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Histological and Biochemical Study of Female Albino Rats (*Rattusrattus*) Treated with Lamotrigine

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Abstract : Epilepsy is one of the most common neurological diseases, affecting at least 50 million people worldwide. Lamotrigine is a newly developed,therefor the present study aims to evaluate the effects of lamotrigine drug on some parameters in female of albino rats.24 female rats used in this study. The animal divided in to four groups(n=6) and each group subdivided into control and treated group. The four treated subgroup administrated drug at doseof 60 mg/kg of body weight for 9,12,14 and 21 day. The results showed that there was significant ($P \leq 0.05$) decrease in body weight when compared with control groups.Therelative organ weight showed significant changes ($P \leq 0.05$) in treated groups. The blood parameters revealed significant changes in treated group except number of monocyte, granulocyte and platelets. The liver enzyme SGOT andSGPT showed significant ($P \leq 0.05$) increase intreatedgroup in comparison with control groups. LH revealed significant ($P \leq 0.05$) decrease compared with control group.Histopathological study revealed the existence of sub piaedema in brain section of group4(treatment group), pneumonia in lung of group 1(treatment group) and hyperplasia in spleen white pulp in group 3(treatment group) in comparison of control group.
Keywords : Epilepsy, Antiepileptic drug, Lamotrigine, Haematological parameters, Histology, Rats.

Introduction:

Epilepsy is a chronic and disabling neurologic disorder and one of the most prevalent neurological disease characterized by recurring seizures. Different types of epilepsy have different causes and their spread depends of age, racial, social class, geographic, or national boundaries[1,2]. It affects approximately 50 mil-lion people throughout the world[3]. Accurate estimates of incidence and prevalence are difficult to achieve because identifying people who may have epilepsy is difficult.

Approximately half of epileptic patients are women[4,5]. Currently, management of epilepsy is mainly based on antiepileptic drugs (AEDs).

Lamotrigine (LTG) C9H7Cl2N5 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[6,7].

(AEDs) are widely used. They are prescribed as standard treatment not only for epilepsies, but for a variety of nonepileptic conditions as well, mainly bipolar spectrum disorders and chronic pain states[8]. A large number of AEDs are available. Since 1990, 16 new (or ‘‘second-generation’’) AEDs have been registered: lamotrigine, vigabatrin, tiagabine, felba-mate, topiramate, gabapentin, pregabalin, levetiracetam, zonisa-mide, stiripentol, oxcarbazepine, eslicarbazepine, rufinamide, lacosamide, retigabine, and perampanel. In many

countries, women constitute the majority of users of these new AEDs[9,10].This may be due to special, women-related safety and tolerability issues(11). During the past 20 years, much attention has been directed toward AEDs and women. Hormonal and metabolic disturbances induced by AEDs, as well as teratogenic and adverse cognitive effects in the offspring of women with epilepsy have come into the spotlight[12,13]At present LTG 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[14].

Material and Methods: Animals:

Experimental Animals:

Female albino rats aged between (8-10)weeks were obtained from the Animal House, Collage of Science, University of Babylon. The rats were housed in wire mess cages under standard condition with 12 hrs.light and 12 hrs.dark cycle during the whole period of experiment. Food and tap water provided *ad libitum*. The animals were divided into 4 experimental groups of 6 rats per group. The daily dose of LTG administrated orally by cavage to each treated animals every morning for 9,12,14,21days.The control of each group administrated with 1.5 water for 9, 12, 14 and 21 days, while the treated one administrated with 60 mg/kg /day of LTG according to body weight for 9, 12, 14 and 21 days.

DrugDosage:LTG obtained from local pharmaceutical supplier, GlascoSmith Kline, Poland. The applied therapeutic dose is 60 mg/Kg body weight. The applied does was orally administrated by cavage for 9, 12, 14, and 21days.

Blood collection: Blood was collected from each rat via the left ventricular cardiac puncture into sterilized EDTA tubes and gel tube to separate the serum quickly and then centrifuged at 3000 g for 5 minutes and the serum separated. The serum samples were stored frozen until used.

Body Weight: Initial and final body weight of the animals was recorded. The relative change in body weight was calculated according to following formula:

Body weight change %= (final weight-initial weight/initial weight)×100

Organs Weight: At the end of the treatment, each rat was sacrificed under ether anesthesia, the liver, kidney, heart, brain, lung and spleen were removed, cleaned from adherent tissues, drying by filter paper and weighted immediately.

