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ANALYSIS OF PHARMACOVIGILANCE DATA AT THE ADVERSE DRUG MONITORING CENTRE PERTAINING TO ANTI TUBERCULAR DRUGS -A RETROSPECTIVE CROSS-SECTIONAL STUDY

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ABSTRACT

Background: The pharmacovigilance programme of India aims to improve patient safety and welfare of Indian population by identifying and analysing new signals from the reported cases and generating evidence based information on safety of medicines. The purpose of this study is to collect the data of adverse drug reactions to the antitubercular drugs and analyse them. India accounts for one fourth of global tuberculosis burden. In 2017, elimination of tuberculosis in India by 2025 was announced as a national goal. Antitubercular drugs are more prone to cause adverse drug reactions. This in turn may lead to poor compliance paving way for the development of drug resistance tuberculosis. Early detection and proper management minimizes this risk. The vision is to communicate the safety information to the health care professionals and public hence reducing the drug related complications. **Methodology:** This is a retrospective cross sectional study of adverse drug reactions reported to the adverse drug reactions monitoring centre regarding the antitubercular drugs. The data collected were from the CDSCO's adverse drug reactions reporting form, reported in the time period of June 2015 – July 2017. **Results:** The demographic pattern, causality, severity of the adverse drug reactions were analysed. 187 adverse drug reactions were reported during the study period which included 133 men and 54 women. The mean age of the reported adverse drug reactions was 46.4±17.59 years. Among the antitubercular drugs pyrazinamide was more prone to cause adverse drug reactions followed by streptomycin. In 62.6% of cases the antitubercular drugs were the probable cause and in 37.4% of adverse reactions ATT were the possible cause. 91.4% of them were non serious and 8.6% of them were serious adverse drug reactions. Most common adverse drug reaction reported was dermatological reactions followed by gastrointestinal and neurological side effects. The study showed that there was a significant association between the causality and seriousness of the adverse reactions encountered. **Conclusion:** This study serves to stress the importance of pharmacovigilance programme, create awareness and intensify the ADR reporting by the health care workers. This is also useful in educating the drug related complications to the patients and the public.

KEYWORDS: Adverse drug reactions, pharmacovigilance, antituberculosis drugs, causality, severity.

BACKGROUND AND INTRODUCTION

The nationwide pharmacovigilance programme was initiated by the Central Drug Standard Control Organisation, New Delhi under the aegis of ministry of Health and Family welfare, Government of India in July 2010. Pharmacovigilance programme of India has 250 Adverse Drug Reactions Monitoring Centres (AMCs) throughout the country. The mission of PVPI is to safeguard the health of Indian population by ensuring the benefits of using medicine outweighs the risks associated with its use.

India accounts for the one fourth of the global tuberculosis burden. An estimated 1.3 Lakh of multi drug resistant tuberculosis patients emerge annually in India. Adverse drug reactions of the anti tuberculosis drugs tend the patient to default the treatment and leads to the emergence of drug resistance.

The purpose of our study is to collect the data regarding adverse drug reactions to anti tuberculosis drugs, analyse them and use the inferences to reduce the risk of drug related harm to the patients. This study also encourages the health care professionals in reporting the ADR.

AIM

To analyse the adverse drug reactions encountered during anti tubercular therapy.

OBJECTIVES

Primary objective

To assess the causality and severity of adverse reactions to the antituberculosis drugs.

Secondary Objectives

1) To study the demographic pattern of patients with adverse drug reactions.
2) To create awareness and motivate various sectors of health care providers and the public about the reporting of adverse reactions.

Study Design

Retrospective cross-sectional study

Study Period

June 2015-July 2017

Study Duration

3 months

MATERIALS AND METHODS

This study was done in the Department of Pharmacology, Coimbatore Medical College after obtaining approval from the institutional ethics committee (No. 0152/2018). The data were obtained from the records maintained in the Adverse drug reactions Monitoring Centre, Coimbatore Medical College, the primary source being the CDSCO's ADR reporting forms received from various hospitals and health care settings. The time period of the study was from June 2015 to July 2017.

