

A Prospective-Observational Study to Assess the Prevalence of Adverse Drug Reactions in MDR-TB Patients at Tertiary Care Hospital in India

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ABSTRACT

Background: Adverse Drug Reactions (ADRs) constitute an enormous burden for the society. The aim of the present study was to detect, document, assess and report the suspected ADRs.

Methods: A prospective-observational study was conducted in the Department of Pulmonary Medicine of a tertiary care hospital for 12 months from April 2014 to March 2015. Patients on RNTCP (Revised National Tuberculosis Control Programme, India) MDR-TB (Multidrug resistant tuberculosis) regimen were enrolled. Detected and suspected ADRs were analysed for causality, severity and preventability using appropriate validated scales and were reported.

Results: A total of 121 ADRs were detected, documented, assessed and reported during the study period. Assessment of severity of the suspected ADRs revealed that 23.14% of suspected ADRs were severe and 28.29% of ADRs were moderate in severity. Causality assessment was done which revealed 61.1% of ADRs were certainly drug-related. The majority of patients who had suffered from ADRs were above 20 years. Ototoxicity was most common (37%) and the drug mostly associated with ADRs was kanamycin (27%). Preventability of ADRs was assessed; and the results revealed that 15.7 % of ADRs were definitely preventable.

Conclusions: Measures to improve detection and reporting of adverse drug reactions by all health care professionals is recommended to be undertaken, to ensure, and improve patient's safety and adherence to MDR-TB regimen.

Keywords: Adverse Drug Reactions (ADR), Prevalence, MDR-TB, India.

INTRODUCTION

World Health Organization (WHO) defines an adverse drug reaction (ADR) as “one which is noxious and unintended, and which occurs in doses normally used in human for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological functions. According to the Centre for Health Policy Research, more than 50 % of the approved drugs were associated with some type of adverse effect not detected prior to approval. Pharmacovigilance or ADR monitoring, launched by WHO in the 1960s in the wake of ‘thalidomide’ disaster, is currently an integrated global effort of more than 70 countries worldwide. After the “thalidomide tragedy” many countries have established drug monitoring systems for early detection and prevention of possible drug-related morbidity and mortality. The use of traditional and complementary drugs (e.g. herbal remedies) may also pose specific toxicological problems, when used alone or in combination with other drugs.²

In India, reported that ADRs due to prescription and over the counter drugs are not available. Most of the advanced countries have set up an adverse drug reaction reporting system at the national level. ADR reporting programs on an institutional basis can provide valuable information about potential problems in drug usage in that institution. Furthermore, reviewing pooled data from diverse geographic, social and medical population enhances the ability to identify rare events and to generate new signals and thus in setting up a sound Pharmacovigilance system in the country. Therefore, setting up of ADR monitoring centers at a more regional or hospital level and integrating them with a sound network can reveal unusual or rare ADRs prevalent in Indian population.

ADR monitoring and reporting activity is in its infancy stage in the developing countries. Lack of well-structured and effective ADR reporting and monitoring programme is a major problem in monitoring the drug safety in Indian populations. The clinicians who prescribe and follow-up on treatment outcomes are best suited to detect adverse reactions in their patients based on information gathered from the patients and their own clinical observations. However, due to the lack of interest and clinical acumen, aptitude and time, many untoward adverse incidents pass unnoticed. Moreover, many physicians are unaware that clinically important ADRs should be reported to the ADR reporting and monitoring centers. As a result, ADRs are often not detected or documented. This could be achieved through establishing or setting up more number of hospital-based or local ADR reporting and monitoring programs that can assist healthcare professionals. It may become a heavy burden on prescribers to ensure that they keep abreast of the evidence regarding ADR to improve the quality of patient care. Therefore, there is a greater and urgent need to create and enhance physicians’ awareness about detection, management, prevention and reporting of ADR. The benefits of pharmacists, pharmacy staffing and clinical pharmacy services to reduce ADRs are documented elsewhere.³ The aim of present study was to estimate the prevalence of adverse drug reactions at a tertiary care hospital in India.

METHOD

This prospective-observational study was conducted in the Department of Pulmonary Medicine at a tertiary care hospital, Surat. Study involves 100 MDR-TB patients. The study was carried out for a

period of 12 months from April 2014 to March 2015 and involved a multidisciplinary spontaneous reporting program that relies on both the prospective and concurrent detection of suspected adverse drug reactions and drug interactions.

