Pattern of Adverse Drug Reactions with DOTS regime in Pulmonary Tuberculosis at tertiary care teaching hospital, Kanpur.

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Abstract: our study aimed at recognising the patterns of ADR prevalent in our tertiary care teaching hospital and research, Kanpur with the implementation of DOTS regime in new Pulmonary TB.
Material & Methods: It was a prospective observational study conducted in the department of Pharmacology in association of Department of Medicine in tertiary care teaching hospital and research centre, Rama Medical College ,Kanpur UP. All the newly diagnosed Pulmonary tuberculosis adult patient enrolled for DOTS regime in intensive phase were followed up for ADRs. The causality and severity were determined by WHO and Hartwig's algorithms respectively.
Results: a total of hundred pulmonary tuberculosis patients were enrolled in our study following the inclusion criteria. A total of 125 ADRs were noted in these six months. Males(71%) had a higher ratio of ADRs than females(29%). Majority of the reactions were associated to the gastrointestinal tract system. Hepatitis(>3x) was serious ADR. Majority of the ADRs were of mild type (81.60 %) and were Probable in 88%. 79% of the patients did not require any modification in the standard regime due to ADRs.
Conclusion: As healthcare workers it is ethically correct to be persuasive, convincing and supportive to the patients for continued treatment despite the mild Adverse Drug Reactions experienced in course. An influential education system of these patients' under-treatment can improve the patient adherence and therapeutic outcome consequently reducing the morbidity and untimely mortality in our country.

Introduction

Tuberculosis (TB) is an ancient disease that has affected mankind for more than 4,000 years. It is a chronic disease caused by an acid-fast bacillus *Mycobacterium tuberculosis* and spreads from person to person through air. India has the highest burden of TB in the world which usually affects the lungs but it can also affect other parts of the body. In the cases of pulmonary TB which is commonly seen in India, may cause symptoms such as chronic cough, pain in the chest, haemoptysis, weakness or fatigue, weight loss, fever, and night-sweats. (1) anti tuberculosis drugs are one of the common prescribed drugs in developed counties like that in india . so are the high ADRs . ADRs contribute largely to global morbidity and mortality due to treatment against TB.

Despite the brief decline in TB notifications observed around the months corresponding to India's two major COVID-19 waves, the National Tuberculosis Elimination Programme (NTEP) reclaimed these numbers. The NTEP has been agile in adopting and adapting newer drugs and treatment modalities. In recent years, the country has made far-reaching progress in the management of TB. (2) One of the challenges of TB is that the pathogen persists in many infected individuals in a latent state for many years and can be reactivated to cause disease. TB is a curable disease with proper and continuous treatment. But if the patient is inconsistent with the chemotherapy of tuberculosis, which are mainly due to side effects of these drugs, lead to development of resistance and the cases of MDR and XMDR TB upsurge. This has urged the need to identify the side effects and adverse effects in new patients in intensive phase under DOTS regime for their early diagnosis and treatment. Also, to further improve the compliance and achieve course completion of a major number of patients to cure TB. This will greatly help in diminishing the countrys' as well as global burden of this disease.Much progress has been made in the recent years about the Tuberculosis and related ADRs, major gaps still persist . these lacunas can be filled in only by completing the drug-course , due reporting of the ADR and prompt management if needed . Our present study aimed to record pattern of adverse drug effects including side effects experienced in newly diagnosed patient of Pulmonary TB in intensive phase who were given Antitubercular drug treatment under DOTS regime.

Material and Methods

This is prospective and observational study carried out on hundred newly diagnosed Pulmonary TB patients . It was a six-month duration trial conducted by the department of Pharmacology in association with Department of Medicine, Rama Medical College Hospital & Research centre, Kanpur UP. All newly diagnosed adult cases of Pulmonary TB of either sex who visited the Medicine department of tertiary care teaching hospital were included in our study. Any patient who was MDR or XMDR TB patient or had comorbid conditions were excluded.

The study was approved by Institutional Ethics Committee Rama Medical College, Kanpur. Detailed clinical history, patient examination and relevant laboratory investigations were documented initially for the eligible patients. These patients were administered antitubercular drugs (in FDC) according to the RNTCP regime. They were requested for regular follow-ups to the hospital and were inquired for compliance, side effects or adverse effects experienced, if any. The data hence obtained was recorded in a tabulated form. Thorough history of the drug compliance and ADR reporting such as the time of onset and drug intake corelation

and the intensity of it was also verified and duly noted in each patients' visit. All the side effects and adverse effects thereafter were analysed and segregated as most common to least common.WHO causality assessment scale as well as Hartwig's severity scale were used to categorise ADR. The data was analysed using descriptive statistics using Microsoft Excel and expressed as percentages.

Table 1: Classification in Gender

Gender	No. of patients prescribed with antitubercular drugs(n=100)
Male	71
Female	29

Table 2:Classification of Age group

Age group (in years)	No. of Patients
20-40	28
41 – 60	56
61-80	12
.> 80	4

Table 3: Percentages of ADR reported

ADR reported as	No of ADR reported(n=125)	Percentage(%)
Abdominal pain	47	37.6
Diarrhea	5	0.04
Rash	9	0.72
Loss of appetite	22	17.6
Pruritis	8	6.40
Joint pain	4	3.2
Body ache	9	0.72
Headache	6	4.8
Nausea /Vomiting	13	10.4

Table 4: WHO Causality assessment of ADRs

Seriousness	Number of ADR(%)
Probable(5-8)	110(88)
Possible(1-4)	15(12)

Table 5: Hartwig's Severity Assessment of ADRs

Grade of Severity	Number of ADR (%)
Mild	102(81.60)
Moderate	21(16.8)
Severe	2(0.01)

