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Original Research Article

A Study on Incidence of Adverse Drug Reaction of Anti-Tubercular Drugs in New Cases of Pulmonary Tuberculosis in a Tertiary Care Teaching Hospital

Mazher Maqusood[1*], Farhan Ahmad Khan[2], Anand Swaroop[3]

[1*]Assistant Professor, Department of TB & Chest,
[2]Professor and Head, [3]PG Student, Department of Pharmacology,
Teerthanker Mahaveer Medical College Hospital and Research Centre, Moradabad, UP, INDIA.

ABSTRACT

Objective: A study on incidence of adverse drug reaction of anti-tubercular drugs in new cases of pulmonary tuberculosis.

Method: It was prospective observational study conducted on Positive pulmonary tuberculosis patients admitted in the ward of T.B and chest and enrolled on the directly observed treatment short course (DOTS) and monitored for ADRs. The causality and severity of adverse drug reaction carried out as per Naranjo scale and modified Hartwig and Siegel scale respectively.

Result: In this study, Out of 263 patient enrolled on DOTS therapy, n= 74(28.14%) patients developed ADRs in which male patient were n= 48 (27.58%) and female patient were n= 26 (29.21%). Total no. of ADRs reported in n=74 patients were n=212. The severity of ADRs were from mild group with n= 161(75.94%) followed by moderate with n= 38(17.92%) and severe n= 13(6.14%). The causality of ADRs reported were probable with n= 158(74.52%) of cases, followed by possible n= 42(19.81%) and definite n=12(5.67%). The most commonly reported ADR was hyperacidity n= 34 (16.03%).

Conclusion: This prospective study conclude that the majority of adverse drug reaction found during the treatment of pulmonary tuberculosis were mild with 75.94% and did not need modification of treatment or administration of specific antidotes followed by moderate with 17.92%, which required discontinuation or change of treatment and antidotes also required and Severe ADRs constituted 6.14% patients which requires intensive medical care.

Key words: Adverse drug reaction, Anti Tubercular therapy, Tuberculosis.

***Correspondence to:**

Dr. Mazher Maqusood, Assistant Professor, Department of TB & Chest, Teerthanker Mahaveer Medical College Hospital and Research Centre. Moradabad.
Email: dmaqusood@gmail.com

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INTRODUCTION

Tuberculosis an infectious disease caused by Mycobacterium tuberculosis, now become the second leading infectious cause of death in the world. Active pulmonary TB incidence estimated around 8 million new cases per year worldwide and approximately cause death 2 million per year.[1]

In 2009, there were an estimated 9.4 million incident cases of TB globally that is equivalent to 137 cases per 100 000 population. Most of the estimated number of cases in 2009 occurred in Asia (55%) and Africa (30%).[2]

Tuberculosis treatment mostly need more than one need more than one drug combination to eradicate tuberculosis bacteria. First line anti-tuberculosis drugs recommended by WHO are combination between isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin.[3]

The necessity use of multidrug regimens has been associated with increased incidence of adverse drug reactions of anti-tubercular drugs. This adverse drug reactions may be mild as well as fatal. Antitubercular agent that commonly use such as, isoniazid, rifampicin and pyrazinamide are highly effective but also can cause hepatotoxicity.

The frequency and nature of Anti-TB induced ADRs have been the matter of concern in many communities. One of the serious ADRs detected in these studies is hepatotoxicity. There are differences in reported rate of hepatotoxicity induced by Anti-TB drugs in different studies.[4]

This reaction could be affected by the genotype of patients receiving these drugs e.g. rapid-acetylator patients are more susceptible for isoniazid induced hepatotoxicity. Studies show that the risk of hepatotoxicity in patients from India is higher than those reported in West (11.5% versus 4.3%).[5]

Studies suggest that more than 5% of the patients on anti - tubercular drugs (ATD) develop ADRs.

Despite the positive therapeutic effects, studies have shown that utilization of multidrug regimens can cause undesirable adverse drug reactions (ADRs) of varying degrees of severity, such as hepatotoxicity, gastrointestinal (GI) disorders, allergic reactions, arthralgia, neurological disorders, and so on.[5-7]

Regarding the difference reported between Asian and Western people in developing Anti-TB induced hepatotoxicity, it is necessary to detect the rate of Anti-TB induced ADRs with emphasize on hepatotoxic reactions in Indian patients, since it could be helpful to revise the therapeutic protocols.

