



TO DETECT AND DO CAUSALITY ANALYSIS OF ADRs OF ANTITUBERCULAR DRUGS USED IN DOTS THERAPY

Dr shashi marko

Assistant Professor Pharmacology, Bundelkhand medical college sagar, Madhya Pradesh India.

Dr J L marko

Associate Professor, pharmacology, Gandhi Medical college, Bhopal, Madhya Pradesh India.

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 therapy.

Introduction

Adverse Drug Reactions (ADRs) are of great concern to the general public, the pharmaceutical industry, the regulatory authorities and the medical profession.

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⁾.

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)⁽²⁾.

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⁽³⁾. 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⁽⁴⁾. 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⁽⁵⁾.

Aims and objectives

1. To do causality analysis of ADRs.
2. To assess and analyze the ADRs According to their demographic distribution, onset, reporting and presentation.

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.

- 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⁽⁶⁾
- b. Naranjo scale⁽⁷⁾
- c. European A.B.O scale⁽⁸⁾

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.

Observation

Total number of patients who were taking DOTS therapy in OPD

(720) and in IPD (100). 62 ADRs detected, in 62 patient, 2 patients were dropped out from DOTS therapy due to ADR. Out of 62 ADRs, 22 ADRs were due to H, 16 ADRs were due to R, 10 ADRs were due to Z and 7, 7 ADRs due to E & S were observed respectively (table.1&2). ADRs reported by treating physician, resident doctor and other health professionals of DOTS center Hamidia Hospital and T.B. Hospital Idgah Hills, Bhopal, during the study period from 15 April 2010 to 15 Dec. 2010. The information thus gathered about ADRs was compiled and analyze in Department of Pharmacology.

TABLE.1 : 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 : TOTAL NUMBERS OF ADR FOR INDIVIDUAL ANTI-TUBERCULAR DRUGS

S. No.	ADRs	H	R	Z	E	S	Total	Percent age
1	GIT Vomiting Abdomen cramps Diarrhea	4 4	4 4	4 1	2 2		10 14	16.12% 22.58%
2	Skin Itching Rash	4 2	2 1		1 1	1	8 4	12.9% 6.45%
3	Musculoskeletal Arthralgia	1		5			6	9.67%
4	CNS P.N. Psychosis	2 2					2 2	3.22% 3.22%
5	Hepatobiliary Hepatitis	3	1				4	6.45%
6	Others Ototoxicity Flu syndrome		2			6	6 2	9.67% 3.22%
Total		22(35%)	16(26%)	10(16%)	7(11%)	7(11%)	62	100%

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

Majority of patients in this study belonged to 31-40 years and 41-50 years of age group, each group had 21% patients, and 90 (20%) were male and 80 (22%) were female followed by 21-30 years age group, here 90 (20%) were male and 70 (19%) were female (Table.3).

Table.3 : SEVERITY OF ADR IN DIFFERENT AGE GROUPS

Age Group	Mild	Moderate	severe	Total	Percentage
12-20	8	3	0	11	18%
21-30	8	9	0	17	27%
31-40	7	8	0	15	24%
41-50	5	9	0	14	23%
51-60	1	4	0	5	8%
Total	29 (46.77%)	33 (53.22%)	0	62	100%

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.4).

Majority of ADR reported were moderate 33 (53.22%) followed by 29 (46.77%) were mild, no severe ADR was reported.

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.5).

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.6).

Total number of ADRs for individual drugs (anti tubercular) drug 22 patients reported to I, 16 patients reported to R, 10 patients reported to P, 7.7 patients reported to E&S respectively.

TABLE 4 : 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
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%)

Table. 5 : SEVERITY OF ADR INVOLVEMENT OF DIFFERENT SYSTEM

S. No.	ADR	Mild	Mod.	Severe	Total	Percent age
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	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 6 : 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 7 : 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⁽⁹⁾. 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⁽¹⁰⁾. Therefore, better approaches must be devised for reporting assessment and management of individuals who present with drug induced disease⁽¹¹⁾.

The study was performed with the ultimate aim of generation of information about ADRs to anti-tubercular 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.

Reference

- Gharaibeh MN, Greenberg H, Waldman SA. Adverse drug reactions: A review. Drug Information Journal 1998; 32:323-38
- Shashikant. Control of tuberculosis. In : S K Sharma. Mohan, Tuberculosis, Newdelhi: jaypee Brother, 2004;556-58.
- Devi S, Ramchandran R, Santha S. Adverse reaction to antituberculosis drugs and their management Bulletin 1997 July and Oct; 4 (3 and 4).

- Tandon. RK, Garg PK. Antituberculosis treatment induced hepatotoxicity. In Sharma S K Mohan, Tuberculosis. Newdelhi; jaypee Brother, 2004;500.
- Stork CM, Hoffman RS. Toxicology of Antituberculosis drugs. In Rom W.N, Gary, S, Tuberculosis. Newyork: Little, Brown and company, 1996; 829-837
- Parthasarathi G, Gogtay N. Causality assessment of adverse drug reactions. Proceedings of the National Training Course on Pharmacovigilance : 2005 Jan. 17-21 ; Mumbai, India.
- Naranjo CA, Busto U, Sellers EM, Roberts EA, Janczek E, Domecq C. et al. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther. 1981;30(2): 239-45.
- Feely J, Williams D. Detecting adverse drug reactions – part II Adverse Drug Reaction Bulle, in 2001; 208 : 795-8.
- Bennett PN, Brown MJ, editors. Clinical Pharmacology. 9th ed. Newyork: Churchill Livingstone; 2003. p. 135-51.
- Hansen KM Detecting, managing and preventing adverse drug reactions International Seminar on Pharmacovigilance & Medication Safety 2005 : 37-9.
- Goodman Gillman- The pharmacological basis of Therapeutics, 11, 1204-1212.