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Case Report

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ANTI-TUBERCULAR DRUGS INDUCED HEPATOTOXICITY- A CASE REPORT

Araveti Lokesh[1], Y. Grace Nithya*[2], Shaik Fouzia[3], Sangaraju Vijayalakshmi[4] and Meda Venkata Subbaiah[5]

[1,2,3,4]Pharm-D, P. Rami Reddy Memorial College of Pharmacy (PRRMCP), Kadapa, Andhra Pradesh, India-516003.
[5]Assitant Professor, P. Rami Reddy Memorial College of Pharmacy (PRRMCP), Kadapa, Andhra Pradesh, India-516003.

***Corresponding Author: Y. Grace Nithya**

Pharm-D, P. Rami Reddy Memorial College of Pharmacy (PRRMCP), Kadapa, Andhra Pradesh, India-516003.

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ABSTRACT

First line anti-tubercular drugs like Isoniazide (10-20%), Rifampicin (10-15%) and Pyrazinamide are potentially hepatotoxic drugs but in case of Ethambutol and Streptomycin are less hepatotoxic drugs. The incidence rate of this adverse effect is found to be 2% to 28%. This is a case report on severe adverse effect focusing on 55 years male patient who brought to hospital with the complaints of abdominal pain which is aggravated and relieving but not of radiating type. Patient is known tubercular from 4 months on regular treatment i.e. Isoniazide, Rifampicin, Pyrazinamide, ethambutol and streptomycin thrice in a week. Based on laboratory and USG abdomen of the patient, he was diagnosed with ATT induced hepatotoxicity through causality assessment. In the management of adverse reaction symptomatic treatment is given and tubercular therapy was altered with Levofloxacin, ethambutol and streptomycin. To prevent and/ minimize drug induced complications and for better management we need to monitor the vitals and systems at risk at regular intervals during therapy.

KEYWORDS: Anti-tubercular drugs, causality assessment, adverse reaction, hepatotoxicity.

INTRODUCTION

Tuberculosis (TB) remains a major global health problem despite the availability of highly efficacious treatment for decades. World Health Organization (WHO) declared TB a global public health emergency in 1993, at a time when an estimated 7–8 million new cases and 1.3–1.6 million deaths occurred each year. In 2010, there was an estimated 8.8 million new cases reported and 1.4 million deaths including deaths from TB among HIV-positive people. In India, TB is a major public health issue with an estimated prevalence of 256 per 100,000 population and 26 per 100,000 populations dying of TB.[1] Although about 85% of TB cases are successfully treated, treatment-related adverse events including hepatotoxicity, skin reactions, gastrointestinal and neurological disorders account for significant morbidity leading to reduced effectiveness of therapy.[2] According to WHO, one third of the population is affected by TB and 1 in 4 adult male deaths is attributed to TB.[3] The incidence rate of anti-TB induced hepatotoxicity is found to be 2% to 28% based on hepatotoxicity diagnosis criteria.[4] The risk factors for anti-TB induced hepatotoxicity includes 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.[5]

First line anti-TB drugs like Isoniazide (10-20%), Rifampicin (10-15%) and Pyrazinamide are potentially hepatotoxic effects but in case of Ethambutol and Streptomycin are less hepatotoxic effects. Acetyl hydrazine, a metabolite of INH is responsible for liver damage. INH should be discontinued if the AST increases to over 5 times the normal value. The occurrence of mortality associated with hepatotoxicity has been reported to be 16 in 500,000 patients receiving rifampicin. A higher incidence of hepatotoxicity has been reported in patients receiving rifampicin with other anti TB agents, and is estimated to be fewer than 4%.[6] A higher incidence of hepatotoxicity has also been reported in patients receiving rifampicin in combination with pyrazinamide for the treatment of latent TB. The side effects and toxicity of the drugs also poses a threat both to the physician and the patients in continuing the therapy. Among the various side effects caused by the TB drugs, damage to the liver caused by most of the important first line drugs is not only a serious challenge encountered in the course of the treatment but also creates difficulties in restarting the regimen. The National treatment regimens for TB patients recommend the use of the five first lines anti-TB drugs Isoniazid (INH),

