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Original Research Article

To study causality and classify severity of adverse drug reactions of Antitubercular drugs used in patients of DOTS therapy

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Abstract: Adverse drug reactions (ADRs) are considered as one among the leading cause of morbidity and mortality. A general knowledge of the various ADRs and their management is essential for the effective management of Tuberculosis. This study was planned for detection, assessment, classification and causality analysis of ADRs to antitubercular drugs used in DOTS Therapy in Hamidia Hospital, Bhopal and T B Hospital Idgah Hills, Bhopal. Information of the ADRs is data based collected from DOTS center with the help of treating physician and other health care professionals in a specialized performa and the assessment of ADRs done with the help of various scales and investigation. Maximum numbers of ADRs were reported among male population within 4 week of starting DOTS therapy. The causality assessment was found to 50% possible and 30.64% probable. Majority of ADRs 53.22% were moderate, and 46.77% were mild. No severe life threatening ADRs were observed during the study period. We found DOTS therapy safer, but regular monitoring is required for ADRs so as to prevent the ADRs at the initial stage.
Keywords: Adverse Drug Reactions (ADRs), antitubercular drugs, DOTS (Directly observed treatment short course) therapy

INTRODUCTION

According to WHO an ADR is any response to a drug that is noxious and unintended, that occurs at doses normally used in humans for prophylaxis, diagnosis and therapy of diseases or for the modification of physiological function. Adverse Drug Reactions (ADRs) are common occurrence in hospital settings and more so in the community and is attributed to the severity and complexity of the disease process, use of multiple drugs, drug interactions [1].

The World Health Organization (WHO) declared tuberculosis (TB) as a global emergency in 1993 [2]. MDR-TB and XDR-TB are strong indicators of TB control programme failures due to multi drug therapy and their ADR. The global estimates of the burden of MDR-TB (511,000 incident cases, 150,000 deaths) and XDR-TB, cases (50,000 cases, 30,000 deaths) [3].

In order to intensify the efforts to control TB the Government of India gradually replaced NTP by the DOTS strategy/programme in 1993 and it is now known as the Revised National Tuberculosis Programme (RNTCP). The objective of this revised strategy is to achieve a cure rate of 85% for infections and seriously ill patients through intermittent (three days a week) supervised short course chemotherapy or the directly observed treatment, short course (DOTS) [4].

Antitubercular drugs, just like other drugs used in clinical practice, are not free from ADRs. The added problem is that combinations of drugs are always used for prolonged periods of time therefore; it is likely that the adverse reactions of one drug may be potentiated by the companion drugs used. Moreover, the Adverse Drug Reactions (ADRs) to the drugs used is one of the major reasons for the patient default for treatment. A general knowledge of the various ADRs and their management is essential for the effective management of TB [5].

All antitubercular drugs can cause adverse drug reactions and may result in ADRs involving almost all system in body, including the gastrointestinal tract, liver skin, nervous system, otovestibular apparatus and the eyes [6]. Numerous clinical trials have

determined that there is a 15% probability of an adverse effect occurring in a patient who is on a multiple antitubercular drug regimen and adverse reactions mostly tend to occur in the first three months of treatment [7].

AIMS AND OBJECTIVES

1. To do causality analysis and assess probable correlation of ADRs to age and sex of patients.
2. To classify the severity of ADRs to antitubercular drugs in to mild, moderate and severe based on the clinical features and investigations.

MATERIAL AND METHODS

The present study was undertaken in the department of Pharmacology Gandhi Medical College Bhopal and TB Hospital Idgah hills Bhopal from 15 April 2010 to 15 Dec.2010 the cases were included all the patients visiting the DOTS Center and those admitted in the medical wards in Hamidia Hospital and TB Hospital Idgah hills Bhopal with suspected ADRs due to antitubercular drugs. The recognition is based on reporting by the patient and by leading questions from the physicians. The history is by far the most important part of any clinical assessment. A detailed drug history for specific diseases including over the counter purchases and intake of other preparations (including herbal, homeopathic) is required [21].

- Information of the ADRs is data based collected from DOTS center with the help of treating physician and other health care professionals in a specialized Performa.
- The assessment of ADRs done with the help of following scales and investigations.

Assessment scale: -

a. WHO assessment scale [8]
b. Naranjo scale [9]
C. European A.B.O scale [10]

Investigations: -

- Liver Function Test.
- Routine haemogram
- Peripheral Blood smear
- Serum creatinine and
- Stool for occult blood,
- Urine routine and microscopy examination,
- Blood urea
- Upper gastrointestinal endoscopy.

Inclusion Criteria: -

1. Patients of all the categories of TB with ADRs to Anti-tubercular Agents visiting in the DOTS center.
2. Patients with ADRs to Anti-tubercular Agents in wards.
3. Patients above 12 years of Age.
4. Patients receiving minimum one Anti-tubercular Agents.