To the best of our knowledge this is the first study for assessing Anti-TB induced ADRs in Western UP patients.

Many minor and major cutaneous adverse drug reactions occur frequently at the doses which are normally used in man. However, these reactions are ignored or they are not reported appropriately to the Pharmacovigilance centres. Hence, this study was aimed in fulfilling the above mentioned lacunae.

AIMS AND OBJECTIVES

This study will be done to identify the incidence of anti-tubercular adverse drug reactions in patients suffering from pulmonary tuberculosis in T.B and Chest Department of Teerthanker Mahaveer Medical College and Research Centre.

India has a tuberculosis control program which is called RNTCP. Under this program, patients that suspected have tuberculosis should do some test series to develop a diagnosis, those test such as tuberculin test, sputum AFB test, culture test, chest x-ray and any other test that necessary for diagnosed.

All tuberculosis patients will be reviewed at first two week after started treatment and there after every month, except if they have an experience of adverse drug reactions, they will be informed to visit the doctor immediately.

METHODOLOGY

This prospective study was conducted on new cases of pulmonary tuberculosis treated in T.B and Chest Department of Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, for a period of 12 months. Around n= 263 patients were enrolled on the basis of inclusion and exclusion criteria.

INCLUSION CRITERIA

- Patient diagnosed with tuberculosis.
- Adult patient (18 years of age and above).
- Normal liver function test before start taking anti-TB drugs regimen.

EXCLUSION CRITERIA

- Patient with abnormal liver function test before start taking anti-TB drugs regimen,
- Paediatric patient (below than 18 years of age).
- Serological evidence of an acute infection with hepatitis B or C and was diagnosed hepatitis
- Patients already taking anti-tubercular drugs.

Research subject enrolled were diagnosed by physician as tuberculosis patient (an outpatient) in Chest Clinic, T.B and Chest Department of Teerthanker Mahaveer Medical College and Research Centre. The Causality Assessment done by Naranjo Scale in the department of Pharmacology. Severity of Adverse drug reaction assessed by using modified Hartwing and Siegel scale.

RESULT

In our study, total number n= 263 patients are included after applying inclusion and exclusion criteria. Among 263 patient, only n=74 (28.14%) patients experienced ADRs during their course of the treatment for Pulmonary Tuberculosis with ATT. As far as the demographic details concerned, out of 74 patients, 48 were male and 26 patients were female (Table 1).

It was observed in the study that the percentage of developing ADRs were less in the female patients n=26 (29.21%) than in male with n= 48 (27.58 %)

On further evaluation and studying the distribution of ADRs, on the basis of age group we found that maximum number ADRs were reported in patient of age group 31-40 years with n=27(36.4%), followed by age group 18-30 years with n= 23 (31.08%), n=16(21.62%) patients in 41-50 years age group, followed by age group 51-60 years with n=06 (8.1%) patients. The least number of ADRs were observed in age group 61-70 years with n=02(2.7%) (Table 2)

Table 1: Sex wise distribution of ADRs among Tuberculosis patient.

S No.	Gender	Number of patient developed ADRs (%)	Number of patient not developed ADRs (%)
1	Male	48 (27.58)	126 (72.41)
2	Female	26 (29.21)	63 (70.78)
	Total	74 (28.13)	189 (71.87)

Table 2: Incidence of adverse drug reaction among pulmonary tuberculosis patients according to age.

S No	Age group (yrs)	Number of patients (%)			
		Not developed ADRs (%)	Developed ADRs (%)	Developed ADRs Male patients	Developed ADRs Female Patients
1	18-30	54 (70.13)	23 (29.87)	12 (52.17)	11 (47.83)
2	31-40	61 (69.31)	27 (30.68)	19 (70.37)	08 (29.63)
3	41-50	37 (69.82)	16 (30.18)	11 (68.75)	05 (31.25)
4	51-60	25 (80.65)	06 (19.35)	04 (66.66)	02 (33.33)
5	61-70	12 (85.72)	02 (14.28)	02 (100)	00 (00)
	Total	189 (71.87)	74 (28.13)	48 (64.86)	26 (35.14)

Table 3: Patient distribution according to life style and occurrence of ADRs.

