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# A CLINICAL CASE REPORT ON PREDICTABLE DRUG-INDUCED LIVER INJURY

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## ABSTRACT
Drug-induced hepatitis is one of the major drug-related problems which a general practitioner encounters in his clinical practice. Predictable Drug-Induced Liver Injury is generally characterized by certain dose-related injury in experimental animal models, has a higher attack rate, and tends to occur rapidly. Injurious free radicals cause hepatocyte necrosis in zones farthest from the hepatic arterioles, where metabolism is greatest and antioxidant detoxifying capacity is the least. Unpredictable or idiosyncratic reactions comprise most types of DILI. These hypersensitivity or metabolic reactions occur largely independent of dose and relatively rarely for each drug, and may result in hepatocellular injury and/or cholestasis. This is a case report focusing on a 46 years female patient who experienced hepatotoxicity after administration of antitubercular drugs, like Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol are the first-line agents in the treatment of Tuberculosis. The patient was receiving anti-tubercular drugs for 6 months and developed hepatitis, which is a severe adverse drug reaction of Antitubercular medications. Naranjo's causality assessment algorithm was used to assess the adverse effect and it indicated anti-tubercular drugs as a probable cause of hepatitis. Hepatotoxicity is typically distinctive or dose-dependent measurements of AST, bilirubin, and alkaline phosphates are adjunctive for monitoring severe hepatocellular injury. We have reported this clinical case because of its scarcity in clinical practice.

**KEYWORDS:** Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol.

## INTRODUCTION
Altered profile of antioxidant enzymes with increased lipid peroxidation indicated that isoniazid and rifampicin-induced hepatotoxicity appeared to be mediated through oxidative stress. Compared with isoniazid, DIH caused by rifampicin occurs earlier and produces a patchy cellular abnormality with marked periportal inflammation. Rifampicin-induced hepatitis has been postulated to occur as a part of systemic allergic reaction and due to unconjugated hyperbilirubinemia as a result of competition with bilirubin for uptake at the hepatocyte plasma membrane. Whether the hepatotoxicity is due to the additive effect of isoniazid and rifampicin or due to their synergistic effect. The increased risk of hepatotoxicity with isoniazid and rifampicin combination has been attributed to the interaction between the metabolism of isoniazid and rifampicin. Acetyl-isoniazid, the principal metabolite of isoniazid, is converted to monoacetyl hydrazine. The microsomal p-450 enzymes convert monoacetyl hydrazine to other compounds resulting in hepatotoxicity. Rifampicin is thought to enhance this effect by enzyme induction. The exact pathogenetic mechanism for the DIH caused by pyrazinamide has not been understood. In patients receiving a combination of isoniazid, rifampicin, and pyrazinamide, two patterns of fulminant liver injury have been observed. An increase in serum transaminase activity which occurs late (usually after one month) has been attributed to pyrazinamide-induced hepatotoxicity while the early increase in transaminases (usually within first 15days) has been attributed to rifampicin and isoniazid-induced hepatotoxicity.[3] For women, several studies report increased risk of hepatotoxicity, but this was not always treatment-limiting or did not achieve statistical significance. One study did show four times higher risk of treatment-limiting hepatotoxicity in women, but with an overall incidence of only 2%. Two other studies showed no increased risk in women.[4] The first 3,4line anti-TB drugs are potentially hepatotoxic. From first-line anti-TB drugs, isoniazid(INH), rifampin(RIF), and pyrazinamide(PZA) cause hepatotoxicity such as 2transaminasitis and fulminant hepatic failure risk factors for anti-TB induced hepatotoxicity include high

alcohol intake, older age, pre-existing chronic liver disease, chronic viral infection due to hepatitis B (HBV) and hepatitis C viruses (HCV), human immunodeficiency virus (HIV) infection, advanced TB, Asian ethnicity, concomitant administration of enzyme-inducers, inappropriate use of drugs and poor nutritional status. The goal of this study was to evaluate the risk factor, alteration in liver enzymes, approach, and outcome of anti-TB drugs induced hepatotoxicity in Manipal hospital patient[s].[2] The goal of this study was to evaluate the risk factor, alteration in liver enzymes, approach, and outcome of anti-TB drugs induced hepatotoxicity in Manipal hospital patients.[2]

**CASE REPORT**

A 46-year-old female patient was brought to the hospital in generalized weakness, aphagia, drowsiness, and insomnia. The patient was diagnosed as pulmonary Koch's 6 months back and she was on regular medication. She was a known case of retroviral disease with ventriculitis and oral candidacies on medications. She had seizures. The patient was brought to the hospital(1st day) with pulse rate 80/min, BP was found to be 110/70 mm Hg and the Respiratory rate was 26/min.The patient was evaluated for pulmonary Koch's and received the following medications: Tablet Levocetirizine5mg OD, Tab. Udiliv300mg TIDTab. Emeset4MG BDTab. Benadon 40mg OD, Tab.AKT4 2100mg OD, Tab.Augmentin 625mg OD. The physician advised the following investigations: MRI BRAIN and Serum Creatinine.

