

Anti-Tuberculous Induced Hepatotoxicity

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Abstract:

Background: Anti-tuberculous drugs can induce liver injury. Although, it is usually mild and transient, but it can be presented in a form of markedly severe liver injury.

Objective: To assess the severity of hepatic injury that can be induced by the anti-tuberculous drugs and to evaluate the effect of different demographic features, duration of therapy and the presence of any other risk factors for liver injury on the frequency of anti-tuberculous drugs induced hepatotoxicity.

Methods: This cross sectional study had enrolled 30 patients who were on quadruple anti-tuberculous therapy regimen (Rifampicin and Isoniazid for 6 months and Pyrazinamide with streptomycin for the initial 2 months). They were randomly selected from those patients who had attend the outpatient clinic or admitted in the medical wards of Al-Yarmouk Teaching Hospital during the period between the 1st of Feb. 2006 to the 31st of January 2007.

Results: This study had enrolled 30 patients, 7 of them were female (23.3% of the sample), and 23 were male (76.7% of the sample). Male to female ratio was 3.28:1. This study revealed that 73.3% of those patients included in this study were older than 50 years old. 86.7% of the sample had less than 3 folds increase in their serum alanine aminotransferase (26 patients), only 4 patients (13.3% of the sample) had more than 3 fold increase in their serum alanine aminotransferase level more than the upper limit of normal range. 73.3% of the sample had increased serum bilirubin level by less than 3 times the upper limit of normal range. 46.7% of the sample (14 patients) were underweight. 70% of the sample (16 patients) had been included in this study within the first 2 months of anti-tuberculous therapy. 7 patients give history of regular alcohol intake (23.3% of the sample). While 4 patients had been discovered to be hepatitis B positive (13.3% of the sample). Jaundice was found in 9 patients (30% of the sample).

Conclusion: This study revealed that severe anti-tuberculous drugs induced liver injury is uncommon, increasing age is an important risk factor. It is unusual to find marked and very high level of alanine aminotransferase and bilirubin in patients using anti-tuberculous drugs. Being underweight can be regarded as a factor that may increase the risk of hepatotoxicity. Most of the cases of liver injury occur early from starting therapy. The presence of other risk factors that can induce liver injury can increase the risk of anti-tuberculous drug induced hepatotoxicity.

Keywords: anti-tuberculous, hepatotoxicity

Introduction:

Treatment of tuberculosis (TB) involves several drugs in combination for six or more months ⁽¹⁾. Many of the commonly used anti-TB drugs are associated with significant potential of causing hepatotoxicity. While the occurrence of drug induced hepatitis is difficult to predict, it has been observed that certain patients are at higher risk of developing drug induced hepatitis during the course of anti-TB chemotherapy. These include patients with pre-existing liver diseases, particularly those associated with chronic viral infection due to hepatitis B, hepatitis C, and HIV, the alcoholics, the elderly and the malnourished ⁽²⁻⁴⁾.

The exact role of regular monitoring of liver function tests in patients receiving anti-TB drugs remains controversial. Certain guidelines only emphasize the need of clinical monitoring without mentioning regular biochemical monitoring ⁽⁵⁻⁶⁾. While a number of authorities recommend routine biochemical monitoring among high risk groups ⁽⁷⁻⁹⁾.

Transient changes in alanine transaminase and bilirubin level are relatively common during anti-TB chemotherapy and do not signify true hepatotoxicity. However progressive rise in alanine transaminase and bilirubin levels is much more ominous. Existing data do not allow reliable prediction of the exact clinical course of asymptomatic patients with moderate degree of biochemical derangement. Opinions, therefore, differ as at what cut-off level of liver dysfunction modification of treatment regimen should be initiated. For the alanine transaminase level. Some recommend stopping the hepatotoxic drugs three times or above that of normal⁽⁸⁻¹²⁾. While others recommend five times^(6-7,13). The recommendations regarding the level of bilirubin are also not uniform⁽¹³⁾. In this introductory chapter, I will try my best to review the important points about drugs induced hepatotoxicity in general, then I will concentrate on the risk and epidemiological facts about anti-TB drugs induced hepatotoxicity.

Drug induced hepatic injury is the most frequent reason cited for the withdrawal from the markets of an approved drug, and it also accounts for more than 50% of cases of acute liver failure in the United States today. More than 75% of cases of idiosyncratic drug reactions result in liver transplantation or death⁽¹³⁻¹⁴⁾.

