Original Research Paper

Volume - 7 | Issue - 5 | May - 2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

PHARMACOLOGY

A CRITICAL ASSESSMENT OF ADVERSE DRUG REACTIONS DUE TO FIRST LINE ANTI TUBERCULAR DRUGS IN DOTS THERAPY

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ABSTRACT Objective of the study is to assess ADR due to DOTS Therapy. 151 patients suffering with Pulmonary / Extrapulmonary tuberculosis were included in the study. 36 patients developed ADR showing incidence of 23.84%. 15 patients showed more than 1 ADR with total ADR to be 52. ADR in Gastrointestinal System was 42.3% ,Cutaneous system ADR was 19.2 % , musculoskeletal system was 11.5 % ,ototoxocity was 9.6 % , nervous system was 7.6 %, liver and biliary system was 5.7 % and others was 3.8 %. 40. 3% of ADR were due to Isoniazid, 25% because of Rifampin, 17.3% due to Pyrazinamide, 7.6% due to Ethambutol and 9.6% due to Streptomycin . 57.6 % cases were of mild grading in severity and 42.3 % were moderate. 67.3% of the cases had a possible relation with the drug. 32.6% ADR were assessed as probable .

KEYWORDS : ADR, DOTS Therapy, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. It mainly affects lungs causing Pulmonary Tuberculosis and other organs like meninges, intestine, bones and joints, lymphatic system, skin and other tissues of the body which is known as Extra Pulmonary Tuberculosis[1]. According to WHO Global TB Report, 2015, out of the estimated global annual incidence of 9.6 million TB cases, 2.2 million were reported to have occurred in India[2]. The Directly Observed Treatment short course (DOTS) therapy used for Tuberculosis treatment mostly needs more than one drug combination to eradicate tuberculosis bacteria. First line anti-tuberculosis drugs in DOTS therapy are isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin[3]. These are used as multidrug regimens and have been known to cause adverse drug reactions . These adverse drug reactions (ADR) may be mild ,moderate or severe which challenges the compliance of the patient with DOTS therapy[4]. Adverse drug reactions also contribute to increased healthcare cost .This is of great concern to the general population, the pharmaceutical industry, the regulatory authorities and the medical profession[5]. Therefore it is important to identify and monitor the ADR due to DOTS therapy and also to create awareness amongst both patients and medical professionals so that it results in better compliance for DOTS therapy. The objectives of this study are to critically assess the Adverse Drug Reactions due to anti tubercular treatment under DOTS therapy in Tuberculosis patients and to carry out the causality and severity assessment of the reported ADR.

METHODOLOGY

The present study is a prospective, observational study conducted at Department of TB and Chest Diseases at Hamidia Hospital Bhopal and Department of Pharmacology Gandhi Medical College Bhopal. The study was carried out from June 2015 to June 2016. The primary objective of the study was to critically assess the Adverse Drug Reactions due to first line anti tubercular drugs under Directly Observed Treatment Short Course (DOTS) strategy in Tuberculosis patients. The secondary objective of the study was to collect demographic details of the patients with ADR to DOTS therapy, to identify the incidence and pattern of ADRs caused and to assess causality and severity of the reported ADR. Diagnosed patients of Pulmonary and Extra Pulmonary Tuberculosis attending the TB and Chest Department Outpatient Department and receiving DOTS therapy were included in the study. Approval and clearance from the Institutional Ethical Committee was obtained before starting the study. All cases which met the inclusion criteria of the study during the time period of the study were included in the study. Total 151 patients met the inclusion criteria. The potential study subjects were interrogated for history in the local dialect and detailed information related to the disease was recorded. A medical specialist carried out a thorough clinical examination for both pulmonary and extra pulmonary TB cases.

INCLUSION CRITERIA :

- All diagnosed cases of Pulmonary/ Extra pulmonary TB through various Lab Investigations.
- Patients undergoing treatment with Category I or Category II regimen of DOTS therapy in the study duration.
- Both Genders suffering with Pulmonary/ Extra Pulmonary Tuberculosis were included.
- Patients more than 12 years of age
- Patients who gave Informed and written Consent for participation in the study.

EXCLUSION CRITERIA :

- All Multi Drug resistant (MDR) / Extensively Drug resistant (XDR) cases.
- Pregnant and lactating mothers.
- Human Immunodeficiency Virus (HIV) infected patients.
- Patients with impaired Renal / Hepatic Function
- Patients suffering with uncontrolled medical conditions like severe anemia, congestive heart failure and Ischemic Heart Disease.
- Patients below 12 years of age.