Exclusion Criteria: -

1. Patients below 12 years of age.
2. Patients who were HIV Positive.
3. Pregnancy.
4. Patients known case of DM.
5. Patients of MDR-TB and XDR-TB.

Information of Patients was reviewed as

- Details concerning the patient's age, sex, occupation, personal history.
- Details regarding history of present illness, details of all medications taken.
- Medication, daily dose, date of starting, stopping the medication and date of onset of suspected ADR.
- Significant past history and the details of medications the patients was taking for any other illness and clinical examination finding with special reference to the adverse reactions.
- Diagnosis and management severity of the ADR, outcomes of the treatment and sequele.

OBSERVATION

Total numbers of patients treated with DOTS therapy were 820. Out of 820, 720 patients were from OPD and 100 were from IPD, (56%) 460 patients were male, (44%) 360 were female.62 ADRs detected, in 62 patients, 2 patients were dropped out from DOTS therapy due to ADRs.

Age & sex wise distribution of ADRs showed –

Among the total number of ADRs 38 (61.29%) were male and 24 (38.70%) were female. Majority of ADRs were 17 (27.41%) from 21-30 year age group followed by 15 (24%) from. 31-40 year age group and 14 (23%) from 41-50 year age group (table.1&2).

The ADRs detected in OPD patients was 48 (77.41%) and IPD was 14 (22.58%) (Table 3).

Table1: Patients Treated With Antitubercular Drugs

Age Group	Male	Female	Total	Percentage
12-20	85	65	140	17%
21-30	90	70	160	19%
31-40	90	80	170	21%
41-50	90	80	170	21%
51-60	85	65	150	18%
> 60	20	10	30	4%
Total	**460(56%)**	**360(46%)**	**820**	**100%**

Table 2: Age & Sex Wise Distribution of ADR

Age Group	Male	Female	Total	Percentage
12-20	6	5	11	17.74%
21-30	10	7	17	27.41%
31-40	8	7	15	24.19%
41-50	10	4	14	22.58%
51-60	4	1	5	8.06%
> 60	0	0	0	0
Total	**38(61%)**	**24(39%)**	**62**	**100%**

Table 3: OPD and IPD wise distributions of ADRs

ADRs	OPD	IPD	Total
GIT	24	4	28
Skin	10	2	12
Musculo	4	2	6
Hepatobiliary	2	2	4
CNS	3	1	4
Other	5	3	8
Total	**48 (77.41%)**	**14 (22.58%)**	**62 (100%)**

Majority of ADR reported were moderate 33 (53.22%) followed by 29 (46.77%) were mild, no severe ADR was reported. According to severity of ADRs involvement of different system: Majority of ADRs seen were gastritis 28 (45%), followed by skin rash 12(19%), arthralgia 6 (10%) and vertigo 6 (10%), followed by hepatitis 4 (6%), peripheral neuropathy 2 (3%), 2 (3%) psychosis 2 (3%) and flu like syndrome 2 (3%) (Table 4).

According to Gender wise distribution of ADR involving different system:

Among total gastritis ADR 28, 16 (57.14%) were male and 12 (42.85%) were female. From 12 skin rashes 5 (42%) were male and 7 (58%) were female. From 6 arthralgia 4 (67%) male and 2 (33%) were female, among 4 hepatitis 3 (75%) were male and 1 (25%) were female. Among 4 CNS ADR-3 (75%) were male and 1 (25%) were female majority of vertigo ADR were seen in males patient, flu like syndrome were also seen in 2 male patients(table.5).

Onset of ADRs after starting anti-tubercular drugs were maximum 17(27%) in 1-2 weeks followed by 14 (23%) ADRs showed onset in 0-1 week and 2-3 week, 13 (21%) in 3-4th week, 3 (5%) in 4-5th week and 1 (2%) in 5-6th week (table.6).

Table 4: Severity of ADR involvement of different system

S. No.	ADR	Mild	Mod.	Severe	Total	Percentage
1	GIT(GASTRITIS) Vomiting Abdominal cramps Diarrhea	 2 4 2	 8 10 2	0	 10 14 4	 16.12% 22.58% 6.45%
2	Skin Itching Rashes	 6 3	 2 1	0	 8 4	 12.90% 6.45%
3	Musculoskeletal Arthralgia	 3	 3	0	 6	 9.67%
4	Ototoxicity Vestibular Symptoms Auditory Symptoms	 1 1	 3 1	0	 4 2	 6.45% 3.22%
5	Hepatobiliary Hepatitis	3	1	0	4	6.45%
6	CNS Periph. Neuropathy Psychosis	 2	 2	0	 2 2	 3.22% 3.22%
7	Others flu like syndrome	2		0		
Total		**29(47%)**	**33(53%)**	**0**	**62**	**100%**

