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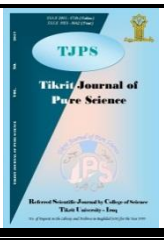

Hematological and Biochemical parameters study of female albino rats treated with lamotrigine drug

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ABSTRACT

The present study was aimed to investigate the possible effects of the anti-epileptic drug lamotrigine (LTG) on some haematological and biochemical parameters in adult female rats. Forty-eight female rats were divided into three groups (each group=16). Group one can be considered as a control group, group two and three administrated lamotrigine drugs orally at a dose of 3.57mg/kg body weight and 7.14mg/kg body weight for 7,14,21,28 day and all groups fed with standard rat feed. The results showed that there were significant ($P \leq 0.05$) changes in haematological parameters in group two and three when compared with the control group during all period except the mean level of corpuscular haemoglobin concentration (MCHC). The liver enzyme aspartate transaminase (AST) and alanine transaminase (ALT) and serum urea, creatinine with calcium, potassium, sodium and chloride ion showed significant alteration in the treated group, the relative organ weight showed significant changes in group two and three in comparison with control group during 7,14,21 and 28 days. Estradiol level in group three increased at 7, 14 and 21 day and decreased at 28 days of treatment when compared with group two and the control group. This study suggested that treatment of healthy female albino rats with therapeutic doses of lamotrigine drug for 28 days generally affect on included parameters in this study.

1. Introduction

Numerous non-epileptic central nervous system disturbances were treated with Antiepileptic drugs (AEDs), in both psychiatry and neurology[1]. AEDs have many mechanisms of action, which comprise modification of c-aminobutyric acid and glutamatergic neurotransmission, and changes of voltage-gated ion channels or intracellular signaling route. These mechanisms of action may describe the efficiency of AEDs in the treatment of epilepsy, bipolar disturbance and neuropathic ache [2**].** Lamotrigine consist of 6- (2,3- dichlorophenyl)-1,2,4-triazine 3,5-diamine C9H7Cl2N5 is a new antiepileptic drug derived from pyrimethamine, which differs from ordinarily available AEDs. It has an effective role in treating both partial and generalized seizure [3].

Lamotrigine effort its antiepileptic activity by blocking the release of excitatory neurotransmitters, especially glutamate and aspartate in the central nervous system [4]. LTG considered as the second generation of anti-epileptic drug (AED) that has been widely used for partial and generalized seizures in adults and children if it's used as monotherapy or in combination with other AEDs [5]. In addition, because of its safety feature, it has been recognized as a first line drug for the treatment of women during pregnancy and childbearing age [6]. LTG display first request linear pharmacokinetics following oral administration, it is rapidly and completely absorbed into the circulatory system with an extreme concentration in plasma after 1–3 hours [7]. Hepatic metabolism is the main path of lamotrigine elimination, unchanged LTG excreted by renal system accounts for less than 10% [8].

In most countries, women constitute the broadly of users of these new AEDs [9]. In a study, mice treated with lamotrigine 6 and 12 mg/kg-1 bm for 21 days showed that a significant increase in total white blood cell count [10]. Healthy rats treated with lamotrigine for different periods noted a significant increase in blood parameters when compared with the control group [11]. There were no significant changes in

hematological parameters among healthy males treated with 50mg lamotrigine [12] Milosheska *et.al.* 2016 [13] showed non-significant differences in serum AST and ALT in patients treated with lamotrigine at dose 50mg/day. After long-term treatment with lamotrigine in male and female rats, no changes were demonstrated in liver, kidney and brain weight [14]. Lamotrigine does not alter the serum concentrations of estradiol when used with another ant-epileptic drug in healthy female [15]. This study aimed to quest the effect of two doses of lamotrigine drug on some haematological, biochemical, ions, estradiol level of a female albino rat for different periods.

2. Materials and Methods

2.1. Drug

Lamotrigine drug was used in the present work which manufactured by ELEA neuroscience Company, Argentina, obtained from a local market (pharmacy) in Hawler province-Iraq. The applied therapeutic dose was 3.57mg/kg bw and 7.14mg/kg bw. The applied doses were orally administrated by gavage once daily for 7, 14, 21 and 28 days. Determination of drug doses were depended on the animal's body weight [16].

