Published in the Slovak Republic
European Journal of Medicine
Has been issued since 2013.
E-ISSN: 2310-3434
2019, 7(1): 35-44

DOI: 10.13187/ejm.2019.1.35
www.ejournal5.com

A Prospective Observational Study on Assessment of Adverse Drug Reactions in Patients taking First Line Antitubercular Drugs at Tertiary Care Teaching Hospital, Nellore

Gobinath Manavalan [a, *], Naina Mohamed Pakkir Maideen [b], Kandukuri Varun [c], K. Charitha Lakshmi [a], P. Kavya Sri [a], CH Sri Durga Padmaja [a], P. Sudharani [a]

[a] Ratnam Institute of Pharmacy, Nellore, India
[b] Dubai Health Authority, Dubai, United Arab Emirates
[c] Department of Respiratory Medicine, ACSR Medical College, Nellore, India

Abstract

Tuberculosis (TB) is a mycobacterial infection, which remains a leading infectious killer globally. Patients' non-compliance, therapeutic failure and drug resistance may result due to the occurrence of adverse drug reactions of Antitubercular drugs. The aim of present study was to identify and analyse the adverse drug reactions caused by first-line antitubercular drugs in DOTS centre and tertiary care hospital in Nellore.

This was a prospective observational study carried out in the Department of Pulmonology at AC Subba Reddy Government Medical College, a tertiary care teaching hospital, Nellore, Andhra Pradesh over a period of six months. During the study period, all the patients receiving treatment with first-line Antitubercular drugs who met the study criteria were included and monitored for adverse drug reactions and subjected to causality assessment.

A total of 260 patients were followed during the study period, out of which 155 patients developed adverse drug reactions. Higher incidence of adverse drug reactions was observed in females (66.66 %) than males (57.77 %). Gastrointestinal system was affected most commonly by the ADRs of first-line antitubercular drugs. Most of the reported ADRs belonged to "possible" category as per WHO and Naranjo scales of causality assessment. And it has been identified that majority of ADRs fall in "mild" category according to Hartwig' scale of severity assessment.

The present study suggests that the involvement of clinical pharmacists in the monitoring and assessment of ADRs of Antitubercular drugs may help to minimize morbidity and improve patient compliance and achieve better therapeutic outcome.

Keywords: tuberculosis, first-line antitubercular drugs, adverse drug reactions, causality assessment, severity assessment.

1. Introduction

Tuberculosis (TB) is a mycobacterial infection, which remains a leading infectious killer globally. It has been estimated that 10.4 million new cases of tuberculosis identified across the world and almost two-thirds of them belong to countries like India, Indonesia, China, Philippines, Pakistan, South Africa and Nigeria, in the year of 2016. In addition, around 1.7 million deaths were reported to be caused by tuberculosis in 2016 (Floyd et al., 2018). TB is classified mainly as

* Corresponding author
E-mail addresses: gobinathmanavalan@ratnampharma.edu.in (G. Manavalan)

Pulmonary TB (PTB) and Extra-pulmonary TB (EPTB). The PTB accounts almost for 85 % of TB cases worldwide and EPTB affects organs such as pleura, lymph nodes, spine, joints, genitor-urinary, nervous system or abdomen and it represents 10 % to 15 % of all the TB cases in the world (Ranzani et al., 2017).

The first line anti- tubercular agents include Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and Streptomycin (Pourakbari et al., 2016) and the second line anti-tubercular agents include Ethionamide, Prothionamide, Cycloserine, Terizidone, Para-aminosalicylic acid (PAS), Rifabutin, Thiacetazone, Fluoroquinolones (Ofloxacin, Moxifloxacin, Ciprofloxacin) and injectables (Kanamycin, Amikacin) (Park et al., 2015). Second line anti-tubercular agents are reported to have low efficacy or higher toxicity or both and hence they used as reserve drugs.

An unpleasant or unintended reaction resulting from the use of a drug administered in normal doses is termed as adverse drug reaction (ADR) (Patton et al., 2018). ADRs are classified into six types including type A (Augmented reactions – dose-related), type B (Bizarre reactions – non-dose-related), type C (Chronic reactions – dose-related and time-related), type D (Delayed reactions – time-related), type E (End of use reactions – withdrawal related), and type F (Failure of therapy) (Edwards et al., 2000). In addition, an adverse drug reaction occurring due to interaction with concomitant medications, is known as adverse drug interactions (Pakkir Maideen et al., 2018; Maideen, 2018).