This study had been designed to evaluate the effect of different demographic features on the frequency of anti-tuberculous induced hepatotoxicity, to assess the severity of hepatic injury that can be induced by the anti-tuberculous drugs, to estimate effect of duration of therapy on the frequency of hepatotoxicity and to find the effect of the presence of any other risk factors for liver injury on the frequency of anti-tuberculous drugs induced hepatotoxicity.

Patients and Methods:

This cross sectional study had enrolled 30 patients who were on quadruple anti-tuberculous therapy regimen (Rifampicin and Isoniazid for 6 months and Pyrazinamide with streptomycin for the initial 2 months) and had elevated liver enzyme. They were randomly selected from those patients who had attend the outpatient clinic or admitted in the medical wards of Al-Yarmouk Teaching Hospital during the period between the 1st of Feb. 2006 to the 31st of January 2007, total number of patients who had been investigated was 215 tuberculous patients. Detailed questionnaire had been prepared including questions about their personnel information and any risk factors for liver injury beside anti-tuberculous therapy. Thorough physical examination had been made for each of the patients included in this study. Blood samples had been sent for liver function tests, renal function tests, and screen for hepatitis viral infection (Hepatitis B and hepatitis C viral infections). All of the patients had been sent for chest X-ray, and abdominal ultrasound.

Result:

This study had enrolled 30 patients, 7 of them were female (23.3% of the sample), and 23 were male (76.7% of the sample). Male to female ratio was 3.28:1. Table-1 shows patients distribution according to their gender.

Age of the patients with anti-tuberculous induced hepatotoxicity ranged between 21-72 year old (51.3 ± 9.56 year old). This study revealed that 73.3% of those patients included in this study were older than 50 year old. Table-1 show patients distribution according to their age.

Serum alanine aminotransferase (ALT, S.GPT) had been increased by 2-14 times the upper limit of normal range (ULN), ($2.4 \pm 1.13 \times \text{ULN}$). 86.7% of the sample had less than 3 folds increase in their serum ALT (26 patients), only 4 patients (13.3% of the sample) had more than 3 fold increase in their serum ALT level more than the upper limit of normal range. Table-2 shows patients distribution according to number of folds increase observed in their serum alanine aminotransferase level.

The increase in bilirubin level was 0.6-5.6 folds more than the upper limit of normal range ($1.5 \pm 0.7 \times \text{ULN}$). 73.3% of the sample had increased serum bilirubin level by less than 3 times the

upper limit of normal range. Table-3 shows patients' distribution according to their observed increase in Serum Bilirubin.

Regarding body mass index of the patients included in this study, it had been found that 46.7% of the sample (14 patients) were underweight, 33.3% of the sample (10 patients) were normal weight and only 13.3% of the sample (4 patients) were obese. Table-4 shows patients distribution according to their body mass index.

Regarding time period between initiations of anti-tuberculous therapy to the inclusion in this study ranged 2weeks-5 months (2.5 ± 0.9 month). 70% of the sample (16 patients) had been included in this study within the first 2 months of anti-tuberculous therapy. Table-5 shows patients distribution according to duration of tuberculosis.

Seven patients give history of regular alcohol intake (23.3% of the sample). While 4 patients had been discovered to be hepatitis B positive (13.3% of the sample).

Jaundice was found in 9 patients (30% of the sample), no hepatomegaly or splenomegaly had been detected in anyone of the patients included in this study. No prothrombin time prolongation had been discovered.

Table-1: Patients' distribution according to their demographic features

Age group (year-old)	Male		Female		M:F	Regardless gender	
	No	%	No	%		No	%
20-29	2	8.7%	0	0%	----	2	6.7%
30-39	0	0%	1	14.3%	----	1	3.3%
40-49	3	13%	2	28.6%	1.5:1	5	16.7%
50-59	6	26.1%	0	0%	----	6	20%
60-69	6	26.1%	4	57.1%	1.5:1	10	33.3%
70-79	6	26.1%	0	0%	----	6	20%
Total	23	100%	7	100%	3.28:1	30	100%

Table-2: Patients' distribution according to number of folds increase in their serum ALT level.

Serum ALT	No	%
$\geq 2 \times \text{ULN} < 3 \times \text{ULN}^*$	26	86.7%
$\geq 3 \times \text{ULN}$	4	13.3%
Total	30	100%

Table-3: Patients' distribution according to folds increase in the serum bilirubin level.

Serum bilirubin	No	%
$< 2 \times \text{ULN}$	12	40%
$\geq 2 \times \text{ULN} < 3 \times \text{ULN}$	10	33.3%
$\geq 3 \times \text{ULN}$	8	26.7%
Total	30	100%

Table-4: Patients distribution according to their body mass index.

