

## **Drug induced hepatitis with anti-tubercular chemotherapy: Challenges and difficulties in treatment**

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### **Abstract**

Tuberculosis is a major health burden worldwide. In Nepal, it is a significant cause of morbidity and mortality. Although better drugs are available for managing tuberculosis, treatment failure is one of the common problems encountered. Among the various causes which can cause treatment interruption, drug induced hepatotoxicity is a common cause. Isoniazid and Pyrazinamide are the common drugs causing hepatotoxicity. Upon occurrence of hepatotoxicity, the hepatotoxic drugs should be stopped and reintroduced as per the available guidelines. The healthcare professional should also counsel the patients for recognizing the early symptoms due to hepatotoxicity which could prevent morbidity.

**Key words:** Adverse effects, Hepatotoxicity, Tuberculosis.

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**T**he cause for Tuberculosis (TB) is known for more than a century and for nearly 50 years we have effective drugs for treating it. However, the world's TB problem is now bigger than before. The exact cause of this is unknown, although it is thought that it could be because of the resurgence of TB due to HIV infection as well as Multiple Drug Resistant Tuberculosis (MDR-TB) due to inefficient management. Each year an estimated eight million new cases and two million deaths occur due to TB world wide.<sup>1</sup> TB is one of the foremost public health problems in Nepal, causing a significant burden of morbidity and mortality, causing an estimated 8,000-11,000 deaths every year.<sup>2</sup> In addition to these, 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).<sup>3</sup> In this article the authors review the existing literature on hepatotoxicity due to the first line ATT drugs and provide an overview regarding the hepatotoxicity and managing the TB in patients developing hepatotoxicity.

### **Clinical manifestations of ATT induced hepatotoxicity**

The clinical presentation of ATT-associated hepatitis is similar to that of acute viral hepatitis. ATT can cause varied degree of hepatotoxicity from a transitory asymptomatic rise in transaminases to acute liver failure and the frequency of hepatotoxicity in different countries varies widely from 2-39%.<sup>4</sup> The occurrence of drug induced hepatotoxicity is unpredictable but it is observed that certain patients are at a relatively higher risk than other populations.

### **Incidence of hepatotoxicity**

The incidence has been reported to be higher in developing countries and factors such as acute or chronic liver disease, indiscriminate use of drugs, malnutrition and more advanced TB have been implicated. A high incidence of viral hepatitis has been reported to coexist in patients with TB in developing countries, resulting in misdiagnosis of ATT-induced hepatotoxicity, especially if serological tests are not performed.<sup>5</sup> A study from Nepal reported the incidence of hepatotoxicity as 8%.<sup>6</sup>

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### Conditions and situations with higher incidence of hepatotoxicity

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.<sup>4</sup> It has been observed in several studies that patients with pre-existing hepatic diseases due to chronic viral infection with Hepatitis B, Hepatitis C, HIV, Alcoholics, the elderly, and the malnourished are at a higher risk of developing drug induced hepatitis compared to the general population.<sup>4</sup> In some studies highest incidence of hepatotoxicity was observed in those who were given empirical ATT without a definitive diagnosis of TB.<sup>4</sup> A Nepalese study reported female gender, disease extent, and poor nutritional status as the risk factors for developing hepatotoxicity.<sup>6</sup>

A recent study from India has reported that age, sex, history of alcohol intake and Body Mass Index (BMI) were not found to be related to the development of hepatotoxicity. However, the presence of HBV infection or an underlying silent chronic liver disease was found to significantly increase the risk of development of ATT induced hepatotoxicity.<sup>4</sup>

One study identified that homozygous 'null' mutation at the GSTM1 gene might predispose an individual to ATT-induced hepatotoxicity.<sup>7</sup>

