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PATTERN OF ADVERSE DRUG REACTION IN PATIENTS ON ANTITUBERCULAR THERAPY REPORTED TO ADR MONITORING CENTRES IN KUMAOUN REGION

Clinical Research

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ABSTRACT

AIM: To evaluate Adverse Drug Reactions (ADRs) due to Anti-Tubercular Therapy (ATT) in a tertiary care hospital in Kumaoun Region.
Introduction: Tuberculosis is affecting one out of three people worldwide. ADRs due to ATT is one of the major cause of noncompliance , hospitalization, drug withdrawl and financial burden to patient during treatment .
MATERIALS AND METHODS: It was a retrospective study conducted at Dr. Sushila Tiwari Government Medical College and hospital. The data was obtained from Suspected ADR Reporting form between January 2019 - December 2019 from Chest and TB department to the ADR monitoring centre attached to the Department of Pharmacology under the Pharmacovigilance Programme of India (PvPI).
RESULTS: Total 164 ADRs were reported from 140 from. Out of which 63.6 % were males and 36.4% were females. Most common ADR reported was related to GIT (43.3%) followed by Metabolic 33.53% and Dermatological (4.9 %). WHO causality scale assessed that 52.3 % of reaction falls under possible and 47.7 % under probable category. Most common drug causing ADRs was Pyrazinamide (44%) followed by Rifampicin (29 %) and Isoniazid (16%).
CONCLUSION: Significant number of ADRs are reported by the use of Antitubercular drugs so there is a need for prompt detection and reporting so that remedial measures are taken in time. Using the therapy rationally and judiciously can decrease the burden of ADRs to society thus benefitting mankind.

KEYWORDS

Adverse Drug Reactions, PvPI, WHO, Tuberculosis

INTRODUCTION

According to World Health Organisation an "Adverse drug reaction can be defined as an noxious, unintended effect which occurs at doses used for diagnosis, mitigation, prevention and treatment of disease." India is second most populous country in the world with one fourth of the global incident TB cases occurring in India annually. Tuberculosis is a communicable disease that is major cause of ill health and leading cause of death from bacillus Mycobacterium tuberculosis. Globally 7.0 million new cases of TB were notified in 2018 –an increase from 6.4 million in 2017. In India new cases rose from 1.2 million to 2.0 million between 2013 and 2018 **[1].**

As per India TB report, in 2019, highest notification of TB cases was from Uttar Pradesh (17%) followed by Maharashtra (10%), Rajasthan (7%), Bihar and West Bengal (5%). Contributing 20 percent of total TB notified patients. Around 4.2 lakh cases out of an all India figure of 21.5 lakh came from Uttar Pradesh.

In Uttarakhand, total 43916 cases were reported. Highest Number of cases were reported from Dehradun district (6623) followed by Haridwar district (4836), Nainital District (3832). It said that India initiated the programmatic management of drug resistant TB (PMDT) in 2007 to address the emerging problem of drug resistant-TB (DR-TB), and the national PMDT scale-up was achieved by March 2013.The treatment success rate among MDR-TB patient in India is about 47% with 20% death rate while 19% patient lost to follow up**.**

The Government of India has declared TB to be a notifiable disease that any doctor who treats any TB patient has to notify it to the government. The government of India gradually replaced the NTP(National tuberculosis Programme) by DOTS (Directly observed treatment for short course) or RNTCP (Revised National Tuberculosis programme) and in December 2019 the name has been changed to National Tuberculosis Elimination Programme **[2]**.

As per new regimen , for new cases- 6 months regimen is followed that includes isoniazid(H), rifampicin(R), pyrazinamide(Z), and ethambutol(E) daily for first 2 months followed by rifampicin(R) and isoniazid(Z) for 4 months. For previously treated cases. HRZE is given daily for 2 months followed by HRZES for next 1 month followed by HRE for 5 months.For MDR-TB , kanamycin (km), levofloxacin(Lfx), ethambutol(E), pyrazinamide(Z), ethionamide (Eto) and cycloserine(Cs) are given for 6-9 months followed by levofloxacin ethambutol, ethionamide and cycloserine for next 18 months **[3]**.

Antitubercular drugs also has many serious adverse drug reactions (ADR) as the treatment of TB almost always involves combination of drugs taken for prolonged period , the occurrence of ADR is quite likely. Moreover, the adverse effect of one drug may be enchanced by the concomitant drugs so it becomes difficult to treat and identify the causative drug causing ADRs. The major adverse reactions to antitubercular drugs caused significant morbidity ,mortality and compromised treatment regimes. Many of the ADR can be prevented or minimized by due diligence. So ADR monitoring becomes a important tool to detect uncommon and sometimes serious ADR ensuring patients safety. Hence we conducted this study to assess the ADRs due to tuberculosis in the tertiary care hospital in Kumaun Region.