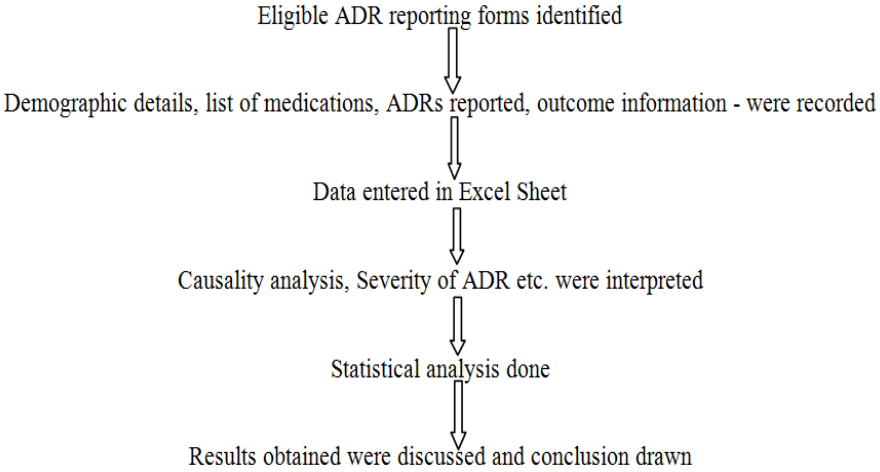
Inclusion Criteria

Adverse drug reactions reported to the AMC, CMC encountered by the anti tuberculosis drugs received in the CDSCO's ADR reporting form from June 2015-July 2017.

Exclusion Criteria

1. ADRs reported for other than anti tuberculosis drugs.
2. ADR forms which were Incomplete.

METHODOLOGY



DATA ANALYSIS TOOLS

Causality Assessment: This was done using WHO Causality assessment Scale.
Severity Assessment: Done using Modified Hartwig and Siegel Scale.

Statistical Analysis

The categorical variables were expressed in terms of frequencies, proportions and percentage. The continuous variables were expressed in terms of Mean and Standard deviation. Test of significance between variables was analysed using chi square test. Analysis were done using SPSS 19 version.

RESULTS

The total number of ADR cases to the ATT drugs reported in the time period from June 2015 to July 2017 was 187. In this 133 were male and 54 were female.

Table 1: Sex distribution.

Sex	No.of patients	Percentage
Male	133	71.1
Female	54	28.9
Total	187	100.0

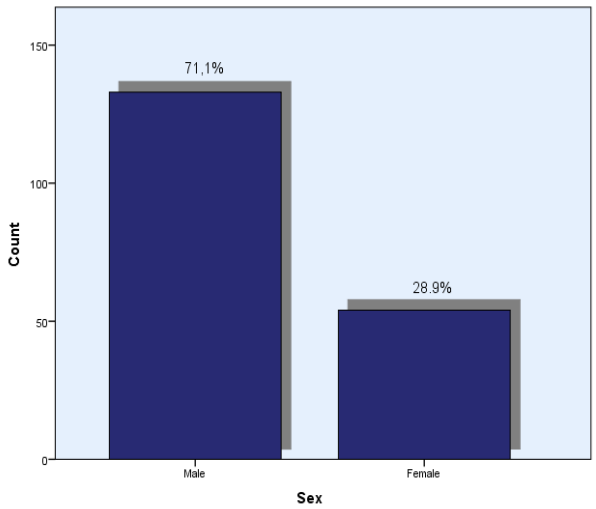


Figure 1: Sex distribution.

The mean age of occurrence of ADR was 46.41±17.59 years.

Table 2: Mean Age and Standard Deviation.

Age	No. of patients	Mean	Std. Deviation
	187	46.41	17.59

Out of 187 ADRs 46 were reported from tertiary care centre and 141 were reported from other centres.

Table 3: Source of information.

