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Original Research Article

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

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ABSTRACT

Background: Treatment of tuberculosis involves giving multiple drugs to the patient which is done to prevent development of resistance besides targeting all bacterial sub-populations. The objective of the present study was to find out the adverse drug reactions (ADRs) of the first line anti-tubercular drugs and to calculate prevalence and causality of these drugs.

Methods: The study was conducted by the Department of Pharmacology, Government Medical College, Srinagar in association with the department of Chest medicine. All patients of tuberculosis on directly observed treatment-short course (DOTS) of either sex or age group were enrolled. An assessment of the causality and allocation of ADRs was done using Naranjo's monitoring scale and WHO-UMC scale.

Results: A total of 57 ADRs with 13 different types were observed in 164 patients, with an overall prevalence of about 34.7%. Thirty seven (64.9%) ADRs were categorized as having a 'probable' causal relationship while 17 (29.8%) was categorized as 'possible' as per the Naranjo's scale. As per the WHO-UMC monitoring scale fifty two (91.2%) were categorized as 'possible' while three (5.3%) were categorized as 'certain'.

Conclusions: Occurrence of ADRs generally results in non-adherance. Timely detection of ADRs through an effective pharmacovigilance programme is the need of hour. The establishment of an active pharmacovigilance centre which was set up in our institution has paved the way to improve the quality of patient care by ensuring safer use of drugs and has helped us to identify and report the various ADR's encountered.

Keywords: Adverse drug reactions, DOTS, Tuberculosis, WHO-UMC

INTRODUCTION

Adverse drug reactions (ADR) usually referred to as a noxious and unintended response to a drug occurring at doses normally used in humans for the prophylaxis, diagnosis and treatment of disease or for modification of physiological function can be a potential factor leading to treatment non -adherence due to increased patient suffering and incur of additional costs because of increased outpatients visits, tests and in more serious instances hospitilizations.[1,2]

Adverse drug reactions adversely affect the quality of life of patients, cause them to lose confidence in their doctors, increase the costs of healthcare, preclude the use of drugs in most patients, resulting in unnecessary investigations and delay in the treatment.[3,4] Adverse drug reactions have been seen to cause 1 out of 5 injuries or deaths per year to hospitalized patients whereas mean length of stay, cost and mortality for ADR patients are double than that for control patients.[5] In relation to mortality a landmark meta-analysis of 39 prospective studies conducted by Lazarou et al, found that Adverse drug reactions resulting in medical management were the fourth to sixth highest cause of death

in emergency services in United States, following only ischemic cardiopathy, cancer and stroke.[6,7]

Data suggests that One-fourth of the world's population is thought to have been infected with *M. Tuberculosis* In 2017, about 10 million people around the world became sick with TB resulting in 1.3 million TB-related deaths worldwide.[8]

The rate of tuberculosis in different areas varies across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests while only 5-10% of the United States population test positive, the reason being attributed to a poor immune system largely due to high rates of HIV infection and the corresponding development of AIDS in the developing countries.[9,10]

The standard anti-TB short course chemotherapy regimen comprised of taking drug combinations of isoniazid, rifampicin, pyrazinamide, ethambutol and /or streptomycin for a period 6-9months.

The WHO has recommended DOTS to be an effective treatment strategy for detection and cure of TB and for controlling the TB epidemic today. Pharmacotherapy of TB consists of giving drug combinations to increase the effectiveness and decrease the emergence of drug resistance. But more the number of drugs, adverse effects are added up too. Incidence of adverse drug reaction's (ADR) being high with these drugs is resulting in more dropouts, change of regime and inadequate or incomplete treatment, all these contributing to emergence of multidrug resistant (MDR) and extensive drug-resistant cases (XDR) strains increasing the morbidity and mortality.[11] Though none of the anti- tuberculosis drug is without adverse reactions but only rarely are the adverse reactions life threatening

Objectives of the present study are to find out the prevalence of adverse drug reactions (ADRs) of the anti-tubercular drugs in patients of tuberculosis on Directly Observed Treatment- Short course (DOTS). And to find out the causality of adverse drug reactions using WHO-Uppsala Monitoring Centre and Naranjo's scale (WHO-UPC) scale.

