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Assessment Of Anti Tuberculosis Drugs Induced ADRs Among In Patients Of TB Ward In Tertiary Care Teaching Hospital.

P.Sireesha[1], S.Nahida Parveen[1], R.B.Achyuth Babu[1], D.Sreekanth[1], G.Divya[2].

[1](Pharm D Intern, *Department of Pharmacy Practice, Sri Padmavathi School Of Pharmacy Tirupati-517501, Andhra Pradesh, India).*

[2]*(Assistant professor, Department of Pharmacy Practice, Sri Padmavathi School Of Pharmacy Tirupati-517501, Andhra Pradesh, India).*

**corresponding author: P.Sireesha*

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Abstract

Background: Tuberculosis(TB) is the airborne communicable disease caused by Mycobacterium tuberculi. which has been one of the common disease affecting human communities. Other than disease related complications there are serious ADRs to the ATT.

Objectives: The main objectives of study was to evaluate the ADRs induced by ATT drugs and also assess causality and severity and informing to PvPI for signal generation and management was provided.

Materials and methods: A study was conducted for 7months at a tertiary care teaching hospital (Mar-Sep) 2019 at SVRRGH hospital Tirupati. Patients who developed at least 1ADR were taken as study subjects. Detection and monitoring of these ADRs was done by interviewing the patients.ADRs were then checked for causality and severity by using Naranjo and Hart wig questionaries respectively.

Results: During the study period 184 patients were admitted in pulmonology ward out of them 70 patients developed 80 ADRs. More number of ADRs were observed in males (57) than females (13). Most common ADR was found to be Gastritis (30) followed by hepatitis (13) then they are classified according to system wise. Causality assessment by Naranjo scale has definite 35%,propable 62.5%,possible 2.5%.Hartwig showed Mild were 31.25%,moderate 40%, severe were 28.75% reported. p value found to be <0.05(0.03).

Conclusion: The present study highlighted the importance of developing strategies to decrease the occurrence ADRs. Early detection of ADRs can be achieved by vigilance programme and proper counselling.As a clinical pharmacist we have the liability to support the patient during the period of ATT therapy.Furthermore strategies are in need of development to improve the patient compliance and therapeutic outcome.

Keywords: Adverse drug reactions, clinical pharmacist, NARANJO and HARTWIGSIEGEL scale, Pharmacovigilance, Tuberculosis.

I. INTRODUCTION

Tuberculosis(TB) is the most rampant communicable disease in the developing countries like India, which can cause morbidity and mortality in people mostly who are in economically productive period of life[2]. Tuberculosis is an infectious air born droplet disease caused by Mycobacterium tuberculi. Mostly effects lungs (pulmonary) but can also other sites (extra pulmonary) which can be curable and preventable.

TB remains one of the major health problems in our country. Twenty–five years ago, in 1993, WHO declared TB a global health emergency according to WHO TB report 2018. However, the probability of developing TB disease is much higher among people infected with HIV; it is also higher among people affected by risk factors such as under nutrition, diabetes, smoking and alcohol consumption. In India, about 1.8 million new cases of TB are detected every year. TB is one of the top 10 causes of death. It is also the leading cause of death from a single infectious agent, ranking above HIV/AIDS according to WHO TB report 2018[4].

World embraces DOTS (directly observed treatment short course) therapy which was introduced by RNTCP in 1993. It includes first line drugs used in combinations; Isoniazid (INH/H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z), Streptomycin (S). It is necessary to use multidrug regimen for prolong period of time to achieve complete cure in the TB patients[1].

For new patients with drug sensitive TB the World Health Organisation (WHO) recommends that they should have six months of TB drug treatment. This should consist of a two month “intensive” treatment phase followed by a four month “continuation” phase.

For new tuberculosis patients Intensive phase treatment 2 months of HRZE, continuation phase treatment 4 months of HR.

