Original Research Article

A study of changes in SGPT and SGOT over time the patients of drug induced hepatitis taking antitubercular drugs

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Abstract

Background: The reported incidence of hepatotoxicity and its clinical types is considerable in the medical literature, ranging from 2.5% to 39% **Methodology:** The study is aimed at studying clinical spectrum of ATT induced hepatotoxicity. Patient attending OPD at a tertiary hospital who are started on AKT and following regularly was included, Patient with tuberculosis who received the full course of ATT without developing hepatitis was formed the control group. The SGPT and SGOT over time the patients of Drug induced Hepatitis taking Antitubercular drugs was monitored. **Results:** At baseline correlation before starting antitubercular drugs. There were 51 patients that is 79.7% showing SGOT and SGPT less than equal to 40, fifteen days after starting antitubercular drugs there were 22 patients that is 62.9% showing SGOT and SGPT less than equal to 40.one month after starting antitubercular drugs. There were 14 patients that is 48.3% showing SGOT and SGPT less than equal to 40.There were 15 patients that is 57.1% showing SGPT between 41 to 120 and SGOT less than equal to 40, two month after starting antitubercular drugs. There were 12 patients that is 63.2% showing SGOT and SGPT less than equal to 40.There were 46 patients that is 95.8% showing SGOT and SGPT between 41 to 120. Three month after starting antitubercular drugs, 12 patients that is 60% showing SGPT between 41 to 120 and SGOT less than equal to 40, 48 patients that is 98% showing SGOT and SGPT between 41 to 120.four month after starting antitubercular drugs There were 40 patients that is 85.1% showing SGOT and SGPT between 41 to 120.Fivemonth after starting antitubercular drugs; There were 37 patients that is 92.5% showing SGOT and SGPT between 41 to 120. Six month after starting antitubercular drugs There were 38 patients that is 88.4% showing SGOT and SGPT between 41 to 120. **Conclusion:** It can be concluded from our study that as the time increases the SGPT and SGOT was raised concurrently; at the base majority of the patients were having the values in the normal range but over the time majority were having the deranged means the antitubercular damage liver over the time.

Key Words: SGPT, SGOT, Drug induced Hepatitis, Antitubercular drugs.

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INTRODUCTION

Introduction :Criteria for anti tuberculous drugs therapy induced hepatitis[1]. Normal liver chemistries prior to starting an anti-TB drug regimen. Patients had to be receiving INH, RIF, PZA, in standard doses, in combination for at least 5 days prior to the development of abnormal liver chemistries. While receiving anti-TB treatment, there had to be an increase in ALT and / or AST to ≥ 120 IU / L (normal ≤ 40 IU / L) and or an increase in total bilirubin to greater than 1.5 mg/dl (normal less than 1.5 mg/dl), with SGOT >SGPT. No other apparent cause for the elevation of liver chemistries. Removal of the medications resulted in a normalization or at least a 50% improvement of the abnormal liver chemistries. Why only some patients who receive AKT develop hepatitis is not clear and several studies searched for host factors, environmental factors or some interaction among various factors. The reported incidence of hepatotoxicity and its clinical types is considerable in the medical literature, ranging from 2.5% to 39% [2,3,4,5,6]. The

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studies were done by steelem.a., Burk R.F., Desprez R.M. *et al*. Teleman M.D, Cheec. B, Earnest A Wang Y.T. *et al* Sharma S.K, Balamurugan A, Saha P. K., Pandey R.M, Mehra N.K e*t al*. Pande J.N, Singh S.P, Khilnani G. C, Khilnani S, Tendon R.K *Et al* Huang Y.S,Chern H.D, SuW.J, *et al* ,Ungo J, Jones D, Ashkin D *et al*. A higher risk of hepatotoxicity has been reported in Indian patients than in their western counterparts[7,8]. These studies were done by singh j gargp. k tendon r. k *et al* dull a.k., moers d. sleadw. w. *et al*. The risk of hepatotoxicity based on data from four prospective Indian studies was 11.5% compared with 4.3% in western publications [9].This study was done by steelem. a, burkr. f, desperezr. m *et al* A study on the incidence and clinical profile of hepatotoxicity due to antituberculosis therapy and the incidence of anti tuberculous therapy induced hepatitis as 8.4%[7,8.] This study was done by singh j gargp. k. tendon r. k. *et al* and other one was singh j aroraa, gargp K. Thakur V. S., Pandeyj. N. Tendon R. K. *et al* Other study done by Mahashur A. A., prabhudesai p.p. *et al*. showed incidence of 11%[11]. The incidence in Nepal study done by Rajanishakyaraob. S, bhavanashrieshtha *et al*. was 8%[12]. While AFMC study done by Col. A.C. Anand, V.S. M, LtCOL A. K. Seth, Lt.col. M. paul, Lt.Col.p.puri *et al* showed incidence of 11% [13]. In western contries, 2 studies conducted, of which first showed incidence of 4.1% and other study showed incidence of 4.5%. Although Not Fully Clear, Such Variations Could Be Due To: The different diagnostic criteria used to define hepatotoxicity, the characteristic and risk factors of the populations studied, The geographic area or the type of monitoring and the tests carried out on patients during follow-up [3,4,5]. The different diagnostic criteria used therefore prevent comparison. Mechanism of AKT Induced Hepatitis: The underlying mechanism of AKT – induced heptotoxicity has not been clearly understood. Isoniazid hydrochloride (INH):Isoniazid Metabolism: Isoniazid is cleared mostly by the liver, primarily by acetylating by N-acetyl transferase 2 (NAT – 2). Acetyl – isoniazid is metabolized mainly to as other minor metabolites [14]. Inter individual variation in plasma elimination half-life (t ½). Independent of drug dose and concentration, is considerable. Individuals with prolonged t ½ have extended exposure to the drug. Genetic polymorphisms of NAT–2 correlate with fast, slow, and intermediate acetylation phenotypes [14]. Microsomal enzymes (e.g., cytochrome P450 2E1) further metabolize isoniazid intermediates through phase 1 pathways [15]. Mechanism of Injury: Oxidative Stress [18]: Reactive metabolites of MAH are probably toxic to tissues through free radical generation [(48)and]nitrogen intermediates. These metabolites generates free radicals such as superoxide, hydrogen peroxide and hydroxy1 radicals. Superoxide, in presence of nitric oxide (NO), preferable react with it resulting in formation of peroxynitratitie, a highly reactive spacies. Further, the free radical sevaenging activities of glutathione-related thiols, and antioxidant glutathione peroxidase and catalase activities, are diminished by isoniazid, but because of that the glutathione reductase activity is increased [17]. The antioxidant N-acetyl – cystine, which is a substrate for glutathione synthesis, inhibits isoniazid induce liver injury [17]. Idiosyncratic Mechanisms [16]: Additional metabolic idiosyncratic mechanisms appear to be operative in INH induced hepatotoxicity. In some individuals, severe drug reaction to INH noted. These reactions are mediated by either immunological mechanism or are idiosyncratic. In these reactions, the metabolites of INH, mono-acetyl hydrazine (MAH) nontoxic diacetyl hydrazine, as well as other minor metabolites modifies the liver protein, Cytochrome P450, which generates these metabolites. The immune reaction directed against this modified CYP produce severe hepatitis in susceptible individuals. The isoniazid metabolite acetyl-hydrazine covalently binds to liver macromolecules, a process mediated by microsomal enzymes [19]. Patients with homozygous cytochrome P450 2 El c1/c1 host gene polymorphism, who have enhanced cytochrome P450 2 E1 activity, in one study had a higher risk of hepatotoxicity, particularly in slow acetylators[15]. TNF – alpha Mediated Apoptosis: A study from the institute of Postgraduate Medical Education and Research in Kolkata, India, investigated the role of TNF – alpha in murine model of hepatotoxicity INH-induced injury was indeed found to be associated with amintransferase elevation and histological changes. Reduced glutathione ratio was taken as evidence of oxidative injury. TUNEL (Terminal Deoxynucleotidy1 Transferase Mediated Deoxyuridine Triphosphate Nick End Labeling) assay confirmed the presence of apoptosis. It is important to note that TNF-alpha expression was increased in the INH-treated mice. Pretreatment of the mice with pentoxifylline (inhibits TNF – alpha production) and gadolinium chloride (deplete kupffer cells) lowered hepatic TNF – alpha levels, decreased aminotransferase levels and decreased hepatic apoptosis. The study concluded those TNF-alpha – blocking strategies may have potential significance in human INH – hepatotoxicity. An increase in serum ALT, previously known as serum glutamate pyruvate transaminase (SGPT), is more specific for hepatocellular injury than an increase in asparte aminotransferase (AST or serum glutamic oxaloacetic transaminase (SGOT]) which can also significantly raised in abnormalities in muscle heart or kidney. Serum enzyme concentrations are measured by functional catalytic assays with normal values established from “healthy” populations. The normal range lies within

2 standard deviations of the mean of the distribution. With 2.5% of persons who are otherwise healthy having concentration above and below the limits of normal on a single measurement populations used to set standard values in the past probably included individuals with occult liver disease, whose exclusion has led to decreases in the upper limit of normal. Increase in alkaline phosphatase and or bilirubin with little or no increase in ALT indicates cholestasis. Alkaline phosphatase concentration may also increase because of processes in bone, placenta, or intestine. An increased concentration of serum χ-glutamy1 transpeptidase, an inducible anzyme expressed in hepatic cholangioles, is useful in distinguishing liver related from other organ-related alkaline phosphatase increases. Jaundice is usually detectable on the physical examination when serum bilirubin exceeds 3.0 mg/dl.

MATERIAL AND METHODS

The study is aimed at studying clinical spectrum of ATT induced hepatotoxicity. Patient attending OPD at a tertiary hospital who are started on AKT and following regularly was 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). Basal LFT level was measured followed by monitoring LFT at interval of every 2 weeks in intensive phase and once in every month in continuation phase. Duration of study was 1 year. These patients was started on ATT at DOTS centre was followed up regularly while they were receiving ATT. In all patient who present with hepatitis while on ATT, sera was analysed for the presence of markers of viral hepatitis, those patients whose results of serologic tests indicates that the hepatitis was of viral orgin are to be excluded. A complete lever function profile including serum bilirubin, serum aminotransferase, total protein and serum albumin and serum alkaline phosphtase was carried out in all patients of both groups. The criteria followed for dignosing hepatitis was clinical manifestations of hepatitis like anorexia nausea vomiting and jaundice along with elevation of serum transaminases more than three times the normal upper limit along with the symptoms of jaundice and elevation of serum transaminases five times above the upper limit of normal without symptoms.Patient with tuberculosis who received the full course of ATT without developing hepatitis was formed the control group.Control group was assessed clinically for response to treatment in view of cough, fever, weight gain, and side effects like nausea and vomiting. and also their liver function test was monitored for every two weeks in the intensive phase and every month in the continuation phase.

RESULT

Table 1: SGOT and SGPT baseline crosstable in the study group

		SGOT base					
		<=40		41-120		>120	
		Count	Column N %	Count	Column N %	Count	Column N %
SGPT base	<=40	51	79.7%	0	0%	0	0%
	41-120	13	20.3%	6	100.0%	0	.0%
	>120	0	.0%	0	.0%	0	.0%
	Total	**64**	**100.0%**	**6**	**100.0%**	**0**	**.0%**

Table 1. shows SGOT and SGPT baseline correlation before starting antitubercular drugs. There were 51 patients that is 79.7% showing SGOT and SGPT less than equal to 40. There were 13 patients that is 20.3% showing SGPT between 41 to 120 and SGOT less than equal to 40. There were no patients showing SGPT levels greater than 120 and SGOT levels less than equal to 40.There was no patient showing SGOT between 41 to 120 and SGPT less than equal to 40. There were 6 patients showing SGOT and SGPT between 41 to 120. There were no patients showing SGOT between 41 to 120 and SGPT greater than 120. There were no patients showing SGPT less than equal to 40 and SGOT greater than 120. There were no patients showing SGOT greater than 120 and SGPT between 41 to120.There were no patients showing SGOT and SGPT greater than 120.

Table 2: SGOT and SGPT fifteen days crosstable in the study group

		SGOT fifteen					
		<=40		41-120		>120	
		Count	Column N %	Count	Column N %	Count	Column N %
SGPT fifteen	<=40	22	62.9%	3	9.1%	0	.0%
	41-120	13	37.1%	30	90.9%	0	.0%
	>120	0	.0%	0	.0%	2	100.0%
	Total	**35**	**100.0%**	**33**	**100.0%**	**2**	**100.0%**

Table 2 : shows SGOT and SGPT correlation fifteen days after starting anti-tubercular drugs. There were 22 patients that is 62.9% showing SGOT and SGPT less than equal to 40.There were 13 patients that is 37.1% showing SGPT between 41 to 120 and SGOT less than equal to 40. There were no patients showing SGPT levels greater than 120 and SGOT levels less than equal to 40. There were 3 patients that is 9.1% showing SGOT between 41 to 120 and SGPT less than equal to 40.There were 30 patients that is 90.1% showing SGOT and SGPT between 41 to 120. There were no patients showing SGOT between 41 to 120 and SGPT greater than 120.There were no patients showing SGPT less than equal to 40 and SGOT greater than 120. There were no patients showing SGOT greater than 120 and SGPT between 41 to 120.There were 2 patients that is 100% showing SGOT and SGPT greater than 120.

Table 3: SGOT and SGPT one month crosstable in the study group

		SGOT one					
		<=40		41-120		>120	
		Count	Column N %	Count	Column N %	Count	Column N %
SGPT one	<40	14	48.3%	2	4.9%	0	.0%
	41-120	15	51.7%	39	95.1%	0	.0%
	>120	0	.0%	0	.0%	0	.0%
	Total	**29**	**100.0%**	**41**	**100.0%**	**0**	**.0%**

Table 3: shows SGOT and SGPT correlation one month after starting antitubercular drugs. There were 14 patients that is 48.3% showing SGOT and SGPT less than equal to 40.There were 15 patients that is 57.1% showing SGPT between 41 to 120 and SGOT less than equal to 40. There were no patients showing SGPT levels greater than 120 and SGOT levels less than equal to 40.There were 2 patients that is 4.9% showing SGOT between 41 to 120 and SGPT less than equal to 40.There were 39 patients that is 95.1% showing SGOT and SGPT between 41 to 120.There were no patients showing SGOT between 41 to 120 and SGPT greater than 120. There were no patients showing SGPT less than equal to 40 and SGOT greater than 120. There were no patients showing SGOT greater than 120 and SGPT between 41 to120.There were no patients showing SGOT and SGPT greater than 120.

Table 4: SGOT and SGPT two month crosstable in the study group

		SGOT two					
		<=40		41-120		>120	
		Count	Column N %	Count	Column N %	Count	Column N %
SGPT two	<40	12	63.2%	2	4.2%	0	.0%
	41-120	7	36.8%	46	95.8%	0	.0%
	>120	0	.0%	0	.0%	3	100.0%
	Total	**19**	**100.0%**	**48**	**100.0%**	**3**	**100.0%**

Table 4 : shows SGOT and SGPT correlation two month after starting antitubercular drugs. There were 12 patients that is 63.2% showing SGOT and SGPT less than equal to 40.There were 7 patients that is 36.8% showing SGPT between 41 to 120 and SGOT less than equal to 40. There were no patients showing SGPT levels greater than 120 and SGOT levels less than equal to 40.There were 2 patients that is 4.2% showing SGOT between 41 to 120 and SGPT less than equal to 40.There were 46 patients that is 95.8% showing SGOT and SGPT between 41 to 120.There were no patients showing SGOT between 41 to 120 and SGPT greater than 120.There were no patients showing SGPT less than equal to 40 and SGOT greater than 120. There were no patients showing SGOT greater than 120 and SGPT between 41 to120.There were 3 patients that is 100% showing SGOT and SGPT greater than 120.

Table 5: SGOT and SGPT three month crosstable in the study group

		SGOT three					
		<=40		41-120		>120	
		Count	Column N %	Count	Column N %	Count	Column N %
SGPT three	<40	8	40.0%	1	2.0%	0	.0%
	41-120	12	60.0%	48	98.0%	0	.0%
	>120	0	.0%	0	.0%	0	.0%
	Total	**20**	**100.0%**	**49**	**100.0%**	**0**	**.0%**

Table 5: shows SGOT and SGPT correlation three month after starting antitubercular drugs. There were 8 patients that is 40% showing SGOT and SGPT less than equal to 40.There were 12 patients that is 60% showing SGPT between 41 to 120 and SGOT less than equal to 40. There were no patients showing SGPT levels greater than 120 and SGOT levels less than equal to 40.There was 1 patient that is 2% showing SGOT between 41 to 120 and SGPT less than equal to 40.There

were 48 patients that is 98% showing SGOT and SGPT between 41 to 120.There were no patients showing SGOT between 41 to 120 and SGPT greater than 120.There were no patients showing SGPT less than equal to 40 and SGOT greater than 120..There were no patients showing SGOT greater than 120 and SGPT between 41 to120.There were no patients that is 100% showing SGOT and SGPT greater than 120.

Table 6: SGOT and SGPT four month crosstable in the study group

		SGOT four					
		<=40		41-120		>120	
		Count	Column N %	Count	Column N %	Count	Column N %
SGPT four	<=40	11	47.8%	7	14.9%	0	.0%
	41-120	12	52.2%	40	85.1%	0	.0%
	>120	0	.0%	0	.0%	0	.0%
	Total	**23**	**100.0%**	**47**	**100.0%**	**0**	**.0%**

Table 6: shows SGOT and SGPT correlation four month after starting antitubercular drugs. There were 11 patients that is 47.8% showing SGOT and SGPT less than equal to 40.There were 12 patients that is 52.2% showing SGPT between 41 to 120 and SGOT less than equal to 40. There were no patients showing SGPT levels greater than 120 and SGOT levels less than equal to 40.There were 7 patients that is 14.9% showing SGOT between 41 to 120 and SGPT less than equal to 40.There were 40 patients that is 85.1% showing SGOT and SGPT between 41 to 120.There were no patients showing SGOT between 41 to 120 and SGPT greater than 120.There were no patients showing SGPT less than equal to 40 and SGOT greater than 120..There were no patients showing SGOT greater than 120 and SGPT between 41 to120.There were no patients that is showing SGOT and SGPT greater than 120.

Table 7: SGOT and SGPT five month crosstable in the study group

		SGOT five					
		<=40		41-120		>120	
		Count	Column N %	Count	Column N %	Count	Column N %
SGPT five	<=40	21	70.0%	3	7.5%	0	.0%
	41-120	9	30.0%	37	92.5%	0	.0%
	>120	0	.0%	0	.0%	0	.0%
	Total	**30**	**100.0%**	**40**	**100.0%**	**0**	**.0%**

Table 7: shows SGOT and SGPT correlation five month after starting antitubercular drugs. There were 21 patients that is 70% showing SGOT and SGPT less than equal to 40.There were 9 patients that is 30% showing SGPT between 41 to 120 and SGOT less than equal to 40. There were no patients showing SGPT levels greater than 120 and SGOT levels less than equal to 40.There were 3 patients that is 7.5% showing SGOT between 41 to 120 and SGPT less than equal to 40.There were 37 patients that is 92.5% showing SGOT and SGPT between 41 to 120.There were no patients showing SGOT between 41 to 120 and SGPT greater than 120.There were no patients showing SGPT less than equal to 40 and SGOT greater than 120..There were no patients showing SGOT greater than 120 and SGPT between 41 to120.There were no patients that is showing SGOT and SGPT greater than 120.

