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Research Article

ADVERSE DRUG REACTIONS ASSOCIATED WITH FIRST-LINE ANTI-TUBERCULAR DRUGS IN A TERTIARY CARE HOSPITAL OF CENTRAL INDIA: A STUDY OF CLINICAL PRESENTATIONS, CAUSALITY, AND SEVERITY

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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 750 bedded tertiary care teaching hospital of central India for the duration of 1 year (May 2013-May 2014). Patients diagnosed with tuberculosis and under treatment with the first-line anti-tubercular drugs were study subjects. Causality, preventability, and severity were analyzed and other parameters such as male to female ratio, most affected system, most common class of drug, and common types of ADRs, were studied.

Results: Nearly 118 patients were started on anti-tubercular treatment of first-line drugs in the study duration. Out of these 45 patients suffered one or more ADRs with a total number of reported ADRs being 91. 57.77% were males. Maximum patients belonged to the age group of 31-40 years (26.66%). The most commonly involved system was hepatic and biliary system (53.33%) followed by gastrointestinal system (51.11%), the most common ADR observed was disturbed liver transaminases (33.33%) followed by nausea and vomiting (28.88%). Causality assessment by Naranjo's scale showed 58.2% ADRs scoring probable, 31.86% were of possible score, whereas 9.8% definite score category. Severity assessment shows 68.88% cases of mild grading, 31.11% of moderate and no case 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 reactions, Multidrug resistant tuberculosis, Extensively drug-resistant tuberculosis, Causality, Naranjo's algorithm.

INTRODUCTION

Morbidity, mortality, social issues, and dual infections like HIV may complicate the overall picture of tuberculosis (TB). For a developing country like India, it not only affects the physical health status but puts forth the financial constraint on health sector.

TB remains one of the major health problems in our country, and it kills more adults than any other infectious disease. In India, about 1.8 million new cases of TB are detected every year, of which one-fifth are extra-pulmonary TB cases [1,2]. An adverse drug reaction (ADR) has been defined as any noxious, unintended, and undesired effect of a drug which occurs at a dose used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions [11].

High incidence of infection has caused a large number of morbidity and mortality which is partly due to serious adverse reactions induced by anti-TB drugs [3,4]. In 1982, the Revised National TB Control Program (RNTCP) reviewed the National TB control program and concluded that it suffered from managerial weakness, inadequate funding, an over-reliance on X-rays, nonstandard treatment regimens, low rates of completion of treatment and a lack of systematic information on treatment outcome [5,6].

Following their commendations of an expert committee, a revised strategy to control TB was tested in 1993 and the RNTCP was started in 1997, and geographic coverage of more than 97% was achieved by the end of 2005 [7]. Directly observed treatment, short course (DOTS) was introduced in India in 1993 as part of RNTCP. The standard anti-TB short course chemotherapy regimen, which comprised of taking drug combinations of isoniazid, rifampicin, pyrazinamide, ethambutol, and/or streptomycin for 6-9 months. The WHO recommended treatment strategy for detection and cure of TB is DOTS, which is the most effective strategy available for controlling the TB epidemic today [8]. Treatment of TB has been revised with time and is treated using the DOTS and revised national TB program. 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. High incidence of infection has caused a large number of morbidity and mortality which is partly due to serious adverse reactions induced by anti-TB drugs [3,4]. Central India carries a burden of this problem to the extent to share a decent percentage of reported cases.

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.

Objectives

To analyze and assess ADRs induced by anti-TB drugs by analyzing the case sheets for studying adverse drug events, 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) [10].

MATERIALS AND METHODS

A retrospective study was undertaken in a tertiary care teaching hospital. 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 May 2013-1st May 2014). Study protocol was approved by institutional ethics committee. Discretion of information acquired was secured, and all the measures to maintain the confidentiality were undertaken, during the study. 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 anti-TB drugs, a combination of four first-line drugs (isoniazid, rifampin, pyrazinamide and ethambutol). Patients of hepatic dysfunction were excluded from the study.

Any ADR marked by consultant physician based on clinical findings, laboratory tests and medical records were included in 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) [10] were studied. Causality which was assessed by Naranjo's algorithmic scale [9] 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 [9]. Severity of ADR (assessed by Modified Hartwig and Siegel Scale) [10]. Examples of ADRs assessed as severe are those that caused the death, directly life-threatening, lengthened hospitalization, or shift to a higher level of clinical care [10].