Identification of an ADR can be useful for the prevention, early detection and management of ADRs. Causality assessment of ADRs is an important step in the ADR monitoring programs and Naranjo's algorithm scale are commonly used to carry out the assessment of causality of the ADRs. Being a source of significant morbidity and mortality, ADRs are responsible for 6 % of hospital admissions and they occur in 10-20 % of hospitalised patients (Cabré et al., 2018). The healthcare costs might be increased by ADRs due to frequent hospitalization, prolongation of hospital stay and additional investigations (Schnippel et al., 2018). It has been reported that ADRs are developed in more than 5 % of patients taking Antitubercular drugs and they include gastrointestinal diturbances, hepatotoxicity, allergic reactions, arthralgia, neurological disorders, and many others (Agrawal et al., 2018).

Monitoring and reporting of ADRs of Antitubercular drugs is very much essential as they can affect the compliance of patients resulting in abrupt discontinuation of treatment leading to multidrug resistance. Clinical pharmacists can play a major role in the assessment of ADRs related to the use of Antitubercular drugs, by which the patient compliance could be improved and the occurrence of multidrug resistance minimised. Hence, this study aimed to involve clinical pharmacists in monitoring and evaluation of ADRs in patients taking first line Antitubercular drugs, in a DOTS centre and tertiary care teaching hospital of Nellore, India.

2. Materials and methods

A prospective observational study was conducted in the Department of Pulmonology at AC Subba Reddy Government Medical College, a 1000 bedded tertiary care teaching hospital, Nellore, Andhra Pradesh and DOTS centre.

Duration of study

The study was conducted for six months from August 2017 to January 2018.

Ethical approval

Institutional Ethics committee of Ratnam Institute of Pharmacy, Nellore and Department of Pulmonology, ACSR Medical College & Govt. General Hospital, Nellore, approved the study.

Patients' selection criteria

The study included the patients receiving first-line anti-tubercular agents, willing to participate in the study and above 12 years of age and the study excluded the patients below 12 years of age, pregnant and lactating women, patients in the categories of MDR-TB and XDR-TB, not willing to participate and the patients having renal and hepatic impairment.

Study Procedure

Pharmacists monitor for the ADRs in patients taking first-line Antitubercular drugs daily, during the study period. Upon the occurrence of suspected ADRs, the concerned physician has been notified and the information such as type of reaction to the drug, outcome of therapy of the patient, etc. documented in the adverse drug reactions monitoring and reporting form.

The causality assessment of ADRs was done by using WHO probability scale (Definite, probable, possible, unclassifiable, unlikely, conditional) and Naranjo's scale (Definite, probable, possible, unlikely), at the end of the study.

Statistical analysis

The data obtained was entered into Microsoft Excel sheet. Descriptive statistics was used to analyse the data.

3. Results

A total number of 260 patients who were on Directly Observed Treatment Short course (DOTS) therapy were enrolled in our study, of which 206 patients (79.23 %) were male and 54 patients (20.76 %) were female (Table 1).

Higher number of patients recruited in the age group between 33-42 years (26.1 %) among that 53 were male and 15 were female, followed by the age group 43-52 years (24.6 %) among them 53 were male and 11 were female. In the age group of 23-32 (18.8 %) 36 patients were male and 13 patients were female and 53-62 years (14.2 %) among them 31 patients were male and 6 female patients were moderately affected. The age group between 63-72 (10.7 %) of total 28 patients, out of that 24 were male and 4 were female and age group of 13-22 (5.3 %) comprises of 9 males and 5 females, the least affected age group (Table 1).

Table 1. Age and Gender wise distribution of patients enrolled in the study

Age	Male	Female	Total No of Patients	Percentage (%)
13-22	9	5	14	5.3
23-32	36	13	49	18.8
33-42	53	15	68	26.1
43-52	53	11	64	24.6
53-62	31	6	37	14.2
63-72	24	4	28	10.7
Total	**206**	**54**	**260**	

The patients affected with tuberculosis (TB) in the study were divided according to the type of TB. Out of 206 male patients 181 patients were affected by pulmonary TB (87.8 %) and 25 patients (12.2 %) were affected by extra pulmonary TB. Out of 54 female patients 43 (79.6 %) were affected by pulmonary TB and 11 (20.4 %) were affected by extra pulmonary TB and total of 86.15 % of pulmonary TB and 13.85 % of Extra pulmonary TB (Table 2).

