World Inventia Publishers

Journal of PharmaResearch

http://www.jprinfo.com/

Vol. 6, Suppl 2, 2017 ISSN: 2319-5622 USA CODEN: JPROK3

Case Report **Full Proceeding Paper**

STUDY OF ADVERSE DRUG REACTIONS IN TUBERCULOSIS PATIENTS

K.Venkateswarlu[1]*,Keerti Tiwari[2], E.Mamatha[2], SaiVivek[2], P.Shravan[3]

[1] *Assistant Professor, Department of Pharmacy Practice, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, INDIA.*

[2] *Pharm D, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, INDIA.*

[3] *Associate Professor, Department of Pharmaceutical, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, INDIA.*

Received on: 05-10-2017; Revised and Accepted on: 08-11-2017

ABSTRACT

T*uberculosis causes a great deal of ill health in the populations of most low-income countries.There may be considerable morbidity, even mortality, particularly with drug-induced hepatitis. These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations. Alternative agents may have greater problems with toxicity, and are often less effective, so that treatment must be prolonged.**Aim:**To identify, monitoring, management and assessment of suspected adverse drug reaction (ADR).* ***Methods:*** *This is aprospective observational study done for a period of nine months from January to September 2016at the inpatient block of Government Hospital Hyderabad,Telangana.Patients who visited the hospital with tuberculosis were reviewed on daily basis and monitored for ADRs. Patient's demographic details are collected and documented. Suspected ADRs were assessed by using standard algorithms.**Results:**A total of 119 patients were reviewed, of which 63 (52.9%) patients met the study criteria who experienced at-least one ADR which was induced by antituberculosis (ATT) drugs. Among 63 patients experienced ADRs, 50(79.36%) were male and 13 (20.63%) were female. In 63(52.9%) patients 80 ADRs were found. Among them 3 (3.75%) reported skin and appendages reactions, 35 (43.75%) reported gastrointestinal system reactions, 7 (8.75%) were liver and biliary system reactions, 19 (23.75%) reported central and peripheral nervous system reactions, 11(13.75%) reported body as a whole general reactions, 1 (1.25%) was vision disorder, 3(3.75%) reported hearing disorder and 1(1.25%) hormonal disorder was found. Most common adverse reactions were found in gastro intestinal system which includes nausea, vomiting, epigastric pain, constipation and diarrhea.**Conclusion:**The present study identified the pattern of ADRs experienced by the patients on ATT. Males had a higher incidence of ADRs. Gastro intestinal system ADRs were the most commonly seen. On evaluation of the causality of ADRs, a majority of them were found to have a 'possible' association with the suspected drugs. Majority of the ADRs were 'mild' in severity. No severe life-threatening ADRs were observed during the study period.*

KEYWORDS*: Tuberculosis, Adverse drug reaction, Severity.*

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. TB is more common among men than women, and affects mostly adults in the economically productive age groups; around two-thirds of cases are estimated to occur among people aged 15–59 years[1]. Treatment for tuberculosis is not only a matter of individual health; it is also a matter of public health[2].

Four major drugs are considered the first-line agents for the treatment of tuberculosis: isoniazid, rifampin, pyrazinamide, and ethambutol. These agents are recommended on the basis of their bactericidal activity,their sterilizing activity and their low rate of induction of drug resistance.

Because of a lower degree of efficacy and a higher degree of intolerability, resistant to first-line drug and toxicity, a number of second-line drugs are introduced .Includes the injectable drugs streptomycin (formerly a first-line agent), kanamycin, amikacin, and capreomycin and the oral agentsethionamide, cycloserine, and PAS.

***Corresponding author:**

K. Venkateswarlu

Assistant Professor,

Department of Pharmacy Practice,

CMR College of Pharmacy,Kandlakoya,Medchal,

Hyderabad,Telangana, INDIA.

Recently, fluoroquinolone antibiotics have become the most commonly used second-line drugs.

Adverse reaction WHO, (1972):A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function.

ADRs of first-line essential Antituberculous drugs:

Rifampicinadverseeffects:The most common adverse event is gastrointestinal upset.Other adverse effects of rifampin include rash (0.8%), hemolytic anemia (1%), thrombocytopenia, and immunosuppression of unknown clinical importance.

Isoniazidadverse effects:The two most important adverse effects of isoniazid therapy are hepatotoxicity and peripheral neuropathy. Other adverse reactions are either rare or less significant and include rash (2%), fever (1.2%), anemia, acne, arthritic symptoms, a systemic lupus erythematosus like syndrome, optic atrophy, seizures, and psychiatric symptoms.