Hematology: The blood sample used for the estimation of WBCs, Lymphocytes, Monocytes, Granulocyte, RBCs, HGB, HCT, and PLT by using Mythic 18 apparatus**.**

Liver Enzyme: The serum used to estimate the liver enzyme (Glutamic oxaloacetate transaminase (GOT), glutamic pyruvictransaminase (GPT)) by usingReflotronKit .

Hormonal Assay: Serum Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH) and Estradiol were measured by usingELISA(using three commercial kits).

Histological Study:Tissue specimens of liver, kidney, heartbrain, lung and spleen were fixed in 10% formalin. Trimming was done on the fixed tissue specimens. Serial alcohol was used for dehydration of the tissue samples. Tissue specimens were cleared in xylene and embedded in paraffin. The paraffin blocks were sectioned at 5 microns thickness by microtome. The obtained tissue sections were collected on the glass slides and stained by hematoxyline and eosin stain for histopathological examination by the light microscope[15].

Statistical Analysis:

Results were shown as Mean±SE for each group. Statistical analysis was performed using SPSS 23. For multiple comparisons, one-wayanalysis of variance (ANOVA) was used. In cases where ANOVA showed significant difference, *post hoc* analysis was performed with least significant. The $p \leq 0.05$ was considered to be statistically significant.

Results:

Body Weights:

The oral administration of LTG at all treatmentperiodsshowedsignificantdecreased in relative body weight ($p \leq 0.05$) in comparison with control group.

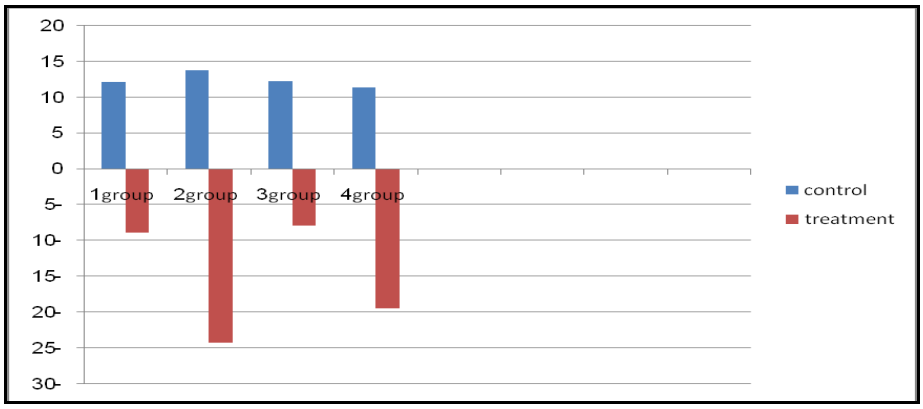


Figure (1): Effect of lamotrigine on body weight of female rats treated for 9, 12, 14 and 21 days.

Organ Weights:

The relative weight of kidneys of treated group (1 and 3) and heart of treated group (1 and 4) showed significant changes($p \leq 0.05$)(Table-1).

Table (1): Effect of Lamotrigine drugin relative weight of organ of female albino rats treated for 9, 12, 14, and 21 days.

Groups	Organ weights/body weight M±S.E					
	Liver	**Kidney**	**Heart**	**Brain**	**Lung**	**Spleen**
Group 1(treated for 9 days)						
Control	a 2.958 ±0.471	a 0.636 ±0.064	ab 0.464 ±0.022	a 0.853 ±0.066	a 0.636 ±0.064	a 0.562 ±0.008
Treatment	a 3.724 ±0.115	ab 0.796 ±0.078	a 0.345 ± 0.024	a 0.860 ±0.0532	a 0.675 ±0.059	a 0.364 ±0.005
Group 2(treated for 12 days)						
Control	a 3.176 ±0.032	ab 0.841 ±0.072	ab 0.417 ±0.028	b 1.104 ±0.051	a 0.653 ±0.104	a 0.508 ±**0.077**
Treatment	a 3.095 ±0.509	ab 0.829 ±0.074	ab 0.593 ± 0.121	b 1.108 ±0.158	a 0.681 ±0.099	a 0.646 ±0.125
Group 3(treated for 14 days)						
Control	a 3.243 ±0.128	b 0.678 ±0.049	ab 0.685 ±0.144	b 0.787 ±0.228	b 0.832 ±0.097	a 0.431 ±**0.046**
Treatment	a 3.648 ±0.368	ab 0.740 ± 0.044	ab 0.614 ± 0.136	b 0.780 ± 0.107	b 0.811 ±0.044	a 0.534 ±**0.125**

Group 4(treated for 21 days)						
Control	a 3.245 ±0.250	ab 0.678 ±0.034	b 0.685 ±0.144	b 0.787 ±0.123	ab 0.732 ±0.022	a 0.431 ±**0.076**
Treatment	a 3.755 ±0.155	ab 0.755 ±0.077	ab 0.429 ±0.013	b 1.035 ±0.069	ab 0.895 ±0.186	a 0.682 ±0.138

*Different symbols mean significant differences

Hematology:

The result of hematological assayshowed that there was significant increase ($p \leq 0.05$)in blood parameters of treated groupscompared with control group with the exception of monocyte and granulocyte numbers, while the platelets numbers showed significant differences in treated one of third and fourth group (Table-2).