Table 2. Pattern of TB of both genders

Age Group	Pulmonary TB		Extra Pulmonary TB	
	Male	Female	Male	Female
13-22	6 (3.3)	2 (4.6)	3 (12)	3 (27.2)
23-32	30 (16.5)	8 (18.6)	6 (24)	5 (45.4)
33-42	51 (28.1)	12 (27.9)	2 (8)	3 (27.2)
43-52	45 (24.8)	11 (25.5)	8 (44)	0 (0)
53-62	25 (13.8)	6 (13.9)	6 (24)	0 (0)

63-72	24 (13.2)	4 (9.3)	0 (0)	0 (0)
Total	181 (87.8 %)	43 (79.6 %)	25 (12.2 %)	11 (20.4 %)

The patients enrolled in our study received Category-I and Category-II type of treatments. The drugs such as Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) comprises Category-I treatment while the drugs like Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (SM) included in Category- II treatment. Out of 206 male patients, 154 patients (74.75 %) received Category-I type of treatment and 52 patients (25.24 %) were received Category-II type of treatment. Out of 54 female patients, 44 were received Category-I (81.48 %) and 10 received Category- II (18.52 %) type of treatments (Table 3).

Table 3. Type of treatment for both gender

Age	**Category –I** (H, R, Z & E)		**Percentage %**		**Category-II** (H, R, Z, E & SM)		**Percentage %**	
	Male	Female	Male	Female	Male	Female	Male	Female
13-22	8	5	5.19	11.36	1	0	1.92	0
23-32	31	11	20.12	25.00	5	2	9.61	20.00
33-42	41	13	26.62	29.54	12	2	23.07	20.00
43-52	36	9	23.37	20.45	17	2	32.69	20.00
53-62	22	5	14.28	11.36	9	1	17.30	10.00
63-72	16	1	10.38	2.27	8	3	15.38	30.00
Total	**154**	**44**			**52**	**10**		

Tobacco is a known risk factor of tuberculosis and tobacco use in the form of smoking and chewing, among our patients has been recorded. Smoking is known to affect the immune system and can render the smokers more susceptible to infections. The results of our study implies that nearly 62.3 % of patients using tobacco in the form of chewing and smoking. Out of these 147 patients were male (90.74 %) and 15 patients were female (9.25 %). Overall 37.69 % of people are nontobacco patients, which comprises 59 male patients (60.2 %) and 39 female (39.79 %) (Table 4).

Table 4. Smoking / chewing tobacco history of patients

Age	**Smoking / Tobacco chewing**		**Percentage**		**Non Smoking / No Tobacco chewing**		**Percentage**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
13-22	7	0	4.76	0	2	5	3.38	12.82
23-32	20	2	13.60	13.33	16	11	27.11	28.20
33-42	34	3	23.12	20.00	19	12	32.20	30.76
43-52	43	5	29.25	33.33	10	6	16.94	15.38
53-62	21	3	14.28	20.00	10	3	16.94	7.69
63-72	22	2	14.96	13.33	2	2	3.38	5.12
Total	**147**	**15**			**59**	**39**		

The alcohol consumption among our patients has also been recorded and it was found that out of 260 patients, 133 patients (51.15 %) consumed alcohol and 127 were non-alcoholic (48.85 %) (Table 5).

Table 5. Gender wise distribution based upon alcohol consumption

Gender	Alcoholic	Non alcoholic
Male	131	75
Female	2	52
Total	133	127
Percentage (%)	**51.15**	**48.85**

Family history is the causative genetic factor in TB and the family history of the enrolled patients were analysed, in which 78 patients have the family history of TB. In this 62 were male (30.09 %) and 16 (29.62 %) were female and that of no family history male 69.90 % and female 70.37 % respectively. Out of the 78 patients age group 33-42 (29.03 %) in male and 43-52 (31.25 %) in female have more affected (Table 6).

Table 6. Patients' family history status

Gender	Family history	No family history
Male	62	144
Female	16	38
Total	**78**	**182**
Percentage (%)	**30**	**70**

Among 260 TB patients recruited for the study, 211 patients (81.16 %) were without any comorbid conditions, while remaining 49 (18.84 %) had one of the co-morbid conditions HIV and Diabetes mellitus. Out of 49 patients (18.84) with comorbidity, 36 were male (73.46 %) and 13 were female (26.53 %). The patients suffering from comorbid conditions included 27 patients of HIV, of which 20 males and 7 females, 22 patients with diabetes mellitus, of which 16 males and 6 females. Patients of age group 43-52 in males (30.55 %), 53-62 (38.46 %) in females have more percentage of co-morbid conditions (Table 7).

Table 7. Co-morbidities status of patients

Age	Co-morbidities		No co-morbidities	
	Male (%)	Female (%)	Male (%)	Female (%)
13-22	0 (0)	0 (0)	9 (5.29)	5 (12.19)
23-32	10 (27.77)	2 (15.38)	26 (15.29)	11 (26.82)
33-42	7 (19.44)	3 (23.07)	46 (27.05)	12 (29.26)
43-52	11 (30.55)	1 (7.69)	42 (24.70)	10 (24.39)
53-62	7 (19.44)	5 (38.46)	24 (14.11)	1 (2.43)
63-72	1 (2.77)	2 (15.38)	23 (13.52)	2 (4.87)
Total	36	13	170	41

During the study period the total of 260 patients were monitored. In which, 155 patients shown ADRs (59.61 %), out of these 119 patients (57.77 %) were male and 36 patients (66.66 %) were female (Figure 1).

