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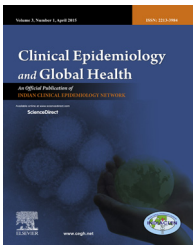

Continuing Education

Prevalence of adverse drug reaction with first-line drugs among patients treated for pulmonary tuberculosis

Abhijeet Singh [a], *Rajendra Prasad* [a,*], *Viswesvaran Balasubramanian* [a], *Nikhil Gupta* [b], *Pawan Gupta* [a]

[a] *Dept of Pulmonary Medicine, V.P. Chest Institute, University of Delhi, India*
[b] *Dept of Internal Medicine, Era Medical College, Lucknow, UP, India*

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ABSTRACT

Adverse drug reactions (ADRs) to first-line anti-tuberculosis drugs are common and may cause associated morbidity and even mortality if not recognized early.[1–3] The overall prevalence of ADRs with first-line anti-tuberculosis drugs is estimated to vary from 8.0% to 85%. They are observed more commonly in the intensive phase and do not differ with intermittent or daily intake of anti-tuberculosis drugs. The occurrence of ADRs may be influenced by multiple factors and may range from mild gastrointestinal disturbances to serious hepatotoxicity, peripheral neuropathy, cutaneous adverse effects, etc. Early recognition and appropriate management of these adverse effects might determine adherence and treatment success.

1. Introduction

India features among the 22 high TB burden countries and has accounted for an estimated one quarter (26%) of all TB cases worldwide.[4] Treatment regimen with multiple first-line anti-tubercular agents (isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin) remains the cornerstone of treatment of tuberculosis. Good bacteriological diagnosis and compliance on treatment are the two main pillars of successful treatment of pulmonary tuberculosis. Adverse reactions to these agents are common and cause significant morbidity and even sometimes mortality if not detected early.[1–3] The World Health Organization (WHO) has defined adverse drug reactions (ADRs) as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[5] Timing, the pattern of illness, the results of investigations, and re-challenge will help attribute causality to a suspected ADR.[6] Various factors such as the dose and time of day at which the medication is administered, patient age, nutritional status, the presence of preexisting diseases or dysfunctions like impaired liver function, impaired kidney function, HIV co-infection, and alcoholism may be related to adverse reactions to anti-tuberculosis drugs.[7] This calls for continued surveillance of

* *Corresponding author*. Tel.: +91 8826406406.
E-mail address: rprasadkgmc@gmail.com (R. Prasad).
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ADRs, especially in public health programs that treat large number of patients, especially in disease like tuberculosis where early recognition and appropriate management of ADRs might determine adherence and therefore therapy success. The aim of this review article is to highlight the current existing prevalence of ADRs in patients receiving first-line anti-tuberculosis treatment (ATT).

2. Prevalence of ADRs with first-line anti-tubercular drugs-global scenario

The data on global prevalence of ADRs with first-line anti-tubercular drugs are scarce. The prevalence of ADRs observed in various studies conducted worldwide ranged from 8% to 85% as mentioned in Table 1.[8–28] This table has focused primarily on those studies that have adopted programmatic treatment approach known as Directly Observed Treatment and Short course chemotherapy (DOTS). The reasons for variation in the prevalence of ADRs across various studies might be related to several possible factors such as: differences in definitions of ADRs terminologies as adopted by clinicians, whether the ADRs were reported subjectively by patient or objectively by clinician on the basis of clinical evidence and monitoring with serial laboratory investigations, the differences in existing co-morbid illnesses such as diabetes, hypertension, or hypothyroidism, and other co-variates including HIV co-infection and variations in the use of specific anti-tubercular drugs including dosage and also pharmacological interactions with other group of drugs particularly anti-retroviral therapy. A study conducted in Nigeria observed that around 14% and 13% incidence of ADRs at 6 months and 8 months, among patients receiving directly observed treatment and short course chemotherapy (DOTS) respectively.[8] In another study conducted by the Hong-Kong Chest Services, ADRs were observed in 21% of patients receiving intermittent therapy.[29] Brazilian National Ministry of Health reported the incidence of minor or mild ADRs in patients treated with the former first-line ATT to range from 5% to 20%.[30] It was also observed that major or severe ADRs were less common (occurring in approximately 2% of the cases, reaching 8% in specialized clinics) and led to the discontinuation or alteration of the treatment. However, another study from a teaching hospital in Brazil reported that 41.1% of the patients presented with minor and 12.8% presented with major ADRs.[31] In a study from Singapore, frequency of ADRs was observed to be 28.7% whereas it was observed to be 29.27% from another study conducted at Hong Kong.[29,32] However, studies have revealed that there are no differential rates of ADRs among patients having intermittent and daily intake of anti-tuberculosis drugs.[33] It was also observed that ADRs were more prevalent in intensive phase than continuation phase.

