PYRAZINAMIDE INDUCED MULTIPLE ADVERSE DRUG REACTIONS: A CASE REPORT


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ABSTRACT

Tuberculosis (TB) is a global pandemic and affects one third of the world’s population. Drug-induced Liver Injury (DILI) is a problem of increasing significance, but has been a long-standing concern in the treatment of Tuberculosis infection in India and much of the developing countries. The liver has a central role in drug metabolism, detoxification, and is consequently vulnerable to injury. Anti tubercular drugs induced liver injury can occur in all age groups including children with significant morbidity and mortality. Intolerance of anti-TB standard therapy, including INH, RIF and PZA is a serious problem in Tuberculosis patients. The clinical spectrum includes asymptomatic elevation in liver enzymes contributes to the liver failure. We report a rare case of Pyrazinamide induced hepatitis along with severe gastritis in a patient infected with newly diagnosed tubercular pericardial effusion and was treated symptomatically by changing the Antitubercular regimens.

KEY WORDS: Tuberculosis, Drug Induced Liver Injury, Pyrazinamide, Gastritis, Hepatitis, Tubercular Pericardial Effusion.

INTRODUCTION

Tuberculosis continues to remain a significant infectious disease across the developing countries. India ranks five in world’s TB population and a country with the highest TB burden. The incidence of TB in India is 1.96 million cases annually, contributing to >300,000 deaths annually, 1000 deaths every day.[1] The most effective anti-tuberculosis therapy is a combination of Isoniazid(INH), Rifampin(RIF), and Pyrazinamide(PZA) for 8 weeks
followed by Isoniazid and Rifampin for a further 4-7 months (standard therapy). Among the first line drugs (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol), the first three have the potential for hepatotoxicity with Pyrazinamide being the cause for Hepatotoxic, followed by Isoniazid and Rifampicin. The use of multidrug regimen for the treatment of TB, such as the combination of INH, RIF and PZA, has been associated with an increased incidence of hepatotoxicity when compared with INH monotherapy used for anti-TB prophylaxis. The incidence of anti-TB-DIH varies worldwide and has been reported to be higher in developing countries where factors such as acute or chronic liver disease, indiscriminate use of drugs, malnutrition and more advanced TB have been implicated. The variation in the incidence of anti-TB-DIH may be related to difference in patient’s condition, drug regimens used investigational methods and the diagnostic criteria defining hepatotoxicity. Despite the development of the prevailing drug regimen, the treatment of Tuberculosis continues to be a problem in patients those who do not tolerate to these drugs regimens. The occurrence of anti-TB drugs induced hepatotoxicity is higher in the developing countries with rates ranging from 8% to 39% compared to developed countries at 3% to 4%, despite similar regimen used.

CASE REPORT
A 51 years old female patient, 65 kg in weight, presented with pricking type of mid sternal pain, lasting for 2-5 sec for 2-3 days, associated with fever for 15 days and dry cough for 4-5 days duration. The patient is a known case of DM and Hypertension for the past 2 years who was on regular medications like Glimipride 500mg BD, Amlodipine 5mg OD respectively. Evaluated for the same, in which ECHO revealed moderate pericardial effusion, admitted for further management. USG and CT-thorax revealed bilateral pleural effusion (L>R). Then the patient was diagnosed with tubercular pericardial effusion. On the second day of hospital stay, she underwent Pericardiocentesis; about 380ml of straw colored hemorrhagic fluid was removed which was exudative, and sent for analysis in which pericardial fluid or other fluids-43 U/L (0.1-30 U/L), and TC-13.7 × 10³/µl was elevated with predominant polymorphs. On day 4, ATT regimen was started (Isoniazid 300mg, Rifampicin 450mg, Pyrazinamide 1500mg), daily. During the stay in hospital, she developed persistent vomiting and gastric irritation, underwent upper GI scopy revealed multiple hemorrhagic erosions in the stomach suggestive of grade III gastritis. On hospital day 7, the patient blood sample showed elevated liver enzymes, alkaline phosphatase 155 U/L (35-104 U/L), SGOT 867 IU/ml (8-32 IU/ml), SGPT 775 IU/ml (10-31 IU/L), Total Bilirubin 3.6 mg/dl (0.2-1.2 mg/dl), LDH 2973 U/L
Based on the elevated liver enzymes and GI scopy report, it was determined Pyrazinamide induced hepatitis and gastritis. In view of gastritis, poor intake of food and blood glucose was in the limit (PPBS-131 mg/dl, FBS- 102 mg/dl, HbA1C-6.0 %). Hence oral hypoglycemic agents was temporarily stopped. Immediately Pyrazinamide was withdrawn and treated symptomatically with Inj. Pantoprazole 40mg IV BD for Gastritis, Domperidone 10 mg BD for vomiting, and Livogen 500 mg for anemia. Anti Tubercular Treatment regimen was changed to Ethambutol 1gm, Rifampicin 450mg, and Isoniazid 300 mg daily. On day 15, Upper GI scopy report was normal; patient was clinically improved and discharged in a stable condition.

DISCUSSION
Pyrazinamide (PZA) is a drug used in the treatment of tuberculosis along with combination therapy. The drug is highly bacteriostatic, but can be bactericidal on actively replicating tuberculosis bacteria. PZA can cause serious adverse reactions, either toxic mediated hepatitis which is very serious and dose related (40-70 mg/kg daily) which may also induce rashes, blood sugar abnormalities, dermatitis, gastritis, arthralgia, are higher when compared to other anti-tuberculosis drugs, based on age and sex.[7] Recent studies suggested that the mechanism of Pyrazinamide induced hepatitis is due to polymorphism and reduced activity of hepatic N-acetyl transferase-2 genes and glutathione-S-transferase which alters nicotinamide acetyl dehydrogenase levels in the liver, which might results in generation of free radical species. There may be shared mechanism of injury for Isoniazid and Pyrazinamide because there is some similarity in molecular structure. It may exhibit both dose dependent and idiosyncratic hepatotoxicity.[5,8]

After reviewing the literature, to the best of our knowledge this is the first case to report with multiple side effects like gastro intestinal disturbances, vomiting, elevated liver enzymes in a single patient. Already the evidences are showing Rifampicin induced gastritis (Showkat Ali Zargar et al.), but the uniqueness of our case is reporting Pyrazinamide induced gastritis and it is confirmed based on the GI scopy report showed normal after stopping the Pyrazinamide. Hence the drug was stopped immediately and the regimen was changed to Isoniazid, Rifampicin, and Ethambutol. During the hospital stay, the patient’s liver parameters, Hematological parameters, GI scopy were frequently monitored and treated symptomatically.
At the time of discharge the patient’s liver parameters showed normal, Hb 9.6 g/dl and the patient was clinically stable.

CONCLUSION
By considering this case report of pyrazinamide induced hepatitis and gastritis. We as a clinical pharmacist suggest to monitor the liver parameters and to perform endoscopic studies in order to evaluate the effects of pyrazinamide.

Tuberculosis patients who are under anti tubercular therapy should be under proper vigilance. Early adverse drug reaction (ADR) findings will pay the way for timely action, to save patients. Further patient safety monitoring is also mandatory during treatments, which needs proper education about the possible ADRs and its management among the Health care professionals.

REFERENCES