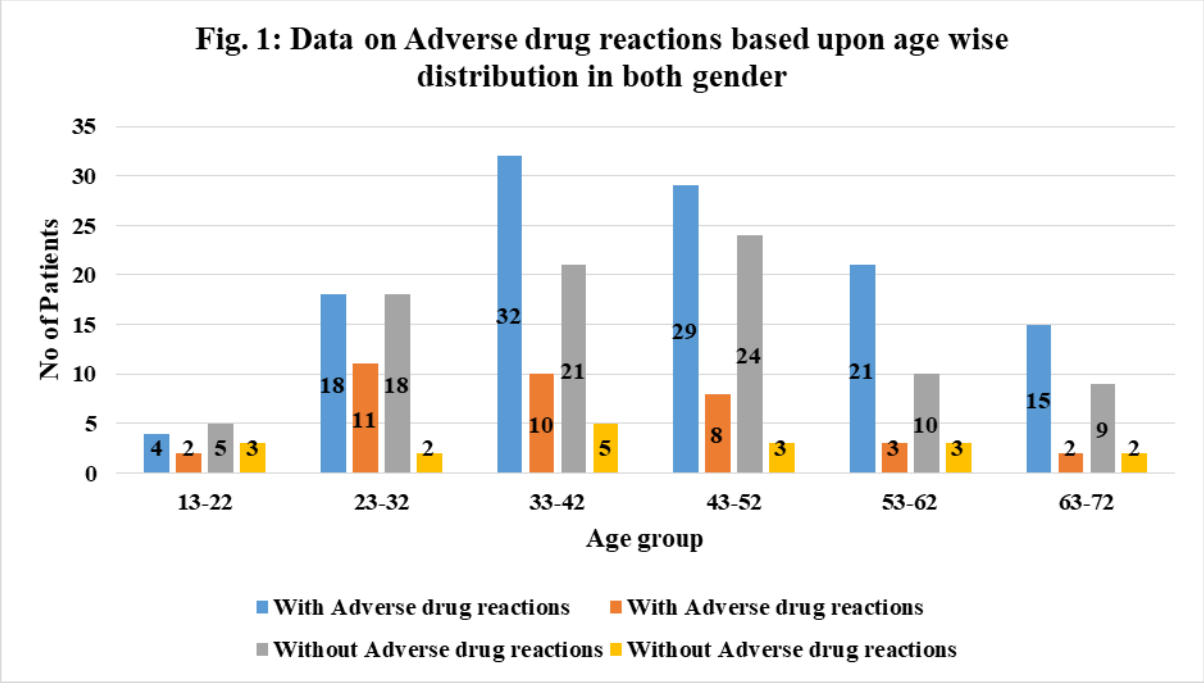

Fig. 1. Data on adverse drug reactions based upon age wise distribution in both genders

In the present study, 76 (49.03 %) patients (65 male and 11 female) developed at least one adverse reaction. A total of 53 patients (41 male and 12 female) had two ADRs and 26 patients (13 male and 13 female) with multiple ADRs. Study reveals that females were more affected by ADRs as compared to male patients. Age group of 33-42 male patients and 23-32 female patients have reported single ADR. Age group of 43-52 male patients and 23-32 female patients were reported two ADRs. Age group of 43-52 of both gender have reported multiple ADRs (Figure 2).

Gastrointestinal system (Gastritis) was the most common system affected followed by Skin (Rashes). Serious ADRs are hepatitis and Odema observe in male patients (0.64 %). Greatest number of ADRs were seen with the use of Isoniazid and Rifampicin. Gastritis (32.9 %), vomiting (21.2 %), giddiness (29 %), headache (2.5 %), anemia (10.9 %), Pruritus (10.9 %), skin rashes (10.9 %), arthralgia (16.1 %), ototoxicity (3.87 %), fever (5.8 %) were the commonest. Serious ADRs like hepatitis and edema (0.64 %) were also observed.