METHODS

The present study was observational longitudinal. After getting approval from the Institutional Ethics Committee, the study was conducted by the Department of Pharmacology in association with the Department of Chest Medicine, Government Medical College (GMC), Srinagar over the period of a one and a half year commencing on 1st April 2016.

The patients coming to the DOTS centre of GMC and associated hospital were studied. The participants were provided with explicit explanation for their inclusion in the study by instituting written informed consent duly translated in local Vernacular.

Inclusion criteria

All patients diagnosed with tuberculosis (pulmonary, extra-pulmonary) on DOTS with first line drugs during study period.

Exclusion criteria

- Patients refusing to give consent for the study
- Patients taking ATT which includes drugs other than first line anti-tubercular drugs
- Patients with underlying organ disease or patients with co-infection like HIV, hepatitis B and hepatitis C.

Handling of ADR reports

Adverse drug reactions (ADRs) were reported spontaneously by patients/ their guardians or the reporting doctor and a questionnaire (active surveillance) was used asking the patient specific questions related to likely ADRs and patient's responses were recorded in the case record form. Once the ADR reports were detected/collected and prepared in consultation with doctors, nurses and pharmacists on duty in OPD, they were scrutinized to prevent any kind of reporting bias on part of investigator.

Causality assessment

Following criteria was used for establishing causal relationship between drug administration and an ADR:

- A temporal (time related) relationship between suspected drug and ADR.
- Improvement after withdrawal of the drug i.e. positive dechallenge.
- A previous exposure to the same suspected drug i.e. pre-challenge.
- The lack of confounding effect t i.e. ADR unlikely to be due to concomitant diseases or due to some other previously consumed medicines.

Based on above mentioned criteria, ADRs were classified as under

Definite

Wherein ADR followed a reasonable temporal sequence from administration of the drug and was confirmed by positive dechallenge or positive rechallenge.

Probable

Wherein ADR followed a reasonable temporal sequence from administration of the drug, was confirmed by dechallenge but was not reasonably explained by the known characterization of patient's clinical state.

Possible

Wherein ADR followed a reasonable temporal sequence from administration of the drug and followed a known response pattern to the suspected drug but could also have been produced by the patient's clinical state or other modes of therapy administered to the patient.

Doubtful

ADR that did not meet the above-mentioned criteria especially if the ADR had no temporal association with the drug use.

On the basis of causality assessment done as above patients were classified into following 3 groups:

- Patients without ADR (either at the time of admission or during hospitalization).
- Patients with ADRs at admission including patients admitted because of ADRs and patients with ADRs which the cause of hospital admission were not.
- Patients with ADRs occurring during their hospital stay.

An assessment of the causality and allocation of ADRs to these different categories was done using Naranjo's monitoring scale and WHO-UMC scale.[12,13]

Statistical analysis

Data was entered in Microsoft Excel. Continuous data was summarized as mean (±) standard deviation or the five number summary as appropriate. Categorical variables were summarized as percentages. Chi-square test was used to test for independence of two categorical variables. Bar charts and pie charts were used for graphical presentation of data.

RESULTS

Table 1 signifies the distribution of the study population according to presence/absence of any ADR. Total 164 patients were enrolled in present study. Out of 164 patients, 57 patients reported ADRs, while as 107 patients did not develop ant type of ADRs during the study period. Overall prevalence of ADRs was 34.80% as per present study.

Table 1: Distribution of study population according to ADR.

ADR	Frequency	Percentage
Present	57	34.8
Absent	107	65.2
Total	164	100

Table 2 shows distribution of the patients in patients presenting with ADRs as per the gender. Out of 57 patients presenting with ADRs, 35 of them were males while as 22 patients were females. There was statistically significant (p=0.0006) relationship between gender and the proportion of the ADRs with 49.3% of males showing ADRs while only 23.7% of the females had ADRs.