Liver Enzyme:

The data showed significant ($p \leq 0.05$) increasedin levels ofSGOT and SGPTintreated groups as compared with control groups(Table -3).

Table (3): Effect of Lamotriginedrug on liver enzyme in female albino rats treated for 9, 12, 14, and 21 days.

Groups	**Liver enzyme in serum**M±S.E	
	SGOT(IU/L)	**SGPT(IU/L)**
Group 1(treated for 9 days)		
Control	a 83±6	bcd 61.066 ±11.833
Treatment	b 193±36	d 85.866±12.066
Group 2(treated for 12 days)		
Control	c 139±42	ab 34.833±3.866
Treatment	abc 197±15.620	abc 55.933±5.285
Group 3(treated for 14 days)		
Control	c 159±5.196	abc 55.933±10.247
Treatment	abc 197±25.324	cd 64.2±4.959
Group 4(treated for 21 days)		
Control	a 98±6	abc 42.15±10.247
Treatment	ac 120.333±39.715	a 55.233±2.940

*Different symbols mean significant differences

Hormonal Assay:

The results showed significant decrease ($p \leq 0.05$) in LH only in treatment groups in comparison with control groups (Table -4).

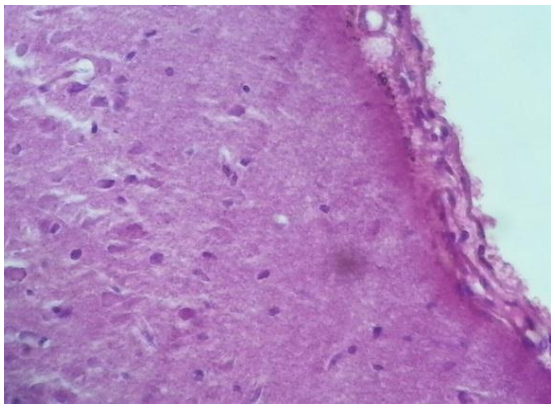
Table (4): Effectoflamotrugine on FSH, LH and Estradiol in serum of female rats treated for 9, 12, 14 and 21 days.

Groups	**HormonesM±S.E**		
	FSH µmol/L	**LH µmol/L**	**Estradiol pg/L**
Group 1(treated for 9 days)			
Control	a 3.122±0.182	ab 0.365±0.00252	a 3.081±0.105
Treatment	a 2.967±0.174	a 0.277±0.033	a 3.1733±0.064
Group 2(treated for 12 days)			
Control	a 2.626±0.021	ab 0.397±0.104	a 3.186±0.051
Treatment	a 2.819±0.157	ab 0.357±0.025	a 2.916±0.318
Group 3(treated for 14 days)			
Control	a 2.647±0.021	c 0.602±0.0003	a 3.266±0.024
Treatment	a 3.017±0.209	ab 0.394±0.034	a 3.180±0.292
Group 4(treated for 21 days)			
Control	a 2.711±0.043	bc 0.499±0.103	a 3.238±0.051
Treatment	a 2.543±0.397	a 0.226±0.004	a 2.655±0.514

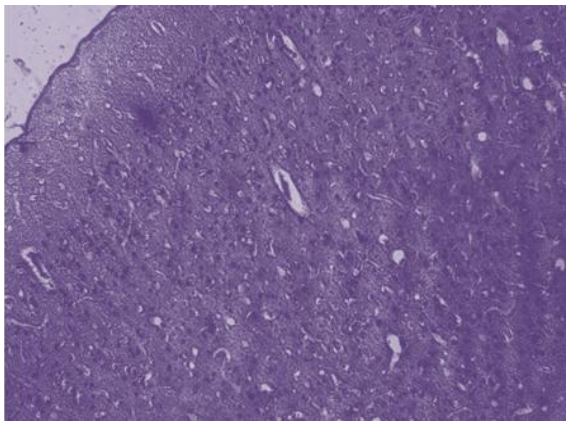
*Different symbols mean significant differences

Histopathological Study:

