Indian Journal of Clinical Biochemistry, 2006, 21 (1) 161-164

CHORONIC EFFECTS OF LAMOTRIGINE ON LIVER FUNCTION IN ADULT MALE RATS

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ABSTRACT

A number of newly developed antiepileptic drugs are currently in use, among them Lamotrigine (LTG) is more common. Despite the extensive use of this drug, it has not been possible to predict the side effects especially the hepatotoxic reactions after long-term treatment. The present study was designed to find out alterations in the activities of liver enzymes after chronic exposure of rats to different dose of LTG. Adults male (Wistar) rats were treated orally with LTG [5 mg/kg body weight or 25mg/kg body wt.] for 60 days. After the experimental period, auto analyzer carried out liver function tests. The liver histopathology was obtained after scarifying the rats.There was a significant increase in the level of ALP, AST, ALT and bilirubin at therapeutic dose of LTG. The increase level of these enzymes and bilirubin at toxic dose were much higher and significant. However, the total protein and albumin significantly decreased at toxic dose of LTG. Elevation of liver enzymes and bilirubin after chronic exposure of rats to high dose of LTG reflects hepatocellular damage that may lead to hepatitis. It is concluded that regular liver function and drug monitoring should follow the treatment with LTG.

KEY WORDS

Antiepileptic, Lamotrigine, and Liver function, Hepatitis.

INTRODUCTION

Lamotrigine (LTG) chemically 6- (2,3- dichlorophenyl)-1,2,4-triazine 3,5-diamine $C_9H_7Cl_2N_5$ is a newly developed antiepileptic drug (AED) derived from pyrimethamine, which is chemically different from commonly available AEDS. It is effective in treating both partial and generalized seizure. LTG most probably exerts its antiepileptic activity by blocking the release of excitatory neurotransmitters, principally glutamate and aspartate in the central nervous system(1, 2). At present it is one of the AEDS, which is frequently used in the medical world. Patients receiving chronic treatment with Lamotrigine in the form of single or polytherapy are at a high risk of developing signs and symptoms of drug toxicity. The most common sources of information on these drug toxicities are case reports and clinical trials which are better reflections of the prevalence and clinical implications of drug toxicity. A case of fatal progressive hepatotoxicity in a patient treated with LTG was reported (2, 3). Liver, particularly, is vulnerable to drug -induced toxicity mainly because of its role as a primary organ of drug elimination and its subsequent exposure to potential toxins. Many commonly prescribed medications including virtually all of the major antiepileptic drugs can cause hepatotoxicity. Hepatic reactions to LTG ranged from transient elevation of hepatic enzymes without clinical signs or symptoms of hepatic dysfunctions to fatal hepatotoxicity (3, 4, 5). In the light of potential toxicity, clinicians prescribing LTG as a single therapy or polytherapy must be alert to the possibility of serious hepatic reactions particularly in case of polytherapy with enzyme inducing agents, each of which may contribute to the overall risk of hepatic dysfunction. The relative role of LTG in elevation of liver enzymes as a whole is difficult to assess on the basis of case reports alone, because of various factors interfering the results.

In this study, animal experiment was designed to rule out the other possible factors influencing the hepatic reaction with LTG and examined the LTG single therapy in two different doses, to evaluate its potential hepatotoxicity by analyzing liver function test in serum

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and hepatocellular damage in liver tissue after chronic exposure of adult male rats.

MATERIALS AND METHODS

Lamotrigine was obtained from local pharmaceutical supplier, Bakhtar Bioshimi Co., Kermanshah, Iran. The rats were obtained from Fasa University of Medical Sciences Animal Research Center, and the device used for biochemical analysis was an auto analyzer, (Hitachi, Japan).

A total number of sixty adult male Wistar rats weighing 180-220 gms had *ad-libitum* access to water and semi synthetic balanced diet, with occasional supply of green vegetables (salad leaves). Rats were caged four per Perspex experimental cages at room temperature (22 - 25ºC). Twelve hours of light and dark cycles were strictly followed in a fully ventilated room .The rats were divided into 3 groups of control and experimental 1 and 2. The control group received vehicle (distilled water) whereas, the experimental groups received Lamotrigine orally by means of gastric tube, as given below

After sixty days of the experimental period the blood samples were collected by heart puncture within 6 to 8 hours of last dose of LTG, liver function tests were carried out immediately after separation of serum using auto-analyzer (Hitachi, Japan) the kits were supplied by Technichon (Germany). Having sacrificed rats, the liver was obtained for histopathology.

