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Causality assessment, severity and preventability of adverse drug reactions due to first-line antitubercular agents

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ABSTRACT

TB (Tuberculosis) is a common infectious disease affecting humans since very long time. Multidrug therapy with its associated adverse drug reactions is one of the major concerns for the management of TB. The current study has been conducted for identifying causality assessment, severity as well as preventability of first-line anti-tubercular agents. All the diagnosed patients of tuberculosis attending TB and chest department of tertiary care hospital of western India and received Anti-TB drugs over 6 months enrolled in the study. Demographic details, suspected drugs/groups, causality assessment, severity assessment, and preventability assessment were analyzed from reported suspected ADR (adverse drug reaction) forms. Throughout the research period of 6 months, 500 patients received Anti-TB drugs. Among them, (10%) 50 patients developed 121 adverse drug reactions. According to the WHO causality scale, 66 (54.54%) ADRs were classified as 'probable' and 53 (43.8%) ADR were 'possible'. More than half of the reactions (31, 62%) were mild on the severity scale while most of the ADRs were definitely (34, 68%) preventable as per the preventability scale. Gastrointestinal system is the most common affected system (54, 47.62%) followed by dermatological disorders (26, 23.01%) and Liver and biliary system (20, 16.52%). Isoniazid (46, 38%) and Rifampicin (40, 33%) were the common cause of first-line antitubercular agents for ADRs. ADRs to antitubercular agents are a major concern for patient compliance. Patient education, intensive reporting, and management can be helpful to improve the outcome of antitubercular therapy.

Keywords: Tuberculosis, adverse drug reactions, anti tubercular drug

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INTRODUCTION

Tuberculosis, a chronic granulomatous disease due to mycobacterium tuberculosis, is leading cause of mortality and morbidity caused throughout the globe even though there is the availability of definitive curative World Health Organization (WHO) approved treatment regimens available (WHO, 2019). To increase TB (tuberculosis) prevention as well as control, the World Health Organization has established a standardized DOTS (directly observed treatment)/Stop TB Strategy. Even though WHO aims to achieve treament success rate of 85%, the actual success rate of treatment treatment remains low (Yang et al., 2019). Many factors such as sociodemographic, economic factors, nutrition, and Human Immunodeficiency Virus (HIV) infection influence the treatment success rate. Moreover, multidrug therapy for a minimum of six months duration and associated adverse drug reaction (ADR) is also responsible for the reduced patient compliance and hence treatment outcome (Ali et al., 2017). For any chronic disease, patient compliance to drug therapy is the key determinant factor for the treatment outcome. Even though it is not possible to completely eliminate the ADR to ATT but proper patient education, consideration of drug interactions and the proper address to ADR can help to improve treatment outcomes (Gupta et al., 2020).

As per WHO, ADR is explained as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function" (Meng Fei et al., 2018). Most of the studies have shown some common ADR such as arthralgia, hepatotoxicity, visual disturbances, allergic reactions, neurological, and gastrointestinal disorders are caused by anti-tubercular agents (Nahid et al., 2016). Amidst all ADR, hepatotoxicity is the major concern related to ATT, along with its frequency ranging from 2–39% in various nations (Anand et al., 2006; Wondwossen Abera et al., 2016). The incidence of hepatotoxicity with ATT is also high in India compared to other nations. As the total incidence of ADRs connected to ATT varies from 5.1% to 83.5%, ADRs connected with antitubercular medicines continue to be of primary concern. It contributes to increased morbidity in patients with tuberculosis (Laghari et al., 2020; Maciel et al., 2010). As a result, it seems that it is required to recognize ADRs and to determine the underlying connection between ADR and drugs Diverse techniques of causality evaluation are available for determining the strength of the association between the occurrence of ADRs and drug (s) exposure (Javadi et al., 2007). The severity of ADRs is connected to the amount to which the ADRs affect the patients' daily life.

Data regarding ADR due to ATT are very few in the West Indian population. Therefore, the present study was designed to provide more insight into ADRs to anti-tubercular agents. The main purpose of this research work was to characterize the pattern of ADRs connected with anti-tubercular treatment, as well as to analyze the severity, causality, and preventability of ADRs associated with anti-tubercular therapy (ATT).

