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ORIGINAL ARTICLE

Safety Evaluation Of Antitubercular Therapy Under Revised National Tuberculosis Control Programme In India

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ABSTRACT

Introduction: The World Health Organization declared tuberculosis (TB) as a global emergency in 1993. To intensify the efforts to control TB, the Government of India gradually replaced the National Tuberculosis Programme by the Directly Observed Short Course Therapy (DOTS) programme which is now known as the Revised National Tuberculosis Programme (RNTCP).

Objectives: The present study was carried out to evaluate the safety of the DOTS therapy by monitoring adverse drug reactions (ADRs).

Methodology: All the TB patients admitted at the DOTS centre Kasturba Hospital, Manipal, and at the DOTS Centre, Udupi, were enrolled as per the study criteria and were monitored for ADRs. The data were evaluated for patient demography, types of TB, types of DOTS treatment, incidence of ADRs, predisposing factors for developing ADRs and the types, onset, management and outcome of the ADRs. ADRs were also assessed for their causality and severity as per the standard algorithms.

Results: Out of 94 TB patients, a majority of them were males (70%) and belonged to the age group of 18-40 years (52%). The incidence of ADRs was 17.02%. Gastritis was the most common ADR and multiple drug therapy was the major predisposing factor. We found that 28.51% of the total ADRs belonged to Type-A ADRs. In 87.1% of the cases, the suspected drug was continued in spite of the ADR, without any complications. On evaluation of the causality of ADRs, a majority of them were found to be 'possible' by both WHO and Naranjo's scales. The severity assessment of ADRs showed that 31(51%) reactions were moderate and 30 (49%) were of the 'mild' nature.

Conclusion: We found DOTS therapy to be safer. But regular monitoring is required for ADRs, so that certain percentage of ADRs can be prevented.

Keywords: Adverse drug reactions, DOTS, India, Tuberculosis.

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Introduction

The World Health Organisation (WHO) declared tuberculosis (TB) as a global emergency in 1993. Southeast Asia

dominates the worldwide distribution of notified cases (36% of the total cases). The global rate of tuberculosis is growing at approximately 1.1% per year[1]. India ranks first in the estimated number of tuberculosis cases, and approximates to1761 (thousands) cases per 10, 49,549 population at the rate of 168 cases per 1, 00, 000 population [1]. Before the advent of the DOTS programme, high prevalence countries like India had a National TB Programme to combat the problem of TB. India's National Tuberculosis Programme (NTP) was started in 1962 (NTP employs a daily regimen of anti-TB drugs) as a truly integrated programme, implemented through District Tuberculosis Centres (DTCs) and peripheral health institutions. After more than three decades, the NTP has made notable, but not spectacular progress. The overall case-finding programmes are about 33% and treatment efficiency is of the same order or worse[2].

In order to intensify the efforts to control TB, the Government of India gradually replaced NTP by the DOTS strategy/programme in 1993 and it is now known as the Revised National Tuberclusis Programme (RNTCP). The objective of this revised strategy is to achieve a cure rate of 85% for infections and seriously ill patients through intermittent (three days a week) supervised short course chemotherapy or the directly observed treatment, short course (DOTS) [3]. Under RNTCP, the doses of first line anti-TB drugs (Isoniazid, Rifampicin, Pyrazinamide, Streptomycin and Ethambutol) were standardized on the basis of body weight and were given in different regimens. All regimens have an *initial intensive phase* lasting 2-3 months, aimed to rapidly kill the TB bacilli, bring about sputum conversion and to afford symptomatic relief .This is followed by a *continuation phase* lasting 4-6 months, during which the remaining bacilli are eliminated so that relapse does not occur [4].

Antitubercular drugs, just like other drugs used in clinical practice, are not free from ADRs. The added problem is that combinations of drugs are always used for prolonged periods of time and therefore, it is likely that the adverse reactions of one drug may be potentiated by the companion drugs used. Moreover, the Adverse Drug Reactions (ADRs) to the drugs used is one of the major reasons for the patient default for treatment. A general knowledge of the various ADRs and their management is essential for the effective management of TB [5]. All antitubercular drugs can cause adverse drug reactions[6] and may result in ADRs involving almost all systems in the body, including the gastrointestinal tract, liver, skin, nervous system, otovestibular apparatus and the eyes [7]. Numerous clinical trials have determined that there is a 15% probability of an adverse effect occurring in a patient who is on a multiple antitubercular drug regimen and adverse reactions mostly tend to occur in the first three months of treatment [8].