Rifampicin (R), Ethambutol (E), Pyrazinamide (P) and Streptomycin (S) Conditions and situations with higher incidence of Hepatotoxicity are fatality due to ATT

induced hepatotoxicity was more likely when jaundice occurred over 6 weeks after the start of therapy, serum bilirubin levels were higher or where treatment was continued despite jaundice.[9] Hepatic dysfunction may be defined as an increase in alanine transaminase (ALT) levels to 1.5 times above the upper limit of normal on at least two consecutive occasions within four weeks of treatment and for patients with increased pre-treatment ALT the elevation had to be greater than 1.5 times the baseline.[10]

CASE REPORT

A 55 years male patient was brought to the Rajiv Gandhi Institute of Medical Science, Kadapa, India which is a tertiary care teaching hospital in conscious state with the chief complaints of abdominal pain since 5 days in right hypogastrium which is an aggrevating and relieving but not radiating type. On physical examination, patient shows icterus and pallor. Patient was known case of tuberculosis since 4 months on regular treatment (Isoniazide (300mg), Rifampicin (450mg), Pyrazinamide (750mg), Ethambutol (800mg) and streptomycin (500mg) thrice in a week).

On the 1st day patient was brought to the hospital with the pulse rate-80bpm, blood pressure-130/80 mmHg and system examination are normal. Patient was treated with following medications:

IVF 1-DNS, 1-RL

Inj. Pantoprazole 40mg

Tab. Iron folic acid 335.5mg

Tab. B complex 67mg

Anti-tubercular drugs (Isoniazide, Rifampicin, Pyrazinamide, Ethambutol and streptomycin)

On day 2nd day patient U/S abdomen reveals that Liver-Echotexture increased by 15cms, Fatty Liver (Grade-II) and mild ascitis. Patient was continued same treatment along with that

Tab. Hepamerz 150mg

Tab. Udiliv 300mg

Stopped Anti tubercular drugs

On day 3rd, 4th, 5th day patient was treated with the same therapy which is in previous day.

On day 6th day patient was recognized with anasarca and jaundice and had pulse rate-80bpm and blood pressure-120/70 mmHg. So he was treated with the following medications

Tab. Lasix 40mg

Tab. Hepamerz 150mg

Tab. Udiliv 300mg

Syr. Lactulose 1.45gm (30ml)

Inj. Pantoprazole 40mg

Tab. Iron folic acid 335.5mg

On day 7th patient complained with similar complaints, so he was continued with the same treatment as in previous day.

The physician advised the laboratory investigations which were represented in the below table no 01 and also an USG abdomen.

Patient's U/S abdomen reveals the Liver-echotexture with increased with 5cm, moderate ascitis.

On the 8th day patient had similar complaints, so he was treated with medication which is as same as earlier day along with that Tab. Aldactone 25mg.

On the 9th day stopped anti-tubercular therapy was altered with the following medications

Tab. Levofloxacin 500mg

Tab. Streptomycin 500mg

Tab. Ethambutol 800mg

Patient was discharged with following medication and come to ask for review after 20 days of therapy.

Tab. Hepamerz 150mg

Tab. Udiliv 300mg

Syr. Lactulose 1.45gm (30ml)

Inj. Pantoprazole 40mg

Tab. Iron folic acid 335.5mg

Tab. Levofloxacin 500mg

Tab. Streptomycin 500mg

Tab. Ethambutol 800mg

Table 1: Patient's investigations.

Parameter	Normal range	1st day	7th day
Total Bilirubin	0.2-1.0mg/dl	6.1mg/dl	3.5mg/dl
Direct Bilirubin	0.1-0.2mg/dl	2.9mg/dl	1.2mg/dl
Indirect Bilirubin	0.3-1.0mg/dl	3.2mg/dl	2.3mg/dl
Alkaline Phosphatases		175U/lit	122U/lit
SGPT	30-65U/lit	259U/lit	63U/lit
SGOT	15-37U/lit	125U/lit	55U/lit

Here we set up the relationship between the suspected drug and adverse reaction observed by performing causality assessment.