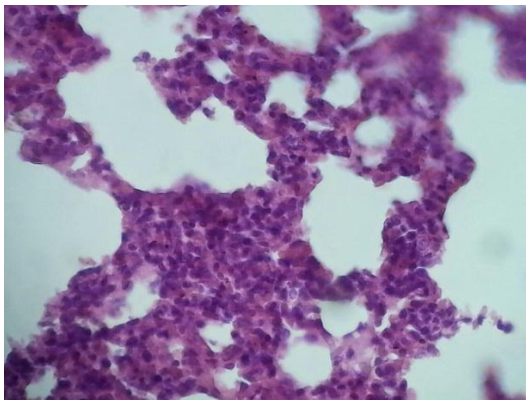
From light microscopy micrographs, the tissue of kidney, liver and heart of all experimental groups showed regular appearance as control tissue groups, while the brain of lamoriginegroups 4 showed sub pia arachnoid edema (Fig.1)when compared with control group (Fig.2). Lung micrograph of group 2 treated with drug characterized by interstitial pneumonia (Fig.3) when compared with control group (Fig.4).The spleen of treated group 3 exhibited hyperplasia in white pulp (Fig.5) unlike the control group (Fig.6).



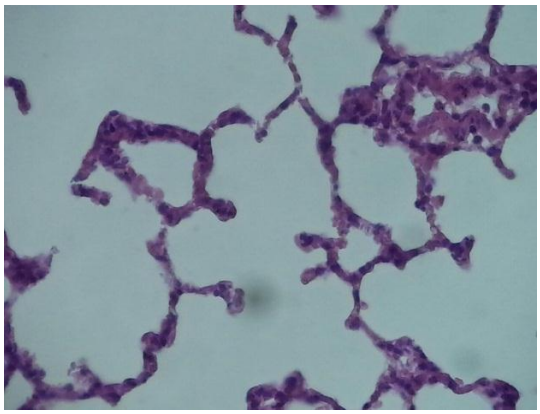
(Figure 2): Photomicrograph of brain section of rats treated with lamotrigine 60 mg/kg of b.w. For 7 and 14 days showing sub piaoedema(HX & E. 40X).



(Figure 1): A photomicrograph brain section of control rat liver showing the normal architecture. (HX & E. 10X).



(Figure 4): A photomicrograph in a spleen section of treated rat with lamotrigine 60 mg/kg of b.w. For7 showingthe interstitial pneumonia (HX & E. 40X).



(Figure 3): A photomicrograph in a section of control rat lung showing the normal architecture. (HX & E.10X)

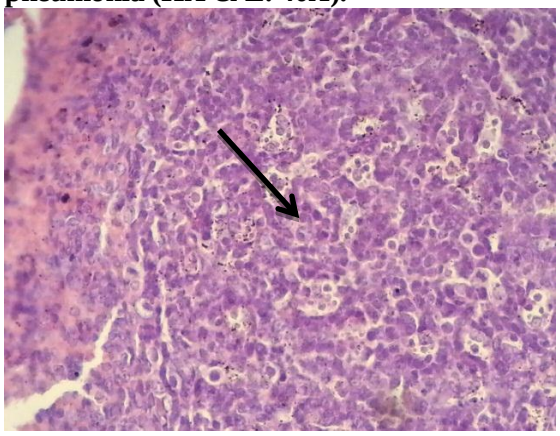
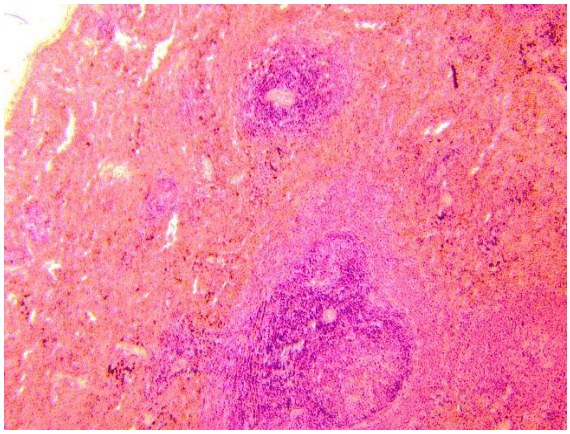


Figure 6): A photomicrograph of a section in the spleen of the treated rat with lamotrigine 60 mg/kg of b.w. For 12 dayshowing hyperplasia in white pulp (black arrow). (HX & E. X40).



(Figure 5): A photomicrograph in spleen section of control rat showing the normal architecture(HX & E. X10).