In various clinical trials, it was found that intermittent short course regimens that are administered thrice weekly, have largely equivalent efficacy as that of the daily regimen [9]. The WHO defines ADR as 'A response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function [10],[11]. Identification of the ADR profile of drugs can be useful for the prevention, early detection and management of ADRs. Identifying the causality and severity assessments of ADRs is an important step in ADR monitoring programs. Naranjo's Algorithm [12] and the WHO Probability Scales [11] are commonly used to carry out the assessment of the causality of the ADRs. Similarly, the Hartwig *et al* Scale [13] is a commonly used scale for identifying the severity of ADRs. Various studies on DOTS vs daily regimen conducted till date, evaluated the efficacy of the dosage regimen [14],[15],[16],[17]. There are studies done to

evaluate the safety in regular regimens; however, very few studies have been done till date to evaluate the safety of the DOTS regimen. Hence, there is a need to study the safety of patients on DOTS through the monitoring of ADRs in a hospital set up. Hence, the present study was undertaken with the following objectives.

1. To collect the demographic details of the patients receiving DOTS therapy

2. To identify the incidence and pattern of ADRs caused by the antitubercular drugs in DOTS patients.

3. To assess the causality and severity assessments of the reported ADRs

Materials And Methods

Study Design

Prospective observational study.

Study Site

The study sites were the DOTS entre, Kasturba Hospital, Manipal, Karnataka, India, and the DOTS Centre, Government Hospital, Udupi, Karnataka, India.

Ethical Committee Approval

The Ethical Committee approval was taken from the Ethical Committee of Kasturba Hospital, Manipal, India.

Study Duration

Eight months (October 2005-May2006)

Operational Modality

All the patients of tuberculosis, admitted in the above centers, were enrolled for the study as per study criteria, by taking their informed consent and were monitored for ADRs. The patient profile of all the patients was maintained by using case sheets to identify the type of treatment (DOTS category), disease classification, the type of patient, date of start and completion of DOTS treatment, record of follow-up and the outcome of the patient's treatment. ADRS are identified or reported by following ways:

1. Participation in ward rounds: Investigators (Pharmacists) participated in ward rounds along with the clinicians and collected the ADR reports.

2. Review of patient case files by the investigators (Pharmacists).

3. Interviewing of the patients by the investigators (Pharmacists).

All the suspected ADRs were also evaluated for their causality using Naranjo's Algorithm [12] and the WHO Probability Scale [11]. Severity assessment was done using the Hartwig *et al* Scale [13].

Results

A total of 94 tuberculosis patients who were on DOTS therapy were enrolled for the study. Out of this, 87 patients were from the DOTS Centre, Govt. Hospital, Udupi, and 7 were from the DOTS Centre, Kasturba Hospital, Manipal. The demographic details of the patients receiving DOTS, are listed in [Table/Fig 1].

(Table/Fig 1) The demographic details of the patients receiving DOTS (n=94)

Parameters		Number	Percentage
Gender	Male	66	70
	Female	28	30
Age group (in years)	Up to 40	49	52
	41-60	33	35
	More than 60	11	12
Type of TB	Pulmonary	90	96
	Extra pulmonary	4	4
Type of DOTS	Category I	38	40
	Category II	52	56
	Category III	4	4
Treatment outcomes	Treatment completed	2	2.12
	Treatment failure	0	0
	Died	3	3.19
	Treatment interrupted (default)	2	2.12
	Transfer out	87	92.55
	Treatment failure	-	-
	Expired	2	2.12
	Treatment interrupted (default)	0	0
	Transfer out	87	92.55
	Treatment failure	-	-
	Expired	2	2.12
	Treatment interrupted (default)	0	0
	Transferred out	3	3.19
	Cured	2	2.12

The Demographic Details Of The Patients Experiencing ADRs

Out of 94 patients, 16 patients developed 21 ADRs with an overall incidence of 17.02%. Among the 16 patients, 11(69%) developed only one ADR and 5 (31%) developed two ADRs each. Among 21 reported ADRs, the highest numbers of ADRs [20 (95%)] were observed in males and the remaining 1 (5%) was observed in a female. Out of 21 ADRs, 9 (42.85%) each, were observed in the age group of 18-40 years and 41-60 years. Three (14.28%) ADRs were observed in the age group of 61 and above. Out of 21 ADRs, 10 (47%) were from patients on Category II of the DOTS therapy, followed by 9 (43%) from Category I and the remaining 2 (10%) were from patients on Category III treatment.

Types Of ADRs

The different types of ADRs reported, are listed in [Table/Fig 2].