ADR Analysis

Later on assessing past and present medical and medication history from the patient, the developed reaction is suspected with anti-tubercular drugs. After analyzing the ADR profiles of the anti-tubercular drugs, it was found that the most suspected drug i.e, isoniazide, rifampicin, pyrazinamide producing hepatotoxicity. We made further assessment to build a relationship between the suspected drug and the developed adverse reaction, through causality assessment with the help of Naranjo's scale, WHO-UMC ADR assessing scale as well as Karch and lasagna scale which were represented in the below table no.02.

Table 2: Causality assessment of suspected ADRs.

ADR	Causality		
	Naranjo's scale	WHO-UMC	Karch and lasagna scale
Isoniazide, Rifampicin and Pyrazinamide induced hepatotoxicity	Probable	Probable	Probable

We made an further assessment on the severity, predictability and preventability through Modified Hartwig and Siegel severity scale, Schumock and Thornton Preventability Scale which were represented in the below table no.03.

Table 3: Severity, Predictability and Preventability of suspected ADR.

Drug	Severity	Predictability	Preventability
Isoniazide, Rifampicin and Pyrazinamide	Moderate - Level 4(b)	Predictable (Type A)	Probably preventable

ADR Management

Usually, management of ADR includes withdrawal/suspension, dose reduction of suspected drug and administration of supportive therapy. Here in this issue, to treat ATT induced hepatotoxicity the drug was withdrawn and a supportive therapy of oral udiliv, hepamerz was given and suspected drugs i.e, isoniazide, rifampicin and pyrazinamide. He was advised to review after 20 days in order to monitor his condition whether it perhaps improved or not after taking the supportive therapy and alteration of anti-tubercular with levofloxacin, ethambutol and streptomycin which were in the part of management of an adverse reaction.

DISCUSSION

In this present issue, we found that anti-tubercular drugs i.e, isoniazide, rifampicin and pyrazianmide induced hepatotoxicity adverse reaction is supported by Schaberg T et al, McNeill L et al, Wong WM et al, Breen RMA et al, Ameer K et al., where they reported the higher incidence of anti-tubercular drugs induced hepatotoxicity. Here the suspected drugs were withdrawn fromn the therapy and altered with levofloaxcin, ethambutol and streptomycin along with the supportive therapy for the management of adverse reaction. Alternatives can be adapted to manage continue streptomycin and ethambutol until liver functions return to normal. This is a weak regimen as it is only streptomycin which is bactericidal while ethambutol is bacteriostatic. Further-more, in case the organisms are resistant to one drug, ft amounts to monotherapy with the other. Therefore, addition of a bactericidal second-line drug, namely a quinalone likely levofloxacin or ciprofloxacin or ofloxacin strengthens the streptomycin and ethambutol combination. To minimize the occurrence of hepatotoxicity liver function tests are to be done before the start of therapy and monitored every 2 weeks during the initial two months in the risk groups like patients with pre-existing liver disorders, alcoholics, the elderly and the malnourished. Close clinical and biochemical monitoring is to be done in hepatitis B carriers also as there is higher incidence of liver dysfunction and symptomatic hepatitis. The patients are to be alerted to report immediately if, symptoms suggestive of hepatitis like loss of appetite, nausea, vomiting, jaundice, occur during the course of treatment; ATT should be stopped immediately if there is a clinical suspicion of hepatitis reaction and then liver function has to be checked.

CONCLUSION

Patients undergoing treatment for tuberculosis needs health education in detail concerning not only adherence and the benefits of ATT but also the side effects. Clinically the patient's condition has to be assessed not only in terms of disease control but also in terms of symptoms and signs of hepatitis on their follow-up.

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