3. Prevalence of ADRs with first-line anti-tubercular drugs – India

The Revised National Tuberculosis Control Program (RNTCP) has adopted the principles of Directly Observed Treatment and Short course chemotherapy (DOTS) and has been treating patients of pulmonary tuberculosis throughout the country since 1998. It has achieved global benchmark of treatment success consecutively for the last five years. The overall prevalence of ADRs with first-line anti-tuberculosis drugs is estimated to vary from 2.3% to 17% in various Indian studies.[10,12,15,20,22–24,26,27] A study conducted by Mehrotra et al. observed that the prevalence of ADRs in the initial intensive phase was 17.39%.[34] Another study conducted at a tertiary institute in Calcutta observed that the overall toxicity was found in 35% cases in the daily regimen group, whereas it was found to be 27.9% in the intermittent regimen group.[22] Data regarding prevalence of ADRs are still scarce and further surveys are required from different geographical areas of India in near future.

4. Gastrointestinal ADRs

Gastrointestinal symptoms are one of the most common ADRs seen with intake of anti-tubercular drugs. Its severity can range from mild symptoms like nausea, vomiting to life-threatening complications. All the first-line anti-tubercular drugs can cause mild gastrointestinal upsets that can be managed symptomatically without change in dosage of drugs. In a study of 893 patients by Shinde et al., it was found that gastrointestinal upset with nausea, vomiting, and abdominal pain were the most common ADRs seen in 12.5% of patients.[35] In another prospective study from China, it was found that gastrointestinal ADRs were seen in 3.74% of 4304 patients and only 7 patients required hospital admissions.[19]

5. Hepatotoxicity

The clinical presentation of ATT-associated hepatitis is similar to that of acute viral hepatitis. ATT-induced hepatotoxicity can manifest as transitory asymptomatic rise in transaminases or acute liver failure. The frequency of hepatotoxicity ranges from 2% to 39% in different countries.[36] An increased incidence of hepatotoxicity has been observed in Indian sub-population when compared to Western population.[37,38] ATT-induced hepatotoxicity in Indian population was observed to be 11.5%. However, a meta-analysis in West found the risk to be 4–28%.[39,40] The occurrence of drug-induced hepatotoxicity is unpredictable though certain patients are at a relatively higher risk than other populations. The incidence has been reported to be higher in developing countries and factors such as acute or chronic liver disease, indiscriminate use of drugs, malnutrition and more advanced TB have been implicated.[41,42] Isolated isoniazid administration resulted in a threefold increase in alanine aminotransferase levels over the normal in 10–20% of these patients.[39,43] A meta-analysis of six studies investigating the use of isoniazid in isolation reported the incidence of hepatitis to be 0.6%.[44] However, recent studies have observed the incidence of clinical hepatitis in patients receiving isoniazid to be lower than previously thought.[39] Hepatotoxicity is rare in children receiving Isoniazid (INH). In a 10-year retrospective analysis, the incidence of hepatotoxicity in 564 children receiving INH for the prophylactic treatment of tuberculosis was observed as 0.18%.[45] The incidence of