Table 8: SGOT and SGPT six month crosstable in the study group

		SGOT six					
		<=40		41-120		>120	
		Count	Column N %	Count	Column N %	Count	Column N %
SGPT six	<40	16	59.3%	5	11.6%	0	.0%
	41-120	11	40.7%	38	88.4%	0	.0%
	>120	0	.0%	0	.0%	0	.0%
	Total	**27**	**100.0%**	**43**	**100.0%**	**0**	**.0%**

Table 8: shows SGOT and SGPT correlation six month after starting antitubercular drugs. There were 16 patients that is 59.3% showing SGOT and SGPT less than equal to 40.There were 11 patients that is 40.7% showing SGPT between 41 to 120 and SGOT less than equal to 40. There were no patients showing SGPT levels greater than 120 and SGOT levels less than equal to 40.There were 5 patients that is 11.6% showing SGOT between 41 to 120 and SGPT less than equal to 40.There were 38 patients that is 88.4% showing SGOT and SGPT between 41 to 120.There were no patients showing SGOT between 41 to 120 and SGPT greater than 120.There were no patients showing SGPT less than equal to 40 and SGOT greater than 120.There were no patients showing SGOT greater than 120 and SGPT between 41 to120.There were no patients showing SGOT and SGPT greater than 120.

DISCUSSION

Laboratory Monitoring: A benefit of ALT and or bilirubin monitoring in preventing or alleviating drug induced liver injury has not been rigorously tested. A recent small nonrandomized report suggested that monitoring may decrease the severity of pyrazinamide induced liver injury. **Disadvantages of Laboratory Monitoring:** Questionable cost – efficacy of frequent testing for rare adverse events, Development and progression of injury between testing events, Unclear enzyme thresholds for medication discontinuation, Confusion of hepatic adaption with significant liver injury. The cost of obtaining AST with ALT is often marginal and may be useful in identifying alchol-related transaminase elevation, where the AST is characteristically higher than the ALT. The diagnosis of a superimposed injury may be difficult with initially abnormal or fluctuating transaminases. Prior laboratory data may be of use in this regard. Monitoring and the use of a potentially less hepatotoxic regimen is generally recommended for those with preexisting liver disease in the hope that superimposed drug induced hepatitis may be detected preclinically and mitigated. Transaminase elevation during the course of anti-TB therapy may in some instances actually represent coincidentally developed hepatitis. In our studyat baseline correlation before starting antitubercular drugs. There were 51 patients that is 79.7% showing SGOT and SGPT less than equal to 40, fifteen days after starting antitubercular drugs there were 22 patients that is 62.9% showing SGOT and SGPT less than equal to 40. one month after starting antitubercular drugs. There were 14 patients that is 48.3% showing SGOT and SGPT less than equal to 40.There were 15 patients that is 57.1% showing SGPT between 41 to 120 and SGOT less than equal to 40, two month after starting antitubercular drugs. There were 12 patients that is 63.2% showing SGOT and SGPT less than equal to 40. There were 46 patients that is 95.8% showing SGOT and SGPT between 41 to 120. Three month after starting antitubercular drugs, 12 patients that is 60% showing SGPT between 41 to 120 and SGOT less than equal to 40, 48 patients that is 98% showing SGOT and SGPT between 41 to 120. four month after starting antitubercular drugs There were 40 patients that is 85.1% showing SGOT and SGPT between 41 to 120. five month after starting antitubercular drugs. There were 37 patients that is 92.5% showing SGOT and SGPT between 41 to 120. six month after starting antitubercular drugs There were 38 patients that is 88.4% showing SGOT and SGPT between 41 to 120. Hepatitis was 7.1%. That is about 5 patients out of which 2 were in 20 to 30 years age group 2 were in 30 to 40 years of age group and one was in 40 to 50 years of age group which is similar to that reported in other indian studies. [11] this studies are done by many indian authors such as mahashur and prabhudesai *et al* an indian study on clinical profile hepatotoxicity due to antituberculous therapy and the incidence Of antitubercular therapy induced hepatitis was 11% in this study(2)The studies done by singhtandon and gargetal. showed incidence of 8.4%[3,14]. The incidence in nepal study which was done by rajanishakyaraobs bhavana shrieshtha *et al* was 8%(132). while afmc study which was done by col. A. C. Anand V.S.M., Lt Col. M. paul, L.t. Col. p.puri *et al* showed incidence of 11% [13].

CONCLUSION

It can be concluded from our study that as the time increases the SGPT and SGOT was raised concurrently; at the base majority of the patients were having the values in the normal range but over the time majority were having the deranged means the antitubercular damage liver over the time.

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