It is essential to take several TB drugs together. If only one TB drug is taken on its own, then the patient will very quickly become resistant to that drug, which means that the drug then won't work.

Table no 1 : Tuberculosis Drugs(RNTCP Guidelines)

First line drugs & Dosage regimen according to body weight	Second line drugs
Isoniazid 5 (mg/kg body weight) maximum (mg) 300	Fluoroquinolones like Levofloxacin, Moxifloxacin
Rifampicin 10 (mg/kg body weight) maximum (mg) 600	Injectables like Amikacin, Kanamycin
Ethambutol 15 (mg/kg body weight)	Other new drugs like Ethionamide, Cycloserine, Linezolid
Pyrazinamide 25 (mg/kg body weight)	
Streptomycin	

I.1.CATEGORIES OF TREATMENT REGIMEN:

For many years the World Health Organisation (WHO) defined four treatment categories for TB[1].

I.1.1.Category 1 was for new smear positive patients with pulmonary TB. $2(H_3R_3E_3)+4(H_3R_3)$

I.1.2.Category 2 was for sputum smear positive patients who have relapsed, who have treatment failure or who are receiving treatment after treatment interruption. $2(S_3H_3Z_3E_3R_3) +1(H_3R_3Z_3E_3)+ 5(H_3R_3E_3)$

I.1.3.Category 3 was for new smear negative pulmonary TB patients (other than those in Category 1), and patients with new less severe forms of extra pulmonary TB. $2(H_3R_3E_3)+4(H_3R_3)$

I.1.4.Category 4 was for chronic cases who are still sputum positive after supervised re-treatment[9].

More the drugs in regimen more the chances of occurrence of adverse drug reactions to patients. Undoubtedly modern drugs have increased life expectancy and improved quality of life for millions of people. However despite of all these benefits, evidence continues to suggest that adverse reactions to medicines are common, though preventable, cause illness, disability and even death[5].

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy[14].

Causality assessment of ADRs is a method used for estimating the strength of relationship between drug(s) exposure and occurrence of adverse reactions. This process is performed to know the severity of the ADR. According to Hartwig and Siegel severity is assessed by the categories of Mild, Moderate and Severe. According to WHO UMC causality assessment criteria. It includes certain, Probable, Possible,Unlikely, Conditional/unclassifiable, Unassessable. According to Naranjo scale Score >9= certain, 5-8=propable, 1-4=possible, <0= unlikely. According to shumock and thrompton preventability scale.Categories include Preventable, probably preventable, not preventable[15,16].

Occurrence of ADRs may lead to consequences like increase in patient discomfort, substantial additional costs because of excess outpatient visits, laboratory tests and other problems like treatment failure, relapse of condition, discontinuation of drugs, development of drug resistance[6].

All these may effect the patient adherence and compliance to treatment[2]. Good patient adherence to treatment regimen is foundation stone to get maximum effect of positive outcome. So early detection and monitoring of ADRs are needed to extemporisation and management of ADR is further required[7].

Therefore it is necessary to be vigilant about any ADR occurring with the use of ATT drugs, so that healthcare professionals might get a clear picture and they can oriented more towards patient counselling and their early management of ADRs can be done effectively[1]. Pharmacovigilance activities can help in obtaining real information of safety and efficacy of medicine when they are being used in the population[7].

II. METHODOLOGY

Study Design: Prospective Observational Study

Study Site : Department Of Pulmonology ,SVRRGGH , Tirupati.

Study Period: 7 Months (March to September)

Study Population: 184

Study Criteria:

Inclusion Criteria:
1. In Patient using ATT Therapy.
2. Newly Diagnosed Patients Of Tuberculosis.
3. Patients Of Either Sex With Age More Than 18yrs.
4. Patients Having No Associated Comorbidities Except HIV.

Exclusion Criteria:
1. Patients Who Are Not On ATT Therapy.
2. Patients Unwilling To Participate.
3. Patients Who are not cooperating.
4. Terminally Ill Patients.