2.2. Animals

Forty-eight healthy adult female albino rats of Wistar strain, Sprague-Dawley, weighing between 125-175gm. Obtained from the animal house in the Department of Biology, College of Education, University of Salahaddin-Erbil were used. The rats were housed in plastic cages under a standard condition at 22±2 ^{o}C temperature with, 12:12 light/dark cycle during the experimental period. They were fed with pellet diet and tap water *ad libitum* at least for 7 days before the experiment. Animals were divided into 3 experimental groups of 16 rats per group. The 3.57mg/kg bw and 7.14mg/kg bw dose of LTG administrated orally by gavage to each treated animals every morning once daily for 7,14,21,28 days according to animal body weight, while the control group administrated with 1 ml water for 7, 14, 21, 28 days.

Blood collection

Blood was collected from each animal through cardiac puncture and collected into sterilized EDTA tubes for evaluation of hematological parameters such as white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hb) concentration, Packed cell volume (PCV) level, red blood cell indices (mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC)) and platelet (PLT) count by using automated hematology analyzer (Japan). Serum was separated using gel tube and centrifuged at 3000 rpm for 15 minutes and then stored frozen until used.

Liver enzymes: Serum used to determine aspartate transaminase, alanine transaminase using the kits for each test by Cobas E411.

Kidney function test: Serum used to estimate, urea and creatinine using the kit for each one.

Ion evaluation: Serum used to evaluate calcium, potassium, sodium and chloride ion levels

Hormonal Assay: Serum used to determine estradiol level using ELISA.

Organs Weight: At the end of the treatment, each rat was sacrificed using ketamine hydrochloride (100mg/ kg bw) the liver, kidney, brain, and lung were removed, cleaned from adherent tissues and weighted.

Statistical Analysis: Data was analyzed using factorial test and Duncan according to the Statistical Package for Social Science (SPSS) system version 20. The level of significance was accepted under level probability 0.05. [17]

Results

Treatment of rat with two doses of lamotrigine drug for 28 days were associated with a significant decrease in haemoglobin concentration in group 3 (7.14mg/kg bw) in days 7, 21 and 28, in day 14 increased significantly, group2(3.57mg/kg bw) decreased significantly in days 14 and 28 when compared with control group. Packed cell volume level decreased significantly in group3 in days 7, and 28, group 2 decreased significantly in days 14 and 28, with a nonsignificant decrease in group 2 and 3 in day 21. White blood cell count decreased significantly in group 3 in days 7 and 21 and increased significantly in day 28 when compared with group 2 and the control group. About platelet count, the statistical analysis showed a significant increase in group 3 in days 7 and 14, with a non-significant increase in both groups in day 28 (Table 1).

Table (1): Mean ± S.E. of lamotrigine drug effect on haemoglobin concentration, packed cell volume, white blood cell count and platelet count of rat treated with 3.57mg, 7.14mg, and control group for 28 days.

Groups	M±S.E. of Haematological parameters			
	Hb gm/dl	PCV %	WBC 10^9 /l	Plate10^9 /l
Treated for 7 days				
Control	12.18±0.40ef	30.85±1.93d	10.70±1.08b	624.75±24.16cd
Group2	13.08±0.28edc	35.13±0.63bc	8.80±0.35cb	676.68±9.52bc
Group 3	11.95±0.21f	30.38±1.02d	6.73±0.83d	741±34.66ba
Treated for 14 days				
Control	13.50±0.14bc	36.83±0.23b	10.88±0.28b	483.71±11.65e
Group2	12.53±0.42edf	32.85±1.30c	10.43±0.72b	795.32±73.87a
Group3	13.88±0.41bac	37.15±1.15ba	10.83±0.36b	731±12.73ba
Treated for 21 days				
Control	14.63±0.08a	39.95±0.22a	10.85±0.52b	643.65±38.83bcd
Group2	14.18±0.17ba	38.13±0.46ba	7.97±0.39cd	735.50±35.72ba
Group3	13.33±0.49bdc	37.63±1.51ba	6.30±0.07d	595.50±27.30cd
treated for 28 days				
Control	13.73±0.36bac	37.23±0.83ba	7.25±1.13cd	566±10.09cd
Group2	12.43±0.26edf	31.38±0.34d	13.65±0.43a	573.75±11.21ed
Group3	13.68±0.28bac	36.78±0.39ba	10.85±0.67b	585.13±9.37ed

