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Case Report

Isoniazid-induced hepatic injury: A case report and its mechanism of liver injury

Hemalatha Selvaraj[1], Kumudha Dhamothrasamy[1*], Kanagaraj Duraisamy[2], Muralikrishnan Dhanasekaran[3]

[1]Faculty of Pharmacy, Karpagam Academy of Higher Education, Coimbatore, Tamilnadu, India. [2]Department of Genearl Medicine,Government Headquarters Hospital, District TB Centre, Erode, Tamilnadu, India. [3]Department of Drug Discovery & Development, Harrison College of Pharmacy, University of Auburn, USA.

Correspondence: Kumudha Dhamothrasamy, Faculty of Pharmacy, Karpagam Academy of Higher Education, Coimbatore, Tamilnadu, India. kumudhachem@gmail.com

ABSTRACT

One of the most frequently used anti-tubercular medications, isoniazid, commonly referred to as Isonicotinic acid hydrazide, is an antibiotic for the treatment of tuberculosis (TB). A prodrug called isoniazid inhibits mycobacterial cellular structures from developing. Isoniazid activation necessitates the presence of KatG, a bacterial *catalase-peroxidase* enzyme present in *Mycobacterium tuberculosis*. Since the liver plays a significant role in the metabolism and detoxification of drugs, it is subsequently susceptible to damage. Hepatotoxicity caused by anti-TB medicines has been documented in 5–28 % of patients who have been treated with anti-TB drugs. In this case, pulmonary tuberculosis was detected in the 43-year-old patient, who was started on ATT category I treatment one month. After a few days, his liver parameters were elevated. Assessment of ADR was revealed by the dechallenging of drugs viz., Ethambutol, Pyrazinamide, Rifampicin, and Isoniazid. When it was discovered that isoniazid caused hepatotoxicity, the drug was withdrawn and the patient was prescribed a RESO regimen. The Naranjo probability scale was utilized to assess the adverse drug effects, and the resultant score "probable" most likely indicated that anti-TB medicines induce hepatotoxicity. This article talks about a case of hepatotoxicity caused by isoniazid, how it was treated, and why the anti-tuberculosis treatment plan had to be changed.

Keywords: ATT regimen, Hepatotoxicity, Isoniazid, Tuberculosis

Introduction

Anti-tubercular (Anti-TB) (ATT) medications are one of the most common causes of idiosyncratic hepatotoxicity worldwide [1-3]. It can be difficult to estimate which of these events corresponds to the most recent international consensus clinical diagnosis of drug-induced liver damage (DILI) [4]. The majority of studies have defined hepatotoxicity as "3 times the high limit of the normal range (ULN) of *alanine transaminase* (ALT) or *aspartate transaminase* (AST) with symptoms (abdominal pain, nausea, vomiting, unexplained fatigue, or jaundice) attributable to liver injury or 5 times the ULN of ALT or AST absence of symptoms [5].

Up to 20 % of individuals using isoniazid alone or in combination with other drugs experienced temporary asymptomatic elevations in liver enzymes that resolved with continuous treatment [6, 7]. The symptoms of ATT drug-induced liver toxicity might range from being without symptoms to a rise in liver enzymes to fulminant hepatic failure [5, 8]. DILI is characterized by a hepatocellular pattern. Hepatotoxicity caused by anti-TB drugs has a burden that is determined not only by its frequency or occurrence but also by its severity and result. The median time between starting therapy and developing clinical symptoms is 16 weeks (ranging from 6 weeks to 6 months) [9-11]. When compared to acute viral hepatitis, anti-TB drug-induced fulminant liver failure is shown to have a poorer prognosis, with a case fatality rate ranging between 0.042 and 0.07 per 1000 people at each given moment throughout treatment [1, 2, 12-14]. In extreme instances, liver biopsy results

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indicate lobular hepatitis, sub-massive to major necrosis, and hydropic hepatocyte degeneration. In cases of rifampicin hepatotoxicity, localized hepatocellular necrosis and apoptosis in zone 3 as well as cholestasis have been seen on histology.

The cause of hepatotoxicity is uncertain despite years of use and the vast majority of individuals who are treated with anti-TB medications globally. Researchers and doctors may be able to find ways to reduce the number of cases of hepatotoxicity and its harmful effects if they look into the possible causes of DILI and the genetic, environmental, and drug factors that make people more likely to be affected by hepatotoxicity.

Isoniazid (INH; isonicotinic hydrazide or isonicotinic acid hydrazide) is a synthetic antibiotic that inhibits *Mycobacterium tuberculosis* from reproducing. Since then, INH has been linked to two hepatotoxic syndromes: mild INH hepatotoxicity and INH hepatitis [15-17]. Mild INH hepatotoxicity is defined as hepatic damage that is subclinical, asymptomatic, and only shown by modestly increased serum *aminotransferases* (generally less than 100 international units/L) [18-20]. It has been reported in up to 20 % of patients prescribed INH [21-25]. Adults are more susceptible than children, although both males and females tend to be equally sensitive. There is no link between race and the rate at which the medication is acetylated in the liver. The majority of cases are self-limited; in general, INH therapy may be continued without dosage modification with careful monitoring. After stopping INH, *aminotransferase* levels usually recover to normal within a few weeks [26, 27].