Study Materials:
Patient data collection form
Informed consent form
Naranjo scale
Hartwig Siegel scale

Statystical Analysis:
The data obtained was analysed by using excel spreadsheet.
p value by using GraphPad Prism 8.0.2.

Data collection method:
A prospective observational study was conducted in inpatient of Department of Pulmonology, SVRRGGH, Tirupati. A specially designed proforma was used for collecting data which includes patient demographics, chief complaints, past medical and medication history, diagnosis, lab investigations, medications prescribed, category using, developed ADR each patient was assessed, this information was collected during ward rounds. Developed ADR was then categorised systematically based on the system involved. Causality was checked by using NARANJO scale, severity of the ADR was assessed by HARTWIG-SEIGEL criteria. Then ADR was managed by giving symptomatic therapy or supportive therapy. Based on the severity of ADR ATT drugs we suggested to take changes like stoppage of drugs, kept on hold for some days, modifying the regimen. Further these occurred ADRs were reported to PVPI for future purposes, signal generation.

III. RESULT

Out of 184 patients only 70 members developed ADRs in that 52 were Males 18 were Females. More number of patients fall under the age group of 51-60(20 members).61 members using Category 1 drugs, Only 9 members using Category 2 drugs. Out of 70 patients ,61 patients developed only 1 ADR, 8 Patients developed 2 ADRs and only 1 patient developed 3 ADRs. Details were given in Table no2.

Table no 2: Demographic and baseline parameters of patients having TB and its association with occurs of ADRs

Parameter	No Of Patients	Percentages (%)
Age Group		
20-30	8	11.43
31-40	12	17.14
41-50	16	22.86
51-60	20	28.57
61-70	12	17.14
71-80	1	1.43
81-90	1	1.43
Category Of TB		
Category 1	61	87.14
Category 2	9	12.86
No Of ADRs	**ADRs In Patients**	
1	61	87.14
2	8	11.43
3	1	1.43

Gender wise distribution	**No of patients**	
Male	52	74.28
Female	18	25.72

Among 70 patients, 80 ADRs are observed most of them are effected with Gastritis (30).Followed by Hepatitis (13),Anaemia (9), Skin rash (8), Erythroderma(4), Arthralgia (3), Vomiting's(3), Vertigo (2), Optic neuritis (2), Pedal edema & Red urine , CKD , Psychosis , Loose stools, Hypokalaemia are each 1 in number respectively.

Table no 3: Distribution based on type of ADRs

Type Of ADRs	People Affected	Percentages (%)	p value
Gastritis	30	37.5	0.0182
Hepatitis	13	16.25	
Anaemia	9	11.25	
Skin Rash	8	10	
Erythroderma	4	5	
Arthralgia	3	3.75	
Vomitings	3	3.75	
Vertigo	2	2.5	
Optic Neuritis	2	2.5	
Red Urine	1	1.25	
CKD	1	1.25	
Psychosis	1	1.25	
Loose Stools	1	1.25	
Hypokalaemia	1	1.25	
Pedal Edema	1	1.25	
Total	80	100	

Total number of ADRs developed in 70 patients were 80 in number with most common being Digestive system related (33), Hepatotoxicity (13), Cutaneous system (12), Haematology (9),Excretory (4),Ophthalmic (2), ototoxicity (2) , Musculoskeletal system (3),CNS (1), Dyselectrolytemia (1).