Means with the same letter are not significantly different

Red blood cell (RBC) count and indices in days 7, 14, 21 and 28 of all experimental group were demonstrated in the table (2). RBC count in group 2 and 3 decreased significantly in days 21 and 28 and insignificantly in day 14, and day 7. Group 2 increased significantly while group 3 decreased when compared with the control group. Both of two groups showed a significant decrease in the level of mean corpuscular volume in days 21 and 28 with a nonsignificant decrease in day 14 and non-significant alteration in day 7, mean corpuscular haemoglobin level decreased non-significantly in days 21 and 28, significant differences in day 14. Mean corpuscular haemoglobin concentration level increased significantly in group 2 and 3 in day 28, non-significant increase in days 7, 14 and 21.

Table (2): Mean ± S.E. of lamotrigine drug effect on red blood cell and RBC indices of rat treated with 3.57mg, 7.14mg, and control group at 28 days of treatment.

Groups	M±S.E. of Haematological parameters			
	RBC 10^{12}/l	MCV fl	MCH pg	MCHC gm/dl
treated for 7 days				
Control	6.05±0.16fe	52.35±0.85dc	20.43±0.59ba	38.17±0.60a
Group2	6.40±0.31dec	56.98±1.29a	20.13±0.49b	38.90±0.84ba
Group3	5.69±0.13f	54.08±1.39bac	20.90±0.27ba	39.18±1.21a
treated for 14 days				
Control	6.38±0.19dec	54.78±0.13bac	20.75±0.21ba	36.38±0.23ba
Group2	6.32±0.21de	53.08±1.42c	20.23±0.39b	38.78±0.57a
Group3	6.00±0.11bdec	56.57±1.33bc	21.73±0.61a	38.50±0.56a
treated for 21 days				
Control	7.20±0.17a	56.85±0.59a	21.18±0.43ba	36.83±0.17ba
Group2	6.58±0.18bdec	55.40±0.68bac	20.55±0.39ba	37.45±0.34ba
Group3	6.72±0.23bdac	53.58±0.89bc	20.13±0.42b	37.63±0.43ba
treated for 28 days				
Control	6.98±0.16bac	55.15±0.81bac	20.45±0.14b	34.23±0.44ba
Group2	6.42±0.12dec	49.68±0.40d	20.28±0.74ba	36.35±3.06b
Group3	6.08±0.14ba	53.50±0.51bc	20.38±0.22ba	38.23±0.34a

Means with the same letter are not significantly different

Table (3) shows that the level of liver enzymes which include aspartate transaminase (AST) and alanine transaminase (ALT). AST level in group 2 increased significantly, while in group 3 decreased significantly in days 7,14 and 28, and both of them changed non-significantly in day 21. The significant decrease observed in the level of ALT in group 3 in days 14 and 21, and non-significantly in days 7and 28. Group 2 decreased non-significantly during all period except in day 14, serum urea and creatinine level increased significantly in group 2 and 3 in day 14, while in days 7,21 and 28 the level decreased gradually.

Table (3): Mean ± S.E. of lamotrigine drug effect on serum AST, ALT, urea and creatinine of rat treated with 3.57mg, 7.14mg, and control group at 28 days of treatment

Groups	M±S.E. of Biochemical parameters			
	AST U/L	ALT U/L	Urea mg/dl	Creatinine mg/dl
treated for 7 days				
Control	191.50±0.65bc	63±1.29a	49.50±1.55a	0.45±0.06b
Group2	211.75±23.05ba	64.25±1.38a	41.75±0.85bc	0.33±0.05c
Group3	147.48±6.28d	61.50±4.11ba	45.23±1.11ba	0.40±0.03cb
treated for 14 days				
Control	154.25±1.89dc	63.75±1.93a	29.52±0.96f	0.35±0.03a
Group2	223.71±28.99ba	51.25±2.39dc	38±041edc	0.40±0.04cb
Group3	138.74±4.59d	51.75±2.87dc	43.50±1.44bac	0.42±0.06cb
treated for 21 days				
Control	155.50±7.93dc	55.25±1.11bc	34.50±3.97edf	0.40±0.07cb
Group2	159.25±6.49dc	49.72±1.49dc	34.19±3.47edf	0.37±0.08cb
Group3	144.75±9.59d	45.51±5.48d	31.25±3.20ef	0.28±0.01a
treated for 28 days				
Control	204.25±12.39ba	64.25±0.48a	38.24±2.81bdc	0.40±0.02cb
Group2	240.50±13.53a	61.22±1.11ba	35.71±1.26bdc	0.33±0.01c
Group3	136.50±9.12d	63.47±0.65a	37±0.41edc	0.36±0.07cb

