Original Article

Adverse effects of first line antitubercular medicines on patients taking directly observed treatment short course: A hospital based study

Abstract

Introduction: Tuberculosis (TB) continues to remain one of the most pressing health problems, with India being the highest TB burden country. India has adopted and enforced Directly Observed Treatment Short course (DOTS) strategy to combat TB. The first line medicines in DOTS are known to cause adverse effects like gastritis, hepatotoxicity and skin allergies. This study was done to determine the occurrence of such adverse effects in patients under DOTS therapy and to assess their impact if any on patient compliance. **Methods:** A hospital based cross-sectional observational study was carried out on all newly diagnosed cases of TB as well as those registered in DOTS centre in Chest and TB department of a tertiary care hospital. A structured proforma was used to collect information regarding adverse effects of medicines under DOTS. Biochemical tests were done after voluntary consent. **Results:** A total of 168 patients (132 male, 36 female) were interviewed for the study. Patients reported adverse drug effects which mainly involved Gastro-intestinal system (39%), Genito-urinary system (32%), Musculo-skeletal system (13%), Central Nervous System (7%), Dermatological (6%), Vestibulo-ocular system (3%). 68.5% of the patients gave consent for biochemical investigations out of which Serum bilirubin (direct) was raised in 52%, Serum albumin was below normal limit in 59% and ESR was raised in 59%. **Conclusion:** Majority of adverse effects were mild. Most commonly encountered symptoms were abdominal. Most patients reported adverse drug effects to be the most likely cause to stop the treatment. Special interventions to cure these mild adverse effects can lead to increased patient compliance and hence a better cure rate. Results also showed that family plays the most important role as a support to combat the illness.

Key words: Tuberculosis, adverse drug effects, hepatotoxicity

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INTRODUCTION

Tuberculosis (TB) continues to remain one of the most pressing health problems, with India being the highest TB burden country, accounting for one-fifth of the global incidence-an estimated 1.96 million cases annually.[1] Approximately 2.9 million people die from TB each year worldwide and about one-fifth of them in India alone.[2] Nearly 500,000 die from the disease >1000/day.[3]

With such fast spreading web of TB, India has adopted and enforced directly observed treatment short course (DOTS) strategy. The first-line medicines included under DOTS viz. isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin are known to cause adverse effects such as gastritis, hepatotoxicity, skin allergies, and visual disturbances.[4-7] Out of these, hepatotoxicity is a potentially serious adverse effect. The risk of hepatotoxicity based on data from four prospective Indian studies was 11.5% compared with 4.3% in western publications.[8]

The currently recommended anti-tuberculosis regimen (DOTS) is usually well tolerated. However, some patients may experience problems, usually due to the bulk of the medicines, a single day's dose consisting of 6-7 tablets. Medicine-related side effects can be minor or major.[9] Therefore, rather than concentrating only on the treatment, the adverse effects of the drugs should also be looked upon for achieving better patient compliance.

Most of the studies which have been conducted in this field dealt with pharmacological aspect of adverse drug effects (ADE), but in our study we have also included the psychological aspect. Long duration of the treatment, a large number of tablets, dependency on medicines can lead to disturbed emotional state among the patients. Different questions have been used to illicit emotional state of the patients.

Studies are being conducted to evaluate the ADE that are most commonly faced by patients taking anti-tubercular treatment, but the need of today is to find out the solution to this problem. In this study various homemade remedies that patient take to relieve their symptoms are also studied. It is very important to study the role of these remedies in curing adverse effects of anti-tubercular therapy (ATT). These homemade remedies can be promoted if proved useful. This will decrease the burden of medicines given for adverse effects to a patient who is already taking seven tablets/day.

Objectives

1. To study the demographic profile of patients diagnosed with TB.
2. To study the ADE and their effect on patients compliance to the treatment.
3. To provide health education to the patients taking DOTS.
4. To study the compliance rate of patients taking DOTS.
5. To study the emotional state of patients and social stigma due to TB.
6. To study the association of lifestyle factors such as alcohol consumption, smoking, diet and occurrence of ADE.

MATERIALS AND METHODS

The study was carried out in the TB and Chest Department of the Hospital Attached to the Government Medical College. It caters to patients coming from both rural and semi-urban region. The study was conducted as hospital-based cross-sectional observational study.

