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Case Report

## Hepatotoxicity Induced by Anti-Tubercular Drugs Therapy: A Case Report

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### ABSTRACT

Anti-tubercular therapy induced liver injury (ATTILI) is the most important risk for the past many years. Many pre-existing factors and conditions like persisting liver injury, female gender, alcohol abuse etc. are important risk factors for the ATT induce liver injury. I read many case reports and literature review for the drugs induce liver injury, and concluded the results, ATT drugs are the most responsible for the liver injury during the therapy periods. The present case was 42-year-old male patient and known case of pulmonary tuberculosis, patients were on the ATT drugs therapy in the last 14 days. After few days of therapy, he produced signs of vomiting (multiple episode), fever (high grade), abdomen pain, coughing, loss of appetite, epigastric discomforts & generalized weakness. On general examination the patient was found to produce signs of Jaundice with yellowish appearance of the sclera. Pulmonologist had firstly withdrawal the anti-tubercular drugs therapy and started the modified anti-tubercular drugs therapy. As a Clinical pharmacist we advise the patients & patients relatives, proper monitoring of liver and renal function test should also be carried out by the health care professional specialist from time to time in order to avoid critical situations.

**Keywords:** Anti-tubercular therapy, Anti-tubercular therapy induced liver injury, Pulmonologist, Hepatotoxicity.

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### INTRODUCTION

Drug-induced liver injury (DILI) is a minor but more significant cause of liver injury across all regions. The incidence rate of anti-tubercular drugs induced hepatotoxicity was found to be 2% to 28% based on hepatotoxicity diagnosis criteria. Antitubercular drug-induced liver injury (ATDILI) is a leading cause of DILI and drug-induced acute liver failure in India and much of the developing world. The clinical manifestation of tuberculosis is characterized by excessive cough, sputum production, unintentional weight loss and loss of appetite, coughing up blood or mucous along with weakness, fatigue, fever, night sweats. It was diagnosed by mantoux skin test, blood test for the presence of Mycobacterium tuberculi, X-ray for the presence of white patches within the lungs <sup>1,2</sup>. Anti-

tubercular drugs like isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) together the cause of defects in liver injury. The abnormalities in SGOT (Serum Glutamate Oxaloacetate Transaminase), SGPT (Serum Glutamate Pyruvate Transaminase) enzymes may lead to hepatitis or liver injury or hepatotoxicity. Hepatitis and hepatotoxicity depend upon the drugs & dose <sup>3</sup>. The enzymes produced by the liver plays a dynamic role in hepatotoxicity (over or under production). From first line anti-TB drugs, isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) causes hepatotoxicity such as transaminasitis and fulminant hepatic failure <sup>4,5</sup>.

Factors implicated in the development of antitubercular treatment induced hepatotoxicity: Advanced age, female sex, alcoholism, underlying liver disease, acetylator phenotype,

N-acetyltransferase (NAT) activity, glutathione S-transferase activity, hepatitis B & C virus, HIV infection, extensive disease, malnutrition have also been observed to be risk factors for the development of the drugs induced hepatotoxicity<sup>6,7,8</sup>.

### CASE STUDY

- ❖ A 42-year-old male, weighing 56 kg who was suddenly came to the emergency department of hospital with the chief complaints of vomiting (multiple episode), fever (high grade), abdomen pain, coughing, loss of appetite & epigastric discomforts.
- ❖ He had a known case of Pulmonary Tuberculosis it means 2 weeks before pulmonologist had diagnosed PTB. He was taking regular first line anti-tubercular drug therapy like Isoniazid, Rifampicin, Pyrazinamide and Ethambutol for last 15 days.
- ❖ Patient had a social and family history of alcoholic & smoking. But patient had occasionally taking alcohol & smoking it means patient had not addicted for alcohol and smoking.
- ❖ He had no past history & family history of hypertension (HTN), diabetes mellitus (DM), thyroid & pulmonary tuberculosis (PTB).
- ❖ On examination the patient was conscious, opening of eyes in response to painful stimuli. At the time of general physical examination PR- 96 bpm, BP-100/70 mmHg, oxygen saturation 92% at the room air and cardiac sounds S1, S2 were positive is noted & abdominal examination revealed epigastric tenderness.
- ❖ At the time of observation Pulmonologist were observed to produce signs of Jaundice with yellowish appearance of sclera. Then pulmonologist was advice the patient for routine laboratory test like CBCs, LFTs, KFTs, USG whole abdomen, Chest X-RAY & viral

serological test. Patients had need for adequate prophylactic treatment to reduce the risk of active TB.