Pyrazinamide adverse effects:Hyperuricemia is a common adverse effect of pyrazinamide therapy; the incidence is probably reduced by concurrent rifampin therapy.

Ethambutoladverse effects:Retrobulbar optic neuritis is the most serious adverse effect; axial or central neuritis and loss of ability to see green.

Streptomycin adverse effects:Ototoxicity and renal toxicity are the most common and the most serious.Vestibular dysfunction is more common and includes loss of balance, vertigo, and tinnitus.

Adherence:Lack of adherence to treatment is recognized worldwide as the most important impediment to cure and likely to cause drug resistant.

- Both patient- and provider-related factors may affect compliance.
  - ✓ Patient-related factors include a lack of belief,existence of concomitant medical conditions, lack of social support; and poverty.
  - ✓ Provider-related factors that may promote compliance include the education and encouragement of patients.
  - ✓ Two other strategic approaches are used: direct observation of treatment and provision of fixed-drug-combination (FDC) products.

Monitoring treatment response and Drug Toxicity:

When a patient's sputum cultures remain positive at greater than 3 months or AFB Smears positive after 5 months indicatestreatment failure and drug resistance [3].

Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite) or those with marked (five to sixfold) elevations in serum levels of aspartateaminotransferase, should be instructed to discontinue treatment and drugs reintroduced after liver function has returned to normal [4].

Hypersensitivity reactions usually require the discontinuation of all drugs and rechallenge to determine which agent is the culprit. To prevent isoniazid related neuropathy, pyridoxine (10 to 25 mg/d) should be added to the regimen given to persons at high risk of vitamin B6 deficiency [5]. Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic acid; however, pyrazinamide treatment should be stopped if the patient develops gouty arthritis [6]. Individuals who develop autoimmune thrombocytopenia secondary to rifampin therapy or the occurrence of optic neuritis with ethambutolis an indication for permanent discontinuation of these drugs [7].Other common manifestations of drug intolerance, such as pruritus and gastrointestinal upset, can generally be managed without the interruption of therapy.

METHODOLOGY

Study site: The study was conducted in the inpatient wards (male and female) of Government teaching hospital having 110 beds.

Study duration: January – September 2016.

Study design: Prospective observational study.

Study population: Patients who were experienced by at-least one adverse drug reaction induced by antitubercular treatment.

Inclusion criteria: Patients who developed at-least one ADR.Patients of either sex.

Exclusion criteria: Patients who have multiple drug resistance or severe illness.Patients who are non cooperative are excluded.

Study procedure: Patients admitted with tuberculosis in medical wards of Government Chest Diseases and Tuberculosis hospital are reviewed on daily basis and included in study as per study criteria and were monitored for ADRs.

ADRS are identified or reported by following ways:

1) Participation in ward rounds (Pharmacists with physicians)
2) Interviewing of the patients by the investigators (Pharmacists).

Adverse drug reaction (ADR) documentation and evaluation form: It includes all the information such as name, age, sex, reason for admission, brief description of reaction, relevant past history of medication, the onset and severity of the ADR experienced the impact of ADR on the treatment and drug involved, dose of the drug, route and frequency time.

All the suspected ADRs were evaluated for their causality using WHO Probability Scale,Naranjo's Algorithm and the Karch and Lasagna scaleSeverity assessment was done using the Hartwig*et al.* Scale. Preventability of an ADR is determined by using Shumock*et al.* criteria. Predictability of an ADR is also determined by using criterias.

RESULTS

During the study period a total of 119 patients were reviewed, of which 63(52.9%) patients met the study criteria that were experienced at-least one ADR which was induced by antituberculosisdrugs.Among 63patients experienced by ADRs, 50(79.36%) were male and 13 (20.63%) were female.

The highest percentage of adverse drug reactions wereobserved in the age group of 39-46 years and 23-30 years comprising of 31.74% and 30.15% respectively, followed by 63-70 years(11.11%), 31-38 years(7.93%), 55-62(7.93%) and 47-54(4.76%).