Discussion:

The data of present study showed that there was significant decrease in relative body weight of treated female rats as compared with control groups.The body weight changes are indicator of adverse side effects of drugs and this reveals that it adversely affect the basic metabolic processes of the experimental animals[16] reported that Lamotrigine-treated patients do not show any change in their weight.[17]reported that there was a significant reduction in body weight of rats observed in antiepileptics fed male rats in comparison to the control group. This controversy of the effect of second-generation antiepileptic drugs on body weight may be due to the different doses used or due to the differences between humans and rats.This might be due to the loss of appetite such effect of higher dose of LTG induced body weight decreased was reported by[18] in adult male rats.[19]Showed that the LTG caused significant decrease of maternal body weight gain comparing with control group. Also[20] obtained that the prenatal exposure to LTG caused decreased in body weight of rat.

Blood forms the main medium of transport for many drugs and xenobiotic in the body and for that matter components of the blood such as red blood cells, white blood cells, hemoglobin, and platelets are at least initially exposed to significant concentrations of toxic compounds. Damage to and destruction of the blood cells are inimical to normal functioning of the body[21]

There was significant alteration in hematological parameters with increased period of drug exposure (except the monocyte, granulocyte and platelets number) which indicate that LTG affect blood cells production. The various blood cells (erythrocytes, leucocytes, and platelets) produced at a turnover rate of about 1 to 3 million per second in a healthy human adult and this value could be altered in certain physiological or

pathological states[22]. Certain drugs including cytotoxic agents affect blood formation rate and the normal range of hematological parameters[23].

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[24,24].

The SGOT and SGPT are good indicators of liver function and biomarkers to predict the possible toxicity of drugs by the increasing of them[25]. These enzyme participate in different metabolic pathways[26].There were significant increases in levels of AST and ALTin treated groups as compared with control groups which reveal that LTG have affect liver function. Significantly elevated levels of liver enzyme often suggest the existence of liver problems.[27]revealed that the LTG caused mild elevation in liver enzyme but not liver cell damage. [28]Found that the discontinuous use of LTG has no effect on liver function and blood hepatic enzyme. Elevated liver enzyme may also be caused by dietary choline deficiency. However, increased levels of liver enzymes do not automatically mean that medical problems exist. Fluctuation of enzyme levels is normal over the course of the day, and they can also increase in response to strenuous physical exercise[29].

[17]Foundsignificant increase in serum GOT and GPT levels in antiepileptics fed male rats treated with Lamotrigine in comparison to the control group.

In present study the significant increase of serum LH level in all groups in compare with control group could be resulted fromLTG –induced stimulationinLuteinizing hormone releasing hormone (LHRH) biosynthesis in the hypothalamus or form direct effect on LH secretion from pituitary which due to increase stimulation of gonadotropins by GnRH[30], [31] showed no significant affection of sex hormones or adrenal and gonadal steroids in patients using Lamotrigine.

(32)showed thatLTG administration increases the follicle stimulating hormone (FSH) and luteinizing hormone (LH) which in turn stimulated estrogen secretion. Increased estrogen secretion results in maturation of graffian follicle followed by ovulation which leads in pregnant animal to embryo detachmen.I think that there is a possible toxic effect of LTG drug on sex organs.The result of present study in accordance with,[33] who found that the LTG caused significant increase in LH of male epileptic patients.It is noticeable that AEDs may also alter endocrine function in both men and women with epilepsy and this variation may lead to clinically significant reproductive endocrine disorders in certain cases.

The spleen weights were increased in female rats at the dose level of 150 μg per rat. Microscopically, 5, 20 and 150 μg per rat CpG 684 caused local inflammatory cell infiltration and hyperplasia of fibrous tissue at injection sites; the treatment of 5 and 150 μg per rat CpG 684 induced enhanced inflammatory reaction in inguinal lymphoid tissue, and the dose of 150 μg per rat induced cell hyperplasia in white pulp of spleen and white pulp expansion. CpG 684 at 150 μg per rat led to decreases in peripheral lymphocyte, serum globulin, glucose, alkaline phosphatase and K

+ levels in female rats, and induced the decrease in serum albumin and total protein in rats of both sexes. The data from this study will provide an important reference for developing CpG 684 as an adjuvant for vaccines of human use. Copyright © 2011 John Wiley & Sons, Ltd.

Histopathological study revealed the existence of pneumonia in lung of group 1(treatment group) sub pia edema in brain section of group 4(treatment group),which may be attributed to an accumulation of liquid as aresult of drug administration[34],and hyperplasia in spleen white pulp in group 3(treatment group) in comparison of control group. Hyperplasia may be due to stress induced because of repeated drug administration[35],but unfortunately we could not find similar studies to compare these results to, neither in female rats nor in humans but may be will used for water treatments[36-41].

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