AN OBSERVATIONAL PROSPECTIVE STUDY OF ADVERSE DRUG REACTIONS IN NEW SMEAR POSITIVE PATIENTS OF PULMONARY TUBERCULOSIS TREATED UNDER DIRECTLY OBSERVED TREATMENT IN CONTINUATION PHASE IN GENERAL MEDICINE OPD AT GULBARGA INSTITUTE OF MEDICAL SCIENCES, KALABURAGI

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ABSTRACT

BACKGROUND

The objective of this study was to study the adverse drug reaction profile of New Sputum-Smear Positive (NSP) patients of pulmonary tuberculosis (PTB) treated under DOTS in category-I, in continuation phase. A prospective observational study was carried out at General medicine OPD, Gulbarga Institute of Medical Sciences, Kalaburagi over a period of three months.

MATERIALS AND METHODS

The study included 180 newly diagnosed TB patients on anti-TB treatment under DOTS. A symptom-based approach was followed for monitoring ADRs. The severity was assessed by Modified Hartwig Scale and causality by WHO-UMC probability scale. Data was expressed as counts and percentages for discrete variables using Microsoft Excel.

RESULTS

Out of 180 patients, 104 patients experienced ADRs with an overall incidence of 57.7%. 56(31.1%) patients showed single ADR whereas 48(26.6%) patients had two or more ADRs. Gastritis alone was present in 45(73.7%) patients followed by itching 4(6.5%), arthralgia 5 (8.1%), jaundice in 3 (4.9%), and generalized weakness 2(3.3%) in patients. Vomiting was present in 34(70.8%) patients, neuropathy in 4 (8.3%) patients, arthralgia in 3 (6.25%) patients, jaundice, itching and generalized weakness in 2 (4.1%) patient each. 61 (58.6%) patients experienced mild, 36(34.6%) had moderate and only 7(6.7%) had severe ADRs.

CONCLUSION

The incidence of ADRs was 57.7% and GI irritation was found to be most common ADR reported by 73.7% patients.

KEYWORDS

Tuberculosis, DOTS, ADRs.

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BACKGROUND

Tuberculosis is one of the major health problems, with India being the highest TB burden country. Directly observed treatment short course (DOTS) was introduced in India in 1993 as part of revised national tuberculosis control program (RNTCP).[1] Combinations of Isoniazid (INH), Rifampicin (RFP), Pyrazinamide (PZA), Ethambutol (EMB), are administered every other day for 6 months.[2] The therapeutic efficiency of DOTS, combination therapy is well defined but certain studies suggest that more than 5% of the patients on anti-tubercular drugs develop ADRs.[3,4]

As the combinations of drugs are used for prolonged periods of time, it is likely that the ADRs of one drug are potentiated by the companion drugs used. All anti tubercular drugs can produce ADRs and involves almost all systems in the body such as gastrointestinal tract, liver, skin, nervous system, otto-vestibular apparatus and eyes.[5] The nature of ADRs also changes due to population variations with respect of genetic, environmental and dietary factors.[6] The Adverse Drug Reactions (ADRs) to the drugs is one of the major reasons for the patients default from the treatment.[6] ADRs not only contribute to the noncompliance to the therapy but because of their severity also lead to stoppage of treatment occasionally which may further lead to development of drug resistance strains. These resistant strains require second line drugs for treatment which have higher cost and more serious adverse drug reactions.[7] ADRs mostly tend to occur in the first three months of treatment.[8] As to the profile of adverse

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drug reactions (ADRs) due to DOTS, there is no report available in patients receiving anti-tuberculosis chemotherapy in Karnataka, India.

The primary objective was to study the adverse drug reaction profile of new sputum smear positive patients of pulmonary tuberculosis treated under DOTS in continuation phase in General medicine OPD, Gulbarga Institute of Medical Sciences, Kalaburagi.

MATERIALS AND METHODS

This observational prospective study was carried out at General medicine OPD, Gulbarga Institute of Medical Sciences, Kalaburagi from 1st Jan, 2018 to 31st Mar, 2018. The study was done after obtaining the approval from institutional ethics committee. The study included 180 consecutively diagnosed TB patients attending OPD of department of general medicine.

Inclusion Criteria

All the new smear positive patients of age >12 years of both sex and willing to participate were included in the study.

Exclusion Criteria

Patients with HIV positive serology and with renal and liver disease were excluded.

After obtaining the written informed consent from the patients, complete present and past history of the patient about the signs and symptoms as well as treatment history was taken in detail. Various laboratory investigations like complete hemogram, complete urine examination, LFTs, RFTs, visual acuity, and fundus examination were done. All the patients received category 1 DOTS as per current RNTCP guidelines. In continuation Phase (IP) DOTS was administered as three drug (3 FDC) fixed dose combinations (Isoniazid 75 mg, Rifampicin 150 mg and Ethambutol 275 mg) according to weight category on daily basis. Patients were followed up by the investigator till the completion of DOTS. The symptom-based approach for monitoring of adverse drug events was followed. Patients who reported any adverse drug event or any symptom were called and managed either on OPD basis or were admitted and managed with appropriate investigations and treatment. Adverse drug reactions were assessed by timing, pattern and back ground frequency. Severity of the ADRs were classified according to Hartwig et al as-

- *Mild reactions which were self-limiting and able to resolve over time without treatment and did not contribute to prolongation of length of stay.
- *Moderate ADRs were defined as those that required therapeutic intervention and hospitalization prolonged by 1 day but resolved in <24 hours or change in drug therapy or specific treatment to prevent a further outcome, and
- *Severe ADRs were those that were life-threatening, producing disability and those that[9] prolonged hospital stay or led to hospitalization, required intensive medical care, or led to the death of the patient. Causality assessment of suspected adverse drug reaction as per WHO-UMC causality assessment scale which quantifies the temporal association as certain, probable, possible, unlikely, conditional/unclassified, unassessable/ unclassifiable.[10]

Statistical Analysis

Data was expressed as percentages for discrete variables and the analysis was made using Microsoft excel.