All patients of either sex and of any age who developed an ADR while on RNTCP MDR-TB regimen during the above mentioned time period were included in the study. During the study period patients were on their routine diet. Patients taking herbal product or any type of supplements were exempted from study group. The protocol of the study was approved by the local institutional ethics Committee. The authors were permitted to utilize the hospital facilities to make a follow up of the prescriptions in the selected department.

ADR Reporting

Newly diagnosed MDR-TB patients on RNTCP regimen were enrolled. Preliminary examination and investigations includes clinical examination, renal and liver function test, serum profile for electrolytes, audiological test, neurological test, ophthalmic fundus examination, and thyroid function test. Various modes of reporting system was adopted including use of ADR notification form, telephone reporting, direct access, referral of patients and personal meeting at every monthly so as to ease the reporting of “suspected” ADRs. Once the suspected ADR was reported, patients’ medical records were reviewed and also patients and or healthcare professionals were interviewed as appropriate to collect all the necessary and relevant data pertaining to the “suspected” ADR.

The details of data collected pertaining to the reported ADR include: description of event, suspected medication, other medications including over the counter medicines and medication on admissions, presenting complaints, past medical history,

allergic status, possible involvement of risk factors of an ADR and previous exposure. Later all the collected data were further reviewed and documented in a suitably designed ADR documentation form.⁸ Then the reported event was subjected to evaluation, and analysed to indicate how likely it was that the implicated drug caused the “suspected” adverse reaction. Suitable ADR documentation form was designed to gather and document as much relevant data as possible pertaining to the reported reaction. The designed ADR documentation form contained the specific details regarding patient demography, description of event, medications suspected, medication used prior to the reaction with their complete dosing regimens, comorbidities, risk factors involved, patient allergic status, causality category, severity, predictability, preventability, management of reported adverse reaction, outcome of management and follow up details.

Criteria for Reportable ADR

In the present study, the World Health Organization (WHO) definition of an ADR was adopted as a criterion for reporting any suspected reaction. The WHO defines an adverse drug reaction as “one which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.”⁷

Assessment of ADR Reports

All the reported events were evaluated, after collecting adequate data from appropriate sources, as to explore the likely involvement of suspected drug in causing the reported event. In assessing the causality, concerned clinician and/or unit chief opinion was obtained. After having assessed the causal relationship between the suspected drug and the adverse reaction, irrespective of their causality category, the

reports were subjected to further analysis including their severity, predictability and preventability of reported reactions.

Causality Assessment

The causality relationship between suspected drug and reaction was established by using WHO and Naranjo's causality assessment scales. The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships and previous patient experience with the medication. The ADR is assigned to a probability category from the total score as follows: *definite* if the overall score is 9 or greater, *probable* for a score of 5-8, *possible* for 1-4 and *doubtful* if the score is 0. The Naranjo criteria do not take into account drug-drug interactions. Drugs are evaluated individually for causality, and points deducted if another factor may have resulted in the adverse event, thereby weakening the causal association.^{1,2,6,10}

Assessment of Severity

The severity of reported reactions was assessed by using Hartwig scale⁴ and was categorized into mild, moderate and severe.

Assessment of Preventability

The preventability of reported ADRs was assessed by using Modified Schumock and Thornton scale⁵ and was categorized as definitely preventable, probably preventable and not preventable. When an event was reported, all patients who experienced an ADR were followed from the day of reporting of an ADR until the completion of treatment to gather updated information

regarding the changes and the progress in the patients' condition and management.

RESULTS

A total of 121 documented ADRs were identified in 100 MDR-TB patients attending Pulmonary Medicine outdoor patient department during the study period. Study involves both male and female patients with mean age of 28.77 ± 9.92 years. (Table 1) Figure 1 show different types of ADRs reported during MDR-TB treatment. Among all ADRs, most common is ototoxicity reported in 26 (21.1%).