MATERIAL AND METHODS:

Study Area:- The study was conducted at the tertiary care centre at Dr. Sushila Tiwari Government Medical College Hospital & TB Chest Institute Haldwani, Nainital. Approval of the Institutional Ethical Committee was obtained for the study.

Study Period and Study Population:- The data was obtained from suspected ADRs reporting forms, between January 2019 to December 2019 from the TB Chest department to the ADRs monitoring centre attached to department of Pharmacology under the Pharmacovigilance Programme of India (PvPI).

STUDY DESIGN:

It was a retrospective study conducted from ADR reporting form, reported from TB chest department, who were treated with anti-tubercular drugs during study period January 2019 to December 2019. The demographic details of the patients were recorded. Details of medication given were also noted. Chief Complaint, past history, drug history were also recorded. Details about the occurrence and nature of ADRs, severity, dechallenge and rechallenge were recorded. Concomitant medications administered were also obtained. Relevant laboratory investigations was also noted. Patients of both sexes and all

ages diagnosed with tuberculosis and treated with chemotherapy for the same, developing at least one ADR during or after the treatment period were included in the study.

STUDY TOOL:

ADR reporting form designed by centre for drug standard control organization (CDSCO) was used to collect data. The reported ADRs were assessed for causality using both WHO causality

assessment scale [4]. The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and categorize into " Certain", "probable", "possible", "unlikely", "conditional", / "unclassified" and "unassesseable"/ "unclassifiable". The data collected, analyzed using Microsoft excel and frequency and percentage were determined for each variable.

RESULTS:

A total of 140 patient were included in the study of which 80 males(63.6%) and 51 females (36.4%) reported ADRs. Mostly the patient under the age group 21-30 reported ADRs.

Table 1: Demographic Details and its association with ADRs.

PARAMETERS	NUMBERS (n=140)	PERCENTAGE
GENDER		
Male	89	63.6
Female	51	36.4
AGE IN YEARS		
0-10	1	0.71
11-20	21	15
21-30	32	22.85
31-40	13	9.3
41-50	20	14.28
51-60	28	20
61-70	17	12.14
71 and above	8	5.71

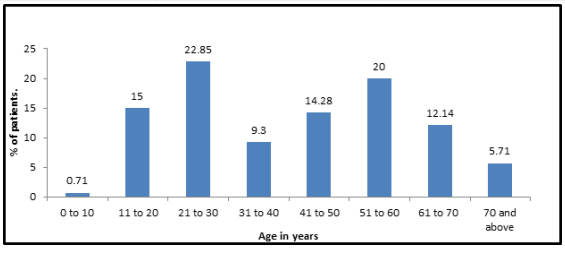

Figure 1: Age Distribution

The most commonly affected system was Gastrointestinal system with 71 ADRs (43.3%) followed by Metabolic System 55 ADRs (33.53%). (Table 2, Figure 2)

Table 2: Incidence of ADRs in different System

System affected	Type of ADRs	Frequency (n=164)	Total Percentage
Gastrointestinal	Hepatotoxicity	62	37.80
	Vomiting	5	3.05
	Loose motions	1	0.60
	Anorexia	1	0.60
	Nausea	1	0.60
	Abdominal Pain	1	0.60
Dermatological	Rash	5	3.05
	Itching	2	1.21
	Eczematous Dermatitis	1	0.60
Nervous	Decreased sleep	1	0.60
	Vertigo	2	1.21
	Peripheral Neuropathy	3	1.82
Metabolic	Hyperuricaemia	55	33.53
Otovestibular	Decreased hearing	2	1.21
	Loss of hearing	3	1.82
Opthalmic	Decreased Vision	3	1.82
	Loss of vision	2	1.21
	Eye toxicity	1	0.60
Haematological	Increased Bilirubin	3	1.82
	Anaemia	2	1.21
	DecreasedLeucocyte count	1	0.60
Others	Weakness	1	0.60
	OralUlcer	1	0.60
Psychiatric	Emotionalquitening	2	1.21
	Agressiveness	3	1.82

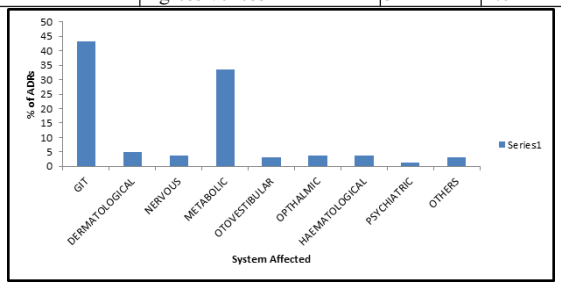

Figure 2: Systemic Distribution of ADRs

Most common drug causing ADRs is Pyrazinamide causing 85 ADRs (44%) followed by Rifampicin causing 56 ADRs(29%) and Isoniazid causing 30 ADRs (16%).