Statistical analysis : The results were subjected to statistical analysis and significance of differences between the mean levels of control and experimental groups was calculated by using Student's paired t-test (two tailed).

RESULTS

The experimental rats exposed to LTG looked apparently normal. No behavioral abnormalities of any kind were observed. The body weights were not significantly different from control group, except that the experimental group exposed to high doses of LTG showed less weight gain. The average total weight gains for control, experimental, one and two were 59.65, 55.40 and 18 gms respectively. Also two of experimental rats treated with higher doses of LTG died after 6th and 7th week of exposure.

The results of liver function tests have been indicated in Table 1. In general the serum levels of various enzymes and bilirubin were elevated in therapeutic and toxic dose of LTG treated rats. The extents of increase in hepatic enzyme levels with toxic doses of LTG were much higher than in therapeutic group.

The liver parenchymal cells in control and lower doses of LTG groups were similar and showed no abnormalities of any kind Fig. 1 and 2 whereas, the toxic doses appear to have a focal scattered coagulative necrosis Fig. 3.

As shown in Table 1: At therapeutic dose of LTG the highest elevation of serum enzyme was observed with ALT (61.3% $p<0.01$) followed by direct bilirubin (86.8% $p<0.01$), ALP (17.9% $p<0.05$), AST (31.6% $p<0.01$) and total bilirubin (27.9% $p<0.05$) whereas, total proteins and albumin were not significantly reduced. Considering the higher dose of LTG the elevation of these enzymes and bilirubin were much higher.

DISCUSSION

The present study indicates that prolonged exposure of rats to LTG results in significant changes in the levels of serum bilirubin and liver enzyme profile. It was observed that long-term treatment with LTG at therapeutic dose affects liver enzymes and bilirubin in a moderate manner than higher dose. The results of liver histopathology also show no liver damage with therapeutic dose, whereas, the hepatocellular damage in most of the rats with higher dose of LTG were seen (Fig. 3). According to our previous study (4) and several other studies long-term treatment with AEDS affects liver enzymes.(6, 7, 8, 9) However, although

Study design

Group	1st week doses	2nd week doses	3rd week onwards
Control (Vehicle)	0.5 ml water	0.5 ml water	0.5 ml water
Therapeutic dose group (5 mg/kg of Lamotrigine)	2.5 mg/kg body wt. / day	5mg / kg body wt. / day (2.5 mg twice)	5 mg/kg body wt. / day
Toxic dose group (25 mg/kg of Lamotrigine)	5 mg/kg body wt. / day	10 mg/kg body wt. / day (5 mg , twice)	25 mg/kg body wt. / day (12.5 mg, twice)

Table 1. Biochemical parameters of rat serum exposed to Lamotrigine for sixty days

Biochemical Parameters	Control Group	Experiment Group I (Therapeutic)		Experiment Group 2 (Toxic dose)	
		(5 mg/kg body wt)	% change	(25 mg/kg body wt)	% change
ALP (U/L)	351.30 ±76.68	405.80* ±64.73	17.9	510.90** ±72.05	45.3
AST (U/L)	160.80 ±27.80	211.60* ±32.07	31.6	290.50** ±36.60	80.0
ALT (U/L)	53.80 ±11.10	86.30** ±14.80	61.3	145.40** ±19.95	170.0
LDH (U/L)	896.90 ±68.70	1001.40 ±87.80	11.6	1227.90* ±98.60	36.9
Total Bilirubin (mg/dl)	0.351 ±0.07	0.449* ±0.08	27.9	0.559* ±0.11	59.0
Direct Bilirubin (mg/dl)	0.129 ±0.02	0.241** ±0.03	86.8	0.332** ±0.04	157.0
Total Proteins (g/dl)	5.91 ±0.52	5.42 ±0.56	-8.2	5.35* ±0.60	-09.4
Albumin (g/dl)	3.14 ±0.29	2.91 ±0.31	-7.4	2.81* ±0.32	-10.47

The values are mean ± SD for 20 rats in each group.
Control group is compared with LTG-treated groups, P values <0.05 is significant.
*= P < 0.05; ** = P < 0.01