Department	No.of patients	Percentage
CMCH	46	24.6
OTHERS	141	75.4
Total	187	100.0

In the reported cases, 93.6% were pulmonary tuberculosis, 2 % were extrapulmonary tuberculosis and 4.3% were multi drug resistant tuberculosis.

The offending drug in most cases was pyrazinamide (72.2%), streptomycin was the next drug to cause ADR mounting to 16.6% of the total.

Table. 4. The offending drug.

Medicines given	N	Percent
Pyzinamide	135	72.2
Streptomycin	31	16.6
Cat-IV	21	11.2
Total	187	100.0

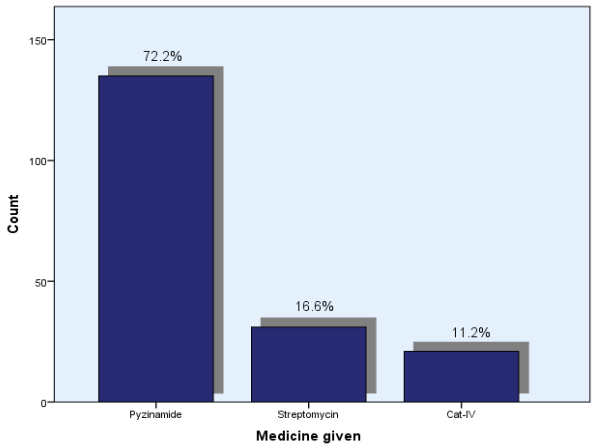


Figure. 2: The offending drug.

The cause for ADR was assessed using standard WHO causality assessment scale. The ATT as the possible cause for the ADR amounted to 37.4% however that as the probable cause for the occurrence of adverse reactions were 62.6%

Table 5: Causality Assessment.

Causality Assesment	Number	Percent
Possible	70	37.4
Probable	117	62.6
Total	187	100.0

The seriousness of ADR was assessed using Modified Hartwig scale. 91.4% of the ADRs occurred were nonserious and 8.6% of them were found serious.

Table 6: Seriousness of the ADR.

Seriousness	No. of cases	Percent
Serious	16	8.6
Non-serious	171	91.4
Total	187	100.0

There was a statistically significant association between the causality of ADR and the seriousness with a P value < 0.000, unadjusted odds ratio being 1 with a 95% confidence interval. (2.14 – 24.53)

Table 7: Association between Causality and Seriousness.

Factors	Category	Total	Serious		Unadjusted odds ratio	95% CI*	P value
			N	%			
Causality	Possible	70(37.4)	13	18.6	7.24	2.14-24.53	<0.000
	Probable	117(62.6)	3	2.6	1		

Among the reported ADRs the dermatological adverse reactions were the highest amounting to 36.9% of the total ADRs. Next is the gastrointestinal side effects amounting to 34.2%. CNS side effects were reported in 11.5% of cases wherein hepatobiliary ADRs were about 4.8%.ADRs pertaining to RS were about 2.7%. one case of chronic kidney disease and two cases of thrombocytopenia were reported.

Table 8: ADRs encountered during tuberculosis treatment.

Adverse Reactions	No.of patients	Percent
Vomiting	64	34.2
Hepatitis	9	4.8
Itching	69	36.9
Giddiness	14	7.5
Loss of Hearing	8	4.3
Difficulty in Breathing	5	2.7
Swelling lower limbs with pain	10	5.3
Fever	5	2.7
Chronic Kidney Disease	1	.5
Thrombocytopenia	2	1.1
Total	187	100.0