After obtaining written informed consent, and as per the Inclusion and Exclusion criteria patients receiving treatment under DOTS regimen (Category I / II) for Pulmonary/Extra Pulmonary TB were enrolled in the study. Patients developing ADR due to anti tubercular treatment under DOTS regimen were critically assessed and the ADR was analysed for Causality and Severity. Incidence of ADR in the study population was calculated .

For every TB patient, a detailed history including drug history, personal history, family history, present and past medical history and history of previous drug reactions was documented in a self developed patient profile Pro forma.

In the Pro forma all the essential information regarding the adverse effects: the onset and severity of the ADR experienced, the impact of ADR on treatment, the drug(s) involved and the date of starting the suspected drugs was recorded.

Information on any past or current occurrence of adverse effects due

to the anti tubercular drugs being administered to them was collected from the patients. Patients were followed at weekly intervals. The causal relationship with the offending / suspected drug(s) was established as definite, probable, possible or doubtful as per the Naranjo Scale[6]. Severity of the reactions were assessed by using Hartwig and Siegel Severity assessment scale[7].

STATISTICAL ANALYSIS

Analysis of Data was performed using MS Excel and Graph Pad Prism. Results were expressed as numbers, frequencies and percentages. Descriptive statistics were used to analyze data regarding incidence, causality, and severity assessment of ADRs.

OBSERVATIONS AND RESULTS

A total of 151 patients met the inclusion criteria and 36 patients developed ADR showing incidence of 23.84%. The Mean age group of the study population was 30.3975 years ± 16.467 years. 15 patients out of 36 developed more than 1 ADR with total number of ADR to be 52. In the present study 23 Females developed ADR when compared to 13 Males . 6 patients of Extra Pulmonary Tuberculosis developed ADR while 30 patients of Pulmonary Tuberculosis developed ADR. 21 patients receiving Category I treatment for Tuberculosis showed ADR while 15 patients receiving Category II treatment showed ADR.

Incidence of Gastro-intestinal symptoms was highest amounting to 42.3%. The incidence of itching with or without rash was 19.2%. 6 cases of joint pain were seen with incidence of 11.5 % . 5 cases of Ototoxicity were observed with incidence of 9.6%. 2 cases of ADR in Nervous System (Peripheral Neuropathy and Psychosis) were observed. The incidence of Hepatotoxicity was 5.7% . Incidence of ADR to other systems was 3.8 % (Table 1).

Total number of ADR for individual drugs under DOTS regimen were : 40.3% (n=21) for Isoniazid (H) which was maximum amongst all the drugs, 25% (n=13) for Rifampicin (R), 17.3%(n=9) for Pyrazinamide (Z), 7.6% (n=4) for Ethambutol (E) and 9.6% (n=5) for Streptomycin (S) (Table 2).

According to Naranjo Scale6 67.3% (n = 35) of the cases had a possible relation with the drug. 32.6% (n = 17) ADR were assessed as probable while none showed Definite Causality with the developed ADR. Severity assessment using Hartwig and Siegel Severity Assessment scale7 showed 57.6 % cases of mild grading, 42.3 % of moderate and no case of severe grading.

TABLE 1 : SYSTEM / ORGAN SPECIFIC DISTRIBUTION OF ADVERSE DRUG REACTIONS

SYSTEM/ ORGAN INVOLVED	ADR	NUMBER OF ADR (n)	%
GASTRO INTESTINAL SYSTEM	Abdominal Cramps	22	42.3
	Nausea & Vomitting		
	Diarrhoea		
SKIN	Itching	10	19.2
	Itching with Rash		
MUSCULO SKELETAL SYSTEM	Arthralgia	6	11.5
OTOTOXICITY	Auditory Symptoms	5	9.6
	Vertigo		
NERVOUS SYSTEM	Peripheral Neuropathy	4	7.6
	Psychosis		
LIVER & BILIARY SYSTEM	Hepatitoxicty	3	5.7
OTHERS	Flu like Syndrome	2	3.8
	Total	52	100

TABLE 2 : TOTAL NUMBER OF ADVERSE DRUG REACTIONS FOR INDIVIDUAL ANTI TUBERCULAR DRUGS

ADR	H (n)	R (n)	Z (n)	E (n)	S (n)
Abdominal Cramps	4	3	2	1	0
Arthralgia	1	0	5	0	0
Auditory Symptoms	0	0	0	0	2
Diarrhoea	2	2	1	0	0
Flu like Syndrome	0	2	0	0	0
Hepatotoxicity	2	1	0	0	0
Itching	3	2	0	0	0
Itching with Rash	3	0	0	2	0
Nausea & Vomitting	2	3	1	1	0
Peripheral Neuropathy	2	0	0	0	0
Psychosis	2	0	0	0	0
Vertigo	0	0	0	0	3
n(%)	21(40.3%)	13(25 %)	9(17.3 %)	4(7.6 %)	5(9.6 %)