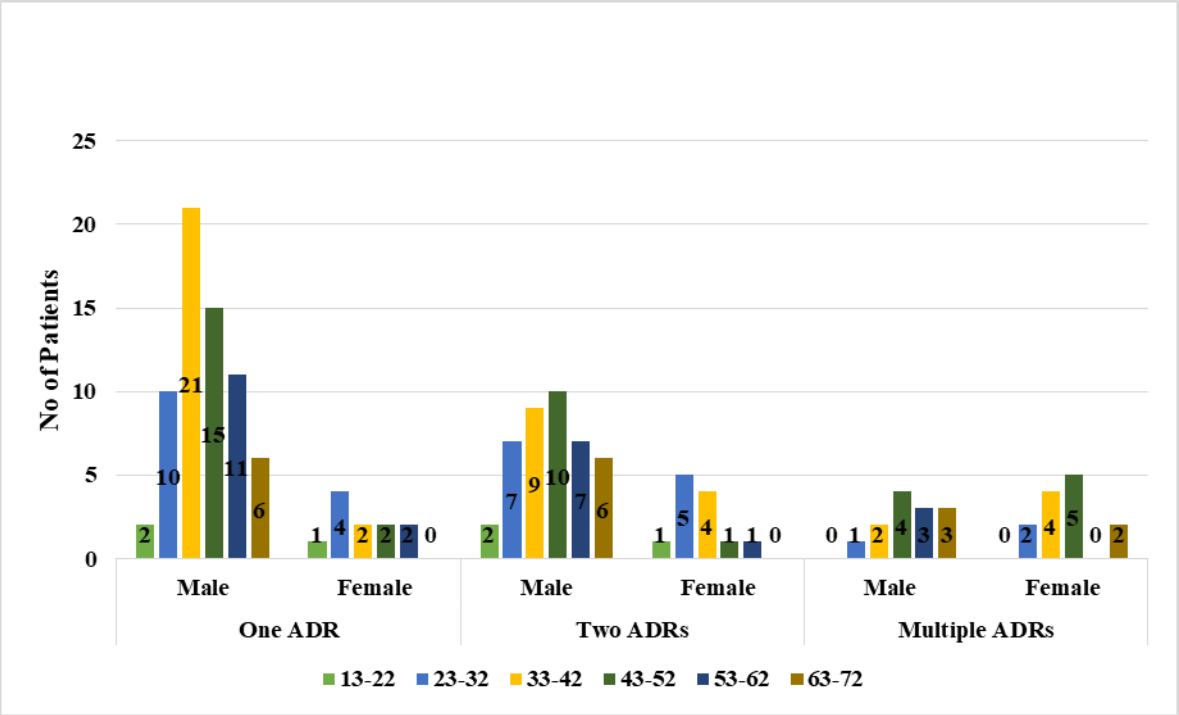

Fig. 2. Number of adverse drug reactions based upon age wise distribution in both genders

Table 8 reveals the ADRs with causative drugs. In which, vomiting is commonly associated with ethambutol and other Anti-tubercular drugs. Rifampicin and Isoniazid produced gastritis. Isoniazid is the causative drug for hepatitis. The incidence of ADRs was increased with increase in the number of drugs in the prescription. The greatest number of ADRs was seen with the use of Isoniazid and Rifampicin. GIT was the commonly involved system.

Table 8. Adverse drug reactions (ADRs) associated with first-line Antitubercular drugs

ADRs	Causative Drugs
Gastritis	Rifampicin, Isoniazid
Anorexia	Rifampicin, Isoniazid, Ethambutol, Pyrazinamide, Streptomycin
Vomiting	Rifampicin, Isoniazid, Ethambutol, Pyrazinamide, Streptomycin
Skin Rashes	Rifampicin, Isoniazid, Ethambutol, Pyrazinamide, Streptomycin
Head ache	Isoniazid, Pyrazinamide
Dizziness	Rifampicin, Isoniazid, Ethambutol, Streptomycin
Optic neuritis	Ethambutol
Peripheral neuritis	Isoniazid
Fever	Pyrazinamide
Redness and Watering of Eye	Rifampicin
Hepatitis	Rifampicin, Isoniazid, Ethambutol, Pyrazinamide

Severity of ADRs encountered during the study period was determined by using the Hartwig Assessment Scale. The results of the assessment revealed that most of the ADRs were mild. 85 patients (63 male, 22 female) showed only mild ADR. 63 patients (49 male and 14 female) showed moderate and 7 male patients showed severe ADR. Age group of 33-42 in male patients showed both mild and moderate ADR whereas 53-62 age group shown severe ADR. In case of female patients, 23-32 age group showed mild and 33-42 age group showed moderate. No severe ADRs reported in female patients (Figure 3).