The present study was conducted on all the newly diagnosed patients of TB in the study period of 2 months (June 2012 to July 2012) as well as the patients who were taking treatment from the DOTS center of the hospital and are registered since January 2012. The patients coming to the Outdoor Department and the patients who were admitted in the Indoor Department of TB and Chest Department were also included for the study. All the patients diagnosed with TB and taking treatment under DOTS during the study period was included for the study. Patients coming for follow up in the outdoor patient department or were registered with other DOTS center and coming to the hospital during the study period were also included. The study was conducted over a period of two months from June 1, 2012 to July 31, 2012.

Month wise data of TB patients (21-60 years) (2012).

Inclusion criteria

All patients diagnosed with TB and undergoing ATT with first-line drugs during the study period.

Exclusion criteria

1. Patients are refusing to give consent for the study.
2. Patients taking ATT, which include medicines other than first line antitubercular medicines.
3. Patients of age <20 years and >60 years.
4. Newly diagnosed patient of TB along with liver diseases (viral hepatitis, chronic liver failure or any other liver disease).

Informed consent

Informed, voluntary and written consent was sought from each candidate before sampling. The purpose of the study, the sample collection procedure and the role of the candidate in the study was explained.

Data collection

The data was collected in these steps:

Step 1

Predesigned questionnaire was used to collect information regarding:

1. Socio demographic profile of the patients.
2. Time dependent side effects of the first-line antitubercular medicines after starting treatment under DOTS.
3. Association of lifestyle factors such as alcohol consumption, smoking, diet and occurrence of ADE.

Step 2

Case record sheet of the patients was filled which included:

1. Vitals of the patient (blood pressure, pulse rate, respiratory rate, temperature, jugular venous pressure).
2. Height, weight, body mass index.
3. Positive findings of physical examination.

Statistical analysis

The data was analyzed by using SPSS version 15 and graph pad.

RESULTS

1. A total of 168 sputum positive patients were studied of different age groups in which 78.6% were male, and 21.4% were female. Maximum of the patients (67.9%) were not aware about the sign and symptom of TB before treatment [Table 1 and Figure 1].

Table 1: Awareness about sign and symptoms of TB before treatment among patients

Age	Awareness about sign and symptoms of TB before treatment		Total	Percentage
	N	Y		
21-30	24	12	36	21.4
31-40	42	6	48	28.6
41-50	18	18	36	21.4
51-60	30	18	48	28.6
Total	114	54	168	100
Percentage	67.9	32.1	100	

Chi-square = 14.41, *P* = 0.0001. 67.9% of the patients were not aware about the sign and symptom of TB before treatment, TB = Tuberculosis

2. A total of 165 sputum positive cases were registered from January 2012 to July 2012, and 141 were suspected case of TB as per the standard definition of RNTCP. Slide positivity rate (SPR) overall was 16.3%, maximum number of patients came in February 2012 (SPR-15.8%) followed by the month of July (SPR-24.7%) [Figure 2].
3. Adverse drug effects, change in urine color was seen in 144 (86%) of the patients followed by anorexia in 108 (64%) of the patients. Anorexia was partly because of the disease as TB is known to cause anorexia. However, the symptom got aggravated upon taking medication. Nausea, vomiting, abdominal cramps, burning sensation in the abdomen, diarrhoea were the next most common drug effects reported by patients [Table 2].
4. Ajwain and lemonade were frequently used as home remedies for relief from ADR. This showed that a major discomfort was due to gastric problems which reportedly subside on home based medication [Table 3].
5. Out of the total patients studied 39% of them responded that they feel sometimes to stop the treatment [Figure 3].
6. The biggest motivation for the continuation of treatment was family pressure followed by knowledge of the severity of the disease [Table 4].
7. It was observed that 28.5% of the patients responded that they suffered from social stigma related to Tuberculosis [Table 5].

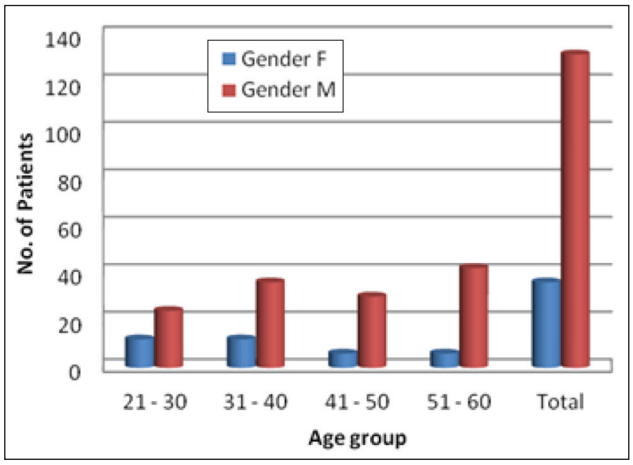

Figure 1: Gender distribution of patients. (A total of 168 sputum positive patients were studied of different age groups in which 78.6% were male, and 21.4% were female)

DISCUSSION

The present study was conducted in the Chest and TB Department of Government Hospital Attached to the Medical College.

