without ADRs that too in group 1only

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