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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

^aDept of Pulmonary Medicine, V.P. Chest Institute, University of Delhi, India

^bDept 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.

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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-variables 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

Table 1 – Characteristics of important studies showing frequency of adverse drug reactions due to first-line anti-tuberculosis drugs.

Study year	Location	Sample size	Study period	Type of regimen	Duration of treatment (months)	Number of drugs in regimens	Incidence of ADRs (%)	Profile of ADRs
Dosumu (2002) ⁸	Nigeria	Group 1–500 Group 2–50	Jan 1996–Dec 1997	DOTS (CAT 1)	6–8	5	Group 1–13 Group 2–14	Group 1 – Arthralgia (4%), Pruritus (2%), Fever (2%), Systemic flu like syndrome (2%), Gastroenteritis-nausea & vomiting (1.6%), Jaundice (1%), Maculopapular rash (0.4%) Group 2 – Arthralgia (4%), Pruritus (2%), Fever (2%), Systemic flu like syndrome (4%), Jaundice (2%)
Yee (2003) ⁹	Canada	430	1990–1999	Supervised/ DOTS	6–8	4	10.70	Rash/Drug fever (4.88%), Hepatitis (2.79%), Severe gastrointestinal upset (2.56%), Visual toxicity (0.23%), Arthralgia (0.23%)
Dhingra (2004) ¹⁰	India	1195	Jan 2002–Jun 2003	DOTS	6–9	5	8.37	Nausea and Vomiting (53%), General aches & Pain (35%), Giddiness (27%), Skin rash & itching (17%), Arthralgia (11%), Hepatotoxicity (1%)
Gülbay (2006) ²	Turkey	1149	1984–2001	DOTS	9	4–5	9.00	Hepatotoxicity – Functional liver disturbance (4.9%), Hepatotoxicity (2.4%), Severe hepatotoxicity (0.8%), Hyperuricemia (including arthralgia) – (2.6%), Ototoxicity (1.7%), Psychiatric changes (0.7%), Cutaneous reactions (0.6%), Flu-like syndrome (0.3%), Gluteal abscess (0.2%), Fever (0.2%), Peripheral neuropathy (0.1%), Changes in visual acuity (0.1%), Hemolytic reaction (0.1%), Change in glucose tolerance (0.1%)
Gholami (2006) ¹¹	Iran	83	Jul 2001–Jul 2002	DOTS	6	4	53.01	Hepatitis (25.9%), Constipation (17.3%), Increased liver transaminases (11.2%), Hyperglycemia (8.7%), Headache (8.7%), Peripheral neuropathy (6.2%), Dysuria (4.9%), Rash (4.9%), Diarrhea (3.7%), Increased uric acid (3.7%), Vision abnormality (2.4%), Prolonged Prothrombin Time (2.4%)
Taher (2006) ¹²	India	1490	Dec 2002–Aug 2005	DOTS	6–9	5	29.00	Nausea and vomiting (11%), Transient gastritis (9%), Elevated serum aspartate aminotransferase or alanine aminotransferase (>50 IU/l) (3%), Elevated serum alkaline phosphatase (>280 IU/l for adults and >840 IU/l for children) (1%), Elevated serum uric acid (>7.4 mg/dl) (3%), Low platelet counts (1.5 lakhs/microliter) (2%)