Table No. 1: Number pattern of ADRs experienced by patients and NumberofADRsinCo-morbiditiespatients

Number of ADRs	Number of cases (n=63)	Percentage
1	48	76.19%
2	12	19.04%
3	03	4.76%
Comorbidites	**Numberofpatients(n=11)**	**NumberofADRs**
CKD+HTN	1	1
DIABETES	2	2
DIABETES+HTN	1	1
AIDS	7	10

In this study total 80 ADRs were reported of which 48 (76.19%) cases experienced only one ADR followed by 12 (19.04%) cases with two ADRs and 3 (4.76%) cases with three ADRs. Co-morbidities like Diabetes, Acquired immune deficiency syndrome (AIDS), Diabetes+Hypertension and Chronic kidney disease (CKD) with hypertension (HTN) were noted. The majority of ADRs was found people with AIDS as co-morbidity. In 80 ADRs 14 (17.5%) ADRs were found in patients with co-morbidities.

Categories of Treatment:Over all 63 patients, 41(65.07%) cases were treated under Category-I drug regimen which includes newly Koch's diagnosed cases, Pleural effusion and other pulmonary infections. 22(34.92%) patients were treated under Category-II drug regimen among relapse cases, treatment failure and defaulters.

Table No. 2: Onset of ADRs reported

Duration of onset	Number of ADRs (n=80)
Within one week	49
Within two weeks	11
Withineightweeks	9
Withinfourweeks	4
Withinthree weeks,Withintwelveweeks,Withinsixteenweeks	2
Within thirty weeks	1

In this study the majority of reactions occurred within one week of treatment followed by within two weeks, within eight weeks and less number of reactions observed in treatment period of three, four, twelve, sixteen and thirty weeks.

Previous allergy to ADRs: Out of 63 patients 6(9.52%) patients had the previous history of drug allergies like vomiting, giddiness, numbness in lower limbs, itching all over the body and 58 (92.06%) had no previous history of drug allergy.

System organ classes involved in ADRs induced by anti-TB drugs:

Among 80 ADRs they were grouped into different system organ classes based on World Health Organization-Adverse Drug Reaction Terminology (WHO-ART).

Table No. 3: System organ classes involved in ADRs induced by anti-TB drugs

System affected by the ADR	Number of ADRs	Percentage
GI system disorders	35	43.75%
Liver and biliary system disorders	7	8.75%
Body as a whole general disorder	11	13.75%
Central and peripheral nervous system disorders	19	23.75%
Hearing disorder,Skinandappendagesdisorders	3	3.75%
Hormonal disorder,Visiondisorders	1	1.25%

In 63(52.9%) patients 80 ADRs were found.Most common adverse reactions were found in gastro intestinal system which includes nausea, vomiting, epigastric pain, constipation and diarrhea.

Drug combinations suspected to cause ADRs:

First line antituberculosis drugs used to treat tuberculosis are Isoniazid(H), Rifampicin(R), Ethambutol(E), Pyrazinamide(Z) and Streptomycin(S) which were used as multiple drug regimen and may cause adverse drug reactions.

Table No. 4: Suspected drugs to cause ADR

Number of drugs suspected to cause ADR	Number of ADRs(n=80)	Percentage
1 (H,E,S)	16	20%
2 (HR)	12	15%
3 (HZE,HRE)	24	30%
4 (HRZE)	28	35%

Highest percentages of ADRs were suspected in the 4 drug combinations comprising of 28(35%), they include mainly Gastro-intestinal system disorders. 3 drug combinations comprising of 24(30%), which include CNS disorders, general body disorders and skin reactions like Steven Johnsons Syndrome (SJS). 2 drug combination suspected to cause ADRs include hepatic disorders and hormonal disorders. 1 drug suspected ADRs constitutes of 16(20%) which includes peripheral nervous system disorders, visual and hearing disorders.

Fate of the suspected drugs:

The suspected drugs were withdrawn in 11 ADRs such as hepatitis, severe gastric intolerance and severe reactions like Steven Johnson's syndrome and in remaining 69 ADRs no change in suspected drug was done.

Management of the ADRs reported:

Among 80 ADRs reported the management of the reported ADRs is listed in Table 5.

Table No. 5: Management of ADRs

Type of management	Number of ADRs (n=80)
Drugs withheld	11
Symptomatic	39
Specific	10
Nil	20

In 11(13.75%)ADRs, ADRs were managed by withdrawing the suspected drugs. Out of these symptomatic treatment was given to 3(3.5%)ADRs whereas in 2(2.5%) ADRs, specific treatment wasgiven and no treatment is given in 6(7.5%)ADRs. In the remaining 59(86.25%) ADRs treatment was continued with drugs with symptomatic, specific treatments of 39(48.75%) and 10(8%) respectively. No treatment was given to 20(25%) ADRs.