Table 2: Distribution and association of ADR with gender in studied population.

Gender	ADR present		ADR absent		Total
	No.	%age	No.	%age	
Male	35	49.3	36	50.7	71
Female	22	23.7	71	76.3	93
Total	57	34.8	107	65.2	164

Chi-square=11.672; P-value=0.0006 (Significant)

Table 3: Distribution of patients presenting with ADR's as per weight.

Weight (kgs)	Frequency	Percentage
Maj ≤20	4	7.0
21-40	3	5.3
41-60	30	52.6
>60	20	35.1
Total	57	100

Table 3 shows the distribution of the patients presenting with ADR's according to the body weight in kilograms (kgs). Majority of the patients (52.6%) presenting with ADRs were having body weight between 41-60kgs, followed by 35.1% in patients having weight of more than 60 kgs. Further 7% patients had weight of less than 20kgs while 5.3% were having a body weight between 21-40kgs.

Table 4: Most common type of ADR's.

Type of ADR		Frequency	%
Gastrointestinal	Decreased appetite	16	28.1
	Nausea/vomiting	13	22.8
Dermatological	Itching	5	8.8
	Rash	2	3.5
Skelton system	Joint pain	5	8.8
Liver	Drug induced liver injury	3	5.3
Renal system	Acute kidney injury	1	1.8
Nervous system	Increased sleep	2	3.5
	Peripheral neuropathy	2	3.5
Others	Increased serum uric acid	1	1.8
	Metallic taste in mouth	3	5.3
	Flank pain	2	3.5
	Pain calf muscle	2	3.5

Table 4 indicates the different types of ADRs reported by studied population. A total of 13 different types of ADRs were reported in the study population. The most common ADR was loss of appetite (28.07%) followed by nausea/vomiting (22.8%), itching and arthralgia each in 8.8%, drug induced liver injury and metallic taste in mouth each in 5.3%. Somnolence, flank pain, rash, peripheral neuropathy and pain in the calf muscle were reported in 3.50% of the patients each. Acute kidney injury and hyperuricemia were reported in 1.75% of the patients each.

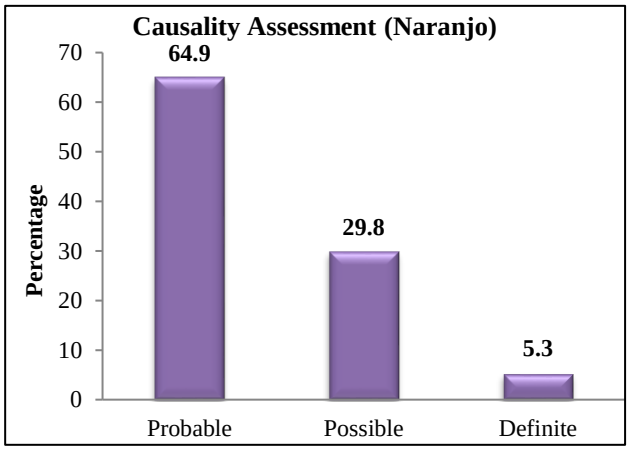

Figure 1: Causality assessment (Naranjo).

Out of a total 57 ADRs, thirty seven (64.9%) were categorized as having a probable casual relationship with the anti-tuberculosis drugs as per the Naranjo's scale and seventeen (29.8%) were categorized as possible as per the Naranjo's scale. Also, three (5.3%) were categorized as definite. The three patients who were categorized as definite were diagnosed as drug induced liver injury (DILI). The suspicious drugs were stopped, and re-challenge was done (Figure 1).