Habit		ADRs occurrence		Total
		Yes (%)	No (%)	
Smoking	Yes	30 (11.44)	96 (36.51)	126 (47.91)
	No	44 (16.74)	93 (35.36)	137 (52.09)
	Total	74 (28.13)	189 (71.87)	263 (100)
Alcohol use	Yes	18 (6.85)	36(13.69)	54 (20.53)
	No	56 (21.30)	153(58.18)	209 (79.46)
	Total	74 (28.13)	189(71.87)	263 (100)

Table 4: Type of detected ADRs induced by Anti-Tubercular Drugs.

S.No	Type of ADRs	n (%)
01	**Increased liver enzymes**	13 (6.13)
02	**Arthralgia**	19 (8.96)
03	**Skin allergy/rashes**	32 (15.09)
04	**Generalized weakness**	24 (11.32)
05	**Dyspepsia**	02 (0.94)
06	**Constipation**	05 (2.35)
07	**Diarrhea**	02 (0.94)
08	**Back pain/muscle pain**	14 (6.60)
09	**Headache**	21 (9.90)
10	**Fever**	06 (2.83)
11	**Hyperacidity**	34 (16.03)
12	**Pain abdomen**	27 (12.73)
13	**Insomnia**	04 (1.88)
14	**vertigo**	09 (4.24)
	Total	212

Table 5: Distribution of Adverse drug reaction by severity according to Hartwing's and Siegel scale scale.

S.No	Type of ADRs	Number of Cases	Frequency%
1	**Mild ADRs**	**161**	**75.94**
	Gastrointestinal	70	33.01
	Generalized weakness	24	11.32
	Neurological	67	31.60
2	**Moderate ADRs**	**38**	**17.92**
	Allergic skin reactions	32	15.09
	Fever	06	2.83
3	**Severe ADRs**	**13**	**6.14**
	Liver dysfunction	13	6.14

Table 6: Causality of ADRs according to Naranjo algorithm.

Causality of ADRs induced by anti-tubercular drugs according to Naranjo algorithm.		
	Percentage	**Frequency**
Probable	74.52	158
Possible	19.81	42
Definite	5.67	12
Total	100	212

According to habit and life style as seen in Table 3, n=126 (47.91%) patients were smokers, n=54 were alcohol users. During study it has been recorded that from n=126 smoking patients n=30 (11.44%) patients develops ADRs and n=96 patients do not develops ADRs. In alcohol consuming patients n=54 (20.53), only n=18 (6.85%) patients were suffered from ADRs.

During the study the major ADRs found was hyperacidity n= 34 (16.03), followed by skin allergy and rashes n=32 (15.09), pain abdomen with n=27 (12.73) ADRs, generalized weakness n=24 (11.32), Headache n=21 (9.90), Arthralgia n=19 (8.96), back pain and muscle pain n=14 (6.60), Increased liver enzymes n=13 (6.13), Vertigo n=09(4.24), Fever n=06 (2.83), Constipation n=05 (2.35), Dyspepsia n=02 (0.94), Diarrhea n=02 (0.94) (Table 4) According to Table 5, the most common ADRs were GI symptoms n=70 (33.01%), the drug which was responsible for these side effects may be PZA and RFP. Around n =13 (6.14%) patients developed Hepatic dysfunction as ADRs, the drug which was responsible for this ADRs may be PZA, RFP and INH and n= 06 (2.83%) patient developed fever and the drug responsible may be RFP.

During the study the causality of ADRs induced by anti-tubercular drugs was found by using Naranjo algorithm. According to Naranjo algorithm the major number of ADRs was detected as probable in n= 158 patient with 74.52 percent, followed by possible in n= 42 patients with 19.81 percent and n=12 patient detected as definite ADRs with 5.67 percent. During the study it was seen that after administration of anti-tubercular drugs no adverse reaction was seen in first 24 hours but the majority of adverse drug reaction was detected in first 10 days which was 75.1 percent which was decreased between days 10-20 by 21% and it was seen that 24.9% of adverse drug reaction occurs between days 21-30 which are moderate to severe drug reaction.