Outcome of the ADR:

In 69(86.25%) events, the patients recovered from ADRs without any complications and in 5 (6.25%) events, the reactions continued, while in 6(7.5%) events, the outcome was unknown as patients got discharged. No fatal reactions were found during the study period.

Pattern of Dechallenge and Rechallenge:In this study the dechallenge and rechallenge of the antitubercular medications was done and the number of cases and outcome of both criteria is summarised in Table 6.

Table No. 6: Dechallenge and Rechallenge of drugs

Criteria	No of cases	Outcome	No of cases regarding outcome
Dechallenge	10	Definite improvement	6
		No improvement	3
		Unknown	2
Rechallenge	9	Recurrence of symptoms	2
		No recurrence symptoms	2
		Absconded	1
		Shifted to other hospital	1
		Not known	2

Out of the 63(100%) cases, dechallenge of the suspected drug was done in 10 (15.87%) cases, and definite improvement of ADR was observed in 6 (9.52%) cases where dechallenge was done. Out of 10 cases of dechallenge, in 9 (14.28 %) cases, rechallenge of drugs was done. In the 9 events of rechallenge, there is no recurrence of symptoms observed in 2(3.17%) cases, recurrence of symptoms in 2(3.17%) and remaining rechallenge cases were not known due to some reasons like the patient is absconded(patient left from hospital without permission), patient is shifted to other hospital and failure of the review by patient.

Table No. 7: Time related classification of ADRs

Time relation	Number of ADRs
Time independent	**2**
Time dependent(n=78)	
Early	**46**
Intermediate	**31**
Immediate	**1**

Based on time relation 78 (97.5%) reactions were found to be time dependent of which 46 were early reactions, 31 were intermediate reactions and 1 immediate reaction was noted and remaining 2 (2.5%) reactions were found to be time independent.

Causality Assessment of reported ADRs:Based on WHO probability, Naronjo scale, Karch& Lasagna scale along the predictablity and preventability of ADR are listed in table-8.

Table No. 8: Causality Assessment of reported ADRs

WHO probability		
Criteria	**Number of ADRs**	**Percentage**
Certain	1	1.2%
Conditional	1	1.2%
Possible	52	65%
Probable	23	28.7%
Unlikely	3	3.7%
Naronjo's scale		
Possible	41	51.25%
Probable	39	48.75%
Karch& Lasagna scale		
Possible	75	93.75%
Probable	5	6.25%
Predictability of ADRs		
Predictable	72	90%
Not predictable	8	10%
Preventability of ADRs		
Definitely preventable	76	95%
Probably preventable	4	5%

According to the WHO probability scale, majority of reactions 52(65%) were found to be 'Possible', followed by 'probable'- 7 (28.7%), 'certain'- 1(1.2%), 'conditional'-1(1.2%) and 'unlikely'- 3(3.7%).

As per the Naranjo algorithm, 41 (51.25%) reactions were 'Possible' and 39 (48.75%) reactions were 'Probable'.

As per the Karch& Lasagna's algorithm the majority of reactions were found to be 'possible'- 75(93.75%) and 5(6.25%) were probable.

Out of 80 ADRs, 72(90%) are predictable and 8(10%) are not predictable.

According to Modified Shumock and Thornton criteria out of 80 ADRs reported 76 (95%) reactions were found to be definitely preventable and 4(5%) reactions were found to be probably preventable.

Severity Assessment of ADRs:

Among 80 ADRs they were assessed for the severity and listed in table-9.

Table No. 9:Severity Assessment of ADRs

Criteria	Number of ADRs	Percentage
Mild		
Level 1	60	75%
Level 2	02	2.5%
Moderate		
Level 3	03	3.75%
Level 4(a)	09	11.25%
Level 4(b)	06	7.5%

Out of 80 ADRs, 62 (77.5%) were mild and 18 (22.5%) were moderate and no severe reactions were reported as per the Hartwig*etal.*scale.

DISCUSSION

Inastudyconducted byLeelavathiDAcharyaetaltheincidenceof ADRsfoundas17.02%ofstudypopulation[8].Inthisstudyhigherincidenceof ADRs52.1%wasseenwhichisconsistentwiththestudyconductedbyK.Ghola mietalatTehran[9].Thesecondmostcommonreactionwascentralandperiph eralnervoussystem,whoseoccurrencewashighercomparedtothatfoundint hestudyconductedbyK.Gholamietal[10],whereitwasfoundtobearound7.35 %.Thethirdmostcommonsystemreactionwasbodyasawholegeneraldisor dersfollowedbyliverandbiliarysystemdisorderconstituting8.75%,whichi sfoundlesscomparabletostudybyK.Gholamietal[11].Skinandappendagesdi sordersconstituting3.75%ofalladversereactionswhichisconsistentwithth estudyconductedbyTanWooiChiangetal[12].

