

Anti-tuberculosis treatment: induced hepatotoxicity – a case report

Poludasari Shravan Kumar, Rachakonda Vidya, Tabassum, Manashwini Jageer

Department of Pharmacy Practice, Malla Reddy Pharmacy College, Dhulapally, Secunderabad,
Telangana, India

ARTICLE INFO

Corresponding author:

Poludasari Shravan Kumar
Department of Pharmacy Practice
Malla Reddy Pharmacy College
Dhulapally, Secunderabad
Telangana
India
Phone: +919553285713
E-mail: poldasarisravan@gmail.com

Key words:

pulmonary tuberculosis, hepatotoxicity,
adverse drug reaction, direct observation
therapy

ABSTRACT

Tuberculosis is a potentially communicable disease that can infect any organ in the body such as bones, kidney, intestine but primarily involves lung parenchyma (Pulmonary tuberculosis). The prevalence of TB is 256 per 100,000 population in India. Hepatotoxicity, gastrointestinal and neurological disorders were some the Adverse Drug Reactions (ADR's) reported that significantly increases the mortality rate which leads to decreased efficacy of the treatment. Hepatotoxicity is the most commonly reported ADR in patients treated with anti-tubercular drugs such as isoniazid, rifampicin and pyrazinamide. Clinical manifestations of hepatotoxicity include abdominal pain, nausea, vomiting, and jaundice. We report the case of a 19-year-old female with complaints of yellowish discoloration of sclera for 45 days associated with vomitings for one week. She had a past medical history of tuberculosis for which she was advised with DOT (Direct Observation Therapy) regimen. A diagnosis of Anti-Tuberculosis Treatment (ATT) - induced hepatotoxicity was made based on the clinical examination and laboratory investigations which was successfully managed by providing supportive care and symptomatic treatment.

INTRODUCTION

Tuberculosis is a potentially communicable disease that can infect any organ in the body, such as bones, kidney, and intestines, but primarily involves lung parenchyma (Pulmonary tuberculosis). *Mycobacterium tuberculosis*, a purple coloured rod-shaped bacterium, is responsible for tuberculosis infection and is spread by droplets of an infected person. Signs and symptoms of tuberculosis include excessive cough with sputum (In severe conditions blood is also seen along with sputum), weight loss, anorexia, fever and night sweat. The prevalence of TB is 256 per 100,000 population in India. Results of various studies concluded that almost 80% of TB cases are completely curable with an effective regimen of Direct Observational Therapy (DOT). Hepatotoxicity, gastrointestinal and neurological disorders were some of the ADRs reported that significantly increases the mortality rate which leads to decreased efficacy of the treatment.

Hepatotoxicity is the most commonly reported ADR in patients treated with anti-tubercular drugs such as isoniazid, rifampicin and pyrazinamide (1). Reports of various studies reveal that anti-tubercular therapy (ATT) induced hepatotoxicity is seen in 5-28% of the patients treated with anti-tubercular drugs (2). Reports of liver function test in ATT induced hepatotoxicity reveals a threefold increase of liver enzymes ALT (Alanine Transaminase) and AST (Aspartate transaminase). Clinical manifestations of hepatotoxicity include abdominal pain, nausea, vomiting, and jaundice. Reports of liver biopsy revealed lobular hepatitis, sub massive to massive necrosis and hydropic degeneration of hepatocytes in severe cases. One hypothesis state that an inflammatory reaction results in production of bacterial lipopolysaccharides which act in combination with drug metabolites to cause hepatotoxicity.

CASE REPORT

A 19-year-old female patient who was a known case of tuberculosis started upon ATT for the previous two months. She discontinued medication for 20 days, restarted medication for TB, continued for 10 days and discontinued again. Then she came to the hospital with chief complaints of yellowish discoloration of sclera for 45 days associated with vomitings for one week. As she had been previously diagnosed with TB, she was prescribed with a combination of Isoniazid (75 mg), Rifampicin (150 mg), and pyrazinamide (400 mg).

After a few days of therapy, the patient experienced symptoms of loss of appetite, constipation and pale skin. Ignoring the symptoms, she continued to take the drugs, which resulted in worsening symptoms such as yellowish discoloration of sclera and vomitings, after which she stopped taking the drugs used in ATT therapy. On examination her vitals were normal and examination of liver parameters were as detailed in Table 1. Serological examinations for hepatitis-B, hepatitis-C, and HIV were negative. Microbiological examination for acid fast bacilli was also found to be negative. No abnormality was detected in the sonography of the abdomen and pelvis (bed side). Chest radiograph, PA view revealed sub-segmental atelectasis noted in the left mid zone. Patient CBP and CUE were found to be normal.