Case presentation

A 43-year-old patient was admitted to the tertiary government hospital in Erode with complaints of abdominal pain, loss of appetite, nausea, vomiting, and generalized weakness. Over 3 weeks, the patient experienced a perfidious and gradually worsening course of symptoms. The subject was a known case of pulmonary tuberculosis, confirmed by a chest X-ray showing lower lobe consolidation. He was on anti-tubercular treatment (ATT) Category I (Rifampicin-150 mg, Isoniazid-75 mg, Pyrazinamide-400 g, and Ethambutol-275 mg) for one month.

The social history of the patient is smoking and alcohol drinking. And he stopped drinking alcohol before the initiation of ATT. In the interview, he said that he didn't consume any nutritional supplements or herbal remedies.

At the time of admission, his physical examination was conscious and oriented with BP (110/80 mmHg), RR (24 bpm), pulse rate (80 bpm), and temperature (36.7 °C). On general examination, he was found icteric with abdominal distension and palpable. He was anemic and had a loss of appetite. His laboratory investigation revealed the presence of jaundice, a sign of hepatomegaly.

His viral markers were found to be negative and his blood glucose level was within the normal range (HbA1c: 6.4%). Based on the laboratory reports, liver function tests and hematological parameters were abnormal. It was suspected that isoniazid induced hepatotoxicity. The variations in laboratory parameters were represented in **Table 1**:

Table 1. A summary of laboratoty investigations of the Patient

Clinical parameters	On admission (after Initiation of ATT)	On day 2	Day15 (At the time of Discharge)	Normal Range
WBC	141X10^3 Cells/mm^3	12.4X10^3 Cells/mm^3	11.6 X10^3 Cells/mm^3	4.5-10X10^3 Cells/mm^3
Platelet	162 X10^3 Cells/mm^3	148 X10^3 Cells/mm^3	152X10^3 Cells/mm^3	150-400X10^3 Cells/mm^3
Hemoglobin	9.8 g/dl	10.6 g/dl	10.8 g/dl	13.5-17.5g/dl
ALP	196 IU/L	188 IU/L	138 IU/L	44-147 IU/L
AST	78 IU/L	62 IU/L	44 IU/L	5-45 IU/L
ALT	121 IU/L	92 IU/L	55 IU/L	5-45 IU/L
Total Bilirubin	3.2 mg/dl	2.35 mg/dl	1.6 mg/dl	0.2-1 mg/dl
Direct Bilirubin	1.4 mg/dl	1.41 mg/dl	1.0 mg/dl	0-0.2 mg/dl
Indirect Bilirubin	1.8 mg/dl	0.94 mg/dl	0.6 mg/dl	0.3-1.0 mg/dl
Albumin	2.64 g/dl	3.22 g/dl	3.28 g/dl	3.4- 5.4 g/dl

The patient's drug regimen was immediately discontinued, and he was given ursodeoxycholic acid tablets (300 mg) orally, metoclopramide injection (10 mg) intramuscularly, pyridoxine 40 mg (OD), and multivitamins.

The same treatment was continued for three days, on the fourth day, the RESO (R: Rifampicin – 450 mg; E: Ethambutol – 800 mg, S: Streptomycin – 750 mg; O: Ofloxacin – 400 mg) regimen was started. After 10 days, liver parameters reached nearly the normal value. At the time of discharge, the patient value of *alkaline phosphatase,* AST, ALT, serum total bilirubin, indirect bilirubin, and direct bilirubin was 138 U/L, 44 U/L, 55 U/L, 1.6 mg/dl, 0.6 mg/dl, and 1 mg/dl, respectively. The condition of the patient improved and on a recent follow-up, there was no elevation of liver parameters.

Using the Naranjo Adverse Drug Reaction algorithm scale, ten questions with yes, no, and unknown responses were collected. On the Naranjo scale, 6, was recorded, indicating "Probable" (6-8). In this case, an adverse effect of antitubercular therapy is probable. Additionally, the sequential association indicates antitubercular-induced toxicity.

Results and Discussion

Acute or long-term liver damage caused by drugs or herbal substances is referred to as drug-induced hepatotoxicity [28]. Asian countries have a greater rate of DIH, which may be attributable to demographic vulnerability, a unique drug metabolism, or the existence of other established risk factors such as HBV infections, malnourishment, and alcoholism [2].

Here we found a 43-year-old male patient who had been diagnosed with TB and was presented in the hospital with chief complaints of abdominal pain, nausea, vomiting, and loss of appetite. The patient was started with CAT-I therapy by ATT for one month. He developed jaundice and an abnormality in LFT. Though the patient was alcoholic and the Naranjo algorithm scale score was 6 "probable" it was found that on cessation of CAT-I drug, liver parameters reached nearly the normal value. Thus, the patient was diagnosed with antitubercular-induced hepatotoxicity and was prescribed second-line treatment.