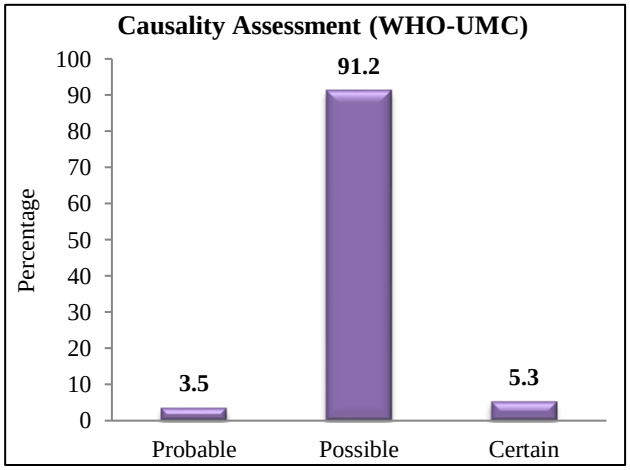

Figure 2: Causality assessment (WHO-UMC).

As per the WHO-UMC Scale for assessing causality of ADR's, two (3.5%) ADRs were classified as probable, fifty two (91.2%) were classified as possible and three (5.3%) were classified as certain (Figure 2).

Table 5 shows duration in weeks at which ADRs presented after the initiation of ATT. Fifty five (96.50%) of the ADRs were reported during intensive phase and only 3.50% of ADRs were reported during continuation phase. As minimum four drugs are used during intensive phase there are increased chances of the development of the ADRs during this phase.

Table 5: Duration (in weeks) at which ADR presented from start of treatment.

Week	Frequency	Percentage
First	13	22.8
Second	17	29.8
Third	9	15.8
Fourth	10	17.5
Fifth	3	5.3
Sixth	1	1.8
Seventh	0	0.0
Eighth	2	3.5
Ninth	1	1.8
Twenty Fourth	1	1.8
Total	57	100

DISCUSSION

Tuberculosis, an infectious disease caused by mycobacterium tuberculosis, is the second most leading cause of death (after cardiovascular diseases) in the world. The World Health Organisation (WHO) declared TB as a global emergency in 1996.TB remains as a major health public health problem in India. India accounts for one-fifth of the global TB incident cases and topping the list among high burden countries. It is estimated that annually around 330,000 Indians die due to TB.

As the drug combinations used for the treatment of Tuberculosis are used for a prolonged period of time, it is likely that the ADRs of one drug are potentiated by the other drugs used in the combination. All anti-tubercular drugs can produce ADRs and involve almost all systems in the body such as gastro-intestinal tract, liver, skin, nervous system, vestibular apparatus and eyes. The adverse drug reactions to the drugs are one of the major reasons for the patients to default from the treatment. ADRs not only contribute to the non-compliance to the therapy but may also occasionally lead to the stoppage of treatment due to their severity and thus lead to development of drug resistance strains. These resistant strains require second line drugs for treatment which have higher cost and more serious adverse drug reactions. ADRs mostly tend to occur in the first three months of treatment.[14]

The present study was conducted by the department of pharmacology in collaboration with the department of chest medicine, Government Medical College, Srinagar between April 2016 to September 2017 to study the side effect profile of first line anti-tuberculosis drugs on directly observed treatment short course (DOTs) and assess their

severity and causality. The proportion of patients with at least one ADR was found to be 34.7% and most of them 77.20% being mild in severity. As per the Naranjo's monitoring scale, 94.7% had a probable/possible and 5.3% had definite causal relationship with anti-tuberculosis drugs; the corresponding figure as per the WHO-UMC scale was almost the same.

Present study was an observational study with bi-weekly follow up during the intensive phase and bi-monthly follow up during the continuation phase. A total of 164 patients were enrolled and followed during these periods that were treated with DOT's.