- ❖ On the same day, pulmonologist prescribed the following drugs to the patient after examination:

1. Injection Pantoprazole - 40mg TDS
2. Injection Ondansetron 2mg TDS
3. Hold the CAT Ist ATT medication therapy and then started modified anti-tubercular therapy regimens i.e. Streptomycin 0.75 gm, Levofloxacin 750 mg, Ethambutol 800 mg.
4. Tablet Hepamerz (L-Ornithine + L-Aspartate) 5mg (1Tab) BD
5. Tablet Levocetirizine - 5mg HS
6. Syrup Liv-52 2tsf TDS
7. Nebulization
8. 4 Bottle normal saline IV – 100 ml/hour

- ❖ On the 2nd day, Blood pressure were recorded as 110/70 mmHg and pulse rate was 85/min. then laboratory reports were collected, according to the laboratory reports patient liver function test (LFT) count was abnormal in the normal limits. However, levels of liver enzymes were extremely elevated, with an aspartate aminotransferase (AST) level of 345 IU/L, alanine aminotransferase (ALT) level of 423 IU/L, alkaline phosphatase (ALP) level of 182 IU/L, total bilirubin level of 2.5mg/dl, direct bilirubin 1.9 mg/dl. Viral markers for hepatitis including hepatitis A, B and C viruses, and human immunodeficiency virus (HIV) all were negative. Chest X-ray was shown non-homogenous opacity with air bronchospasm noted in right lobe suggestive of consolidation. (Table-1 & Fig.1)

**Table 1: Laboratory Investigation**

S. N.	Parameter	Test value (Day-1)	Test value (Last Day)	Normal value
1.	SGOT	345	69	17-59 IU/L
2.	SGPT	423	58	9-52 IU/L
3.	ALP	182	138	38-126 IU/L
4.	Total Bilirubin	2.5	1.4	0.2-1.3 mg/dl
5.	Direct Bilirubin	1.9	0.6	0.0-0.8 mg/dl



**Figure 1: Chest X-Ray**

- ❖ On the 3<sup>rd</sup> day, patient complaint of whole-body ache, fever and nausea, so doctors prescribed with tablet paracetamol 500 mg SOS for the fever and body ache. Blood pressure was normal i.e. 120/70 mmHg and pulse rate were 76 beats/min with SPO2 concentration 99.2%.
- ❖ On the 4<sup>th</sup> day, patients complain loss of appetite, bitter in mouth & taste, Pulmonologist was done the nutritional assessment and the patient was on soft liquid, diet, food, moderate protein and low-fat liquid and same treatment was continued. Pulmonologist had made a provisional diagnosis of anti-tubercular drug induced hepatotoxicity.
- ❖ On 5,6,7<sup>th</sup> day, no fresh complaints were seen and temperature was normal, blood pressure was 110/70 mm/hg, respiratory rate was 22 beats/min, pulse rate was 78 beats/min with SPO2 concentration 98%. All liver function tests (LFT) reports were found normal.
- ❖ On 8<sup>th</sup> day, upon normalization of patient conditions, pulmonologist stopped the modified ATT therapy, and then started the CAT 1<sup>st</sup> DOTS Therapy (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Pyridoxine) with proper monitoring of routine LFT investigation.
- ❖ On 9,10<sup>th</sup> day, no fresh complaints were seen and temperature was normal, blood pressure was 110/70 mm/hg, respiratory rate was 24 beats/min, pulse rate was 79 beats/min with SPO2 concentration 99%. Then pulmonologist made the final diagnosis as the based-on case assessment of anti-tubercular drugs induced hepatotoxicity.
- ❖ Staying 11<sup>th</sup> days in hospital, patient was discharge with appropriate medication chart and patient counselling. The discharge medication includes:
  1. Tablet Isoniazid 300mg OD - (4 months)
  2. Tablet Rifampicin 450mg OD - (4 months)
  3. Tablet Ethambutol 800mg OD - (4 months)
  4. Tablet Pyrazinamide 1200mg OD - (4 months)
  5. Tablet Pyridoxine 20 mg OD (HS) - (4 months)
  6. Syrup Liv-52 2 TSF, TDS
  7. Tab Pantoprazole 40 mg OD, BBF
  8. Review after one months in OPD with the LFT reports.

## DISCUSSION

Anti-tubercular drugs induced hepatotoxicity is common in the tuberculosis patients. It is a serious problem and it was reported that 2-28% of TB patients experiences drug related hepatotoxicity during the treatment of patients. Incidence rate of the TB patients in India is 8-36%. According to the many studies, overall incidence of serious adverse effects was three time higher with pyrazinamide then with isoniazid or rifampicin. Almost all the anti-tubercular drugs are metabolized by the liver and when the therapy lasts for a long time there are increased chances of hepatotoxicity and liver injuries<sup>9,10</sup>.