Table no 4: Systemwise distribution of ADRs

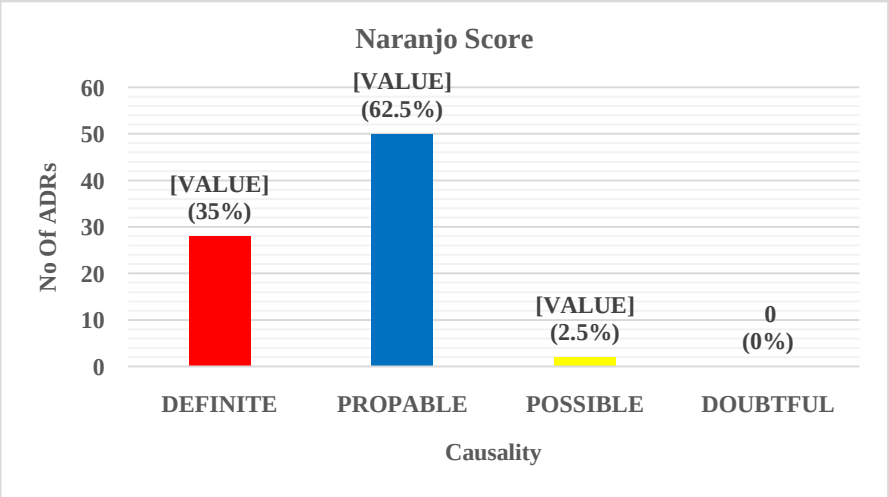
System Involved	No Of ADRs	Percentage(%)	p value
Digestive	33	41.25	0.0306
Hepatotoxicity	13	16.25	
Cutaneous	12	15	
Haematology	9	11.25	
Excretory	4	5	
Ophthalmic	2	2.5	
Ototoxicity	2	2.5	
Musculoskeletal	3	3.25	
CNS	1	1.25	
Dyselectrolytemia	1	1.25	
Total	80	100	

Then causality of ADRs were checked using the NARANJO scale in that Definite were 28, Probable were 50, Possible were 2 in the total of 80 ADRs. Then severity of ADRS were assessed by using the modified HARTWIG & SIEGEL scale out of 80 ADRs mild were 25, moderate were 32, severe were 23.

Table no 5: Casuality of ADRs according to Naranjo Scale and severity according to Hartwig & Siegel Scale.

Naranjo Score	No Of ADRs	Percentage(%)
Definite	28	35
Propable	50	62.5
Possible	2	2.5
Doubtful	0	
Hartwig &Siegel Scale		
Mild	25	31.25

Moderate	32	40
Severe	23	28.75



Tuberculosis has been a public health problem affecting our nation for long, inviting attention of physicians, public health specialists, researchers and policy makers in new, efficient, cost effective, pragmatic and different ways to tackle with this burden. One out of every 3 persons in the world are infected with mycobacterium tuberculosis[8].In our study we found 70 members developed 80 ADRs among the 184 patients who are on the ATT drugs according to RNTCP guidelines.

Majority of ADRs are reported in males(52) than females(18) which was supported by Athira B *et al*., It may be due to the fact that males are having higher risk factors like smoking, alcoholism and drug addiction than females and population of males are higher in this studyalso might be one of the reason[2].

Most of the ADRs are found in the age group of 51-60(20 ADRs) were identified polypharmacy due to the comorbid condition can also be one of the cause for development of ADR. Out of total 80 ADRs reported was gastritis (30) which shows the similar results like Athira *et al*., Followed by CLD(13), Rash in(8) patients, (9)members experienced Anemia.These results are similar to Shinde etal, Reena Verma etal[21,3]. Arthralgia seen in(3) patients, Vomiting's (3) patients, Erythroderma in (4) patients[8]. The only ADR suspected to be induced by Ethambutol was vision abnormality such as Blurred vision / Optic neuritis observed in (2) members[17,8].Vertigo seen in (2) patients[18].Where only 1 patient developed Psychosis, Loose stools, Hypokalaemia and red urine.