(Table/Fig 2) Types of ADRs (n=21)

System affected by the ADR	Types of ADRs	Number	Percentage
Gastrointestinal	Gastritis	8	38.09
	Hepatitis	2	9.52
	Anorexia	1	4.76
Skin	Skin reactions	3	14.28
Nervous system	Peripheral neuropathy	1	4.76
	Dizziness	1	4.76
	Psychosis	1	4.76
Others	Ototoxicity	1	4.76
	Vertigo	1	4.76
	Weakness	1	4.76
	Arthralgia	1	4.76

Predisposing Factors

The commonest predisposing factors for the development of ADRs were multiple drug therapy in 8 cases (38.09%) and there were no predisposing factors in the 8 (38.09%) cases. Dose, age, and alcoholism were found to be the other predisposing factors in 1 (4.76%), 3 (14.28%) and 1 (4.76%) cases, respectively.

Time Of Onset Of ADRs

Out of the 21 ADRs, most of them [7(33.33%)] occurred within a week of treatment, followed by 6 (28.57%) in the second week, 3 (14.28%) in the third week and 1(4.76%) each in the fourth, fifth and sixth weeks of the initiation of DOTS treatment. Two (9.52%) of the ADRs occurred on the first day of the treatment itself.

Management Of ADRs

In 3 (14.28%) cases, the ADRs were managed by withdrawing the suspected drugs. Out of these, in 2 (9.52%) cases, symptomatic treatment was given whereas in 1(4.76%) case, specific treatment was given. In 18 (85.71%) cases, the drug was continued in spite of the occurrence of ADRs. Out of these, in 9 (42.85%) cases, symptomatic treatment was given, whereas in 9 (42.85%) cases, no treatment was given. In none of the cases was the dose of the drug altered/reduced.

Outcome of the ADR

In 13 (61.90%) cases, the patients recovered from ADRs without any complications and in 6 (28.57%) cases, the reactions continued on discharge, while in 2 (9.52%) cases, the outcome was unknown as patients got discharged. There were no fatal reactions during the study period.

Pattern Of Dechallenge And Rechallenge

Out of the 21 cases, dechallenge of the suspected drug was done in 3 (14.28%) cases, in 18 (85.71%) cases, there was no dechallenge of the drug, and definite improvement was observed in all the 3 (14.28%) cases where dechallenge was done. Out of 3 cases of dechallenge, in 2 (9.53 %%) cases, rechallenge of drugs was done, whereas in one case (4.76%), there was no rechallenge done. In both the cases of rechallenge, there is no recurrence of symptoms observed.

Number Of Drugs Involved In ADRs

Among 21 ADRs, 6 (28.57%) ADRs were caused by single drug, whereas in the other 15 (71.42%), ADRs were suspected to be

caused by more than one drug. It was found that 47% of ADRs were caused by the CAT II regimen, which may due to a majority of patients receiving the CAT II DOTS treatment and it included a 5 drug combination as compared to CAT I (4 drug combination) and CAT III (3 drug combination).

Causality Assessment

According to the WHO probability scale, a majority of reactions 47(77.04%) were found to be 'Possible', followed by 'Unassessable'- 7 (11.47%), 'certain'- 5 (8.19%) and 'Probable'- 2 (3.27%). As per the Naranjo algorithm, 54 (88.52%) reactions were 'Possible', 5 (8.19%) reactions were 'Unlikely' and 2 (3.27%) reactions were 'Probable'.

Severity Assessment Of ADRs

Out of 61 suspected drugs causing 21 ADRs, 31 (51%) reactions of ADRS were moderate, 30 (49%) were mild and no severe reactions were reported as per the Hartwig *etal* scale.

Discussion

The recent WHO guidelines on the treatment of tuberculosis mentions extra pulmonary tuberculosis to be accountable for 20-25% of reported cases, being relatively more frequent in children and persons with HIV infection, whereas in our study, 4% were of the extra pulmonary type and the remaining were of pulmonary tuberculosis. It could be so, as children and HIV patients were not included in the present study [18]. While evaluating the treatment category, it was observed that a majority of the patients received CAT II DOTS treatment. It shows that these patients were of either type relapse or failure or treatment after default (Total of 52 numbers). A large number of patients (87) were transferred out to their local DOTS Center for further treatment. Three patients died because of tuberculosis itself.

The overall incidence of ADRs in the study was found to be 17.02%, which is almost double as compared to that found in the study carried out by Dhingra *et al [19].*, which showed that 8.37% of ADRs occurred in patients on DOTS treatment at the New Delhi Tuberculosis Center. Other studies by Dosmu *et al*[20]. showed around 14% and 13% incidence of ADRs in 6 months and 8 months, in patients on DOTS therapy, respectively. A study conducted by the Hong-Kong Chest Services showed around 21% reactions in the intermittent therapy. These variations could be attributed to the number of patients included in each study [14],[15]. Moreover, in our study, many patients were on the Category II regimen with five drugs and this could also have contributed to a high incidence of ADRs.