RESULTS

In the study duration, 118 patients were started on anti-tubercular treatment (ATT) of first-line drugs. Of these 45 patients suffered one or more ADRs with a total number of reported ADRs being 91. Of 45 patients, 26 cases (57.77%) were males, and 19 cases (42.22%) were females. Maximum patients belonged to the age group of 31-40 years (26.66%) followed by 21-30 years (22.22%) and 11-20 years (17.7%) (Fig. 1).

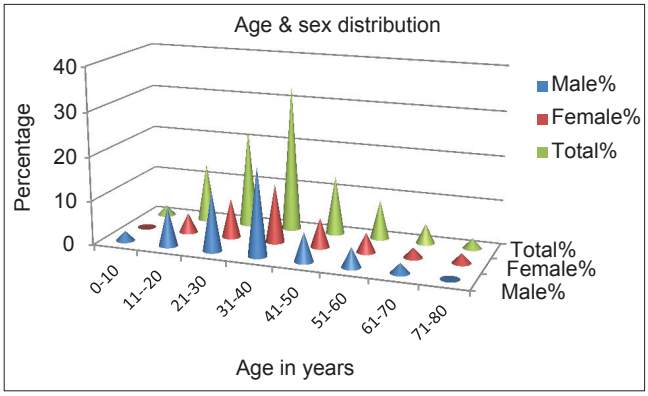
The most commonly involved system was hepatic and biliary system (53.33%) followed by gastrointestinal (GI) system (51.11%), dermatological (28.88%) CNS and PNS (22.22%), fever and flu-like syndrome (13.33%), optic neuritis and blurred vision (11.11%) & metabolic system (11.11%), renal toxicity (4.44%), gout and arthralgia (4.44%), hematological toxicities (2.22%) (Fig. 2).

The most common ADR observed was disturbed liver transaminases (33.33%) followed by nausea and vomiting (28.88%). 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 about 13.33% each. Blurred vision and optic neuritis (11.11%), metabolic disturbances including hyperglycemia (11.11%) were also recorded. Diarrhea was reported in 8.88% patients.

Other ADRs also included peripheral neuritis (4.44%), arthralgia and with increased blood uric acid level (4.44%), pruritis (4.44%), peripheral neuritis (4.44%), increased blood urea (2.22%), and urinary complaints like dysuria (2.22%) (Fig. 3).

Causality assessment (Naranjo's scale)

Nearly 45 cases of ADRs were analyzed in which about 91 ADRs were reported. After assessment, 58.2% scored probable, 31.86% were of possible score, whereas 9.8% were in definite score category (Fig. 4).



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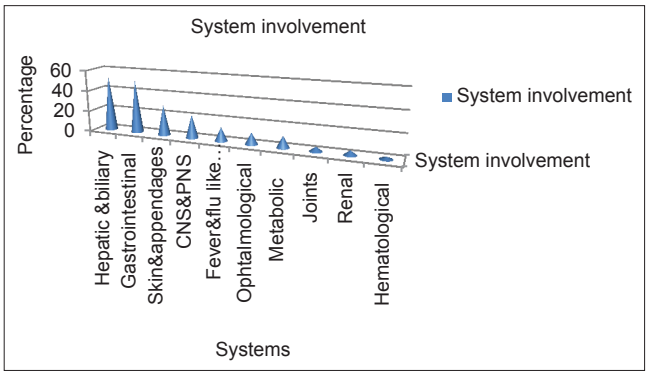

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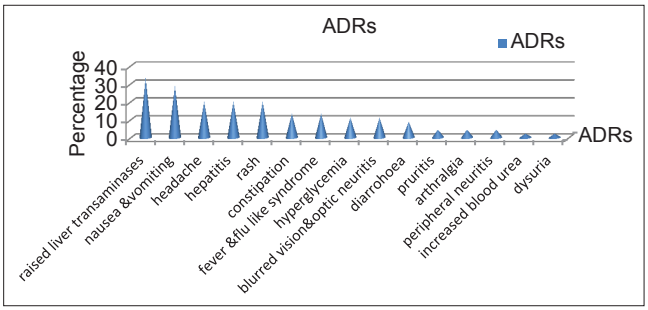


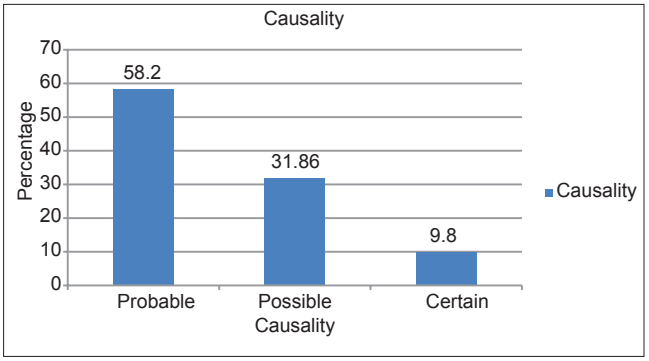
Fig. 3: ???