In present study the maximum number patients (52.43%) had weight between 41-60 kilograms and the population used by Sinha et al, was similar to current study population as far as weight is concerned. In a Study done by Iyer et al, TB patients (80%), weighed below average for Indian reference adult man (60kg) and women (50kg).1[5,16] The overall prevalence of ADRs in present study was 34.7%. A study conducted in a tertiary care hospital, Lahore, Pakistan by Aamir et al, reported similar findings with incidence of 40.2%.[17] Similar results have also been reported by Hassan et al.[18]A study conducted in a tertiary care hospital, Manipal, India by Sinha et al, reported an ADR incidence of 69.01%.[15] Another survey in Malaysia reported an ADR incidence of 15.8%; while a study done in Gujarat, India reported an incidence of 7.9%.[19,20]

One possible explanation of this variation could be differences in detecting methods of ADRs. As to whether ADRs were collected based on face to face interview with patients and chart review, or retrospectively from patient's medical records, besides genetic makeup could also have played a role.

Authors used both the WHO-UMC scale and Naranjo's monitoring scale for causality assessment. All the ADRs reported in the present study were causally related to the anti–tuberculosis drugs prescribed. Out of 57 ADRs, 37 (65%) were categorised as having a probable causal relationship with the anti-tuberculosis drug while 17 (29.7%) were categorised as possible as per the Naranjo's scale, further 3 (5.3%) ADRs were categorised as definite. As per the WHO-UMC scale for assessing causality, 52 (91.20%) ADRs were classified as possible, 2 (3.50%) were classified as probable and 3 (5.30%) were classified as certain. Ramanath et al, reported similar findings with most (92.97%) ADRs showing a possible causal relationship.[21] Similar results have been reported by Damasceno et al.[22] Present study had three certain/definite (5.30%) cases in which re-challenge was done and offending drug was found to be pyrazinamide. A study conducted by Verma et al, categorised 9.8% of the cases as definite/severe.[11] In present study, the prevalence of ADRs was more common in males (49.3%) as compared to females (23.7%). Athira B et al, reported similar findings with highest numbers (68.81%) of ADRs being observed in males.[23] Similar results have also been reported by Dedun et al, but there are some studies suggesting females to be at higher risk of developing more ADRs.[20,24] It might be because they pass through life stages like pregnancy, menarche and menopause that has an impact on the drug response.[25] Studies done by Aamir et al, and Hassan et al, also had found ADRs to occur more commonly in females than males.[17,18]

A total of 57 ADRS were noted among 164 patients enrolled in the study. The most common ADR presented were gastro-intestinal symptoms found in (50.9%) of the cases. Allergic Skin manifestation in form of itching and pruritis were reported in 12.28%, while as arthralgia was reported in 8.8% of the ADRs. Three ADRs (5.26%), each of drug induced liver injury (DILI) and metallic taste in the mouth were reported in the study, followed by 2 ADRs each of flank pain, sleep, peripheral neuropathy and pain in calf muscles. A study done by Sinha et al, also reported the frequency of ADRs in form of gastro-intestinal symptoms was found in (53.52%) of the patients while as ADRs related to skin manifestation was reported in 8.45% of the patients according to the same study.[15] Similarly Athira et al**,** found that the majority of the ADRs were related to was gastro-intestinal tract, followed by skin reactions.[23] Similar results have been reported by **S**ood et al, Hassan et al, and Sribaddana et al.[18,26,27] However study done by Aamir et al, had reported joint pain as the most common ADR while as a study done by Kurniawati et al, found skin reactions as the most common ADRs.[17,19] Another study done by Kheirollah et al, found that the most common ADR was hepatitis.[28]

CONCLUSION

The occurrence of ADRs generally results in non-adherence and frequent dropouts which makes the treatment more complicated because of the development of resistance. Timely detection of ADRs through an effective pharmacovigilance programme is the need of hour. The establishment of an active pharmacovigilance centre which was set up in authors' institution has paved the way to improve the quality of patient care by ensuring safer use of drugs and has helped us to identify and report the various ADR's encountered. By monitoring the patients closely, the ADRs can often be avoidable by adjusting the doses or if required, the withdrawal of the particular drug causing them.

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