Kishore (2008) ¹⁴	Nepal	326	Jan 2001–Dec 2006	DOTS	6–9	5	12.27	Elevated hepatic enzymes/Hepatitis (57.14%), Gastritis (9.52%), Arthralgia (9.52%), Erythematous/macular rash (7.14%), Interstitial nephritis/Renal failure (4.76%), Nausea/Vomiting (4.76%), Peripheral neuritis (2.38%), Vestibular neuritis (2.38%), Defective vision (2.38%)
Chhetri (2008) ¹³	Nepal	137	Jan 2005–Jun 2005	DOTS	6–9	5	54.74	Tingling and burning Sensation in extremities (11.03%), Joint Pain (10.34%), Bodyache (10.34%), Epigastric burning (10.34%), Generalized itching/rashes (10%), Anorexia/Nausea/Vomiting (9.66%), Vertigo/Dizziness (6.21%), Headache (4.83%), Weakness (3.45%), Tinnitus (2.41%), Ataxia (1.72%), Constipation (1.03%), Diarrhea (1.03%), Miscellaneous (7.93%)
Tak (2009) ¹⁵	India	94	Oct 2005–May 2006	DOTS	6–9	5	17.02	Gastritis (32.09%), Hepatitis (9.52%), Anorexia (4.76%), Skin reactions (14.28%), Peripheral neuropathy (4.76%), Dizziness (4.76%), Psychosis (4.76%), Ototoxicity (4.76%), Vertigo (4.76%), Arthralgia (4.76%)
Jeong (2009) ¹⁶	Korea	105	6 months	Supervised/ DOTS	6–8	5	57.00	Dermatologic (9%), GI trouble (8%), Arthralgia (6%), Visual change (6%), Hepatotoxicity (4%), Fatigue or malaise (6%), Dizziness (4%), Fever (1%)
Maciel (2010) ¹⁷	Brazil	79	2003–2006	Supervised/ DOTS	6	4	83.54	Joint pain (14.48%), Skin edema or irritation (or both) (8.54%), Memory loss (7.12%), Acne (6.88%), Itching (6.65%), Epigastric or abdominal pain (or both) (5.46%), Nausea or vomiting (or both) (4.98%), Muscle pain (4.41%), Headache (3.55%), Painful limbs (3.55%), Chest pain (2.74%), Somnolence (2.69%), Cough/sore throat/presence of secretion (2.69%), Pulmonary rhonchi or sounds (or both) (2.37%), Weakness/dyspnea (2.22%), Eye irritation (2.22%), Decreased visual acuity (2.22%), Dysuria (1.67%), Swelling of joints or bone (or both) (1.42%), Hepatomegaly (1.42%), Insomnia (1.42%), Petechiae or bleeding (or both) (1.42%), Alopecia (1.18%), Myalgia (1.18%), Loss of appetite (1.18%), Dizziness (1.18%), Adenopathy (0.94%), Intolerance to light (0.94%), Tremors (0.94%), Anemia (0.47%), Confusion or lack of attention (or both) (0.47%), Fever (0.47%), Lymph node enlargement (0.47%), Depression (0.23%), Sweats (0.23%)

Table 1 (Continued)

Study year	Location	Sample size	Study period	Type of regimen	Duration of treatment (months)	Number of drugs in regimens	Incidence of ADRs (%)	Profile of ADRs
Gillani (2012) ¹⁸	Malaysia	653	Jan 2008–Jun 2010	Supervised/ DOTS	6–12	4	15.8	Skin reaction-itchiness, rashes (7.8%), Gastrointestinal reactions-nausea, vomiting, GI upset (2.5%), Hepatotoxicity-hepatitis (2.6%), Central nervous system reactions-dizziness, headache (0.3%), Skin along with gastrointestinal reactions (0.8%), Skin along with central nervous system reactions (0.9%), Gastrointestinal along with central nervous system reactions (0.6%), Gastrointestinal along with skin reaction and muscle ache (0.2%), and Skin reaction along with flu like syndrome (0.2%)
Lv (2013) ¹⁹	China	4304	Oct 2007–Jun 2008	DOTS	6–9	5	17.33	Liver dysfunction (6.34%), Gastrointestinal disorders (3.74%), Arthralgia (2.51%), Allergic reactions (2.35%), Nervous system disorders including ototoxicity (2.04%), Hematologic system disorders (0.70%), Renal impairment (0.07%), Others (0.05%)
Sinha (2013) ²⁰	India	102	Jul 2009–Dec 2010	DOTS	6–9	5	69.01	Anorexia (31.58%), Vomiting (28.95%), Nausea (21.05%), Burning epigastrium (18.42%), Generalized weakness (16.9%), Liver dysfunction (15.49%), Allergic skin reactions (8.45%), Neurological (2.82%), Fever (2.82%)
Qureshi (2013) ²¹	India	50	1.6 years	DOTS (CAT 1)	6	4	60.00	Nausea (56%), Vomiting (30%), Dyspepsia (24%), Abdominal pain (20%), Loss of taste (14%), Diarrhea (4%), Malaise (16%), Jaundice (8%), Skin rash (2%)
Mandal (2013) ²²	India	83 (Intermittent regimen-43) (Daily regimen-40)	Jan 2010–Dec 2011	DOTS (Intermittent & daily regimens)	6–9	5	Intermittent regimen – 25.58 Daily regimen – 35.00	Intermittent regimen – Gastrointestinal disturbance (9.30%), Raised serum transaminase (6.98%), Clinical jaundice (2.32%), Vertigo (4.64%), Itching & rash (2.32%), Peripheral neuropathy (0.00%), Arthralgia (0.00%) Daily regimen – Gastrointestinal disturbance (15.00%), Raised serum transaminase (0.00%), Clinical jaundice (7.5%), Vertigo (0.00%), Itching & rash (5.00%), Peripheral neuropathy (2.50%), Arthralgia (5.00%)