The physician advised the following medications (Table 1) following the cessation of anti-tubercular drugs. Alternative drugs such as streptomycin, ethambutol, levofloxacin were prescribed for treatment of TB. Patient was diagnosed with ATT induced hepatotoxicity with marked elevations of bilirubin (hyperbilirubinemia) and increased hepatocellular enzymes (SGOT, SGPT, ALP). Laboratory values of liver function test on different days are shown in Figure 1 and Figure 2, respectively.

Table 1 Medication chart

Brand name	Generic name	Dose
Inj Zofer	Ondansetron	4 mg
Tab Udiliv	Ursodeoxycholic acid	300 mg
Hepamerz sachets	L aspartate granules	3 gm
Syp Lactulose	Lactulose	15 ml

Figure 1 Reported values of various liver enzymes [ALP, SGOT AND SGPT] on different days during hospitalisation

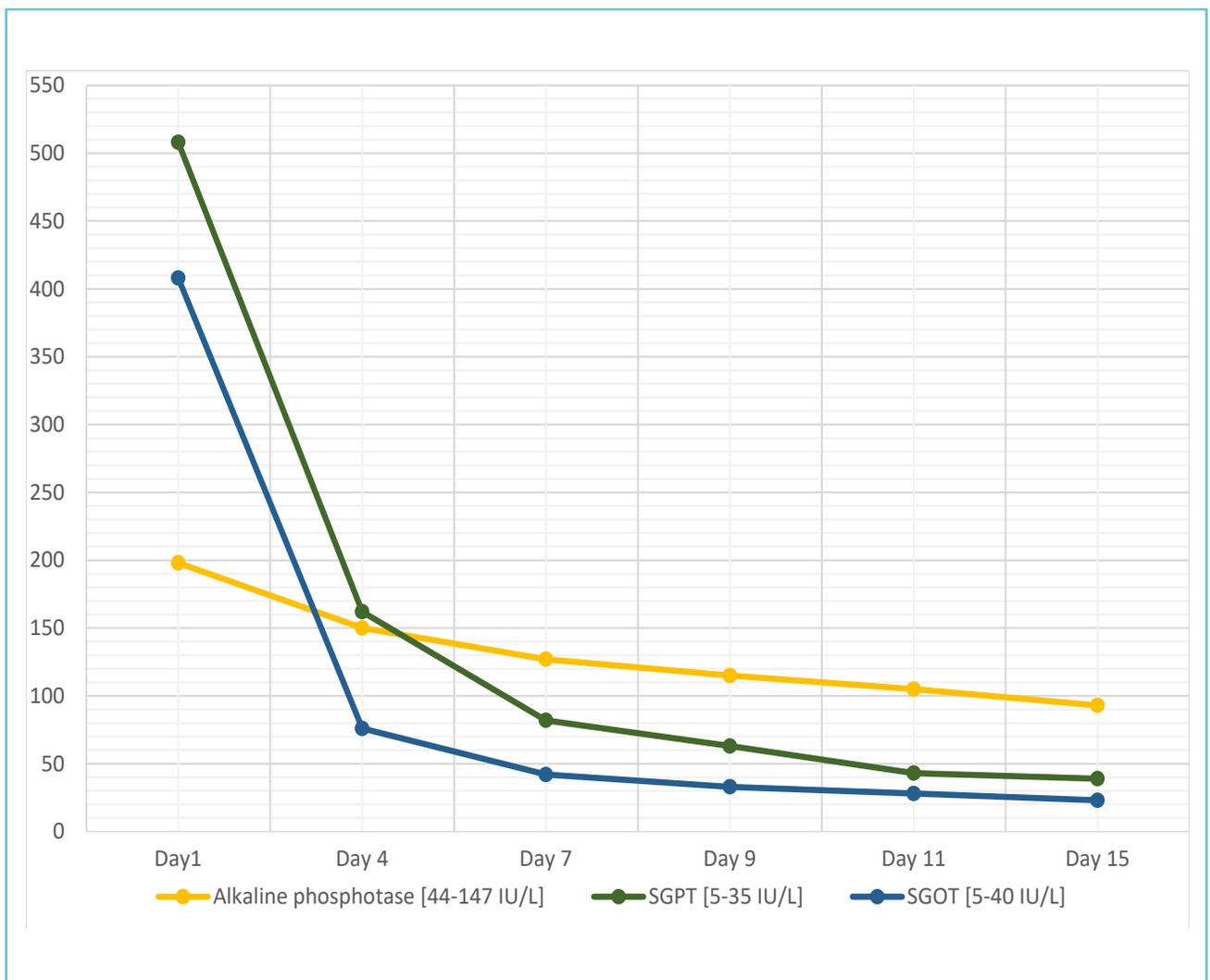