RESULTS

Out of the total 180 patients, 104 patients experienced ADRs with an overall rate of 57.7%. 56 (31.1%) patients showed single ADR whereas 48 (26.6%) patients had two or more ADRs (Table 1).

ADR	Number of Patients	Percentage
1 ADR	56	31.1
≥ 2 ADR	48	26.6
No ADR	86	47.7
Total	**104**	**57.7**

Table 1. Adverse Drug Reactions (ADRs) in Patients

Table 2 Adverse drug reactions in patients (N=180).

Gastritis alone was present in 45(73.7%) patients followed by itching 4(6.5%), arthralgia 5(8.1%), generalized weakness 2 (3.3%) hypersensitivity 1(1.6%) and jaundice in 3(4.9%) patients. Two or more ADRs were present in 48(26.6%) patients. Gastritis was common in all the patients. Out of these vomiting was present in 34 (70.8%) patients, neuropathy in 4(8.3%) patients, arthralgia in 3(6.25%) patients, hypersensitivity in 3(6.25%) patients, jaundice in 2(4.1%) patients, itching in 2(4.1%) patients and generalized weakness in 2(4.1%) patients as shown in (Table 2).

Adverse Drug Event	No. of Patients	Percentage
Single Adverse Drug Reaction		
Gastritis	45	73.77
Itching	4	6.5
Hypersensitivity	1	1.6
Arthralgia	5	8.1
Jaundice	3	4.9
Generalized weakness	2	3.3
Total	**61**	**33.8**
Two or More ADRs		
Gastritis + vomiting	34	70.8
Gastritis + neuropathy	4	8.3
Gastritis + arthralgia	3	6.25
Gastritis + hypersensitivity	3	6.25
Gastritis + generalized weakness	2	4.1
Gastritis + jaundice	2	4.1
Gastritis + itching	2	4.1
Total	**48**	**26.6**

Table 2. ADRs Profile of Patients

Out of the total 180 patients, 61 (58.6%) patients experienced mild ADRs, 36 (34.6%) patients had moderate and only 7 (6.7%) patients had severe ADRs. (Table 3). On causality assessment using WHO causality assessment scale all the ADRs were possible in nature.

ADR Nature	No. of Patients	Percentage
Mild	61	58.6
Moderate	36	34.6
Severe	7	6.7
Total	**104**	**57.7**

Table 3. Severity Assessment of ADRs (N=180)

DISCUSSION

The incidence of adverse drug reactions in our study was 57.7% and GI irritation (gastritis) was found to be the most common ADR reported by 7.7% patients. Patients with mild ADR did not require any treatment.

Symptoms of gastritis started within a week of the start of treatment. In almost all the patients with gastritis and vomiting, change in dietary habits was recommended. Additional Proton pump inhibitor or histamine antagonist was prescribed in those in which alone dietary advice could not bring relief. None of these patients were dechallenged. Since gastritis is the most common reported ADE, change in dietary habits like low fat diet, bland diet and consumption of cold milk should be recommended in these patients. Peripheral neuropathy was present in 4 patients. All the patients presented after one month of start of treatment. It was mild to moderate in nature. All the patients were given additional pyridoxine 100 mg daily. None of the ATT was stopped and patients improved without any other intervention.

Hypersensitivity reaction to ATT was present in 3 patients. One patient had severe hypersensitivity reaction immediately after the first dose of treatment; The reaction subsided immediately after stopping the R (dechallenge). Re-challenge was not done in this patient due to ethical reasons. All the four first line drugs can cause hypersensitivity reactions, but it is found to be most common with R.[11] Another patient had vasculitis after 1 week of the start of treatment. The patient was admitted and the reaction subsided within a day on its own. The causal association of ATT drugs was not ascertained in this case. Out of total 104 patients, single ADR was experienced by 56 (31.1%) patients and more than one ADR were experienced by 48 (26.6%) patients.

In the study conducted by Acharya et al in Karnataka, the incidence of ADRs was 17.02%, with more preponderance in males and gastritis was the commonest complaint.[12] In another study conducted by Dhingraet al in New Delhi, GI symptoms were most common symptoms and were present in 53% of patients. In the study from Nepal by Khetri et al, the incidence of ADR was 54.74% with equal prevalence in males and females.[13] Commonest ADR was central nervous system. Two studies from Russia by Chukanov and Tashpulatova reported an incidence of 72.8% and 60.2% respectively.[14] The incidence of ADRs may vary from population to population in different regions to a great extent. Our study findings are similar with the previous study done by Sharma A et al.[15]

Onset of the ADRs is an important factor as some of them appeared very early and others delayed. In our study about 80% of the ADRs occurred within the first week of therapy. In the study by Dhingra, 67% of the ADRs occurred in the first four weeks. The average lag in start of treatment and appearance of adverse drug reaction was immediate reaction to 120 days. As some of the ADRs would appear early and would gradually increase while others present only in the initial period and gradually subside with passage of time. Since DOTS is a combination therapy, it is very difficult to find a causal relationship between individual drug and ADE without de-challenging it which was done only in one patient. Even in that case two medications were stopped, and risk of re-challenge was not found feasible.

CONCLUSION

Identification of adverse drug reaction profile of drugs is not only useful in prevention, early detection and management of ADRs but also helps in drawing long term strategies of treatment with appropriate schedules.

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