Dalal (2014) ²³	India	150	Oct 2011–May 2013	DOTS	6–9	5	19.33	Gastrointestinal tolerance – Nausea/Vomiting/ Gastritis (12.67%), Itching without rash (1.3%), Itching with rash (1.3%), Arthralgia (2.67%), Peripheral neuropathy (1.3%), Drowsiness (1.3%), Hepatotoxicity (2%), Ototoxicity (0.67%)
Verma (2014) ²⁴	India	118	May 2013–May 2014	DOTS	6	4	38.14	Raised liver transaminases (33.33%), Nausea and vomiting (28.88%), Hepatitis (20%), Headache (20%), Rash (20%), Constipation (13.33%), Fever (13.33%), Flu-like syndrome (13.33%), Blurred vision and optic neuritis (11.11%), Hyperglycemia (11.11%), Diarrhea (8.88%), Peripheral neuritis (4.44%), Arthralgia 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%)
Farazi (2014) ²⁵	Iran	940	May 2010–Mar 2014	DOTS	6–9	5	Major – 5.8 Minor – 22.8	Hepato-biliary system (35.7%), Gastrointestinal tract (22%), Musculo-skeletal system (19.5%), Skin and appendages (15.3%), Peripheral nervous systems (3%), Hematologic system (1.2%), Ototoxicity (1.2%), Visual system (1.1%), Renal system (0.9%)
Sivaraj (2014) ²⁶	India	100	Jun 2003–Feb 2006	DOTS & Non-DOTS (50 each)	6–12	5	Group 1–58 Group 2–132	Group 1 – GIT (16%), Hepatotoxicity (8%), Hematological toxicity (8%), Dermatitis (12%), Fever/Flu like symptoms/Arthralgia/Gout (14%) Group 2 – GIT (32%), Hepatotoxicity (24%), Hematological toxicity (24%), Dermatitis (16%), Optic neuritis (4%), Ototoxicity (2%), Fever/Flu like symptoms/Arthralgia/Gout (30%)
Athira (2015) ²⁷	India	511	Jul 2013–Nov 2013	DOTS	6–9	5	18.20	Gastrointestinal problem (38.09%), Skin reaction (30.48%), Hepatotoxicity (14.28%), Arthralgia with hyperuricemia (1.90%), Hearing problem (0.95%), Vision problem (0.95%)

Note: Many authors have quoted different terminologies for describing various adverse drug reactions associated with anti-tuberculosis drugs. Therefore, these terminologies have been retained as described in abovementioned studies published by the authors. The reader may refer to these studies for further details.

hepatotoxicity was observed to be more in children receiving both INH and rifampicin. In a retrospective study of 430 children treated with both INH and rifampicin, hepatotoxicity was observed in 3.3%.⁴⁶ Transitory and asymptomatic increases in the serum levels of bilirubin and hepatic enzymes occurred in 5% of patients with Rifampicin. When Isoniazid was used in combination with Rifampin, the incidence of hepatitis was observed to be 2.7%. Cholestatic hepatitis occurred in 2.7% of the patients receiving Rifampin in combination with Isoniazid and was 1.1% when Rifampicin was received in combination with ATT other than Isoniazid.³⁹ Pyrazinamide is the most hepatotoxic of the drugs.^{44,47} Studies from Nepal reported the incidence of hepatotoxicity in patients receiving ATT to range from as 8% to 35%.^{48,49} In a study in Pakistan, it was found that ATT-induced hepatotoxicity was seen in 67 (19.76%) out of 339 patients and was seen more common in smear AFB-negative patients.⁵⁰ However, incidence of hepatotoxicity from studies from Brazil and Japan was similar to Indian population.^{51,52} The risk of hepatotoxicity from ATT drugs was influenced by clinical and genetic factors.⁵³ In a study done by Singh et al., ATT-induced hepatotoxicity presented as jaundice in 61% patients followed by prodromal symptoms in 39% and life-threatening complications in 16.6%.⁵⁴ Studies have also observed that 0.01% of patients taking ATT are at a risk of developing Acute liver failure (ALF) and the contribution of ATT in magnitude of ALF population may be even higher in countries in which tuberculosis as well as hepatitis virus(es) are endemic.^{39,55} In the study conducted in nearly 1200 acute liver patients in India, ATT was the cause in 5.6% of cases and three-fourths (76%) of ATT-ALF patients died within 5 days of hospitalization.⁵⁶