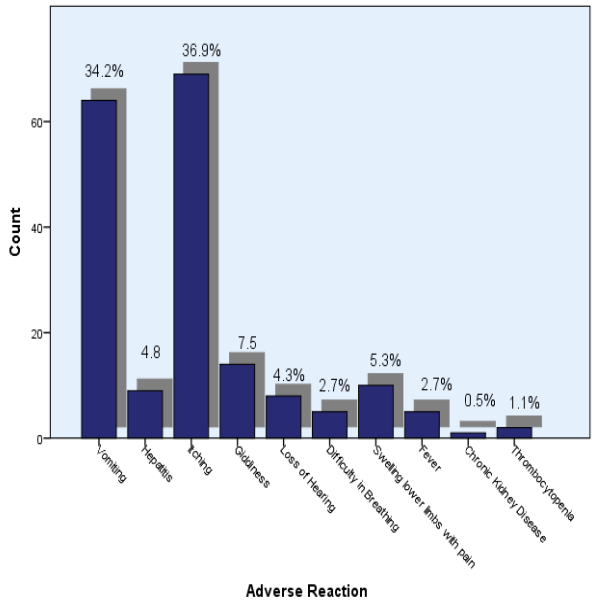


Figure 3: ADRs encountered during tuberculosis treatment.

DISCUSSION

The pharmacovigilance programme of India is intended to identify and analyse the new signals from the reported cases, generate evidence based information on the safety of medications and communicate the information to the health care system and the public. Thus safe treatment can be ensured.

Tuberculosis is an airborne infectious disease which continues to be a challenge to the public health. The drugs used to treat tuberculosis, like most other drugs can cause adverse drug reactions owing to the multidrug regimen and prolonged therapy.

This study analyses the adverse drug reactions encountered during the treatment of tuberculosis, which were reported to the ADR monitoring centre, from June 2015 – July 2017.

The total number of cases reported in the study period of two years was 187. Males account for 71.1% and females were 28.9%. This male preponderance coincides with the study conducted by Amit Kumar Singh, Niharika Paut with 78.6% reported ADR were encountered by male patients.[5] Another study done by Banu Eris Gulbay et al also showed that 76.2% male had ADRs.[2]

In this study the mean age of patients reported with ADR was 46.41 years with the a standard deviation of 17.59 years. This is the productive age group. Tuberculosis itself confers economic burden to the family and country while ADR becomes an added burden. This age group of occurrence of ADR matches with various studies viz., Houda Elkhabbazi et al[1], Banu Eris Gulbay el al[2], Fivy Eurniawati, Syed Azhar Syed Sulaiman and Syed Wasif Gillani[3], Waseem Saeed, Arshad Naseem, Jamal Ahmed[6], Daphne Yee et al.[9]

Among the antitubercular medications, most of the ADRs reported to the ADR monitoring centre were attributed to Pyrazinamide (72.2%). ADRs due to Streptomycin amounted to 16.6% of the total cases. In the study done by Daphne Yee et al, the incidence of ADRs due to Pyrazinamide were more than that of other drugs which agrees with our study.[9]

In the study, the causation of ADR was assessed using WHO causality assessment scale which showed that for 37.4% of ADRs ATT being the possible cause and for 62.6%, ATT was the probable cause. The study conducted by Athira B, Manju CS and Jothi E in Kerala also reported that the majority reactions were probable (68.57%) and 20% were possible reactions.[16] This is in consistence with our observations.

Modified Hartwig scale was used to evaluate the seriousness of the ADR. We found that though 91.4% of the ADRs reported were nonserious, we have to stress on 8.6% of cases which were serious. The occurrence of nonserious ADRs might lead to the discontinuation of the medications whereas serious ADRs, when left undiagnosed could lead to fatal complications. This is consistent with the study conducted by Daphne Yee et al that had 9% of incidence of serious ADRs. This study conducted by Syed Mohammad et al., showed that ADRs belonged to mild to moderate level of severity whilst none belonged to severe level.[4] In contrast to this serious ADRs occurred in patients taking first line antitubercular drug.[7]

The analysis of the ADRs in this study showed that the majority were dermatological adverse reactions. This was similar to the observations of Fivy Kurniawathi et al.[3] Gastrointestinal side effects accounted to 34.2% of the observed ADRs. This is comparable with the results obtained by Amit Kumar Singh, Niharika Pant in their study.[5]

Although the antitubercular drugs are more prone to produce hepatotoxicity, the hepatobiliary side effects

noted in our study was 4.8%. The hepatotoxicity reported by Banu Eris Gulbay et al was about half of our observation (2.4%), whereas Fivy Kurniawati et al found 2.6% of hepatotoxicity in their study.[2,3]

CONCLUSION

This study highlights the causality, severity and outcome of the ADRs encountered with the use of antitubercular drugs. It also explains the demographic pattern of Tuberculosis patients having ADR to ATT drugs.