In present study we distinguished the members based on the number of ADRs they have been affected with. Where 61 members developed only 1 ADR, 8members developed 2 ADRs, only 1 member developed 3 ADRs. Most of the patients are on Category 1 than category 2 similar to study done by Kumarjit Sinha etal..,[10]

The best way to establish the causal relationship between a drug and its effect is done by causality assessment scales like NARANJO scale which consists of 10 questionnaires with some points. As per Naranjo scale Definite(28), Probable(50), Possible(2), Doubtful(0).In order to take proper initiatives towards the management of ADRs it is essential to assess the severity of the ADRs. Hartwig scale is widely used for this purpose. Our study shows that Mild(21), Moderate(32), Severe(23) are in number[18,19,12].

More the number of drugs in the prescription more the occurrence of ADRs[13].ADRs are unintended effects developed due to the usage of ATT are observed in the patients which is found to be one of the reason for the dropouts. These ADRs were collected by us during the ward round participation. The gathered ADRs were reported to PvPI and also suggested to physicians for the further management of ADRs.

In most of the cases ADRs can be detected early by counselling the patients regarding the drugs and difficulties of therapy which may provide some knowledge to patients and care takers about the ADR and their consequences. There by they can inform to health care professionals, so that they can be managed properly without causing morbidity and mortality.

Management was given based on the severity of the ADR in which 30 patients continued ATT therapy as they are mild in nature. In moderate condition patients ATT was holded for few days in 28 patients who are prescribed with some symptomatic therapy. Stopped the ATT therapy was seen in 17 patients where some patients stopped ATT by themselves and some persons stopped by the advice of health care professionals. Pattern of dechallenge and rechallenge was done in only limited patients like erythroderma and severe hepatitis

cases. Where causating drug was kept in hold and remaining drugs were continued with some symptomatic therapy. In case of Hepatitis modified regimen was prescribed[18,13,20].

Suggestions are given based on the severity of the ADR in the patient. In case of anemia management was undertaken based on the levels of haemoglobin. HB in the range of 10-12 then continue the ATT with some lifestyle modification, nutritional diet. HB in the range of 8-10 then hold the ATT for few days with IFA supplements, blood transfusion. HB less than 8 then stop the ATT for that blood transfusion and IFA supplements where given.

Hepatitis, if it is severe then stop ATT and start SLE regimen to the patient. In moderate condition hold the ATT for few days and hepato protectants were given.In mild condition continue ATT with some life style changes are suggested.Optic neuritis is the severe form of ADR where the condition can be reversed by the stoppage of the ATT.Gastritis in the severe form then stop the ATT and symptomatic treatment was given. In moderate condition hold the ATT for few days symptomatic treatment was given. In the mild condition continue the ATT and protective agents were suggested.

In case of rashes if they are severe stop the ATT straightway and given specific therapy to reduce itching and hives. In moderate situation hold for few days then soothening agents were given to control itching and rashes. In mild condition continue ATT with some lifestyle changes like don't expose to sun directly. Similar suggestion were given to the erythroderma patients where the rashes arise lately after usage of ATT for 3-4 months[20].Outcome of ADRs most of them were recovered, some of them were in the stage of recovering and only some patients details were not available.

All the collected ADRs were reported to PvPI for the further management. Vigilance programme was useful for signal generation, early detection of ADRs and interactions, discover increase in the frequency of ADRs. This further provides effective communication to public there by improvising the health needs, safe use of medicines among the patients.Hence implementation of good patient care oriented programmes will be helpful in all hospitals by inclusion of clinical pharmacist to support the patients in improvising their quality of life and finally they can achieve positive therapeutic outcome.

P value was calculated found to be 0.03 (<0.05) was considered significant.

IV. CONCLUSION

Even though there is high success rate by usage of ATT, we still observe considerable treatment failure because of lack of awareness in patients about the ADRs and the occurrence. a liable person like clinical pharmacist plays a major role by communicating with patients regarding ADR and their complications. Thus promoting chances for early detection of these ADRs where they can be managed without dropouts of therapy. Finally development of drug resistant strains can be decreased and better healthy life can be achieved. Strategies like educational campaigns might improve more ADR reporting by the patients voluntarily so that proper management can be initiated.

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