Causality assessment through WHO scale indicated that 61.16% were certain, 26.45% were probable. Causality assessment of suspected ADRs using Naranjo's scale showed that 57.85% of them were definite, 26.45% were probable and the rest of them categorized as possible and doubtful. The severity of 51.24% of reactions (using Hartwig scale) was reported as moderate and 23.14% considered as severe. On the basis of Modified Schumock and Thornton scale, 15.70% and 36.36% reactions of the suspected ADRs were definitely and probably preventable, respectively. (Figure 3) 36% of all ADRs was suspected due to pyrazinamide and 27% were due to Kanamycin.

DISCUSSION

Number of Patient with MDR-TB increasing these days. We have limited number of drugs to combat with life threatening disease. In last few years we haven't seen any new drug development process for such infectious disease. Presently available drugs have limited efficacy and require multiple drugs for cure. These drugs have grave side effects. Study was conducted to evaluate drug induced ADRs and to assess causality, severity.

According to the present findings the ADRs in the patients were more documented

in males. Sex ratio patients might be an intervening factor but does not seem to be a major determinant.

MDR-TB is increasing now days and we have limited numbers of drugs for treatment. Seven drugs are included in RNTCP MDR-TB regimen. These drugs have grave side effects and most of them are moderate to severe variety. In this study most common ADR was ototoxicity and is suspected due to kanamycin.⁹ In four patients it requires to stop injection kanamycin. Pyrazinamide was the most common drug responsible for majority ADRs. Early diagnosis and reporting of severe form of ADRs can prevent life time suffering for patient. Attempt should be made to use alternatives and to find risk factors.

Under-reporting is a major problem even in western countries where the pharmacovigilance system is well established. In India the major problem is a lack of proper system of pharmacovigilance. Our ability to anticipate and prevent such ADRs can be facilitated by the establishment of standardized approaches and active reporting of suspected ADRs by all healthcare professionals including physicians, dentists, nurses and pharmacists.

CONCLUSIONS

This study strongly suggests that there is greater need for streamlining of hospital based ADR reporting and monitoring system to create awareness; and to promote the reporting of ADR among healthcare professionals of the country. Measures to improve detection and reporting of ADR by all health care professionals should be undertaken, to ensure patient's safety.

Conflict of Interests

Authors have no conflict of interests.

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Table 1. Demographic and clinical characteristics of MDR-TB Patients treated with anti-tubercular medication

Sr. no	Characteristic	Patients (n =100)
1	Age	28.77±9.92
2	Sex (M/F)	61/39
3	Weight(kg)	44.57±7.94