Patients' classification	BMI	Smoker diabetics	
		No	%
Underweight	< 20	14	46.7%
Normal	20-25	10	33.3%
	26-30	2	6.7%
Obese	31-35	3	10%
	36-	1	3.3%

Table-5: Patients distribution according to duration of tuberculosis.

Time since starting anti-tuberculous therapy	No	%
< 1 month	5	16.7%
1-2 months	16	53.3%
> 2 months	9	30%
Total	30	100%

	40		
Severely obese	>40	0	0%
Total		30	100%

Discussion:

Liver injury in patient on anti-tuberculous treatment often presents the clinician with a difficult problem of management. A reversible moderate increase in transaminase levels occur in about 15-39% of patients on anti-tuberculous treatment⁽¹⁵⁻²⁰⁾. A slight increase in transaminases should not lead to discontinuation of treatment, with the consequent risk of developing drug resistance of the mycobacterial strain. However, it is difficult to predict whether minor abnormalities of the liver function conceal the initial stage of a severe hepatotoxic reaction⁽²¹⁾.

This study revealed that with increasing age, the frequency of anti-tuberculous drugs induced hepatotoxicity would be higher, 73.3% of the sample were older than 50 year old. Those younger than 40 year old comprised only 10% of the sample. Kopanoff et al, had a conclusion that being older than 35 year old, make you at a high risk group in regard to INH hepatotoxicity, with an incidence of 1.2% at the age of 35-49 compared to 4.6% of those older than 65 year old⁽²²⁾. Some authority recommend that those older than 35 year old should receive frequent serum transaminase assays during the first 2 months of therapy and be tested monthly thereafter⁽²⁰⁻²¹⁾.

Being female can be regarded as a risk for more frequent hepatotoxicity, not only anti-tuberculous induced one, but all types of hepatotoxicity. This study showed that 23.3% of the sample were female. The mechanism for this higher risk of drug induced hepatotoxicity among females is not so well explained, but epidemiological evidence suggest that role of female gender in creating this higher risk. In one study, women accounted for 79% of reactions due to acetaminophen and 73% of idiosyncratic drug reaction⁽²³⁾. In regard to anti-tuberculous drug induced hepatotoxicity and especially INH induced liver injury, it had been shown that both men and women tend to be equally vulnerable to mild liver injury⁽²⁴⁻²⁵⁾. But the effect of gender appear more overtly in cases of more severe cases of INH hepatitis⁽²⁶⁻²⁷⁾. Dossing et al, estimated a sex related frequency of liver injury during anti-tuberculous treatment of about the same frequency which had been estimated by this study (36% of the sample included in Dossing et al study)⁽²¹⁾.

It is well known that most of the cases of anti-tuberculous drug induced hepatic injury are of mild type, 10-20% of them presented subclinically with just mild elevation of serum aminotransferase, that is usually less than 100 U/l i.e. <5 times the upper normal limit⁽²⁴⁻²⁵⁾. This study revealed that 86.7% of the sample had elevated serum transaminase of more than twice the upper limit normal but less than 3 times that limit, a finding which is in agreement with the findings of other studies. It is not uncommonly, mildly elevated pretreatment liver enzymes encountered among TB patients without any other evidence of liver disease. When these patients are given the full treatment regimen, their enzyme levels are often observed to revert to normal and this phenomenon is presumably related to the resolution hepatic tuberculous microgranuloma⁽²⁸⁾.

This study revealed that 46.8% of patients with anti-tuberculous drugs induced liver injury were underweight. It had been reported that malnutrition can be considered as a risk factor for liver injury among those who are receiving anti-tuberculous drugs^(22,29-31). This finding could be explained by the fact that underweight can be regarded as an indirect evidence for the severity of tuberculous disease affecting the patient and making him losing weight to the degree that made him underweight or suffering from malnutrition.

This study revealed that 70% of patients with liver injury discovered by this study within the first 2 months after initiation of therapy. Clinical features – Approximately one-half of cases of INH hepatitis occur within the first two months after initiation of therapy; the remaining cases occur as late as 14 months^(30,32). The clinical features are indistinguishable from acute viral hepatitis⁽³³⁾. At

presentation, most patients complain of fatigue, malaise, anorexia, or nausea, with or without vomiting. Approximately one-third have generalized flu-like symptoms, while some experience right upper quadrant pain. These symptoms generally appear days to several weeks before the onset of clinical jaundice, which is the presenting feature in approximately 10 percent of cases^(33, 53-64).

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