MATERIALS AND METHOD

Over six months, prospective observational research has been conducted at the Department of Tuberculosis as well as respiratory diseases at a tertiary care teaching institution in western India. The research has been carried out after approval from the institutional ethics committee (No. GMERS/MCG/IEC/12/2019, dated 20/04/2019), and signed informed consent has been obtained from all of the participants. All patients who were put on first line anti tuberculosis drugs (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol with customization in therapy, if any) and developed ADR were enrolled in the study. In order to assess and manage ADRs in the study population, medical charts and laboratory reports have been reviewed to prescribe drugs. The occurrence of ADRs has been determined based on laboratory reports (liver dysfunction and hematologic disorders), along with symptomatology (neurological disorders, arthralgia, allergic reactions, and gastrointestinal disorders) reported by caregivers or patients along with physical examination by paediatricians and clinicians (if laboratory reports could not identify ADRs). The authors have decided the liver dysfunction based on serum ALT (alanine aminotransferase), serum AST (aspartate aminotransferase) along with total

bilirubin that has been two times higher than the upper normal limit (ALT is 34 IU/L, AST is 31 IU/L along with 1.2 mg/dl total bilirubin) in our laboratory. The term "hepatotoxicity" was described as a rise in either the ALT or AST, which was larger than three times the upper normal limit, or a rise in total bilirubin which was greater than two times the upper normal limit (Lv et al., 2013).

All of the reported adverse drug reactions (ADRs) from TB patients were thoroughly reviewed and analyzed. These features of suspected ADRs have been assessed based on the following critical elements: 1. patient initials, 2. reaction date (onset), 3. gender, 4. description of the problem or reaction, 5. indications for use, 6. suspected medication(s), 7. concomitant medical products such as herbal remedies and self-medication, 8. re-challenge, 9. de-challenge and 10. results. Additional details were also collected in ADR forms like ADR management, co-morbidities, concomitant medications, concerning previous allergies, along with outcome.

Data pattern, extent, severity, duration of the reactions, and outcome of the reaction were clinically scrutinized, interpreted, and analyzed for suspected drugs. MeDRA (Medical Dictionary for Regulatory Activities) coding was done for all the suspected adverse drug reactions (Org., 2020). MeDRA is standard and internationally accepted specific medical terminology used for ADR classification. It has a hierarchical structure with five levels. Through the hierarchy, basic Low-Level Terms (LLTs) are grouped under preferred terms (PT). High-Level Terms (HLT) are used to group clinically relevant PTs together, and relevant High-Level Group Terms (HLGT) are used to group relevant HLTs together in System Organ Classes (SOC). The ADRs narrative elaboration scores for root cause of the reactions were assessed by the WHO – Uppsala Monitoring Centre (WHO-UMC) causality assessment scale (WHO, 2013). Here, the causality assessment was done to establish the relationship between the drug and the adverse reaction by using the same scale and it was classified into certain, probable, possible, unclassifiable, unlikely and unclassified categories (Table 1). According to the Modified Hartwig and Siegel scale, the ADR severity has been determined (Hartwig et al., 1992). The Modified Hartwig and Siegel scale categorizes ADR severity as mild, moderate or severe depending on characteristics such as length of hospitalization, need for treatment change, along with disability caused by the ADR. The Modified Schumock and Thornton scale divides preventability into three categories: those that are certainly preventable, those that are possibly preventable, and those that are not definitely preventable (Schumock & Thornton, 1992). In Section A, there are five questions, and in Section B, there are 4 questions. All of the responses are classified as either "Yes" or "No." ADRs have been considered "definitely preventable" if the response to one or more of the questions in Section A was "yes." After we determined that all of the responses were negative, we moved on to Section B. ADRs have been considered "probably preventable" if the answer to one or more of the questions in Section B was "yes." We go on to Section C if all of the answers have been negatives. There were no preventable adverse events in Section C.

Data Analysis

Data has been entered in Microsoft Excel version and the results were analyzed using descriptive statistics. Results were presented in tables, pie charts and bar diagrams in appropriate proportions and percentages. Throughout the study, the confidentiality of study participants was maintained.