One hundred and forty-one patients out of 165 registered came for follow-up during the study period, a compliance rate of 84% was

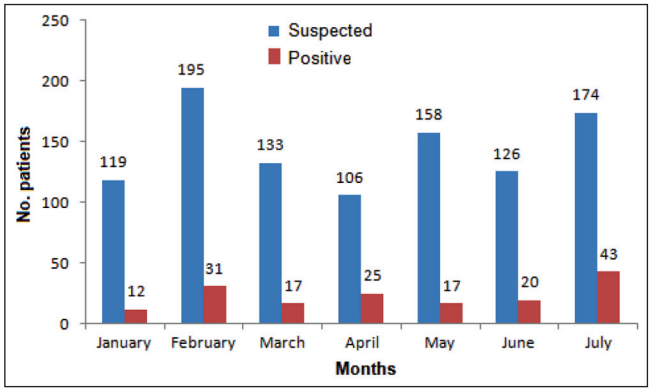

Figure 2: Month wise distribution of tuberculosis patients. (Out of 165 registered cases 141 patients could be contacted, and 27 patients who were registered with other directly observed treatment short center and came to this hospital for follow up. So the total sample size was 168)

Table 2: ADE in different age groups

ADE	Age				Total	Percentage
	21-30	31-40	41-50	51-60		
Nausea/vomiting	18	6	6	12	42	5.6
Abdominal cramps	12	18	12	0	42	5.6
Diarrhea	18	12	0	0	30	4.0
Constipation	0	0	0	12	12	1.6
Anorexia	24	36	24	24	108	14.3
Itching/skin irritation	6	12	12	6	36	4.8
Cutaneous eruption	12	0	0	0	12	1.6
Visual disturbance	12	0	0	0	12	1.6
Hearing disorder	6	0	0	6	12	1.6
Tingling sensation	6	6	6	6	24	3.2
Numbness	6	0	18	6	30	4.0
Change in urine color	30	30	36	48	144	19.0
Frequency of micturition	24	18	18	36	96	12.7
Joint pain	6	6	12	12	36	4.8
Lethargy	6	24	18	12	60	7.9
Burning sensation in abdomen	12	12	18	18	60	7.9
Total	198	180	180	198	756	100.0

Change in urine color was seen in 144 (86%) of the patients followed by anorexia in 108 (64%) of the patients, ADE = Adverse drug effects

Table 3: Homemade remedies used by patients to relief ADR

Age	Homemade remedies to relieve ADR					Total	Percentage
	No	Ajwain	Cold water, lemonade	Lemonade	Mulekha, isabgol		
21-30	30	0	4	2	0	36	21.4
31-40	36	4	2	5	1	48	28.6
41-50	30	4	0	0	2	36	21.4
51-60	34	8	2	0	4	48	28.6
Total	130	16	8	7	7	168	100.0
Percentage	77.4	9.5	4.8	4.2	4.2	100.0	

***Significant at 0.1% level of significance, Ajwain was used by 9.5% of patients to get relief from ADE, ADE = Adverse drug effects, ADR = Adverse drug reaction

Table 4: Reasons or motivation for the continuation of treatment

Age	Motivation to continue the treatment					Total	Percentage
	Knowledge of the severity of disease	Family pressure	Doctor	Other patients getting cured	Any other		
21-30	12	24	6	6	0	48	20
31-40	18	18	18	18	0	72	30
41-50	18	12	12	6	0	48	20
51-60	18	30	18	6	0	72	30
Total	66	84	54	36	0	240	100
Percentage	27.5	35	22.5	15	0	100	

***Significant at 0.1% level of significance (for motivation to continue the treatment), The biggest motivation for the continuation of treatment was family pressure followed by knowledge of the severity of the disease