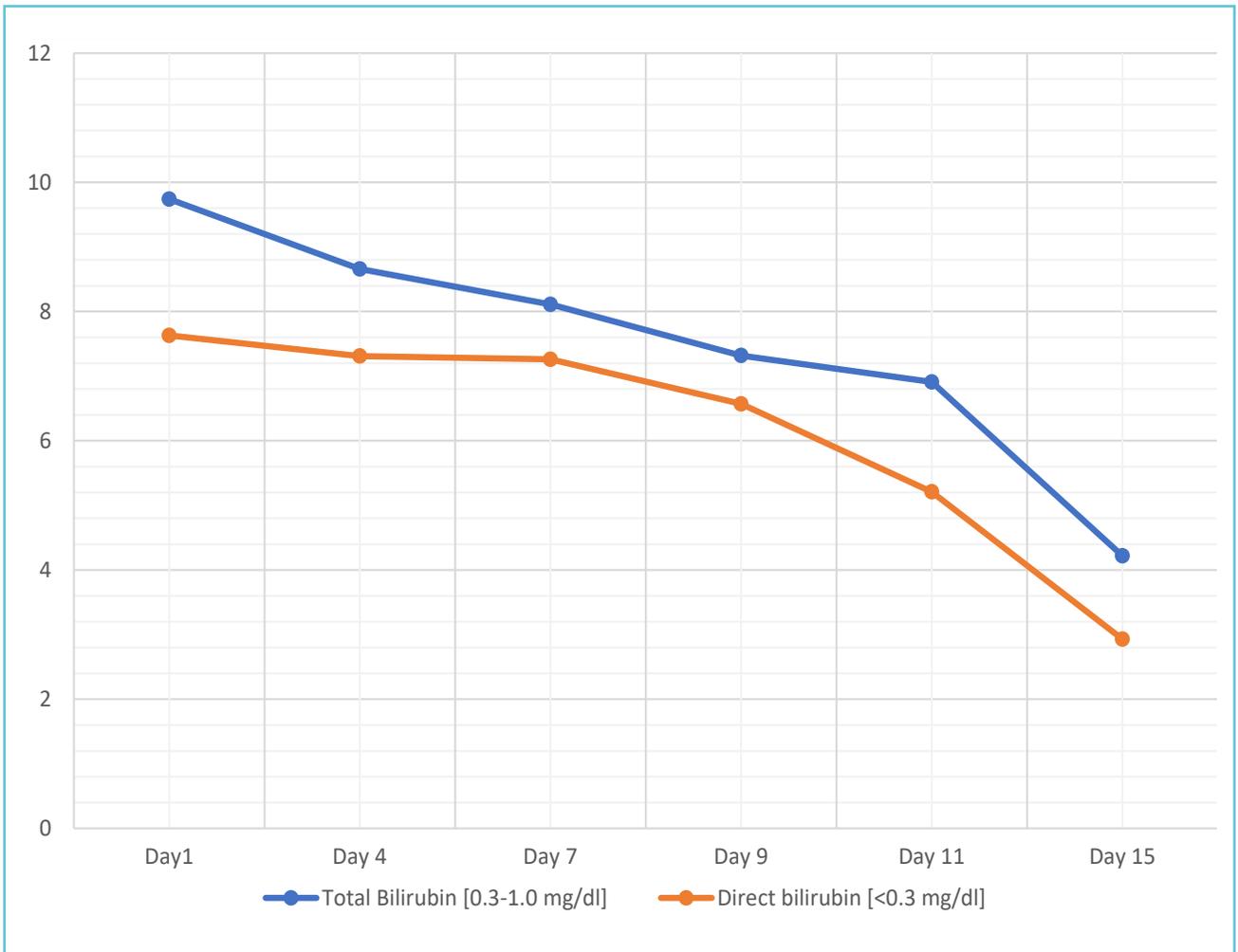


Figure 2 Reported values of bilirubin on different days during hospitalisation



DISCUSSION

Currently, there are 10 drugs approved by the U.S. FDA for the treatment of tuberculosis, namely: Isoniazid, Rifampin, Pyrazinamide, Ethambutol, Rifapentine, Streptomycin, Cycloserine, Capreomycin, P-Aminosalicylic acid, Ethionamide. Fluoroquinolones such as Levofloxacin, Moxifloxacin and Gatifloxacin are also used in the treatment of drug resistant tuberculosis and in patients who are unresponsive to first line drugs, even though they are not approved by FDA for treatment of tuberculosis (3). Tuberculosis is a mycobacterial disease, treatable with anti-tubercular therapy. Commonly used drugs are Isoniazid,

Rifampicin, pyrazinamide and Ethambutol. All these drugs are used in combination for a few months (2-6 months).