RESULT AND DISCUSSION

During the study period of 6 months, 500 patients with tuberculosis were attended to receive antitubercular drugs at outpatient and in-patient department of TB and chest, tertiary care teaching hospital. 50 patients were there who developed 121 ADR. The results of this research recommend that ADR caused by antitubercular drugs continue to be a problem for drug adherence because they can prolong hospitalization, result in treatment discontinuation, and result in treatment failure. The occurrence of ADR in the current study is 10 % which is similar to other studies that reported incidence of ADR among antitubercular drugs from 5.1 % to 23 % (Maciel et al., 2010). The study from Brazil shows that the incidence of ADR was 83.5% (Farazi et al., 2014). The analysis of ADR forms shows that adult patients experienced more ADR (43) from age 15 to 50 years (86 %), elder patients (>50 years

of age) experienced 7 (14%) and no pediatric patients (<14 years age) experienced any ADR. The reporting of ADRs caused by ATT along with their risk factors in children is limited. Hence, our study included ADR reported in adults.

Concerning patient gender, females experienced more ADR than males (54 %) in this study. In the global scenario, male suffers more from tuberculosis than females (Imam et al., 2020). Some studies in India and other countries also found out that male experienced more tuberculosis and more ATT-induced ADR than female patients which are consistent with our result. Similarly, male predominance of tuberculosis was also seen in young adult and elderly patients (Francoise et al., 2019). As males are usually more social, more labour-based work than females in which chances of transmission of disease are more. Second, males are likely to have a smoke, take alcohol and drug addiction which is an increasing risk of contracting tuberculosis. Our study shows a contrasting result to other studies. It is likely that females are more aware about their health and therefore, early diagnosis and treatment started in females which lead to more ADR. This finding might be explained by gender-related variations in pharmacokinetics and immunology, along with hormonal considerations at various times of life, such as menarche, pregnancy, pre-menopausal and post-menopausal phases, which all influence drug response and are discussed in more detail below. The connections between contraceptive medications and anti-TB treatments may potentially contribute to the incidence of ADRs in some patients (Meng Fei et al., 2018). Generally, Females have a leaner body mass, lower hepatic clearance, variations in cytochrome P450 enzyme activity, altered stomach motility, and a lower glomerular filtration rate as compared to males, among other characteristics (Alomar, 2014; Rademaker, 2001).

Table 1. WHO-UMC Causality Categories

Causality term	Assessment criteria (all points should be reasonably compiled)
Certain	•Event or laboratory test abnormality, with plausible time relationship to drug intake •Cannot be explained by disease or other drugs •Response to withdrawal plausible (pharmacologically, pathologically) •Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible) •Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because the information is insufficient or contradictory • Data cannot be supplemented or verified

Table 2: Classification of ADRs according to MedDRA

Sr no.	Medra SOC	SOC case	PT	PT no.
1	Gastrointestinal disorders	54	Vomiting	22
			abdominal pain	10
			Nausea	10
			Gastritis	7
			diarrhoea	4
			redness gum	1
2	Skin and subcutaneous tissue disorders	26	Itching	13
			Rash	6
			burning sensation	3
			Pruritus	2
			maculopopular lesion	1
			Acne	1
3	Hepatobilliary disorders	20	icterus sclera	11
			yellow coloring urine	4
			yellow coloring skin	5
4	Musculoskeletal and connective tissue disorders	4	pain in leg	2
			Burning sensation	2
5	Nervous system disorders	8	behaviour change	2
			Vertigo	2
			Weakness	2
			Lethargy	1
			speech disorders	1
6	Investigations	2	urine output decreased	2
7	Respiratory, thoracic and mediastinal disorder	1	dyspnoea	1
8	Immune system disorders	1	facial oedema	1
9	Eye disorders	1	eye redness	1
10	Ear and labyrinth disorders	1	hearing decreased	1

Note: Medra-Medical Dictionary for Regulatory Activities, PT-preferred term, SOC- system organ class

System organ class analysis

As per Medra classification of ADR shown in Table 2, Gastrointestinal disorders were the most affected system with 47.62 % of 121 all ADRs reported from 50 ADR forms which is comparable to other studies (Farazi et al., 2014; Javadi et al., 2007; Meng Fei et al., 2018). The symptoms of it experienced by the patients are vomiting, abdominal pain, nausea, diarrhea etc. Patients who developed gastrointestinal symptoms were reassured, managed symptomatically and advised to take ATT after a meal (Javadi et al., 2007; Laghari et al., 2020). Another system affected was skin and subcutaneous tissue disorders (23.01%) followed by yellow coloration of sclera and urine (16.52%). The rate of dermatological adverse reactions to anti-TB medications in our research was 23.01%, which was greater than the rate in other studies (Farazi et al., 2014; Sharma et al., 2020). The incidence of hepatotoxicity induced by ATT is 16.27 % in this study which is also similar (between 3.5% and 16.2%) to other studies published by other countries (Ohkawa et al., 2002). It is the most significant cause to reduce effectiveness of drug by decrease drug adherence or further leads to treatment failure (Ohkawa et al.,

2002; Sharma et al., 2002). Hence, TB patients on anti-TB medication should have their liver function monitored every month.