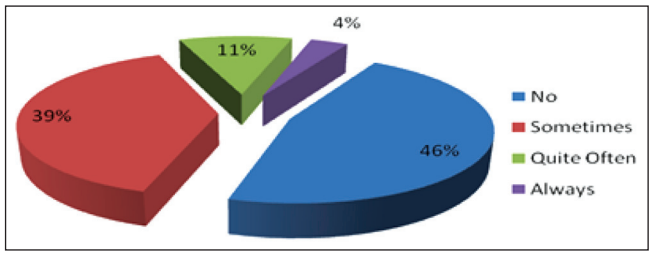

Figure 3: Distribution of patients (%) feel like stopping the treatment

observed. Such high compliance rates could be due to the efficient counseling of the patient in DOTS centers. During the study period a total of 168 (141 registered in our DOTS center and 27 registered in other DOTS centers, who came for follow-up in our chest and TB OPD) patients were interviewed, out of which 132 were male, and 36 were female.

Maximum numbers of patients were in the age group of 31-40 and 51-60. 42 patients in the age group of 31-40 (25%) were not aware about signs and symptoms of TB before treatment. ADE were the most likely cause to leave the treatment as reported by patients (38%).

Patients reported to be having 16 types of ADE which mainly involved gastrointestinal system (39%), genito-urinary system (32%), musculoskeletal system (13%), central nervous system (7%), dermatological symptoms (6%), the vestibular system and ocular system (3%). This is similar to the findings of Chhetri *et al.* in Nepal.[10]

Majority of ADE were reported in age group of 21-30 and 51-60 years. This correlates well with the study by Chhetri *et al.*[10]

Table 5: Patients suffering with emotional problems secondary to social stigma

Age	Suffer from any emotional disturbances secondary to social stigma related to TB		Total
	N	Y	
21-30	24	12	36
31-40	36	12	48
41-50	24	12	36
51-60	36	12	48
Total	120	48	168

Chi-square = 1.4, P = 0.23. 28.5% of the patients responded that they suffered from social stigma-related to TB, TB = Tuberculosis

However in another study by Yee *et al.*, age above 60 years was associated with an increased incidence of ADE due to anti-TB medicines.[11]

There was a marked association of alcohol consumption and smoking with increased incidence of ADE in the age group 51-60 years. Study conducted by Kurniawati *et al.* also showed that the association between drug-induced ADE and addiction (alcohol, smoking) is significant.[12]

Ajwain and lemonade were frequently used as home remedies for relief from ADR. This showed that major discomfort was due to gastric problems which reportedly subside on home based medication. The biggest motivation for the continuation of treatment was family pressure, which can be used as a tool to increase patient compliance rate. Patient's family can be the target population to spread education regarding the disease [Table 4].

It was observed that 29% of patients suffered from emotional problems secondary to social stigma. Results of similar kind were also

reported in a study conducted by Karim *et al.* which concluded that social stigma was more common in females.[13] This results are due to less awareness about the disease and its treatment. It was observed that 61% of patients had full faith in the treatment. This significant value of faith among patients is quite motivational from treatment point of view, because only when the patients have faith the treatment can bear results [Figure 3].

In the present study, 68.5% of the patients gave consent for biochemical investigation. On biochemical examination, it was found that serum bilirubin (direct) was raised in 52% of the patients and serum albumin was below the normal limit in 59% of the patients, but there was no marked sign of hepatotoxicity in any of the patient. In 31% of the patient blood urea was raised, and ESR was raised in 59% of the patients. Study by Shakya *et al.* have also shown that there is derangement of liver function tests present in patients who are taking anti tubercular medicines for a long time.[14]

CONCLUSION

Adverse drug effects was observed in patients taking anti TB treatment, majority of symptoms were mild which included abdominal symptoms in the maximum number of cases. However, majority of the patients reported that ADE will be the most likely cause to leave the treatment. There was no marked sign of hepatotoxicity in patient taking anti tubercular treatment. Special intervention and knowledge to cure these mild adverse effects can lead to increased patient compliance. The study also showed that family plays the most important role to combat the illness. Family pressure played a very important role in increasing patients' compliance to the treatment. Most patients had faith in the treatment and were interested in continuing the treatment.

Though less than half patients were under DOTS category 2, but efforts should be made to bring this number to zero. More studies should be conducted to evaluate what leads to treatment failure and decreased compliance rate among patients. Studies should be conducted to evaluate the benefits of palliative care for TB patients.

Efforts should be made to treat the adverse drug reactions and also provide emotional support to the patients.

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