Severity assessment using modified Hartwig and Siegel scale

Assessment shows 68.88% cases of mild grading, 31.11% of moderate, and no case of severe grading were reported in the study duration (Fig. 5).

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. ADRs resulting in dropouts, insufficient treatment, and cost of treating ADRs are an essential component and have to be addressed. 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 [12]. 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% [13]. This shows the high incidence of ADRs with anti-tubercular drugs. In our study also, many ADRs were reported which needed hospitalization like 20% cases with hepatitis, a few cases with severe vomiting, associated



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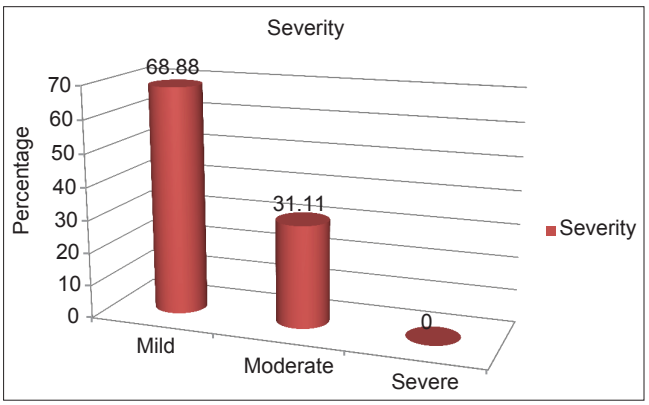

Fig. 5: ???

fever in some patients also needed inpatient care. It has been estimated that 10-20% of isoniazid recipients develop elevated liver enzymes [19]. In our study, incidence in males was found to be high about 58%. 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 [14]. Though there are studies which have found the incidence to be higher in females. They suggest females are at higher risk of developing ADRs [20]. It might be because they pass through life stages like pregnancy, menarche, etc., which modify the drug response [21]. Studies from the UK and Canada also reported females to have a significantly higher incidence of ADRs due to ATT drugs [22]. In our study, the highest percentage of patients was found in the age group 31-40 years about 27% followed by 21-30 years of age group (22%). 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 [15]. 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 [16]. 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 our study, the most commonly involved system was hepatic and biliary system (53.33%) followed by GI system (51.11%) with nausea vomiting in about 29% cases, constipation in about 13.33% cases whereas, diarrhea was reported in 8.88% cases., In 2012, Shinde *et al.* reported 12.65% of GI upset cases and 6.27% of hepatotoxicity cases caused by first-line anti-TB agents [17]. Khalili *et al.* reported that ADR including hepatotoxicity can be one of the main reasons for poor adherence, and it will result in interruption and change in the treatment [18]. Treatment interruption or change of drugs both can result in inadequate or improper treatment and can further affect the course of the disease and may also result in the emergence of drug-resistant strains which can further limit the options. Other types of ADRs that were seen included hepatitis (20%), headache (20%), and rash in also about 20% patients. Fever flu-like syndrome accounted for about 13.33%. Blurred vision and optic neuritis (11.11%), metabolic disturbances including hyperglycemia were seen in about 11.11% patients. Other ADRs also included peripheral neuritis (4.44%), arthralgia, and with increased blood uric acid level (4.44%), pruritis (4.44%), peripheral neuritis (4.44%), increased blood urea (2.22%), and urinary complaints like dysuria (2.22%).

Causality assessment was done using Naranjo's scale. All 45 cases of ADRs were analyzed in which about 91 ADRs were reported. After assessment, 58.2% scored probable, 31.86% were of possible score, whereas 9.8% were in definite score category. Severity assessment using modified Hartwig and Siegel scale showed 68.88% cases of mild grading, 31.11% of moderate and no case 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. MDR-TB and XDR-TB are not only difficult to treat with limited options, second-line drugs have more toxicities and treatment being a lot more expensive than the first-line drugs with effectiveness reported to be lower. 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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