Results

Widely held, the patients reported had more than one ADR. There were hundred patients enrolled for our study among who 71 were males and 29 were females (Table 1). 41- 60 years age group had the maximum patients (56%) followed by that in 21-40 years (28%). The incidence of "New TB case" was lower in adults above sixty years (Table 2). A total of 125 ADRs were collected from the patients. We observed in gastrointestinal system, ADR were on a higher tone than others such as abdominal pain, loss of appetite, nausea-vomiting and diarrhoea in descending order. Some patients reported pruritis(rash), joint pains and general malaise with headache (Table 3) On further assessment on the WHO probability scale (Table 4), we noted that many ADRs fell under the category of probable ADR (110; 88%) and the rest were possible ADR(15;12%). When explored on the Hartwig's scale (Table 5), majority of the reporting were non serious or mild type (102, 81.60%). Remaining were moderate (21;16.8%) and serious (02;0.01%) which were managed promptly. Hepatitis was a serious ADR observed and the patient was off the study. There was no mortality in any patients due to ADR from chemotherapy in the study period at our hospital.

Although, in 21% of all patients, the standard treatment regime had to be modified due to non-compliance and intolerance of the associated side-effects. Rest 79% were continued on the typical regime laid with supportive treatment for ADRs.

Discussion

Our research for ADRs caused by Antitubercular treatment in newly diagnosed Pulmonary tuberculosis with intensive phase regime revealed 125 ADRs in total. ATT associated ADRs were found to have summed up to a major burden of the total ADRs when compared with other class of drugs. Males were predominately affected than females. The results collected by us are in coherence with the study conducted by Athira B et al.(3) and Jayapriya et al.(4) This could be explained by higher male admission to the hospital during the study period. The most common age group noted was 41-60 years. Manju et al.(5) also had maximum patients falling in middle age of 41-55 years. Most frequent ADR were those related to the gastrointestinal tract. We noted that abdominal pain and loss of appetite were the main complaints. Nausea and vomiting were associated with the initiation of chemotherapy. Mild symptoms mainly from the gastrointestinal tract were managed symptomatically. 45 % of the ADRs in GIT were reported by Shareef J et al.(6) Farazi A et al.(7) also found a higher incidence of gastrointestinal ADR reporting on Iranian patients. A study by Jayapriya et al. and Athira B. et al. also confirmed the same. Charumathi A et al.(8) validated that the most common system involved is that

of GIT. Manju et al. came across higher number of Gastrointestinal system involved ADR. Oral administration of bactericidal drugs on empty stomach may be a major reason for abdominal symptoms. There were no drug modifications done in 79% of subjects. However, 21% demanded a change in the standard regime who were turning noncompliant or were intolerant to adverse effects. General malaise, bodyache and joint pain, rash and pruritis trail the aforesaid. Serious liver damage and Hyperuricemia were seen in two patients respectively and were withdrawn from the study. It was also summed that the ADRs could become serious requiring hospitalization. Deranged Liver transaminases(>3x) were serious reactions noted which definitely required curbing the treatment strategy or were followed up more frequently with regular reporting of liver enzymes. Liver dysfunction was also noted by Farazi et al. where patients suffered increased levels of AST & ALT which was serious medically. Our study also suggested that raised liver enzymes is a serious ADR. Athira B et al.(3) showed that hepatotoxicity was a serious ADR reported. The results were further confirmed by another study done by Charumathi et al.(8) which indicated that Pyrazinamide was most toxic drug followed by isoniazid . A combination of both drugs could lead to potential hepatotoxicity. Alongside, elevated uric acid concentrations (2%) were among other serious ADR which were certainly due to Rifampicin use.(5) Farazi et al.(7) documented hyperuricemia with the Antitubercular treatment in Iranian patients. Uric acid elevation were also noted by Athira B et al.(3) in a very small number of patients. She documented it in two patients with the usage of Pyrazinamide which was reversed with stopping the drug. The ADRs in 81.60% of patients were mild type which didn't require radical treatment. Manju et al.(5) documented 79.6% were non serious ADRs. Nevertheless Shareef et al.(6) differed to our data to documented 36.4% as mild ADRs as against 60.7% of moderate ADRs. Athira B et al.(3) examined that, out of 105 adverse drug reactions, 68.57% were moderate and 31.42% were mild reactions which is unlike our study. The difference could be due to differences in patient population and available preparation of the drugs. The present study also explored and documented that most of the ADR were on the "probable" scale of assessment(110,88 %). Shareef et al. quoted that the adverse drugs reactions were found to be 'probable' by both WHO and Naranjo scales in his study in patients on ATT. The causality assessment. Athira B. et al.(3) also showed that 68% of the ADR data was "probable". Studies by Jayapriya et al.(4) and Manju et al.(5) were alike to ours on causality assessment of ADRs with ATT.

Our study had few limitations. We conducted a single-centric short-term trial in a limited cross section of patients. We included only intensive phase pulmonary tuberculosis adult patients who were prospectively observed. Many more such ADR reports would be desirable for a prudent approach to this mammoth task of diminishing the cases which turn to MDR and XMDR TB only due to intolerance to adverse drug reactions ultimately leading to noncompliance.

Summary and conclusion:

Tuberculosis is a national health burden commonly associated with a range of Adverse drug reactions. Subsequently these reactions lead to intolerance to treatment culminating in non-compliance. (9) The consequences of ADRs burden on the healthcare system are both economically and physically challenging to a patient as well as to the country. Hence, robust actions will be pragmatic to diminish the conversion of these newly diagnosed patients ultimately to MDR or XMDR TB. Early diagnosis, management and counselling for the continuance of treatment is the pressing priority.

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