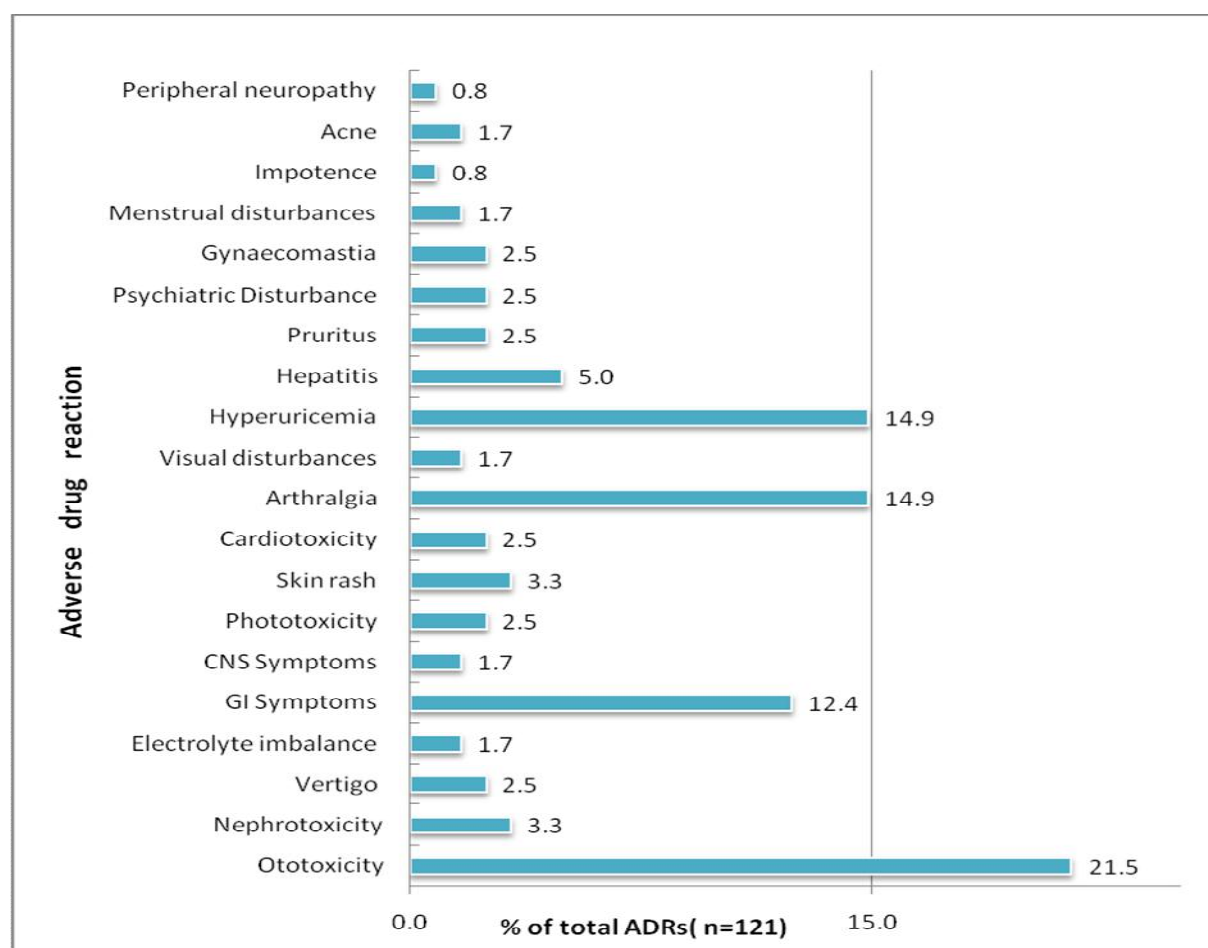


Fig. 1: Percentages of adverse drug reactions. (n=121)