According to a study, the incidence of drug induced liver injury in India is between 8-36%. Incidence of drug induced hepatotoxicity is higher in Asian countries due to ethnic susceptibility, unusual drug metabolism and due to other risk factors, such as alcoholism, malnutrition and other infections such as hepatitis B (4).

Isoniazid causes peripheral neuropathy and hepatotoxicity (elevated serum transaminases and serum bilirubin), Rifampicin causes immune-allergic reactions and hepatotoxicity (elevated

serum transaminases, alkaline phosphate and serum bilirubin), pyrazinamide causes joint pains (increased serum uric acid) and hepatotoxicity (elevated serum transaminases and serum bilirubin).

These three drugs isoniazid, rifampicin and pyrazinamide have high potential of inducing hepatotoxicity and clinical manifestations of hepatotoxicity include nausea, vomiting, weakness, fatigue and yellowish discoloration of eyes. These side effects can be due to one/two or all of the 3 drugs and some of the patients are not able to tolerate these and as a result stop taking anti-tubercular drugs which leads to decreased effectiveness of the treatment. Hepatotoxicity with ATT drugs increases with following factors such as concomitant usage of other hepatotoxic drugs, age, alcohol abuse and pre-existing liver disease. According to a study, pyrazinamide is 3 times more potent than isoniazid or rifampicin in precipitating serious adverse events (5).

In the present condition, the patient was on a therapy with the ATT drugs like Isoniazid, Rifampicin and Pyrazinamide for two months. After a few days of therapy, she produced signs of loss of appetite, constipation and pale skin. Later, the patient developed signs such as yellowish discoloration of sclera and vomitings.

The pathophysiology of ATT induced hepatotoxicity is explained by four different mechanisms which include direct toxicity, idiosyncratic damage, induction of liver enzymes and allergic reactions.

Direct toxicity is due to production of free radicals which damages the liver tissue and this is dose related. Idiosyncratic damage is due to hypersensitivity reactions and may be a genetic or acquired variations in the metabolic pathway. Induction of liver enzymes may increase the hepatotoxic potential of the drugs. Allergic reaction is caused due to a reactive metabolite.

CONCLUSION

In summary, this is a case of a patient who developed hepatotoxicity following the intake of anti-tubercular drugs which is managed by providing supportive care. It is essential to educate the patients about the possible ADRs associated with the drugs used in the treatment of tuberculosis. Physicians must counsel their patients about signs and symptoms of hepatotoxicity and encourage them to report them as soon as possible.

TAKE HOME MESSAGES/ LEARNING POINTS:

- In pulmonary tuberculosis, a Sputum smear test should be performed once every two or three months to monitor the progression of disease until the end of treatment. If smear test was found positive, the patient must be reevaluated and effectiveness of therapy must be considered.
- Patient should be advised to take full course of treatment although patient might feel better after taking medications for a short span of time.
- Patients advised with DOT therapy is recommended to undergo frequent liver function check-ups, which include serum bilirubin, aminotransferases, alkaline phosphatase as most of the drugs used in DOT therapy has the potential to induce hepatotoxicity.



Authors' contributions

Shravan and Vidya: Collection of the data and preparation of manuscript.

Tabassum and Manashwini: Review of literature and edited the manuscript.

REFERENCES

1. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Eur Respir J*. 1996 Oct;9(10):2026-30. doi: 10.1183/09031936.96.09102026. PMID: 8902462.
2. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM; U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002 Dec 17;137(12):947-54. doi: 10.7326/0003-4819-137-12-200212170-00007. PMID: 12484709.
3. Chapter 6: Treatment of tuberculosis disease-Center for Disease Control can be accessed from <https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf>.
4. Singla R, Sharma SK, Mohan A, Makharia G, Sreenivas V, Jha B, Kumar S, Sarda P, Singh S. Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity. *Indian J Med Res*. 2010 Jul;132:81-6. PMID: 20693595.
5. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med*. 2003 Jun 1;167(11):1472-7. doi: 10.1164/rccm.200206-626OC. Epub 2003 Jan 31. PMID: 12569078.