The study showed that there was a statistically significant association between the causality of the ADR and its seriousness. This implies that when an ADR occurred due to antitubercular drug, it should be closely monitored and treated accordingly to avoid the consequences.

There was a strong association between the seriousness of the ADR and recovery of the patients from the ADR. The recovery from the ADR is essential for the uninterrupted intake of antitubercular medications.

This study throws light on common ADR s encountered during the course of antituberculosis treatment. It alarms the Healthcare Professionals as well as the patients to watch out for the ADRs. It also serves to stress the importance of Pharmacovigilance programme and to intensify the ADR reporting. Early identification of ADRs and its proper management ensures compliance of the patients to antituberculosis drugs and prevents the emergence of Drug resistance.

Limitations

The limitations of the study are, it is a retrospective study and the sample size is small.

REFERENCES

1. Elkhabbazi, Houda, Rajaa Benkirane, and Abderrazak Khadmaoui. "Evaluation Of Adverse Effects Of Antituberculosis In El-Idrissi Hospital, Kenitra, Morocco," n.d., 6.
2. Gülbay, Banu Eriş, Özlem Ural Gürkan, Öznur Akkoca Yıldız, Zeynep Pınar Önen, Ferda Öner Erkekol, Ayşe Baççıoğlu, and Turan Acıcan. "Side Effects Due to Primary Antituberculosis Drugs during the Initial Phase of Therapy in 1149 Hospitalized Patients for Tuberculosis." *Respiratory Medicine* 100, October 2006; 10: 1834–42. https://doi.org/10.1016/j.rmed.2006.01.014.
3. Kurniawati, Fivy, Syed Azhar Syed Sulaiman, and Syed Wasif Gillani. "Adverse Drug Reactions of Primary Anti-Tuberculosis Drugs Among Tuberculosis Patients Treated in Chest Clinic." *Life Sci.*, 2012; 3(1): 8.
4. Naser, SyedMohammad, Manab Nandy, Parvin Banu, Arghya Banerjee, Suhrita Paul, Indrashis Podder, and Mayukh Mukherjee. "Adverse Drug Reaction Monitoring through Active Surveillance of Antitubercular Therapy in an Urban Tertiary Care Center." *Community Acquired Infection*, 2016; 3(2): 51. https://doi.org/10.4103/2225-6482.184913.
5. Singh, AmitKumar, and Niharika Pant. "Adverse Effects of First Line Antitubercular Medicines on Patients Taking Directly Observed Treatment Short Course: A Hospital Based Study." *International Journal of Medicine and Public Health*, 2014; 4(4): 354. https://doi.org/10.4103/2230-8598.144063.
6. Waseem Saeed, Arshad Naseem, Jamal Ahmed. "Retrospective Audit Of Patients Treated For Mdr-Tb In Re-Treatment Category"J Ayub Med Coll Abbottabad, 2009; 21(2).
7. O.S. Michael1, O.M. Sogaolu2, F.A. Fehintola1, O.M. Ige2 and C.O. Falade1. "Adverse Events To First Line Anti-Tuberculosis Drugs In Patients Co-Infected With Hiv And Tuberculosis" Ann Ibd. Pg. Med., 2016; 14(1): 21-29.
8. AliasgharFarazi,1,2 MasoomehSofian,1 MansourehJabbariasl,3 andSaraKeshavarz4 Adverse Reactions to Antituberculosis Drugs in Iranian Tuberculosis Patients Hindawi Publishing Corporation Tuberculosis Research and Treatment, 2014; 412893: 6. http://dx.doi.org/10.1155/2014/412893
9. Daphne Yee, Chantal Valiquette, Marthe Pelletier, Isabelle Parisien, Isabelle Rocher, and Dick Menzies Incidence of Serious Side Effects from First-Line Antituberculosis Drugs among Patients Treated for Active Tuberculosis Am J Respir Crit Care Med., 2003; 167: 1472–1477. DOI: 10.1164/rccm.200206-626OC on January 31, 2003 Internet address: www.atsjournals.org
10. R A M Breen, R F Miller, T Gorsuch, C J Smith, A Schwenk, W Holmes, J Ballinger, L Swaden, M A Johnson, I Cropley, M C I Lipman Adverse events and treatment interruption in tuberculosis patients with and without HIV coinfection http://thorax.bmj.com/Thorax: first published as 10.1136/thx.2006.058867 on 14 July 2006.
11. YinYinXia1, DaiYuHu2, FeiYingLiu3, XiaoMengWang4, YanLiYuan 5, DeHuaTu6, YiXinChen7, LinZhou8, LiZhenZhu9, WeiWeiGao9, HongYuanWang1, DaFangChen1, LiYang10, PingPingHe1, XiaoTingLi1, YingJianHe1, FengSun1 and SiYanZhan*Study protocol Design of the Anti-tuberculosis Drugs induced Adverse Reactions in China National Tuberculosis Prevention and Control Scheme Study (ADACS)Background Xia et al. BMC Public Health, 2010; 10: 267. http://www.biomedcentral.com/1471-2458/10/267
12. Anupa Khatri Chhetri1, Archana Saha2, Sharat Chandra Verma3, Subish Palaian4, Pranaya Mishra5, Pathiyil Ravi Shankar6 A study of adverse drug reactions caused by first line anti-tubercular drugs used in Directly Observed Treatment, Short course (DOTS) therapy in western Nepal, Pokhara J Pak Med Assoc, October 2008; 58: 10.
13. B Kakande | MD RJ Lehloenya | BSc, MBChB, FCDerm(SA) Drug Reactions Associated With