The most efficient method for preventing the transmission of the disease is with anti-TB treatment, although occasionally treatment is interrupted by unfavorable occurrences. Antitubercular medications can cause a variety of side effects, such as acute renal injury, gastrointestinal problems, rashes, optic neuritis, and liver toxicity Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol are the first-line (Category I) anti-TB medications. Since these medications are predominantly metabolized by the liver, they are the leading factor in drug-induced hepatotoxicity with anti-TB therapy. There are four ways in which ATT causes hepatotoxicity, including direct toxicity, idiosyncratic damage, the production of liver enzymes, and an allergic reaction. The initial hepatocyte destruction might be additionally augmented by subsequent inflammation. They then follow phase I and phase II reactions. The mitochondrial respiratory chain is first inhibited in ADTH, which leads to an increase in reactive oxygen species (ROS) and a decrease in adenosine triphosphate (ATP). Damage to the inside of cells can be brought on by ROS production, ATP depletion, and mitochondrial damage. Hepatocytes eventually decide to undergo apoptosis and necrosis.

Mechanism of liver injury

The liver is where INH is primarily metabolized and excreted. Cytochrome P4502E1 (CYP2E1) and N-acetyltransferase-2 (NAT2) are two vital enzymes in the metabolic pathway that influence the risk of hepatic injury. Isoniazid is converted to acetyl isoniazid by the enzyme NAT2, which is subsequently hydrolyzed to form acetyl hydrazine. CYP2E1 may oxidize the latter to make *N*-hydroxy-acetyl hydrazine, which can then be dehydrated to become acetyl diazine. Acetyl diazine can be a toxic byproduct in and of itself, or it can degrade into reactive byproducts such as acetyl radical, acetyl onium ion, and ketene (all of which can bind covalently to hepatic macromolecules and cause liver damage). Further acetylation of acetyl hydrazine to non-toxic diacetyl hydrazine is carried out by the enzyme NAT2. As a result, delayed acetylation leads to the buildup of both the parent molecule and mono-acetyl hydrazine. INH suppresses the acetylation of acetyl hydrazine even more. Furthermore, direct hydrolysis of INH without acetylation creates hydrazine, which might harm the liver [29]. Slow acetylators have a ten-fold increase in INH metabolism via this minor route, especially when rifampicin is used [30]. The hepatic NAT2 gene is polymorphic in humans, and rapid acetylation is associated with one or more wild-type NAT2*4 alleles, while slow acetylation is related to two or more variant alleles of the NAT2 gene [31]. Acetylation activity *in vitro* decreases when the NAT2*4 > NAT2*7 > NAT2*6 > NAT2*5 alleles are inherited [32-34]. In their initial study, which involved genotyping acetylator status in 224 participants receiving anti-TB treatment, Huang, *et al*. found that individuals with NAT2 genotypes associated with delayed acetylation had a four-fold risk of developing INH-induced hepatotoxicity [35] and Likewise, a recent meta-analysis of 14 trials with 474 cases and 1446 controls led to the same conclusions, with a 4.6 odds ratio favoring slow acetylators [36]. Additionally, serious hepatotoxicity was more likely to develop in slow acetylators than in rapid acetylators. Those with the NAT2*6/6 and NAT2*6/7 genotypes were at a much greater risk than those with other genotypes. The same researchers looked at whether CYP2E1 genetic polymorphisms affected vulnerability to anti-TB drug-induced hepatic toxicity. CYP2E1 activity is inhibited when INH is administered. Under the inhibitory impact of INH [37], subjects who were homozygous for the CYP2E1 c1 allele (wild type) showed greater enzyme activity than those who carried one or more CYP2E1 c2 alleles. When compared to the other genotypes, patients with CYP2E1 c1/c1 were 2.5 times more likely to develop hepatotoxicity, according to research including 318 people on anti-TB treatment. When CYP2E1 c1/c1 was coupled with slow-acetylator conditions, the risk of hepatotoxicity rose sevenfold. In 218 ATT-taking subjects, Bose *et al*. in India examined the effects of the NAT2 and CYP2E1 (promoter and intron 6 regions) polymorphisms on ATT hepatotoxicity. There was a higher prevalence of the NAT2*5/*7 and NAT2*6/*7 genotypes in the anti-TB DILI group (slow-acetylator). Although CYP2E1 c1/c1 was present in both the DILI and non-DILI groups, the genotypes C/D or C/C were three times more likely to result in anti-TB DILI. The same study showed that the risk of DILI went up when the NAT2 gene polymorphism was combined with the CYP2E1 C/D or C/C genotype [33, 38, 39].

Conclusion

The basis of avoiding and controlling any drug-related illnesses is determining the root cause and ruling out the specific medication that causes hepatotoxicity. The toxicity of a drug can have a significant influence on the disease's outcome and the patient's quality of life. So, this kind of case study about injuries caused by drugs adds to what is already known about the subject.

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