The reason why some patients receiving ATT develop hepatitis is not clear and many studies were done to search for host factors, environmental factors

or interaction among various factors and also on genetic factors and acetylator status. The time required for the metabolites to reach hepatotoxic levels is much earlier with INH plus rifampicin treatment than INH alone and this has been shown to be synergistic rather than additive. Recent studies show that polymorphism of N-acetyl transferase 2 (NAT2) genes and glutathione-s-transferase (GST) are the major susceptibility risk factors for ATT induced hepatitis. Slow acetylators of NAT2 develop more severe hepatotoxicity than rapid acetylators making it a significant risk factor.<sup>8</sup>

### Hepatotoxic effects of ATT drugs

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 base line.<sup>9</sup> Transient changes in ALT and bilirubin levels are relatively common during ATT and do not signify true hepatotoxicity. However, the progressive rise in ALT and bilirubin levels is much more dangerous. But the recommendations for the modification of treatment regimen and the cut-off level of liver dysfunction have not been standardized. Some authors recommend stopping the hepatotoxic drugs if the ALT level increases by three times or more compared to that of normal, while others recommend five times. The hepatotoxic effects of the ATT drugs can be classified based on the potential of ATT drugs to cause hepatotoxicity and the details are listed in Table 1.

**Table 1:** Hepatotoxic potential of first line ATT drugs

Hepatotoxic potential	Drugs
High	INH, Rifampicin, Rifabutin, Pyrazinamide
Less	Streptomycin, Ethambutol

### Isoniazid (INH)

Approximately 10-20% of patients during the first 4-6 months of therapy have a mild hepatic dysfunction shown by mild and transient increase in serum AST, ALT and bilirubin concentration. But in some patients the hepatic damage may be progressive and cause fatal hepatitis. 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.

A prospective cohort study of 11,141 patients receiving INH preventive therapy reported a rate of

hepatitis lower than that previously reported. Of these, 11 patients (0.10% of those starting, and 0.15% of those completing therapy) developed clinical hepatitis.<sup>10</sup>

From January 1991 through May 1993, liver transplant centres in New York and one in Pennsylvania collected data on patients who had hepatitis attributed to INH therapy. Eight patients were on INH monotherapy on the usual dose of 300 mg daily (to prevent TB) at the time of onset of hepatitis. Histological evaluations showed massive or

sub massive hepatic necrosis, with cholestasis in 2 patients.<sup>11</sup>

Hepatotoxicity is rare in children receiving INH. In a 10-year retrospective analysis, the incidence of hepatotoxicity in 564 children receiving INH (10 milligrams per kilogram per day (mg/kg/day) to a maximum of 300 mg/day) for the prophylactic treatment of tuberculous was 0.18%.<sup>12</sup> However, the incidence of hepatotoxicity in children receiving INH and rifampicin for TB was 3.3% in another retrospective study (14 of 430 children).<sup>13</sup>

### **Rifampicin**

Transient abnormalities in liver function are common in the initial stages of therapy. But in some cases it may cause severe hepatotoxicity, more so in those with pre-existing liver disease, forcing the physician to change treatment and opt for liver friendly treatment.

Rifampicin causes transient elevations in hepatic enzymes usually within the first 8 weeks of therapy in 10% to 15% of patients, with less than 1% of the patients demonstrating overt rifampicin-induced hepatotoxicity. 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%.<sup>14</sup> A higher incidence of hepatotoxicity has also been reported in patients receiving rifampicin in combination with pyrazinamide for the treatment of latent TB.<sup>15,16</sup> This data has led to the recommendation that this regimen should generally

not be offered for the treatment of latent tuberculosis<sup>17</sup>.

### **Pyrazinamide**

The most common adverse effect of this drug is hepatotoxicity. Hepatotoxicity is dose related and may occur any time during therapy.