CONCLUSION

The present study identified the pattern of ADRs experienced by the patients on ATT. Males had a higher incidence of ADRs. Gastro intestinal system ADRs were the most commonly seen. On evaluation of the causality of ADRs, a majority of them were found to have a 'possible' association with the suspected drugs. Majority of the ADRs were 'mild' in severity. No severe lifethreatening ADRs were observed during the study period.

This study showed that the incidence of ADRs was high (52.9%) with first line anti-TB drugs (DOTs therapy). Majority of the patients felt that after taking their treatment the condition become worsening, but truly speaking which is caused due to ADR of ATT, this shows wrong conception about treatment. This was minimised by clinical pharmacist involvement in interviewing the patient and counselled to meet the medical officer, thereby encouraging the DOTS provider (pharmacist/ health care professional) to address the problem. This study concluded that there is a need of a close monitoring system for proper detection of ADRs caused by antiTB drugs. Counselling of patients for timely prevention, detection and management of ADRs will helps in minimising the further occurrence of ADR.

ACKNOWLEDGEMENT

The thesis made me come out with new experiences under the guidance, support of all the following people.I was extraordinarily fortunate in having K.Venkateswarlu as my research guides.E.Mamatha and Sravan as co-worker.I thank themfor their help, support and constant encouragement throughout the progress of this work. It was really a great experience working under them and their guidance, which was of immense help in my project work without which it would have been an unachievable task.

REFERENCES:

1. France. Global Tuberculosis control: WHO report.Chapter 1 Introduction. **2011**; p.3-5.
2. Fauci,Braunwald,Kasper,Hauser,Longo,Jameson,Loscalzo.Harris on'sPrinciple'sofInternalMedicine,17thed. USA: The McGraw-Hill Companies.Chapter150,Tuberculosis, **2008**; p.970.
3. Fauci, Braunwald, Kasper, Hauser, Longo, Jameson, Loscalzo. Harrison's Principle's of Internal Medicine, 16thed. USA:The McGraw-Hill Companies. Chapter 150, Tuberculosis,**2005**;p. 953.
4. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am J RespirCrit Care Med. **2000**;161:1376–1395.
5. Barbara G. Wells JTD, Terry L. Schwinghammer, Pharmacotherapy Hand book. 7 ed.: The McGraw-Hill Companies, Inc.; **2009**.
6. Parthasarthi G, Karin N, Milap C Nahata. A Text of Clinical Pharmacy Practice,Essential Concepts of Skills, 1st Edition, Orient Longman, India **2001**;84-97.
7. Poon-chuen Wong. Current Management of Pulmonary Tuberculosis. Medical Bulletin**2008**;13(12):24-26.
8. Eric J Forget and Dick Menzies. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf**2006**;5(2):231-249. doi:10.1517/14740338.5.2.231.
9. Tak D, Acharya L , Gowrinath K, RaoPadma G, Subish P. Safety Evaluation of Antitubercular Therapy Under Revised National Tuberculosis Control Programme in India. JClini and Diagn Res **2009**;3:1395-1401.
10. Mohammad Reza Javadi, Gloria Shalviri, KheirollahGholami, JamshidSalamzadeh, GolshanMaghooli, SeidMahdiMirsaeedi. Adverse reactions of anti-tuberculosis drugs in hospitalized patients: incidence, severity and risk factors.PharmacoepidemDr S**2007**;16:1104-1110. doi:10.1002/pds.1468.
11. SouravGhosh, Sanjay KR. Malik, Arvind Gupta, RohitChaudhary. A Prospective, observational Cohort Study to Elicit Adverse Effects of Anti-Tuberculosis Drugs among Patient Treated for Active Tuberculosis. T Ph Res **2010**;3:10-16.
12. Kishore PV, SubishPalaian, PradipOjha,Shankar PR.Pattern of Adverse Drug Reactions Experienced by Tuberculosis Patients in a Tertiary Care Teaching Hospital in Western Nepal. Pak J Pharm Sci**2008**;21(1):51-56.

How to cite this article:

K. Venkateswarlu et al. STUDY OF ADVERSE DRUG REACTIONS IN TUBERCULOSIS PATIENTS. J Pharm Res 2017;6(Suppl 2):61-65.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil