

# A study of the various factors associated with drug induced hepatitis in the patients taking antitubercular drugs at tertiary health care centre

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## Abstract

**Background:** Antituberculous therapy induced hepatitis is an important cause of morbidity and mortality in developing countries where the incidence of pulmonary tuberculosis is high. **Aims and Objectives:** To study the various factors associated with Drug induced Hepatitis in the patients taking Antitubercular drugs at tertiary health care centre. **Methodology:** Patient attending OPD at a tertiary hospital who are started on AKT and following regularly will be included. Patient from CAT 1 and from CAT 2 attending OPD who are started on AKT was included (pulmonary and extra pulmonary and CAT1 and CAT 2) During one year June 2009 to May 2010. The qualitative variables was analysed by chi- square test. for the comparison of quantitative data, the students t test was applied. The values of  $p < 0.05$  were regarded as significant. **Result:** The Category of DOTS Treatment, BMI, Sex, Alcohol Intake etc. were not significantly associated with the development of Hepatitis ( $P > 0.05$ ). **Conclusion:** It can be concluded from our study that Correlation between age, sex and incidence of ATT induced hepatitis is controversial and requires further studies. In our study occurrence was more in young males. Correlation between incidence of ATT induced hepatitis and nutrition is controversial and it is more common in people with low BMI in our study. Chronic alcoholism is not an independent risk factor. However history of prior alcohol induced hepatitis or alcohol induced liver disease has been well established as risk factor for drug induced hepatitis.

**Key Words:** Drug induced Hepatitis, Antitubercular drugs, Risk factors of Drug induced Hepatitis.

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Received Date: 14/05/2017 Revised Date: 28/06/2017 Accepted Date: 20/07/2017

DOI: <https://doi.org/10.26611/10213112>

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	Accessed Date: 26 July 2017

## INTRODUCTION

Antituberculous therapy induced hepatitis is an important cause of morbidity and mortality in developing countries where the incidence of pulmonary tuberculosis is high. The incidence of pulmonary tuberculosis is high in

developing countries<sup>1,2</sup>. The incidence for tuberculosis in India is 1.68/1000 population<sup>3,4</sup>. For treatment of pulmonary tuberculosis, multidrug therapy is used worldwide so as to prevent development of drug resistance. The drugs used as first line multidrug therapy are:

1. Isoniazid
2. Rifampicin,
3. Pyrazinamide
4. Ethambutol.
5. Streptomycin.

However rifampicin, isoniazid and pyrazinamide all are hepatotoxic<sup>5</sup>. Despite the availability of effective chemotherapeutic agents that exist to treat this illness, hepatotoxicity from first line drugs such as isoniazid (INH), rifampicin and pyrazinamide is common and may limit their use<sup>6</sup>. Several studies has shown that alcohol

use<sup>6,7,8</sup> increasing age<sup>9,10,11,12</sup>, nutritional status<sup>13,14</sup>, presence of chronic liver disease<sup>11,12,13</sup> and infection by hepatitis b virus<sup>20</sup>, infection by hepatitis c virus<sup>15,16</sup>, certain genetic factors<sup>10,11,12</sup> concomitant use of other hepatotoxic drugs<sup>14</sup> have been reported to increase the risk of antituberculosis drug induced hepatotoxicity<sup>13,14</sup>. The exact mechanism of this liver toxicity remains unclear. Populations such as those with human immunodeficiency virus (infection), the elderly, substance abusers and immigrants from countries with a high incidence of TB are more likely to develop DIH<sup>17</sup>. However results have been reported by other workers and consensus regarding their role is lacking<sup>18,19</sup>. Role of genetic factors has been suggested by some workers<sup>20</sup>. There are no definite recommendation as to whether AKT should be stopped (all drugs) and what should be the schedule for reintroduction of these agents<sup>21</sup>. In view of above the present study is undertaken to study the incidence of AKT induced hepatitis and role of clinical markers in development of AKT induced hepatitis.

### MATERIAL AND METHODS

Patient ATTending OPD at a tertiary hospital who are started on AKT and following regularly will be included. Patient from CAT 1 and from CAT 2 ATTending OPD who are started on AKT was included (pulmonary and extra pulmonary and CAT1 and CAT 2) During one year June 2009 to May 2010 These patients will be started on ATT at DOTS center and will be followed up regularly while they were receiving ATT. The age, sex body mass index and chronic alcoholism affect the development of ATT induced hepatotoxicity and the factors predisposing were studied. The qualitative variables was analysed by chi-square test. for the comparison of quantitative data, the students t test was applied. The values of p<0.05 were regarded as significant. The results are expressed as the mean plus minus SD

### RESULT

**Table 1:** Category wise Distribution Of Hepatitis In The Study Group

		Presence of hepatitis			Total
		Hepatitis	No hepatitis		
category	CAT I	Count	3	37	40
		% of Total	4.3%	52.9%	57.1%
	CAT II	Count	2	28	30
		% of Total	2.9%	40.0%	42.9%
<b>Total</b>		<b>Count</b>	<b>5</b>	<b>65</b>	<b>70</b>
		<b>% of Total</b>	<b>7.1%</b>	<b>92.9%</b>	<b>100.0%</b>

Applying chi square test p value is 0.893 which is not statistically significant

**Table 2:** Correlation of BMI and hepatitis

		Presence of hepatitis		Total	
		No hepatitis	Hepatitis		
BMIcat	<=18.5	Count	28	3	31
		% of Total	40.0%	4.3%	44.3%
	>18.5	Count	37	2	39
		% of Total	52.9%	2.9%	55.7%
<b>Total</b>		<b>Count</b>	<b>65</b>	<b>5</b>	<b>70</b>
		<b>% of Total</b>	<b>92.9%</b>	<b>7.1%</b>	<b>100.0%</b>

By Application of Chi Square Test P Value Is 0.649 Which Is Not Statistically Significant

**Table 3:** Correlation of sex and hepatitis

		Presence of hepatitis		Total	
		Hepatitis	No hepatitis		
Sex	Male	Count	4	43	47
		% of Total	5.7%	61.4%	67.1%
	Female	Count	1	22	23
		% of Total	1.4%	31.4%	32.9%
<b>Total</b>		<b>Count</b>	<b>5</b>	<b>65</b>	<b>70</b>
		<b>% of Total</b>	<b>7.1%</b>	<b>92.9%</b>	<b>100.0%</b>

By Applying Chi Square Test, P Value Is 1 Which Is Not Statistically Significant

**Table 4:** Correlation of Alcohol Intake and Hepatitis

		Presence of hepatitis		Total	
		No hepatitis	Hepatitis		
Alcohol	A	Count	11	1	12
		% of Total	15.7%	1.4%	17.1%
	NA	Count	54	4	58
		% of Total	77.1%	5.7%	82.9%
<b>Total</b>		<b>Count</b>	<b>65</b>	<b>5</b>	<b>70</b>
		<b>% of Total</b>	<b>92.9%</b>	<b>7.1%</b>	<b>100.0%</b>

By Application of Chi Square Test P Value Is 1 Which Is Not Statistically Significant

### DISCUSSION

Even though studies have reported that the risk of ATT induced hepatitis increases with advancing age<sup>16, 17</sup> done by telemanm. d, cheec.b, earnest. c.r, selft.h. *et al.* the highest incidence being in individuals greater than 50 years of age. Our study shows the incidence of hepatitis is more in younger age group this is in accordance with nepal study done by rajanishakyarao and bs bhavana shriestha. Similar result was shown by some indian studies. where asno significant correlation was found in afmc study done by scientists as above and two other studies from Spain done by fernandezvillar, r.vazquez, gallado, f.ulloa, v.leiro, m.mosteiro, l.pifieirothus the role for older. Age on incidence of ATT induced hepatitis remains controversial. Also the population studied in this study is of younger age group predominantly also the incidence of tuberculosis is more in younger age group. Females are considered as having higher risk and it was linked to various causes such as lower biotransformation

and subsequent clearance of exogenous molecules due to lower level of microsomal enzymes, slow acetylator enzymatic pattern. However as per popular belief that females are at more risk of developing ATT induced hepatitis. And also studies showing more incidence in female sex.<sup>25</sup> This studies were done by Kopanoff, E., Sander, Caras *et al* our study showed no significant correlation between female sex and incidence of hepatitis. Similar has been reported by previous three studies<sup>18</sup> out of the 69 patients who developed hepatotoxicity in Nepal study 47 were males. Aims study also showed more males affected that is 33 out of 60 patients done by Tanejad, P., Kaurd, Desprez, M *et al*. Also the number of females in the study group was small. Under nutrition has been considered as a risk factor for development of ATT induced hepatitis in the literature and shown to affect the incidence of ATT induced hepatitis. The depletion of glutathione store and slow rate of liver enzyme metabolism was considered responsible. The same is shown by various studies<sup>22</sup> done by Gronhagen-Riska, C., P. E. Hellstrom, and B. Froseth. Indicators were used to assess undernutrition such as BMI, serum albumin level, serum cholesterol level. We used BMI as indicator of under nutrition. In our study incidence of hepatitis was more in patients with low BM. Chronic alcoholism causes liver damage, hepatitis and cirrhosis this is thought to increase the risk of hepatitis in patients on ATT. Chronic alcoholism has been stated as important risk factor for hepatitis and studies also shows same results. However in our study we did not find significant correlation between chronic alcoholism and ATT induced hepatitis. This is in accordance to results found by 3 studies previously done<sup>23</sup> because they did not have alcohol induced liver disease. Scientists name as mentioned above. Also all the 5 patients who developed hepatitis were not having previous history of hepatitis in our study. We also assessed time of development of hepatitis in patients out of 5 patients who developed hepatitis in our study, two developed within fifteen days and three developed within second month this was in accordance to the results obtained in various studies done previously stating that hepatitis is common in first 8 weeks of therapy. This also supports the possibility of immunological mechanism for induced hepatotoxicity. Patients enrolled in this study were taking combination of drugs. Due to this reason it is difficult to conclude which drug was the main culprit for causing hepatitis. Although isoniazid is the main culprit causing hepatic injury, role of other drugs is also there previous studies conducted have proven that the risk is in the order of isoniazide+rifampicin greater than isoniazid. Isoniazid greater than pyrazinamide. pyrazinamide greater than rifampicin. rifampicin greater than

ethambutol.<sup>24</sup> These studies were done by Garibaldi R, Drusin, Freibes, Gregg M.

## CONCLUSION

Correlation between age, sex and incidence of ATT induced hepatitis is controversial and requires further studies. In our study occurrence was more in young males. Correlation between incidence of ATT induced hepatitis and nutrition is controversial and it is more in common in people with low BMI in our study. Chronic alcoholism is not an independent risk factor. However history of prior alcohol induced hepatitis or alcohol induced liver disease has been well established as risk factor for drug induced hepatitis.

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Source of Support: None Declared  
Conflict of Interest: None Declared