In the Centre for Diseases Control (CDC) update, 48 cases of hepatotoxicity were reported in association with a 2-month regimen of Rifampin-pyrazinamide for the treatment of latent tuberculosis between October 2000 and June 2003. Thirty-seven patients recovered and 11 died of liver failure. Of the 48 reported cases, 33 (69%) occurred in the second month of therapy.<sup>17</sup>

### **Ethambutol**

There are fewer reports of hepatotoxicity with Ethambutol in the treatment of TB. Abnormal liver function tests have been reported in some patients taking ethambutol; however, these patients were also taking other antiTB drugs known to cause liver dysfunction.<sup>18</sup>

### **Streptomycin**

No hepatotoxicity has been reported.

### **Recommendations for managing ATT induced hepatotoxicity and restarting the therapy**

The national TB guidelines of Nepal provide information regarding the management of ATT induced hepatotoxicity and the details regarding the restarting of TB drugs in patients developing hepatotoxicity. The details are listed below in Box 2.

#### **Box 2: National recommendations for managing ATT induced hepatotoxicity and restarting the therapy**

- If a drug induced hepatitis is diagnosed, ATT drugs are to be stopped
- Wait until the jaundice resolves ( A severely ill patient may die without TB drugs)
- It is strange but fortunate that in most cases the patient can restart the same drugs without hepatitis returning.
- If jaundice returns, and the patient has not completed the intensive phase, give him two months of Streptomycin, INH and Ethambutol followed by 10 months of INH and Ethambutol.
- If the patient has completed the intensive phase, give him INH and Ethambutol until he has had a total of 8 months treatment for Short Course Chemotherapy (SCC) or 12 months for standard regimen.

#### **Box 3: BTS recommendations for restarting the therapy in patients developing hepatotoxicity**

- INH should be introduced initially at a dose of 50 mg/day, increasing sequentially to 300 mg/day after 2–3 days if no reaction occurs, and then continued.
- After a further 2–3 days without reaction to INH, rifampicin at a dose of 75 mg/day can be added, increasing to 300 mg after 2–3 days, and then to 450 mg (<50 kg) or 600 mg (>50 kg) as appropriate for the patient's weight after a further 2–3 days without reaction, and then continued.
- Finally, pyrazinamide can be added at a dose of 250 mg/day, increasing to 1.0 g after 2–3 days and then to 1.5 g (<50 kg) or 2 g (>50 kg).

An approach of sequential introduction of the drugs in the order: isoniazid, rifampicin, pyrazinamide with daily monitoring of the patient's clinical condition and liver function tests have been recommended by the British Thoracic Society (BTS, 1998).<sup>19</sup> The BTS recommendations are listed in Box 3.

In one study, after the detection of ATT-induced hepatitis, the likely offending drugs (H, R and P) were discontinued and reintroduced sequentially one after the other with challenge doses of INH, rifampicin and pyrazinamide with regular bilirubin and aminotransferases levels. The study concluded that continuation of ATT after development of jaundice was associated with a high fatality rate. It was possible to re-introduce INH in 96% and rifampicin in 88% of patients with ATT induced hepatotoxicity.<sup>4</sup>

#### **Strategies to minimize the occurrence of hepatotoxicity**

Liver function tests are to be done before the start of treatment 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.<sup>9</sup>

#### **Responsibilities of the healthcare professionals**

Health education has to be provided to all patients undergoing treatment for tuberculosis in detail regarding not only adherence and the benefits of ATT but also the side effects. 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; 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. ATT should be stopped immediately if there is a clinical suspicion of hepatitis reaction and then liver function has to be checked; if the ALT levels rise to three times or above or serum bilirubin levels rising to two times or above the upper limit of normal values without hepatitis symptoms.

#### **Conclusion**

Since TB is a common problem in Nepal and drug induced hepatotoxicity is one of the common problems associated with ATT therapy, this issue gains importance. Patients on ATT therapy should be counselled thoroughly for the early detection of hepatotoxicity and on occurrence of hepatotoxicity the patients should be managed appropriately.

Although the occurrence of hepatotoxicity due to ATT drugs is not totally avoidable, a systematic approach can definitely be helpful in minimising not only the incidence but also the morbidity.

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