In this case study, a 42-year-old male patient weighing 56 kg who was Suddenly came to the emergency department of hospital. He had a known case of Pulmonary Tuberculosis. He was taking regular first line anti-tubercular drug therapy for last 15 days. Patient had social and family history of smoker and alcoholic. But patient was occasionally taking alcohol & smoking it means patient was not addicted for alcohol and

smoking. Patient had no past history & family history of hypertension (HTN), diabetes mellitus (DM), thyroid, pulmonary tuberculosis (PTB). In the emergency department junior resident doctor were examination the patient he was conscious, opening of eyes in response to painful stimuli. At the time of general physical examination PR- 96 bpm, BP-100/70 mmHg, oxygen saturation 92% at the room air and cardiac sounds S1, S2 were positive noted and observed the signs of Jaundice with yellowish appearance of sclera. Then pulmonologist was advice the patient for routine laboratory test like CBCs, LFTs, KFTs, USG whole abdomen, Chest X-RAY & viral serological test. Pulmonologist need for adequate prophylactic treatment to reduce the risk of active TB was explained to the patient. Staying 8<sup>th</sup> days in hospital, upon normalization of patient conditions, pulmonologist stopped the modified ATT therapy, and then started the CAT 1<sup>st</sup> DOTS Therapy (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Pyridoxine) with proper monitoring of routine LFT investigation. On 9,10<sup>th</sup> day, no fresh complaints were seen and temperature was normal, blood pressure was 110/70 mm/hg, respiratory rate was 24 beats/min, pulse rate was 79 beats/min with SPO2 concentration 99%. Then the pulmonologist was made the final diagnosis as the case of anti-tubercular drugs induced hepatotoxicity. On 11<sup>th</sup> day, patient was discharge with appropriate medication and patient counselling.

In this case study highlights anti-tubercular drugs therapy (ATT) induced Hepatotoxicity. During the follow-up, after initiation of ATT regimen the patient liver function tests was found to be abnormal and it is suspected as anti-tubercular drugs therapy induced Hepatotoxicity, which is effectively managed by with drawl of causative drugs (Isoniazid and Rifampicin, Pyrazinamide). INH and RIF are the common drugs and mainly used in the treatment of tuberculosis. The effectiveness of therapy with these drugs is about 25-92%. Minimum duration for INH therapy is for 9 months and some strategies follow a 4-month therapy with INH and 2 months RIF therapy. Other alternatives include RIF therapy for 4 months and RIF or PYZ therapy for 2 months. In all these cases the adverse effects and resistance towards these drugs are very much higher. Hence recent studies suggest a combined therapy with INH-RIF for about 3-4 months producing excellent therapeutic activity. The rate of hepatotoxicity by INH-RIF therapy is about 2.6% while it is low with its individual therapy, 1.1% and 1.6% respectively. Isoniazid and Rifampicin when given together acts upon the P450 enzymes, INH induces the formation of acetyl hydrazine which covalently binds with liver proteins. Hepatotoxicity with ATT drugs increases as concomitant other hepatotoxic drugs are administered, female gender, age, alcohol abuse, pre-existing liver disease etc. This is one of the major exacerbating factors<sup>11,12</sup>.

## CLINICAL PHARMACIST ROLE

As a clinical pharmacist we need to be made aware of these potentially fatal adverse effects associated with anti-tubercular therapy via conduction of quality-based seminars, conferences, published medical literature and learning programmes and health care camps. The following strategies must be followed in order to prevent and minimize the morbidity & mortality of ADR associated with anti-tubercular drugs therapy:

- ✓ LFTs must be done, before and after the initial start-up drugs therapy and to analyse the enzymatic conditions of liver.
- ✓ Face to face monthly assessment and patient education for adverse drug events are essential.

- ✓ Health education must be provided to the patients undergoing anti tubercular drugs therapy on the action of the drugs and the side effects associated. This would help the patients identify the symptoms and immediately stop the therapy and take it to pulmonologist notice.
- ✓ The patients must report if loss of appetite, nausea, vomiting, jaundice appear during the course of treatment.
- ✓ ATT must be withdrawn if any suspicious signs and symptoms appear. ATT therapy is not to be continued until jaundice or hepatotoxicity is diagnosed.

### CONCLUSION

- ✓ The Pulmonologist and Clinical Pharmacists could help the patients out by making them understand the adverse effect and side effects of each drugs so that immediate withdrawal of the drug could be done by the patient itself and letting it know to the pulmonologist. This would prevent the further worsening of the condition, remaining as the exacerbating condition in most of the cases.
- ✓ We need to monitor the vitals, LFTs & other risk at regular intervals during the therapy. As a clinical pharmacist role, we prevent and minimize drug induced complications & ADRs, Proper patient counselling & education is most important for the better management of patients.

### ABBREVIATIONS

TB: Tuberculosis

ATT: Antitubercular Therapy

INH: Isoniazid

RIF: Rifampicin

PYZ: Pyrazinamide

SGOT: Serum Glutamate Oxaloacetate Transaminase

SGPT: Serum Glutamate Oxaloacetate Transaminase

DILI: Drug Induced Liver Injury

ADR: Adverse Drug Reaction

HIV: Human Immunodeficiency Virus

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