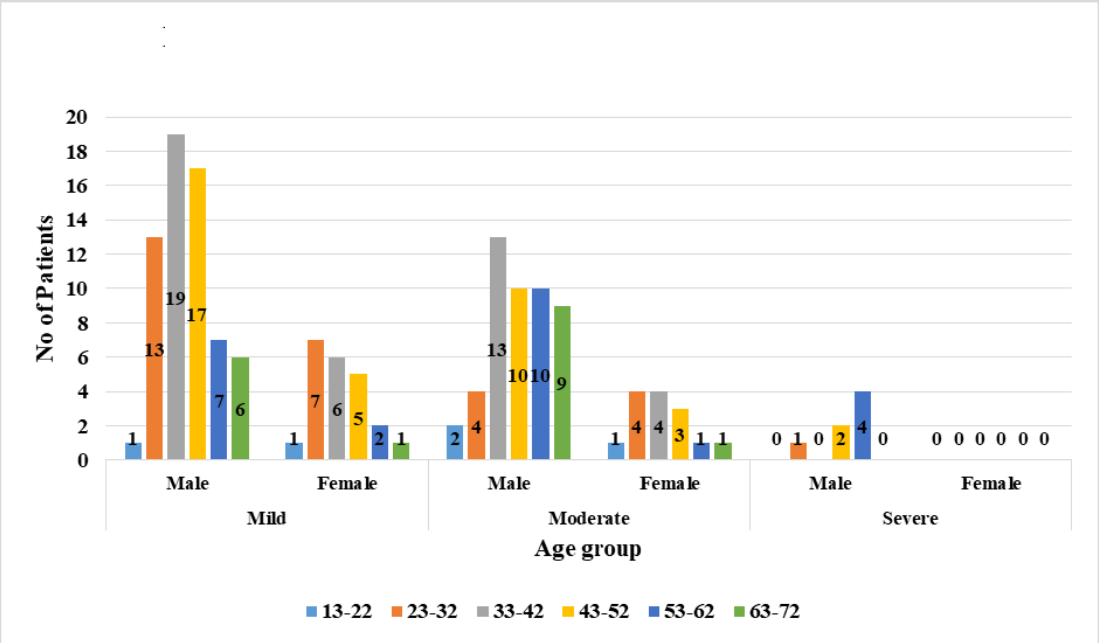

Fig. 3. Severity of adverse drug reactions based upon age wise distribution in both genders

Figure 4 shows the Causality assessment of ADR based on Naranjo's Causality assessment scale. The result showed that most of the encountered ADR were possible (54.83). Age group of 33-42 male patients showed more possible, whereas for female patients both 23-32 and 33-42 age groups were more possible for ADRs.

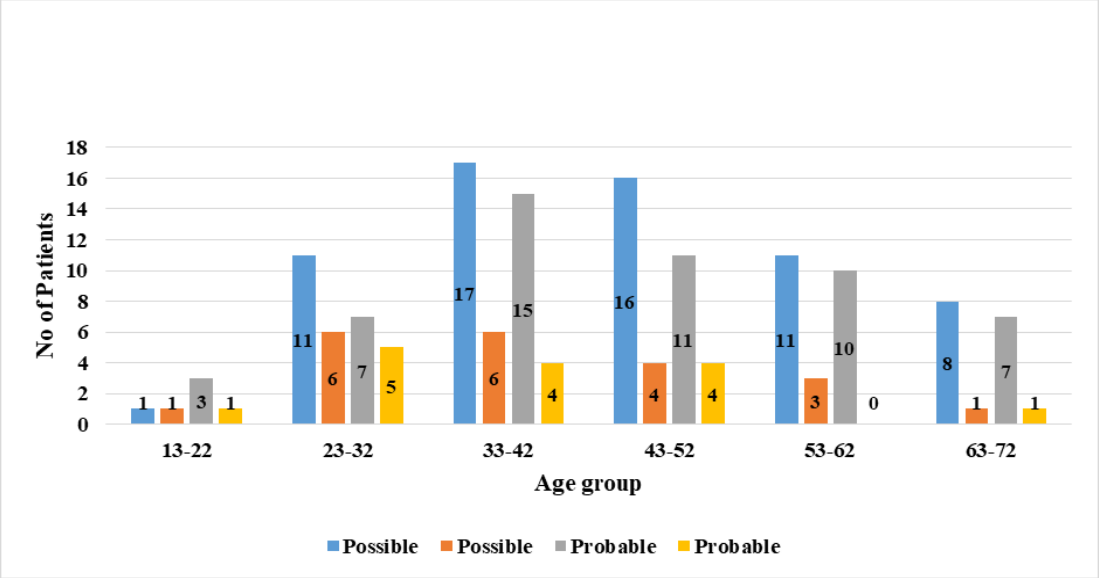

Fig. 4. Assessment of adverse drug reactions based upon age wise distribution in both gender