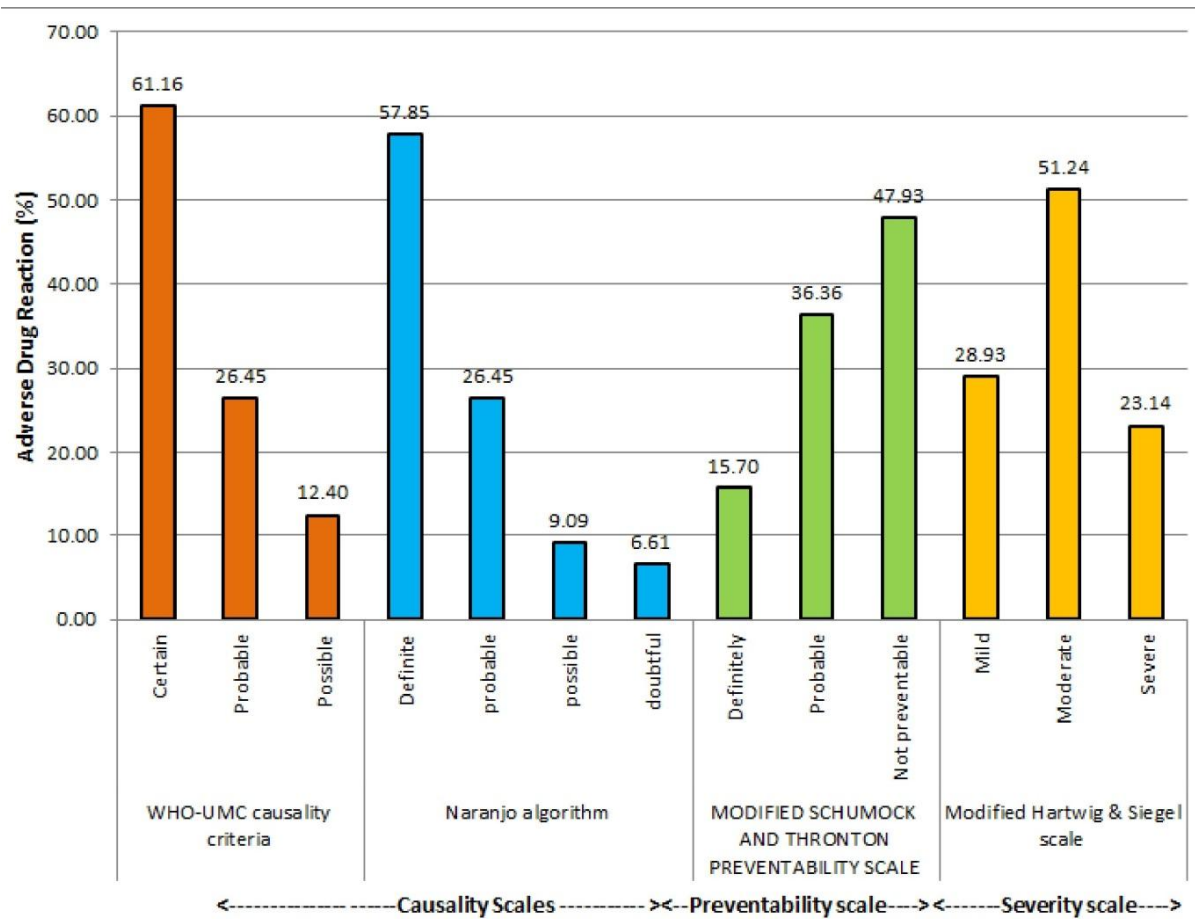


Fig. 2: WHO-UMC causality scale, Naranjo algorithm, Modified Schumock and Thornton preventability scale and Modified Hartwig & Siegel scale. (n=121)

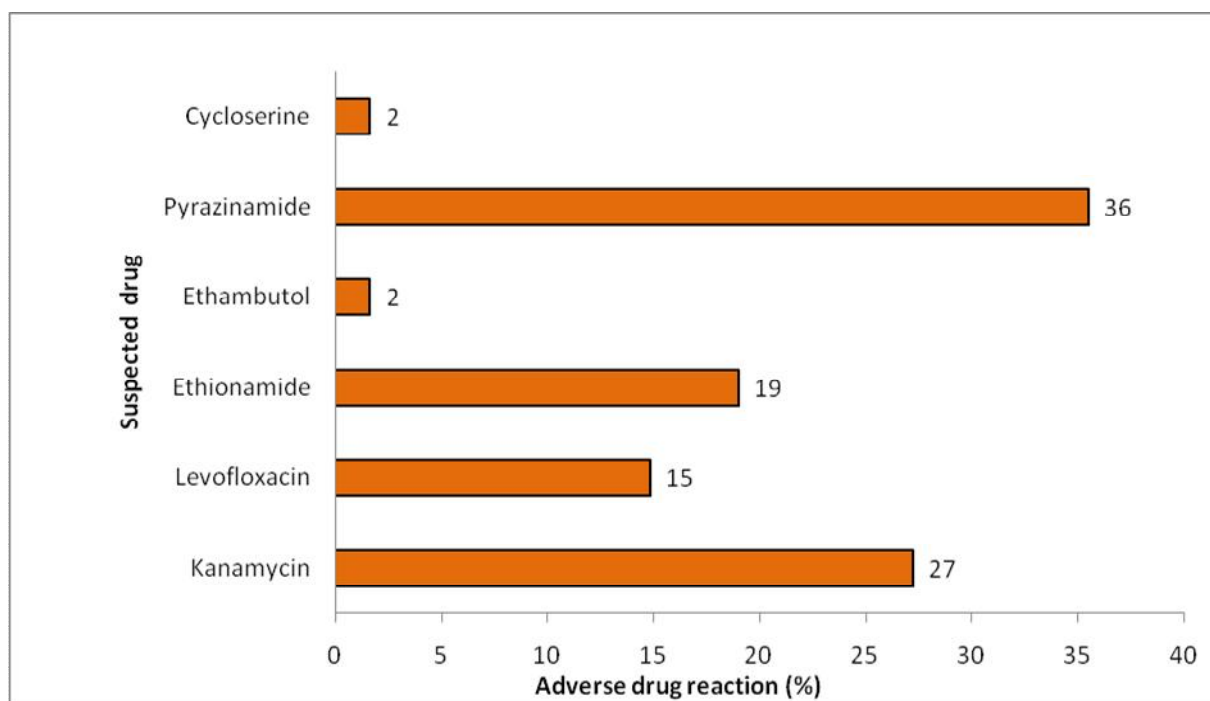


Fig. 2: Suspected drug for adverse drug reaction. (ADRs in %) (n=121)