Antituberculosis Drugs Current Allergy & Clinical Immunology, December, 2015; 28: 4.

14. H. Simon Schaaf, Stephanie Thee, Louvina van der Laan, Anneke C. Hesseling & Anthony J. Garcia-Prats Adverse effects of oral second-line antituberculosis drugs in children, Expert Opinion on Drug Safety, 2016; 15:10, 1369-1381, http://www.tandfonline.com/loi/ieds20
15. Kocfa Chung-Delgado1,2*, Alejandro Revilla-Montag1,2, Sonia Guillen-Bravo1,2, Eduardo VelezSegovia1,2, Andrea Soria-Montoya1,2, Alexandra Nun ˜ez-Garbin1,2, Wilmer Silva-Caso1,2, Antonio Bernabe-Ortiz1 Factors Associated with Anti-Tuberculosis Medication Adverse Effects: A Case-Control Study in Lima, Peru www.plosone.org, November, 2011; 6(11): e27610.
16. Tauseef Nazir*, Sameena Farhat, Mohd Adil, Zuryat Asraf Adverse drug reactions associated with first line anti-tubercular drugs, their prevalence and causality assessment in patients on Directly Observed Treatment Short-course (DOTS) in a tertiary care hospital. http://dx.doi.org/10.18203/2319-2003.ijbcp20185174
17. Shamiya Sadiq1, Vijay Khajuria2, ViShal r. Tandon3, annil mahajan4, jang B. Singh5 Adverse Drug Reaction Profile in Patients on Anti-tubercular Treatment Alone and in Combination with Highly Active Antiretroviral Therapy Journal of Clinical and Diagnostic Research, Oct, 2015; 9(10): FC01-FC0410.7860/JCDR/2015/13452.6652