| **Parameters Test values Normal** |
|---|
| **LFTS**<br>Bilirubin -total 2.25mg/dl 0-1.2mg/dl<br>Bilirubin-Direct 2.03mg/dl 0-0.3mg/dl<br>Bilirubin-indirect 0.22mg/dl 0-0.8mg/dl<br>SGOT/AST 60 IU/L 0-32mg/dl<br>SGPT 34 IU/L 0-33mg/dl<br>ALP110IU/L |
| **BIOCHEMISTRY**<br>Serum.Albumin 2.9g/dl 3.5-5.2g/dl<br>Serum.Globulin 4.6g/dl 1.8-3.4g/dl<br>A/G Ratio 0.63 1.1-1.8<br>Total protein 8.7g/dl 6.4-8.3g/dl<br>Serum.creatinine 0.40mg/dl 0.6-1.1mg/dl<br>Serum.Sodium 132mmol/L 134-145mmol/L |
| **CBP**<br>Prothrombin time 14.8sec 10.5-13.1sec<br>Haemoglobin 8.4g/dl 12-15g/dl<br>Haematocrit 26.7% 34-48%<br>MCV 67.4fl 80-96fl<br>MCH 21.2pg 27-31pg<br>MCHC 31.4g/dl 32-37g/dl<br>RDW 26.1% 11.6-14%<br>Platelet count 421000/cu.mm 150000-400000/cu.mm |
| **USG**<br>Abdomen Grade I fatty liver<br>Small uterine fibroids |
| **MRI BRAIN**<br>Ependymal enhancement is seen in the supratentorial ventricular system predominantly in the temporal horn, atrium, and body of the right lateral ventricle. Edema is seen in adjacent parenchyma. S/O Ventriculitis. Gliotic changes noted in the left cerebellum, around the 4th ventricle, and in the vermis with small calcifications in the cerebellum. As compared to the previous MRI, oedematous changes in the periventricular regions of the cerebrum have reduced. Know the case of RVD+V with ventriculitis. |

**Investigations**

On the 2nd day, B.P. was normal i.e. 120/70 mm Hg and heart rate 81/min with SPO2 concentration 99.2%. On the 3rd day, the nutritional assessment was done and the patient was not interested to take food and the same treatment was continued. On 4th day she was in semi confused state and bedridden. On the 5th day, Due to the above drugs, the patient had experienced hepatitis, jaundice, headache, decreased urine output. Tab.AKY4 cause hepatotoxicity in this patient so it was stopped and instead of this Tab. Isoniazid only given. B.P was recorded as 110/80 mm Hg, pulse rate was 82/min, spo2 was 96%, respiratory rate was 20/min. On 6th day no fresh complaints were seen and the temperature was normal, B.P. 110/80, R.R. 20/min, P.R. 101/min with SPO 2 concentration 98%. the patient was diagnosed as

the case of anti-TB drug-induced hepatitis. A patient was with no fresh complaints and a plan for discharge was made. On 11th day the patient was discharged with appropriate discharge medication chart and patient counseling.

## DISCUSSION

Anti-TB drugs induced hepatotoxicity is a serious problem and it was reported that 2-28% of TB patients experience drug-related hepatotoxicity (DIH) during the treatment. Drug-induced liver injury(DIH) has replaced viral hepatitis as the most common cause of acute liver failure. Drug-induced liver injury is diagnosed only after excluding viral hepatitis. The incidence rate of drug-induced hepatotoxicity in India is 8-36%. The higher incidence of DIH was found in the Asian countries which may be due to ethnic susceptibility, the inherent peculiarity of drug metabolism, and/or the presence of various known risk factors such as HBV infection, malnutrition. According to a study, the overall incidence of serious adverse effects was three times higher with Pyrazinamide than with 9 isoniazid, or rifampicin. Malnutrition is one of the main risk factors which aggravates the anti-TB induced hepatotoxicity. In this case, the patient was not interested to take food. In this case, hepatitis was seen in the patient. Nutritional assessment was done and the patient was on malnutrition during the treatment. Taking all the information under consideration, a causality assessment of the entitled medical conditions was done by using Naranjo Causality Assessment Algorithm and the results indicated Antitubercular agents are possible to cause hepatotoxicity with Naranjo score. Upon discharge, the patient was counseled regarding the medications and course of the treatment. The discharge medication includes Tab.Qutipin25mg OD, Syp.Zincovit 8mg OD, Tab.Dexa8mg OD, Inj.Zosyn 4.5g 8th hrly Inj. Metronidazole 500mg 8th hrly, Inj.Rantac50mg 12th hrly

## CONCLUSION

We reported a clinical case of drug-induced predicable liver injury due to ATT- Rifampicin in A 46-year-old female patient LTBI. Although hepatotoxicity is a well-known side effect of INH, mortality rates remain low as reported in the literature. It is important for clinicians and pharmacists to appropriately follow up patients, counsel them on the signs and symptoms of hepatotoxicity, and encourage them to report it. Tuberculosis patients under the ATT, when TB treatment is instituted, jaundice occurring within 1 to 7 days should suggest rifampicin toxicity. However, if only indirect Hyperbilirubinemia is found and if hemolysis is excluded the patient may be restarted on rifampicin with close monitoring of bilirubin. Since Rifampicin is the most important first-line anti-TB drug it is very important to restart this drug to have a satisfactory response to ant TB therapy.

## Conflict of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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