6. Peripheral neuropathy

Peripheral neuropathy occurs in approximately 20% of patients treated with Isoniazid.¹³ This was similar to findings of a study in Pakistan where peripheral neuropathy characterized by tingling and burning sensation in the hands and feet was the commonest ADR observed with Isoniazid. The other anti-TB drug known to cause peripheral neuropathy is Ethambutol, but very rare in comparison to Isoniazid. In a study conducted by Koju et al., peripheral neuropathy was experienced by only 18.57% of the patients.⁵⁷ In the existing literatures also, occurrence of peripheral neuropathy is considered rare with the recommended doses of Isoniazid used in DOTS strategy. In a study of 893 patients by Shinde et al., on patients started on first-line ATT, it was observed that 5.04% of patients had peripheral neuropathy and 0.22% had acute psychosis.³⁵

7. Psychiatric disorders

Isoniazid-related psychiatric disorders can manifest as psychosis, obsessive-compulsive neurosis, and mania, loss of memory and death.⁵⁸ The first description of psychotic symptoms due to Isoniazid was by Mandel et al., who reported three such cases in 1956.⁵⁹ The mechanism of production of isoniazid-related psychiatric disorders is not clearly known, but Isoniazid is known to interfere with several metabolic

processes essential for the normal functioning of the neuron. Isoniazid causes deficiency of vitamin B₆ by causing excessive excretion of the vitamin, which in turn leads to a disturbance of normal tryptophan metabolism. There is great variability in the clinical features of Isoniazid-induced psychosis in the various reported cases. Jackson, in 1957, reported five cases of Isoniazid-induced psychosis that presented with excessive argumentation, mental depression, euphoria, grandiose ideas, and complex delusions; none of these patients had any previous history of mental illness.⁶⁰ Agarwala et al. reported symptoms of restlessness, irritability, emotional instability, agitation, apprehension, and fluctuation in behavior after Isoniazid therapy.⁶¹ Bedi et al. reported a case of Isoniazid psychosis in a 74-year-old, who developed restlessness, irritability, aimless activity, and incongruous actions 10 days after starting isoniazid therapy.⁶² Tiwari et al. reported a case of Isoniazid-induced psychosis with disturbed sleep, restlessness, and abnormal behavior. The durations of psychotic symptoms in these case reports varied widely, i.e. 7–45 days, 7 days, 10 days, and 120 days.⁶³ A review of all cases of drug-induced seizures reported to the California Poison Control System revealed that of 386 cases, 23 (5.9%) were due to Isoniazid.⁶⁴ In a study of 83 healthcare workers who received a 6-month course of Isoniazid, 34 (41%) developed an ADR. In 26 of these 34 patients, toxicity resulted in discontinuance of therapy.⁶⁵ Toxic psychosis developed while under treatment with Isoniazid in 5 cases seen at Louisiana.⁶⁶ In Peru, severe psychiatric syndrome occurred in approximately 1% of tuberculosis cases between 1991 and 1999.⁶⁷ In Turkey, out of 1149 patients with established tuberculosis who initially received ATT therapy, neuropsychiatric manifestations were observed in 0.7% of patients.²

8. Retro-bulbar neuritis

Ethambutol is one of the important first-line drugs in the treatment of tuberculosis. Carr and Henkind et al. first described the ocular ADRs of Ethambutol therapy in 1962.⁶⁸ Retro-bulbar neuritis is the most important potential ADR from Ethambutol. It is reversible in most cases and is related to the dose and duration of treatment, but may occasionally become irreversible resulting in permanent visual disability, especially in the older population.⁶⁹ The reported incidence of retro-bulbar neuritis when Ethambutol is taken for more than 2 months is 18% in subjects receiving greater than 35 mg/kg/day, 5–6% with 25 mg/kg/day, and less than 1% with 15 mg/kg/day.^{70,71}

9. Ototoxicity

Streptomycin predominantly affects the vestibular system. Audiometry data suggest that the incidence of ototoxicity may be as high as 25%.⁷² Prazic and Salaj et al. found audiologically defined lesions in 36% of a group of 975 children treated with Streptomycin sulphate for pulmonary tuberculosis.⁷³ Hearing loss has also been reported in infants of tuberculous mothers treated with streptomycin during pregnancy.⁷⁴ Familial occurrence of drug-induced toxicity has also been reported.⁷⁵