DISCUSSION

The aim of present study was to find out the ADRs of anti-tubercular drugs (DOTS). In this prospective study, total of n=263 patients were enrolled on DOTS, in which 74 patients were developed ADRs. The total number of ADRs was found to be n=212. During the study, we observed that males constitutes the major population of study group that was n= 174 (66.15) against females patients n= 89 (33.94). This male predominance may be due to the fact that male patient having more habit of smoking, alcoholism and drug addiction, also men are socially active and contact more persons and visit multiple places than female. These

risks make them more vulnerable for tuberculosis infection. According to Tak DK et al,[8] study he found the incidence of ADR was to be 17.02%, But in our study incidence is more 28.13%. This may because this area of Western UP is endemic for Tuberculosis.

In our study, it has been seen that majority of ADR was seen in age group of 31-40 years. The result is in contrast by Yee et al,[9] where due to anti- tubercular drugs the gender of age over 60 years was associated with increased incidence of ADRs.

Among total n=212 adverse drug reactions, the highest number of ADRs was observed in female n= 110 than male n= 102 were seen. Most of literature says that the female gender is the one of the predisposing factor for ADRs. Female are considered as a more risk factor than male for occurrence of ADRs due to anti-tubercular drugs as studied by Yee et al and Shakya et al.[10] It has been also considered that female patient having more risk of ADRs because of their small body size and to their body weight as compared to male patient. And it might be because they passes through various stages of life like pregnancy, menarche etc which changes the drug response. This suggests that important precaution should be followed while prescribing the anti-tubercular drugs to minimize the adverse drug reaction.

From different life style factors in this study it was seen that the ADRs in smokers was 11.44% and alcohol users developed ADRs in 6.85%. In the similar study conducted by Gronhagen Riska C et al,[11] alcohol users were having more risk for development of ADRs induced by Isoniazid and Rifampin.

After complete evaluation majority of adverse drug reaction was hyperacidity 16.03% and it was followed by skin allergy and rashes 15.09% and this was followed by pain abdomen 12.73% followed by generalized weakness 11.22% which was followed by head ache 9.90% and this was followed by vertigo 4.24%, fever 2.83%, constipations 2.35%, dyspepsia 0.94%, diarrhea 0.94%. Philadelphia tuberculosis control program suggested if the skin reaction developed due to antimicrobial use primary step to control the ADRs is to discontinue of the drug until the ADRs not resolved and after the identification of causative agent the drugs can be re started.[12]

In our study the Naranjo algorithm is used in the causality assessment of adverse drug reaction which is based on the score on the basis of points assigned to each of the ten questions. According to Naranjo scale majority of reaction was probable with 158 (74.52%), followed by possible 42 with 19.81% and definite with 12 with 5.67%. Severity of Adverse drug reaction assessed by using modified Hartwing and Siegel scale. For proper management of ADRs it is necessary to assess the severity of ADRs. During study it was found that out of 212 adverse drug reaction occurred by anti-tubercular drugs mild ADRs was 161 (75.94%) followed by moderate ADRs with 38 (17.92%) and severe ADRs was 13 (6.14%).

CONCLUSION

The study conclude that the occurrence of adverse drug reaction due to the anti-tubercular drugs used for treatment of pulmonary tuberculosis in the ward of Teerthanker Mahaveer Medical college and hospital Moradabad, India shows that the majority of adverse drug reaction found during the treatment of pulmonary tuberculosis was mild group with 75.94% and did not need modification of treatment or administration of specific antidotes followed by moderate ADRs with 17.92% which required discontinuation or change of treatment and antidotes also required severe ADRs was in 6.14% patients which requires intensive medical care. The study also shows that the pulmonary tuberculosis is more prevalent in age group of 31-40 years. Adverse drug reaction is more prevalent in female patients. The major detection of adverse drug reaction is from gastrointestinal system. It was also concluded that majority of causality of ADRs was probable which was 74.52% followed by possible 19.81% and definite 5.67%.

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