A study conducted by Ormeod *et al* [21]. showed that 64 patients had single adverse drug reactions, while 3 patients suffered from two drug reactions in each case, giving a total of 70 ADRs, whereas in the present study, 11 patients had single adverse drug reactions, while 5 patients suffered from two drug reactions in each case, giving a total of 21 ADRs.

Most of the literature says that the female gender is the one of the predisposing factors for ADRs and also, a study conducted by Daphne *et* al [22] showed that the female gender is at a high risk of developing ADRs. But in the present study, males developed more ADRs, and it could be because more numbers of males were included in the study. A study conducted by Daphne *et al* [22] showed that ADRs occur in patients above the age of 60 years. But in the present study, a majority of ADRs were observed in patients with ages below 60 years. It could be because less number of patients with ages above 60 years were included in this study.

The most common ADR was gastritis, out of which 3 occurred within the first week, two occurred within the second week and the remaining three occurred within the third week, whose occurrence was less as

compared to that seen in the study by Dhingra *et al* [20], where it was around 53%. The second most common reaction was skin reaction, whose occurrence was comparable to that found in the study conducted by Dhingra *et al* [19], where it was found to be around 17%. The third most common reaction was hepatitis- 9.52%, whose occurrence was more as compared to that found in the studies conducted by Dhingra *et al* [19] and Zierski *et al* [16], where it was found to be around 1% and 3.6-4.6%, respectively.

Vestibular symptoms (Vertigo and Ototoxicity) were noted in two patients who were on DOTS CAT II regimen, aged 47 years and 62 years respectively, in the fourth and seventh week of treatment. The patients were referred for ENT consultation for the confirmation of Ototoxicity. Still, streptomycin was continued, as only a few doses were left. No confirmatory test of Audiometry was done to confirm Ototoxicity, since the patients were poor.

A 62 year old patient developed INH induced psychosis within the first week of treatment and the drug was withdrawn immediately. Antipsychotic drugs were given, after which the reaction subsided and after 4 days, rechallenge was done and there was no further complaint. Peripheral neuropathy occurred in one patient and the predisposing factor was found to be alcoholism. Symptomatic treatment (Diclofenac sodium) was given and the complaint continued, as pyridoxine (specific treatment) was not available in the government hospital set-up. Other reactions observed within a week of treatment were dizziness and anorexia and those observed within the second week were weakness and arthralgia. A number of patients were included in the each study and it was found that various predisposing factors like age, sex, genetics, race, pharmacokinetic parameters, etc, might contribute to the variation in incidences of different ADRs at different sites.

Multiple drug therapy was noticed to be a major predisposing factor for 38.09% of the ADRs. 14.28% of the ADRs were age related and in one patient, it was due to an alcohol habit while in another patient, it was due to an increased dose of pyrazinamide. In the first four weeks, around 76.18% of the ADRs occurred within four weeks of DOTS therapy, which was approximately similar to that found by Dhingra *et al* [19], where it was found to be around 67%.

Causality assessment using standard methods is probably the best way to establish the causal relationship between a drug and its effect. The Naranjo algorithm [12] 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. On a scale with a maximum of 13 points, scores greater than 9 confirmed the adverse reaction by the incriminate drug. A score of 5-8 was considered as 'probable', while a score of 1-4 was categorized as 'possible' ADR. In our study, we found a majority of the ADRs to be 'possible'.

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 [13] is widely used for the purpose. This scale categorizes the adverse drug reactions into different levels as mild, moderate or severe, which is helpful in deciding whether hospitalization is required or not. The severity assessment of the reported ADRs revealed that most of the ADRs were mild and moderate. Among the reported ADRs, 28.57% were type A reactions which were dose related, pharmacologically predictable and were likely to improve if the medicine was withdrawn e.g. pyrazinamide induced hepatitis due to increased dose administration. Hepatitis due to DOTS, CAT I, INH induced psychosis and peripheral neuropathy is also dose related and others include dizziness, weakness which was common with ATT drugs. Others (71.43%) belonged to type B, which were unrelated to

the known pharmacological actions of the drug and were generally unrelated to the dosage of the drug.

Conclusion

An incidence of 17.02% of ADRs was identified under the Revised National Tuberculosis Control programme in India. Males had a higher incidence of ADRs. In general, the number of ADRs was high in males. Gastritis was the most common ADR and multiple drug therapy was the major predisposing factor. In 87.1% of the cases, the suspected drug was continued in spite of the ADR, without any complications. On evaluation of the causality of ADRs, a majority of them were found to have a 'possible' association with the suspected ADRs. Nearly half- 31(51%) of the ADRs were 'moderate' in severity. No severe life threatening ADRs were observed during the study period. Most of the ADRs belonged to the 'mild' or 'moderate' severity category. We found DOTS therapy safer, but regular monitoring is required for ADRs, so as to prevent the ADRs at the initial stage.

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