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ADVERSE DRUG REACTION MONITORING OF FIRST LINE ANTI- TUBERCULAR DRUGS IN A TERTIARY CARE HOSPITAL - A RETROSPECTIVE STUDY.

Pharmacology

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ABSTRACT

Objective: The objective was to study the adverse drug reactions (ADRs) associated with first-line anti-tubercular drugs for clinical presentations, causality, and severity. **Methods:** A retrospective study was undertaken in a tertiary care teaching hospital of India for the duration of 1 year (January 2019 - December 2019). Patients diagnosed with tuberculosis and under treatment with the first-line anti-tubercular drugs were study subjects. Causality, outcome and severity were analyzed and other parameters such as male to female ratio, most affected system, , and common types of ADRs, were studied. **Results:** Nearly 130 patients were started on anti-tubercular treatment of first-line drugs in the study duration. Out of these 60 patients suffered one or more ADRs with a total number of reported ADRs being 105. 67% were males. Maximum patients belonged to the age group of 31-40 years (30%). The most commonly involved system was hepatic and biliary system (60%) followed by gastrointestinal system (40%), the most common ADR observed was disturbed liver transaminases (40%) followed by nausea and vomiting (25%). Causality assessment by Naranjo's scale showed 60% ADRs scoring probable, 25% were of possible score, whereas 15% definite score category. Severity assessment shows 66% cases of mild grading, 32% of moderate and 2% cases of severe grading was reported in the study duration **Conclusions:** Vigilance regarding these ADRs occurrences can result in early diagnosis and thus, proper management can be instituted earliest. This will build confidence of patients and will decrease the dropouts which in turn can result in decrease chances of developing drug-resistant strains.

KEYWORDS

adverse drug reaction, antitubercular drugs, causality, severity, outcome

INTRODUCTION

Undoubtedly modern drugs have increased life expectancy and improved quality of life for millions of people. However, despite all these benefits, evidence continues to suggest that adverse reactions to medicines are common, though often preventable, cause illness, disability and even death. As per WHO pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicines-related problems". During the last few decades health professionals and the public have started to recognize morbidity and mortality due to medicine as one of the major health hazards [1]. Tuberculosis (TB) is caused by bacteria of the Mycobacterium tuberculosis complex. It is one of the oldest diseases known to mankind and was as well as still been responsible for huge death toll worldwide. India is the country with the highest burden of TB.

Anti-tubercular drugs are mainly classified as first- and second-line drugs. Conventionally, there are five first-line drugs: H (Isoniazid), R (Rifampicin), Z (Pyrazinamide), E (Ethambutol), and S (Streptomycin). Second-line drugs include the aminoglycosides kanamycin and amikacin, the polypeptide capreomycin, PAS, cycloserine, terizidone, the thioamides ethionamide and prothionamide and several fluoroquinolones such as moxifloxacin, levofloxacin and gatifloxacin. All these first line drugs have been associated with various side effects. Some of the frequently encountered side effects of these first line drugs are:

Isoniazid: Hepatitis, peripheral neuropathy, rashes.

Rifampicin: Orange urine/body fluids (sweat), flulike syndrome, hepatitis.

Pyrazinamide: Hepatitis, hyperuricemia, arthralgia, rashes.
Ethambutol: Optic neuritis (red-green color blindness), hyperuricemia.

Streptomycin: Ototoxic effects, generally manifesting as dizziness, vertigo.

These are just few side effects been mentioned here and they just represent a sector of the vast canopy of side effects produced by anti-tubercular drugs.

Incidence of 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 extensively drug-resistant cases (XDR) strains increasing the morbidity and mortality. This study is being carried out to estimate the burden of problem in our hospital so that clear picture can be obtained and physician be oriented more to provide counseling and also diagnose these ADRs as soon as possible as early management improves the outcome. Furthermore, ADR reporting practice was stressed upon during collection of data. [2]