Table 5: Gender Wise Distribution of ADR Involving Different Organ System

S. No.	ADR	Male	Female	Total
1	GIT	16	12	28
2	Skin	5	7	12
3	Musculoskeleton	4	2	6
4	Hepatobiliary	3	1	4
5	CNS	3	1	4
6	Others	8	0	8
Total		**38(61%)**	**24(39%)**	**62**

Table 6: Onset of ADR

S. No.	ADR	0-1 Wks	1-2 Wks	2-3 Wks	3-4 Wks	4-5 Wks	5-6 Wks	Total / %
1	GIT (Gastritis)	10	10	4	4			28 (45.16%)
2	Skin Rashes & Itching	2	4	4	2			12 (19.35%)
3	Musculoskeletal Arthralgia		2	2	2			6 (9.67%)
4	Oto-toxicity				3	2	1	6 (9.67%)
5	Hepatobiliary Hepatitis			2	1	1		4 6.45%)
6	CNS Peri Neuropathy Psychosis	 2	 1	 1				2 (3.22%) 2 (3.22%)
7	Other Flu Like Syndrome			1	1			2 (3.22%)
Total		**14 (23%)**	**17 (27%)**	**14 23%)**	**13 21%)**	**3 5%)**	**1 (2%)**	**62 (100%)**

Organ system involvement in different age group, due to ADRs to anti-tubercular drugs were Gastritis 28 (45%), skin rash 12 (19%), arthralgia 6 (10%), Hepatitis 4 (6%), CNS 4 (6%) and 8 (13%) were

reported with others. Maximum patient of gastritis found in 12-50 years of age group (table.7)

Table 7: organ system involvement in different age groups

Age Group	GIT	Skin	Muscu.	Hepatob.	CNS	Others
12-20	6	4	0	0	0	1
21-30	6	4	1	1	2	3
31-40	7	3	3	1	0	1
41-50	6	1	2	1	1	3
51-60	3	0	0	1	1	0
> 60	0	0	0	0	0	0
Total	**28(45. %)**	**12(19%)**	**6(10%)**	**4(6%)**	**4(6%)**	**8(13%)**

The causal link between the ADRs and the suspected anti-tubercular drug by Who scale, certain relationship was established between the anti-tubercular drug and ADRs in 12 (19.35%) patients while 19 (30.64%) probable and 31 (50%) ADRs were categorized as possible (table.8).

Type A, ADRs were found to be the 35 (56%) and Type B, ADRs were 27 (44%)(table.9).

Table 8: causality assessment (WHO scale) of ADR

Drug Anti-Tubercular	No. of ADR	Certain	Probable	Possible
H	22	4	7	11
R	16	2	5	9
Z	10	3	2	5
E	7	0	2	5
S	7	3	3	1
Total	**62**	**12(19%)**	**19(31%)**	**31(50%)**

Table 9: types of ADR

Anti-Tubercular Drugs	No. Of ADR	Type-A	Type-B
H	22	8	14
R	16	11	5
Z	10	5	5
E	7	5	2
S	7	6	1
Total	**62**	**35(56%)**	**27(44%)**

DISCUSSION AND CONCLUSION

Since there can be no hope of eliminating all the adverse effects of drugs it is necessary to evaluate pattern of adverse reactions [11]. There is a special need for systemic collection of information on ADRs in India due to wide variation in genetic, nutritional, environmental and disease patterns [12]. Therefore, better approaches must be devised for reporting assessment and management of individuals who present with drug induced disease [13].

The study was performed with the ultimate aim of generation of information about ADRs to antitubercular drugs of DOTS center in Hamidia Hospital and TB Hospital Idgah Hills, Bhopal to add knowledge about the safety of medicines and prevention of ADRs.

During the study period from 15 April 2010 – 15 Dec 2010, 62 patients with ADRs to anti-tubercular drugs were detected by spontaneous reporting from the health care professionals of Hamidia Hospital, Bhopal. This was accomplished using the notification slip, telephonically 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. Compiled and analyzed the study their demographic distribution, onset, causal

relationship to anti-tubercular drugs (WHO scale) type, Nature and severity.

Maximum numbers of ADR were reported among male population with in 4 week of starting DOTS therapy. The causality assessment was found to 50% possible and 30.64% probable. Gastrointestinal system (Gastritis) was the most common system affected followed by Skin (Rashes).

Majority of ADRs 53.22% were moderate, and 46.77% were mild. No severe life threatening ADRs were observed during the study period. We found DOTS therapy safer, but regular monitoring is required for ADRs, so as to prevent the ADRs at the initial stage.

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