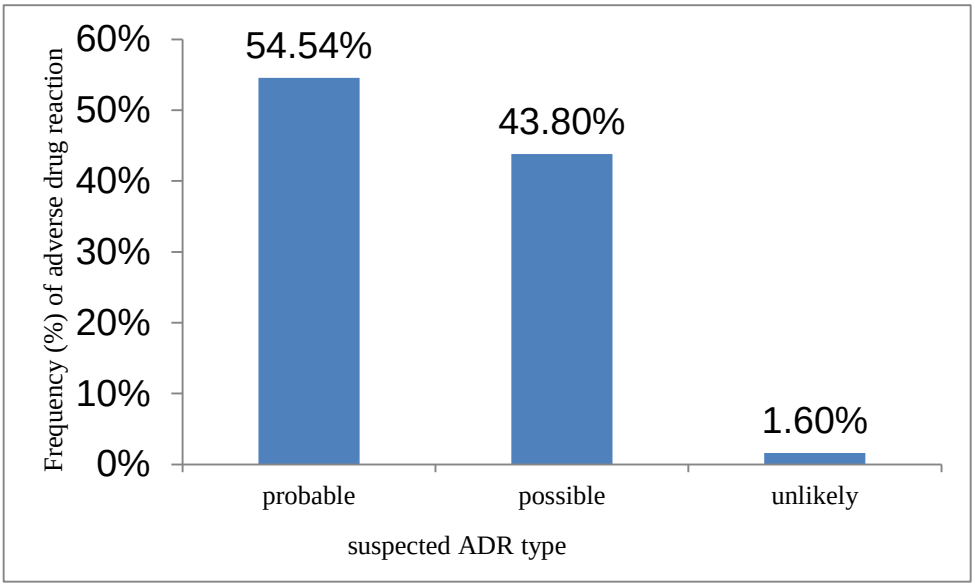

Figure 1: Causality assessment of reported ADR according to WHO-UMC Scale

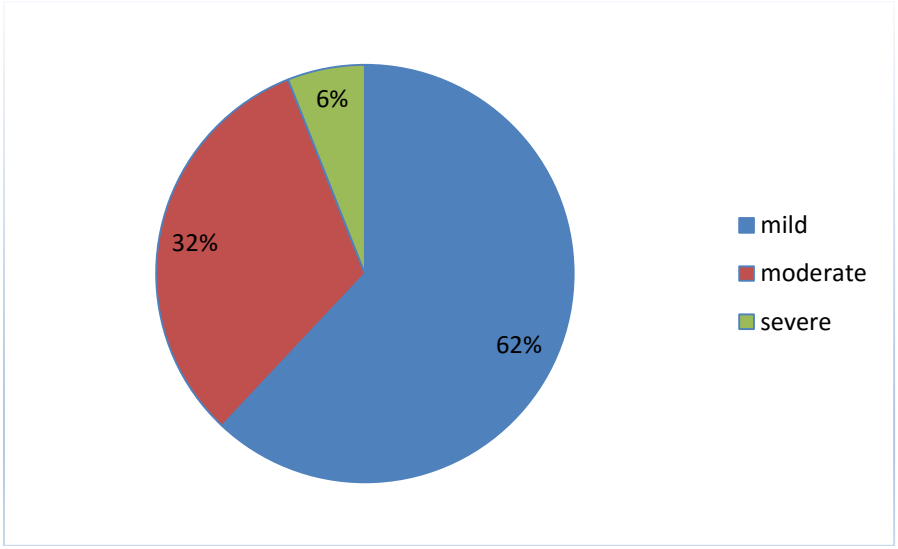

Figure 2: Severity assessment of reported ADRaccording to modified Hartwig and Siegel scale