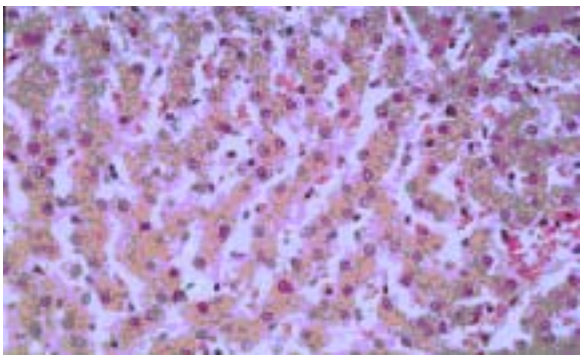

Fig. 1. Normal rat liver parenchyma in control group (H & E 400X)

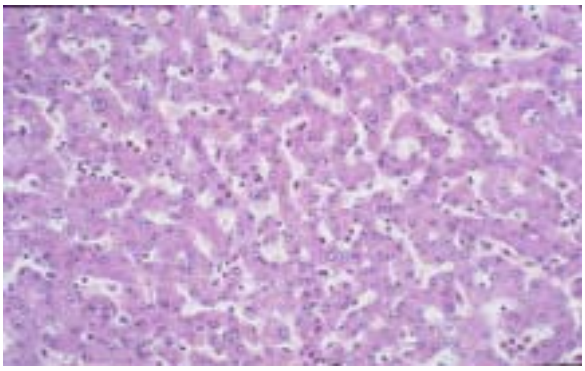

Fig. 2. Histopathology of rat's liver after exposure to therapeutic dose of LTG (H & E 400X)

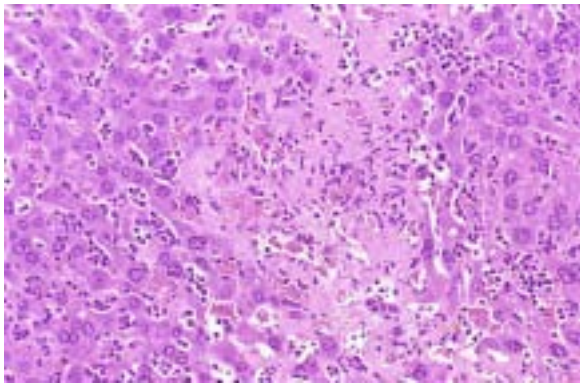

Fig. 3. Focal necrosis of rat's liver with high dose of LTG (H & E 400X)

we have a considerable increase level of liver enzymes but increased bilirubin level was not parallel to the extent of increase liver enzyme and liver damage with high dose of LTG.

The long-term treatment of therapeutic dose of LTG did not have any effect on body growth rate; on the contrary, higher doses of LTG retarded the body growth of rats as compared with control groups. This might be due to loss of appetite. Such an effect of LTG induced decreased body growth rate at toxic dose was not reported in the literature to the best of our knowledge.

A case of fatal hepatotoxicity with other clinical signs and symptoms such as rash and fever, elevated liver

function tests and other clinical sequelae of hepatic failure in a patient treated with Lamotrigine were reported. The liver damage is documented in serial liver biopsies, which show approximately 50% of hepatocyte necrosis (3).

In another postmortem case report a peripheral blood concentration of 54 mg/l and liver tissue concentration of 220 mg/kg of LTG, led to death in which, the manner of death was undetermined. However, in our study the two cases of the rats death with high dose of LTG might have been due to the liver failure. Although in our study the blood therapeutic and toxic levels of the LTG was not determined, other studies reported a serum therapeutic levels of 2-14 mg/l (10).

In another study (11), three children suffering from seizures were treated with lamotrigine. In one child, this therapy led to relatively severe hepatic failure due to aggressive therapy. His liver function and blood hepatic enzymes became normal after discontinuation of the drug. In contrast, some other studies reported Lamotrigine as a safe and effective medication. Meldrum reported a moderate protein binding and no induction of liver enzymes by Lamotrigine at therapeutic dose. The lower dose of LTG caused a mild elevation of liver enzymes but no liver cell damage (12).

Having considered various reports in the related literature on LTG therapy it may be concluded Lamotrigine as a safe and effective medication, yielding better responses at therapeutic dose as monotherapy when compared with other AE drugs with reference to quality of life and suppression of side effects (12,13), which are valuable in providing over all improvement, disease free period and quality of life.

In general it was concluded that a careful monitoring of liver function tests and drug monitoring should be done while treating the patients with Lamotrigine, while aggressive dose should be avoided as far as possible, especially with those who have complicated acute systemic disorders.

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