Table 3: Causality Distribution of ADRs

Suspected Drug	Type	Number (n=193)	Total Percentage
Isoniazid	**Probable**	**17**	**16**
	Possible	**13**	
Rifampicin	**Probable**	**13**	**29**
	Possible	**43**	
Pyrazinamide	**Probable**	**45**	**44**
	Possible	**40**	
Kanamycin	**Probable**	**4**	**2**
Ethambutol	**Probable**	**12**	**6**
Streptomycin	**Probable**	**1**	**0.5**
Cycloserine	**Probable**	**5**	**2.5**

Most of the ADRs were Possible 101(52.3%) followed by Probable 92 (47.7%).(Table 3, Figure 3)

Table 3: Causality Distribution according to WHO Causality Scale.

Causality	Number(n=193)	Percentage
Probable	92	47.7
Possible	101	52.3

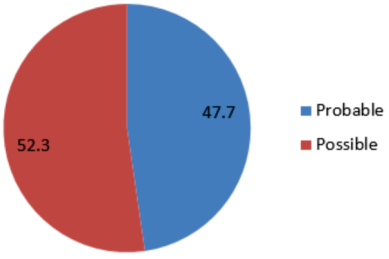

Figure 3: Causality Distribution

DISCUSSION:

To identify the Adverse drug reactions, their treatment and improving compliance is very important aspect of Tuberculosis treatment. PvPI is making tremendous efforts in this regard and it has proven to be an effective way in process of signal generation.

In our study, total 164 ADRs were reported from 140 ADR reporting forms out of which 63.6% patients were male and 36.4% patients were female. Males are more prone to ADRs due to anti tubercular drugs because of higher incidence of smoking, alcoholism and improper diet. It was in correlation with the study done by Gaur et.al which showed that 66% of ADRs were in male **[4].**Mostly the ADRs were prevalent among 21-30 years of age followed by 41-50 years of age similar to most studies showing increased risk of ADRs among Adult Patients **[5,6]**

In our study the most common system affected was GIT (43.3%) followed by metabolic (13.65%). This is in as per the study wherein 82% had gastrointestinal side effects, and 5/3 percent had dermatological side effects **[7].** Among GIT the most common ADR

being hepatotoxicity and vomiting, this was in accordance to the ADR reported by other workers **[8].** This drug related hepatotoxicity is usually seen within the initial few months of intensive phase of antitubercular chemotherapy. It is always good to have liver function test done before starting therapy [**9].**Health care professions have the responsibility to counsel the patients regarding signs and symptoms of hepatotoxicity.

Most common drug causing ADR was Pyrazinamide (44%) closely followed by Rifampicin (29%) and Isoniazid (16%) similar finding was noted by [8,10] some researchers whereas Russian reported streptomycin as the most common drug causing ADR [**11].** There can be difference in the drug causing these ADRs depending on the genetic make up, regime followed , dose of the drug and compliance to therapy. In our study severe cutaneous adverse reaction rates with anti- TB drugs were (4.9%) lower than other studies (4.8% to 6**%)** In this study, visual toxicity due to ethambutol occurred in 6 patients (3.65%) which was slightly higher than reported result in the study of Yee et al. (0.2%)[**12].** Assessment of the WHO causality scale indicated 52.3 % of the reactions were possible and 47.7% of ADRs were probable. Majority of the ADRs were in possible relationship to the suspected drug which was in accordance to study done by Kishore *et.al* **[8].**

CONCLUSION:

Good management of active tuberculosis treatment includes the initiation and the completion of anti-TB therapy with minimal complications. The antitubercular drugs cause significant adverse effects so there is a need for prompt detection to decrease morbidity and mortality. Pharmacovigilance should be promoted and a holistic approach should be adopted by health care professional, drug regulations, drug manufacturers policy makers and the government. Judicious use and rational prescribing reduce the burden of ADRs in the society and benefit the mankind.

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