In a large Indian study with short course chemotherapy regimes in the treatment of patients with pulmonary tuberculosis, 16.1% of the patients given Streptomycin developed vertigo which was severe in 5% cases.⁷⁶ In 10% of these patients, the drug had to be stopped. Reduction of dosage was needed in about 20%. In another series of 1744 patients treated with various ATT, 10.3% developed intolerance to streptomycin. Involvement of the VIII cranial nerve was the commonest (46.8%) untoward reaction.⁷⁷ Neff et al reported intolerance to streptomycin in 12.9% of their cases. In this series, also, vestibular and auditory dysfunction was the commonest.⁷⁸

10. Immunological and hematological ADRs

In a Brazilian study, Rifampicin-induced thrombocytopenia, leukopenia, eosinophilia, hemolytic anemia, agranulocytosis, vasculitis, acute interstitial nephritis, and septic shock occurred in 0.1% of the patients.^{39,79} However, few Asian studies reported allergic reactions with first-line ATT to be between 2.02% and 2.35% and hematological adverse effects to be 0.1–0.7%. Author in his work on hematological abnormalities during ATT found that thrombocytopenia, characterized by a rapid lowering of the platelet count in sensitive individuals was observed. Generally, the most common offending agent for the causation of thrombocytopenia secondary to anti-tubercular drugs is Rifampicin.^{80–82} Isolated case reports showing thrombocytopenia following administration of Pyrazinamide,^{80,83} Isoniazid, Ethambutol are found in literature and are attributed to an immunological phenomenon. Streptomycin is very rarely implicated as a cause of thrombocytopenia. Kant et al. reported thrombocytopenia secondary to Rifampicin, Ethambutol, and Pyrazinamide in a single individual.⁸⁰

11. Arthralgia

Pyrazinamide and ethambutol are two anti-tuberculous drugs that have been reported to induce hyperuricemia in non-gouty patients leading to arthralgia.⁸⁴ The metabolite pyrazinoic acid is likely responsible for the hyperuricemic effect. The mechanism is related to pyrazinoic acid, the principal metabolite of pyrazinamide oxidized by xanthine oxidase, which inhibits the renal tubular secretion of uric acid.⁸⁵ Hyperuricemia has been reported in 43–100% of patients treated with pyrazinamide (alone or in combination).⁸⁶ Gouty attacks have also been associated with patients taking pyrazinamide. Ethambutol can also cause hyperuricemia by decreasing renal uric acid clearance, but it does so less consistently and to a lesser degree than pyrazinamide. In a study by Dhingra et al. on patients receiving DOTS therapy general aches and pains were complained by about 35%.¹⁰ However, in a study by Shinde et al., arthralgia was seen in 0.67%³⁵ which was lower in comparison to reported incidence of 2.57% in Chinese patients receiving ATT.¹⁹

12. Renal toxicity

Aminoglycosides produce renal toxic effects due to their accumulation in the renal tubules. Such effects are more

common in elderly individuals and in patients with a history of kidney disease. The risk of nephrotoxicity is less and range around 2% while using streptomycin.^{87,88}

13. Cutaneous ADRs (CADRs)

Pyrazinamide has been described to cause various skin reactions like maculopapular rash, erythema multiforme, exfoliative dermatitis, and DRESS syndrome. Among the first-line drugs, pyrazinamide is the commonest cause of CADR (2.38%), followed by streptomycin (1.45%), ethambutol (1.44%), rifampicin (1.23%), and isoniazid (0.98%).^{3,89} It is not uncommon for exfoliative dermatitis to occur with more than one of the four drugs. It is unclear whether renal failure predisposes to increased occurrence of CADRs. So far, no definite association exists between preexisting renal insufficiency and increased incidence of CADRs. The incidence of ethambutol induced rash is found to be 0.5%.⁹⁰ The author reported a rare occurrence of exfoliative dermatitis secondary to ethambutol and pyrazinamide in a 18-year-old female.⁹¹ Patients receiving Isoniazid can develop antinuclear antibodies during the use of the drug. Less than 1% develops systemic lupus erythematosus, the incidence of which is the same in both genders. Isoniazid administration can also worsen pre-existing lupus.⁹²

14. Other ADRs

Few case reports on Isoniazid-induced gynecomastia among patients treated with ATT.^{93,94} A rare occurrence of anaphylactic shock due to streptomycin was also reported.⁹⁵

15. Conclusion

The treatment of tuberculosis can cause a variety of ADRs. Accurate diagnoses and knowledge of the pharmacological properties of the drugs involved will allow professionals to tailor their approach to each individual case in near future.

Conflicts of interest

The authors have none to declare.

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