Material and methods

A retrospective study was undertaken in Guru Nanak Dev hospital attached to government medical college Amritsar. Data were collected from the medical record section and department of TB and chest by reviewing patient's files. Data were analyzed for the ADRs that occurred in the specified period of 1 year (1st January 2019 – 31st December 2019). Suitable study design for ADR profile study was developed for compiling the data. Inclusion criteria consisted of all patients of either gender. The patients diagnosed with pulmonary TB and on treatment under DOTS regimen were included in the study. These patients were on antiTB drugs, a combination of four first-line drugs (isoniazid, rifampin, pyrazinamide and ethambutol). Patients of hepatic dysfunction were excluded from the study. Patients with similar signs and symptoms as adverse drug reactions of antitubercular drugs were also excluded from the study. All the results were calculated in percentages and proportions. Common ADRs, common drugs accounting for ADRs, systems involvement, causality assessment (assessed by Naranjo's algorithmic scale) [9], Severity of ADRs (Modified Hartwig and Siegel Scale) were studied. Causality which was assessed by Naranjo's algorithmic scale is the most common assessment tool of ADR, and verifies the chances of whether an ADR is essentially due to the drug or it is the result of other causes, the likelihood is consigned by the score, termed as definite, probable or possible. Severity of ADR (assessed by Modified Hartwig and Siegel Scale) was also recorded as mild, moderate and severe. Examples of ADRs assessed as severe are those that caused the death, directly life-threatening, lengthened hospitalization, or permanent disfigurement of any organ or body part. Adverse drug reactions reported in intensive treatment phase and maintainance treatment phase was also noted. Outcome of adverse drug reactions as recovered fully, recovering, not recovering, unknown and fatal was also reported.

Results

Table 1 : Gender distribution of patients showing adverse drug reactions.

Gender	Number of patients
Male	40
Female	20

Table 2: Distribution of age groups of patients showing adverse drug reactions

Age group (years)	Number of patients (percentage)
0- 10	3 (5%)

11 – 20	7 (12%)
21-30	14 (23%)
31-40	18 (30%)
41-50	9 (15%)
51-60	6 (10%)
> 60	3 (5%)

Table 3 : Distribution of various systems for the adverse drug reactions

System	Number of adverse drug reactions (percentage)
Hepatic and biliary	63 (60%)
Gastrointestinal	42 (40%)
Dermatological	37 (35%)
CNS and PNS	32 (30%)
Fever and flu like symptoms	21 (20%)
Ophthalmological	16 (15%)
Metabolic	13 (12%)
Renal	3 (3%)
Joints	2 (2%)
Hematological	2 (2%)

Table 4 : Distribution of adverse drug reactions in patients

Adverse drug reaction	Number of adverse drug reaction (percentage)
Disturbed liver transaminases	42 (40%)
Nausea and vomiting	26 (25%)
Hepatitis	21 (20%)
Rash	21 (20%)
Erythema	11 (10%)
Urticaria	5 (5%)
Constipation	11 (10%)
Fever	11 (10%)
Flu like symptoms	11 (10%)
Blurred vision and optic neuritis	16 (15%)
Headache	21 (20%)
Peripheral neuritis	5 (5%)
Dizziness	5 (5%)
Hyperglycemia	13 (12%)
Arthralgia and increased uric acid levels	5 (5%)
Anaemia	1 (1%)
Thrombocytopenia	1 (1%)
Diarrhea	5 (5%)

Table 5: Causality assessment of various adverse drug reactions reported in patients.

Causality assessment	Number of adverse drug reactions (percentage)
Probable	63 (60%)
Possible	26 (25%)
Definite	16 (15%)

Table 6: Severity assessment of adverse drug reactions in patients.

Degree of severity	Number of adverse drug reactions (percentage)
Mild	69 (66%)
Moderate	34 (32%)
Severe	2 (2%)

Table 7 : Adverse drug reactions encountered in which treatment phase of drugs.

Treatment phase	Number of adverse drug reactions
Intensive	90
Maintainance	15

Table 8 : Outcome of adverse drug reactions

Outcome	Number of adverse drug reactions
Recovered fully	55
Recovering	20
Not recovering	2
Unknown	26
Fatal	2

In the study , 130 patients were started on anti-tubercular treatment (ATT) of first-line drugs. Of these 60 patients suffered one or more ADRs with a total number of reported ADRs being 105. Of 60 patients, 40 cases were males, and 20 cases were females (table 1). Maximum patients belonged to the age group of 31-40 years (30%) followed by 21-30 years (23%) and 41-50 years (15%) (table 2). The most commonly involved system was hepatic and biliary system (60%) followed by gastrointestinal (GI) system (40%), dermatological (35%) ,CNS and PNS (30%), fever and flu-like syndrome (20%), ophthalmological (15%) & metabolic system (12%), renal toxicity (3%), gout and arthralgia (2%), hematological toxicities (2%) (table 3). The most common ADR observed was disturbed liver transaminases (40%) followed by nausea and vomiting (25%). Other types of ADRs that were seen included 20% cases of hepatitis, headache, and rash each. Constipation and fever and flu-like syndrome accounted for 10% each. Blurred vision and optic neuritis (15%), metabolic disturbances including hyperglycemia (12%) were also recorded. Diarrhea was reported in 5% patients. Other ADRs also included peripheral neuritis (4.44%), arthralgia and with increased blood uric acid level (5%), dizziness (5%), peripheral neuritis (5%), anaemia (1%) and thrombocytopenia (1%) (table 4). Causality assessment (Naranjo's scale) Nearly 60 cases of ADRs were analyzed in which about 105 ADRs were reported. After assessment, 60% scored probable, 25% were of possible score, whereas 15% were in definite score category (table 5). Severity assessment using modified Hartwig and Siegel scale Assessment shows 66% cases of mild grading, 32% of moderate, and 2% cases of severe grading were reported (table 6). Appearance of adverse drugs in the intensive treatment phase was 90 and in maintainance treatment phase was 15 (table7). Outcome of adverse drug reactions in patients was recovered fully in 55% , recovering in 20%, not recovering in 2%, unknown in 26% and fatal in 2%.(table 8).