DISCUSSION

The present study is a Prospective Observational Study. A total number of 151 patients of both Pulmonary and Extra Pulmonary Tuberculosis meeting the inclusion criteria were included in the study. A total 36 patients developed Adverse Drug Reactions showing an incidence rate of 23.84 %. 15 patients out of total 36 patients developed more than 1 ADR with total number of ADR to be 52. A study from Nepal showed an incidence of 12.27% (Kishore PV et al[8]). A study from Manipal, India (Tak.DK et al[9]) showed an incidence of 17.02%. There is a wide variation in the incidence of ADR depending on the place and time of the study.

In the present study Females developed more ADRs than Males . Yee et al[10] and Kishore PV et al[8] also show females to be more susceptible to developing ADR to anti tubercular treatment. Generally, females are considered to be more at risk of ADR due to their smaller body size and body weight compared to males or it might be because females pass through life stages like pregnancy, menarche etc., which modify the drug response. But the result was statistically non significant.

In our study patients of Extra Pulmonary Tuberculosis developed only 16.6% (n=6) of total 36 patients developed ADR while patients of Pulmonary Tuberculosis developed 83.3 % (n=30) ADR of total 36 patients. This is in correlation with study Tak DK et al[9] which showed 4 % incidence of ADR in Extra Pulmonary Tuberculosis patients. Patients receiving Category I treatment for Tuberculosis showed 58.8 % (n=21) ADR out of the total 36 patients who developed ADR , while patients receiving Category II treatment showed 41.6 % (n=15) . The observation was statistically non significant.

Adverse Drug reactions of Gastro-intestinal System developed within 2 weeks of initiation of the therapy. Symptomatic treatment was given in most cases and hospitalization was rarely required. 10 cases of itching with or without rashes were seen and they developed within 2 to 4 weeks of initiation of therapy. Anti histaminic drugs were given for the symptomatic treatment of itching and rashes. Muscle and joint pains specifically in the back developed within 2 weeks of starting the therapy. Pain was mild in nature and was relieved by analgesics. Ototoxicty included Auditory symptoms like tinnitus and hearing loss and Vestibular symptoms like vertigo which developed after 4 weeks of initiation of therapy. Peripheral Neuropathic symptoms included sensation of tingling. It was treated by giving supplements of pyridoxine 100 mg/day. In cases of Psychosis the drug was withdrawn. In cases of hepatotoxicity the drug was immediately withdrawn and was reintroduced after the reaction subsided.

Overall the incidence of ADR in Gastrointestinal System was highest constituting 42.3% (n=22) of total 52 ADR (Table 1). This is comparable with studies like Dhingra et al11 (53%), Kishore PV et al8 (53%).

The Naranjo Scale6 is widely used in carrying out the causality assessment of ADRs. According to Naranjo Scale6 67.3% (n = 35) of the cases had a possible relation with the drug. This was in variation with Tak D.K et al9 (88.52%) and Kishore et al8 (20%). 32.6% (n = 17) ADR were assessed as probable while none showed Definite Causality with the developed ADR.

Severity assessment using Hartwig and Siegel Severity Assessment scale7 showed 57.6 % cases of mild grading, 42.3 % of moderate and no case of severe grading. A study by Sivaraj, et al12. also reported the majority of reactions to be mild (68.97%).

The present study indicates that the pattern and spectrum of AD was similar to those observed in other studies with some difference in the pattern and the individual causative drugs.

CONCLUSION

This study showed that about 23.84 % of TB patients who received DOTS therapy developed one or more ADRs during treatment. The reactions were Mild and Moderate in nature but these side effects may still result in poor compliance of the patient to make a judgment for stopping the medications which is a cause of occurrence of drug resistance and increased economic burden. It is also essential to give an alert card to the patient to warn against the future exposure. A further more elaborate population-based prospective study, though very tedious and cumbersome, may help to generate more extensive and accurate data thus providing a greater awareness regarding the overall incidence, prevalence and pattern of ADR and their causative drugs seems to be worth undertaking and also form an important aspect of Pharmacovigilance Programme.

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