4. Discussion

It is necessary to evaluate pattern of adverse reactions, as there can be no hope of eliminating all the adverse effects of drugs. There is a special need for systemic collection of information on ADRs in India due to wide variation in genetic (family history), life style (smoking, drinking alcohol) and disease patterns. ADR monitoring and reporting in hospitals is an important program to identify and quantify the risks associated with use of drugs. This information may be useful in identifying and preventing suspected ADRs while generally enhancing the knowledge of prescribers to deal with ADRs more effectively. Early detection of ADRs helps to modify the doses or the drug

regimen to minimize toxic effects. Similar studies can be used as reference for iatrogenic ADRs and assessment of prevention of expected adverse drug reactions. ADR reporting and monitoring in a tertiary care hospital should be continuous and ongoing process to keep a record of newly marketed drugs and medicinal products. This helps in providing baseline data regarding the safety of those drugs. Serious ADRs account for prolonged hospitalization, increased morbidity and also economic burden. Hence, ADR monitoring is considered as an important activity, as it justifies the benefit versus risk ratio of drugs.

This study was performed with the ultimate aim, to generate information about ADRs to anti tubercular drugs prescribed at DOTS centre in Nellore, Andhra Pradesh, to add knowledge about the safety of medicines and prevention of ADRs. During the study period from August 2017 – January 2018, 62 patients with ADRs to anti-tubercular drugs were detected by spontaneous reporting from the health care professionals of the DOTS therapy centre, Nellore. This was accomplished using the notification slip, telephonic conversation or communicating personally. The patients suffering from ADRs were examined by physician and information about the adverse event was recorded in the ADR form. Information about ADR in patients satisfying the inclusion criteria were recorded in the case report.

Our Study reveals that females were more affected by ADRs as compared to male patients. Previous studies have revealed similar findings (Nemagouda, 2014; Maqusood et al., 2016; Shareef et al., 2018). Female patients have reduced body size to body weight ratio, compared to males, which might be the reason for high prevalence of ADRs among them. Our present study also found that gastrointestinal system was involved commonly in the ADRs of first-line Antitubercular drugs. Various studies have also noted the same (Gor et al., 2008; Sinha et al., 2013; Singh et al., 2015).

In our present study, WHO Causality assessment scale (Zaki, 2011) and Naranjo causality algorithm scale (Naranjo et al., 1981) have been employed to evaluate causality assessment of the suspected adverse drug reactions. Majority of the reported ADRs belonged to the possible category and the rest of the ADRs were found as probable, as per WHO Causality assessment scale and Naranjo's scale.

Hartwig Assessment Scale was used to carry out the severity assessment of ADRs and the scale is categorized into mild, moderate and severe levels (Hartwig et al., 1992). Hartwig's scale helps to decide whether hospitalization is required or not for an adverse drug reactions developed. Though the incidence of ADRs due to first line antitubercular drugs used in the DOTS centre, Nellore was high, majority of the reported ADRs were classified as mild and did not need modification of treatment or administration of specific antidotes. In addition, majority of the patients were seen to have mistaken the symptoms of ADR with the disease being treated.

5. Conclusion

Our current study indicates that gastrointestinal system was affected more commonly by the ADRs of first-line Antitubercular drugs. As per the Hartwig's scale, majority of the reported ADRs were classified as mild. In addition, most of the ADRs had a "possible" relationship with the suspected drugs, as per the causality assessment done by using WHO Causality assessment scale and Naranjo causality algorithm scale. The current study stresses on more intensive implementation of ADR monitoring and reporting to provide optimum patient care and to obtain therapeutic outcome. The involvement of clinical pharmacists in detecting and monitoring of adverse drug reactions might help to improve the patient adherence, minimize drug resistance and achieving better therapeutic outcome.

6. Acknowledgement

We would like to express our gratitude to our college chairman Mr. Ratnam garu for supporting our study.

References

Agrawal et al., 2018 – *Agrawal, A., Bhosale, U.A.* (2018). A prospective pharmacovigilance study to evaluate adverse effect profile of first line anti-tubercular drugs in newly diagnosed sputum positive patients. International Journal of Basic & Clinical Pharmacology, 7(2): 283-7.

Cabré et al., 2018 – *Cabré, M., Elias, L., Garcia, M., Palomera, E., Serra-Prat, M.* (2018). Avoidable hospitalizations due to adverse drug reactions in an acute geriatric unit. Analysis of 3,292 patients. *Medicina Clínica* (English Edition), 150(6): 209-14.

Edwards, Aronson, 2000 – *Edwards, I.R, Aronson, J.K.* (2000). Adverse drug reactions: definitions, diagnosis, and management. *The lancet,* 356(9237): 1255-9.