DISCUSSION

TB is posing a major hazard to the health authorities and the medical fraternity by emerging as a serious problem causing high morbidity and mortality rates. Its association with HIV infection and drug resistance causing MDR-TB and XDR-TB is making this disease difficult to treat day by day. ADR associated with these drugs further complicates the picture. In a study conducted in Iranian population hospitalized in the general ward, ADR has been reported as the cause of admission for 8% of patients [3]. In another study conducted for detecting anti-infectives induced adverse reactions in Iranian hospitalized patients, the total rate of hospitalization because of an ADR was estimated as 2.2% [4]. This shows the high incidence of ADRs with anti-tubercular drugs. In our study, the most commonly involved system was hepatic and biliary system (60%) followed by gastrointestinal (GI) system (40%), dermatological (35%) ,CNS and PNS (30%), fever and flu-like syndrome (20%), ophthalmological (15%) & metabolic system (12%), renal toxicity (3%), gout and arthralgia (2%), hematological toxicities (2%) (table 3). The most common ADR observed was disturbed liver transaminases (40%) followed by nausea and vomiting (25%). Other types of ADRs that were seen included 20% cases of hepatitis, headache, and rash each. Constipation and fever and flu-like syndrome accounted for 10% each. Blurred vision and optic neuritis (15%), metabolic disturbances including hyperglycemia (12%) were also recorded. Diarrhea was reported in 5% patients. Other ADRs also included peripheral neuritis (4.44%), arthralgia and with increased blood uric acid level (5%), dizziness (5%), peripheral neuritis (5%), anaemia (1%) and thrombocytopenia (1%) (table 4). In our study, incidence in males was found to be high about 67%. It may be due to the fact that the males are having higher risk factors like smoking, alcoholism, and drug addiction to get TB than females and men are socially more active and visit public places more often. These risks make them more vulnerable for TB infection [5]. Though there are studies which have found the incidence to be higher in females. They suggest females are at higher risk of developing ADRs [6]. It might be because they pass through life stages like pregnancy, menarche, etc., which modify the drug response [7]. Studies from the UK and Canada also reported females to have a significantly higher incidence of ADRs due to ATT drugs [8]. In our

study, the highest percentage of patients was found in the age group 31-40 years about 30% followed by 21-30 years of age group (23%). Edoh and Adjei, also found a higher incidence of TB in the age group of 21-40 years with the highest peak of 29.7% in the group of 31-40 years [9]. This is probably because the people in this age group are involved in TB infectious activities like smoking, alcohol intake, etc., which results in the weakening of immunity [10]. Immunity plays a major role in the pathogenesis and manifestations of the disease. The major ADR burden is borne by liver and GI tract. Hepatotoxicities share the major percentage of ADR profile of these drugs. Hepatotoxicities are major adverse effects of all three main anti-TB drugs, isoniazid, rifampin, and pyrazinamide. In 2012, Shinde et al. reported 12.65% of GI upset cases and 6.27% of hepatotoxicity cases caused by first-line antiTB agents [11]. Severity assessment using modified Hartwig and Siegel scale showed 69% cases of mild grading, 34% of moderate and 2% cases of severe grading. A study by Sivaraj, et al. RNTCP regimens with and without DOTS, also reported the majority of reactions to be mild (68.97%).

CONCLUSION

Anti-tubercular drugs may cause high incidences of ADRs ranging from mild to severe. This can cause not only significant morbidity or mortality; cost of treating them can also increase the burden on our health resources. Vigilance regarding these ADRs occurrences can result in early diagnosis and thus, proper management can be instituted earliest. This will build confidence of patients and will decrease the dropouts which in turn can result in decrease chances of developing drug-resistant strains.

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