Causality and severity assessment

Causality assessment according to WHO scale is shown in Figure 1, 54.54% ADR were classified as 'probable' followed by 32% ADR were as 'possible'. Since no patients were subjected to a rechallenge due to safety or ethical concerns, we were unable to uncover any evidence of a clear association. Our findings are comparable with other studies done in Spain, India & Pakistan (Saqib et al., 2018; Sevilla-Sanchez et al., 2017; Sundaran et al., 2018). A possible explanation is that most of the ADR were detected in 2 months of intensive phase only. This finding is similar to earlier studies (Lv et

al., 2013). Hence, early detection of ADR occurred by directly observed short-course therapy (DOT). The severity assessment is essential to carry out in order to take proper management of ADR. Figure 2 shows the modified Hartwig and Siegel scale, which categorizes most ADR as mild (62%), moderate (32%), or severe (13%). Thus, the majority of ADEs found were of a minor kind. The mild ADR (62%) require no change in treatment with suspected drug followed by (32%) moderate ADR class which help clinician for deciding whether hospitalization is essential or not for particular ADR. Due to the severity of the ADR, only 6% of the patients required acute medical treatment in the hospital (Hartwig et al., 1992). In contrast to present findings, utilizing a similar scale, 61.4% of moderate occurrences were recorded in India (Sriram & Senthilvel, 2013). The Causality assessment has been done by Modified Schumock and Thornton 1991 preventability scale as shown in Figure 3, with the majority being classified as definitely (68%) followed by probably (32%) in accordance with another study that utilized identical criteria and found that 66.7 percent of avoidable ADRs may have been prevented in India (Sevilla-Sanchez et al., 2017). At this point, we need to intensify large-scale efforts for creating safer and higher-quality health care systems in order to address the problem appropriately, with a focus on the prescription and monitoring phases for prevention.

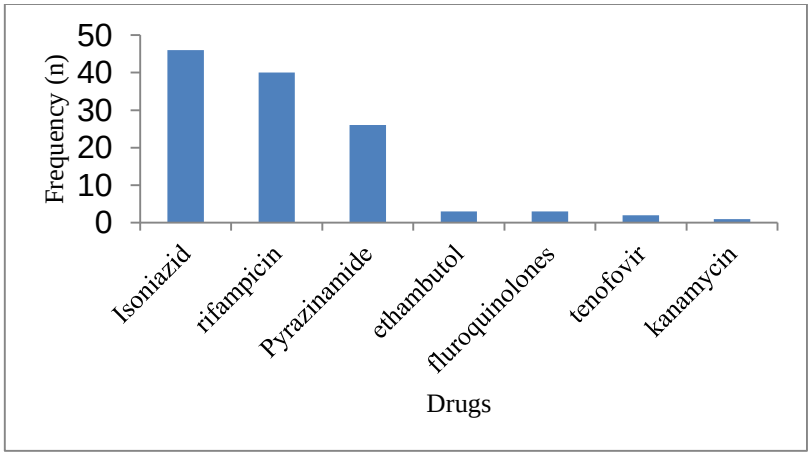

Figure 3: Antitubercular drug responsible for ADR (121 drugs/50 ADR)

Drug class analysis

Among first line antitubercular drugs, Isoniazid was most usual drug responsible for frequent ADR reports (38%) followed by rifampicin 33%, pyrazinamide 21.48% as shown in Figure 3. Directly Observed short-course therapy is a combination regimen of isoniazid, rifampicin pyrazinamide and ethambutol. The efficacy or toxicology of a certain medicine might therefore be extremely difficult to determine. In spite of this, a thorough understanding of the pharmacokinetics and potential side effects of medications utilized in combination would allow a physician to recognize ADR and treat patients with anti-TB therapies in a safer as well as effective manner. Other drugs like fluoroquinolone, tenofovir and aminoglycoside were also responsible from ADR. The study's strength is that we gathered and evaluated all of the accessible data for the specified time period, and the results may be representative of the reality of tuberculosis care in Gandhinagar, Gujarat. We had certain limitations like finding of our result can't be generalized to the whole country due to small sample size. Second, because rechallenge was not done in all patients following a dechallenge, only a small number of cases could be classified as definite.

CONCLUSIONS

Majority of ADR were mild as per severity classification and maximum ADR fell under the category of “probable” in causality assessment. This study provided a good overview of adverse drug reactions associated with anti TB drugs. Many ADR were found to be preventable in nature.

Consequently, it must intensify large-scale efforts to create healthcare systems that are safer and of greater quality in order to effectively address the problem. Our study had a drawback in that it did not look at the influence of adverse drug reactions on TB therapy.

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