Floyd et al., 2018 – *Floyd, K., Glaziou, P., Zumla, A., Raviglione, M.* (2018). The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. *The Lancet Respiratory Medicine,* 6(4): 299-314.

Gor, Desai, 2008 – *Gor, A.P., Desai, S.V.* (2008). Adverse drug reactions (ADR) in the inpatients of medicine department of a rural tertiary care teaching hospital and influence of pharmacovigilance in reporting ADR. *Indian journal of pharmacology*, 40(1): 37.

Hartwig et al., 1992 – *Hartwig, S.C, Siegel, J., Schneider, P.J.* (1992). Preventability and severity assessment in reporting adverse drug reactions. A*merican Journal of Health-System Pharmacy,* 49(9): 2229-32.

Maideen, 2018 – *Maideen, NMP* (2018). Thiazolidinediones and their Drug Interactions involving CYP enzymes. *A J Physiol Biochem Pharmacol.*, 8(2): 47-54.

Maqusood et al., 2016 – *Maqusood, M., Khan, F.A., Swaroop, A.* (2016). A Study on Incidence of Adverse Drug Reaction of Anti-Tubercular Drugs in New Cases of Pulmonary Tuberculosis in a Tertiary Care Teaching Hospital. *IJMRP,* 2(3): 53-6.

Naranjo et al., 1981 – *Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruiz, I., Roberts, E.A., Janecek, E., Domecq, C., Greenblatt, D.J.* (1981). A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology & Therapeutics,* 30(2): 239-45.

Nemagouda, 2014 – *Nemagouda, S.* (2014). The Antitubercular Drug Induced Adverse Effects in Registered Cases under RNTCP–Dots Programme in Bijapur. *Journal of Evolution of Medical and Dental Sciences,* 3(19): 5255-62.

Pakkir Maideen et al., 2018 – *Pakkir Maideen, N.M., Manavalan, G., Balasubramanian, K.* (2018). Drug interactions of meglitinide antidiabetics involving CYP enzymes and OATP1B1 transporter. Therapeutic advances in endocrinology and metabolism, 9(8): 259-68.

Park et al., 2015 – *Park, S.I., Oh, J., Jang, K., Yoon, J., Moon, S.J., Park, J.S., Lee, J.H., Song, J., Jang, I.J., Yu, K.S., Chung, J.Y.* (2015). Pharmacokinetics of Second-line Anti-Tuberculosis Drugs after Multiple Administrations in Healthy Volunteers. *Antimicrobial agents and chemotherapy,* AAC-00354.

Patton, Borshoff, 2018 – *Patton, K., Borshoff, D.C.* (2018). Adverse drug reactions. *Anaesthesia,* 73: 76-84.

Pourakbari et al., 2016 – *Pourakbari, B., Mamishi, S., Mohammadzadeh, M., Mahmoudi, S.* (2016). First-line anti-tubercular drug resistance of mycobacterium tuberculosis in IRAN: a systematic review. *Frontiers in microbiology,* 7: 1139.

Ranzani et al., 2017 – *Ranzani, O.T., Rodrigues, L.C., Waldman, E.A., Carvalho, C.R.* (2017). Estimating the impact of tuberculosis anatomical classification on treatment outcomes: A patient and surveillance perspective analysis. *PloS one,* 12(11): e0187585.

Schnippel et al., 2018 – *Schnippel, K., Firnhaber, C., Berhanu, R., Page-Shipp, L., Sinanovic, E.* (2018). Direct costs of managing adverse drug reactions during rifampicin-resistant tuberculosis treatment in South Africa. *The International Journal of Tuberculosis and Lung Disease*, 22(4): 393-8.

Shareef et al., 2018 – *Shareef, J., Nandakumar, U.P., Bhat, M.* (2018). A Study on Assessment of Adverse Drug Reactions in Patients with Tuberculosis in a Tertiary Care Teaching Hospital. *Journal of Applied Pharmaceutical Science*, 8(04): 099-104.

Singh et al., 2015 – *Singh, A., Prasad, R., Balasubramanian, V., Gupta, N., Gupta, P.* (2015). Prevalence of adverse drug reaction with first-line drugs among patients treated for pulmonary tuberculosis. *Clinical Epidemiology and Global Health,* 3: S80-90.

Sinha et al., 2013 – *Sinha, K., Marak, I.T., Singh, W.A.* (2013). Adverse drug reactions in tuberculosis patients due to directly observed treatment strategy therapy: Experience at an outpatient clinic of a teaching hospital in the city of Imphal, Manipur, India. *The journal of association of chest physicians,* 1(2): 50.

Zaki, 2011 – *Zaki, S.* (2011). Adverse drug reaction and causality assessment scales. *Lung India,* 28(2): 152.