Means with the same letter are not significantly different

A significant increase of liver weight was observed in group 3 in days 7 and 21 and non-significantly in group 2 and 3 in days 14 and 28. Right, and left kidney weight increased significantly in group 3 in day 7. Lung weight decreased significantly in group 3 in day 7 while brain weight increased significantly in group 2 and 3 in days 14 and 28 and non-significantly in days 7 and 21. (Table 4).

Table (4): Mean ± S.E. of lamotrigine drug effect on the liver, right and left kidney, lung, and brain of rat treated with 3.57mg, 7.14mg and control group at 28 days of treatment.

Groups	M±S.E. of Organ weight mg				
	Liver	R. kidney	L. kidney	Lung	Brain
treated for 7 days					
Control	5.83±0.22dc	0.62±0.04b	0.52±0.03c	1.57±0.19a	1.70±0.08cbd
Group2	6.87±0.52ba	0.70±0.05ba	0.57±0.02bc	1.30±0.07ba	1.72±0.02cbd
Group3	7.50±0.15a	0.76±.03a	0.69±0.06ba	1.19±0.12b	1.79±0.06cb
treated for 14 days					
Control	6.28±0.08bdc	0.72±0.05ba	0.63±0.02bac	1.47±0.01ba	1.48±0.01e
Group2	7.31±0.39ba	0.73±0.02ba	0.67±0.03bac	1.42±0.09ba	1.70±0.02cbd
Group3	7.15±0.33ba	0.75±0.05a	0.72±0.05a	1.47±0.15ba	1.82±0.01b
treated for 21 days					
Control	7.08±0.11ba	0.69±0.01ba	0.67±0.02ba	1.49±0.07ba	1.60±0.03cbd
Group2	6.39±0.10bdc	0.62±0.05b	0.58±0.04bc	1.29±0.07ba	1.65±0.03d
Group3	5.52±0.14d	0.61±0.01b	0.58±0.01bc	1.22±0.04b	1.69±0.03cd
treated for 28 days					
Control	6.62±0.27bac	0.73±0.05ba	0.66±0.04ba	1.41±0.02ba	1.53±0.03a
Group2	6.99±0.67ba	0.68±0.02ba	0.64±0.05bac	1.38±0.08ba	1.68±0.04cd
Group3	7.23±0.16ba	0.72±0.03ba	0.65±0.04ba	1.40±0.07ba	1.79±0.06cb

Means with the same letter are not significantly different

Effect of lamotrigine on estradiol level observed in fig. (1). A significant increase was shown in group 2 and 3 in day 7, nonsignificant increase in days 14 and 21 with a significant decrease in day 28 when compared with the control group.

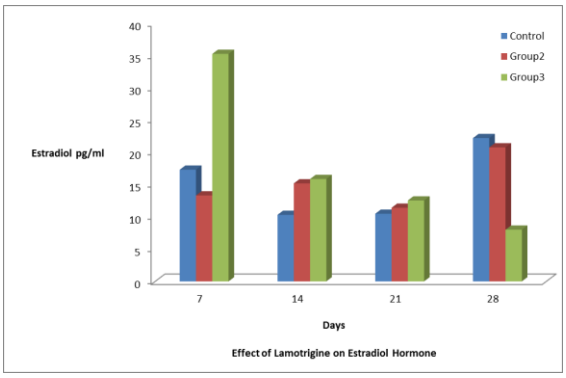

Figure (1): Effect of lamotrigine on serum estradiol level after days 7,14,21 and 28 in female rat treated with 3.5mg,7.14mg, and control group.

Figure (2) demonstrated a significant increase in calcium ion level in group 2 and 3 in days 14 and 21 with non-significant changes in days 7 and 28.

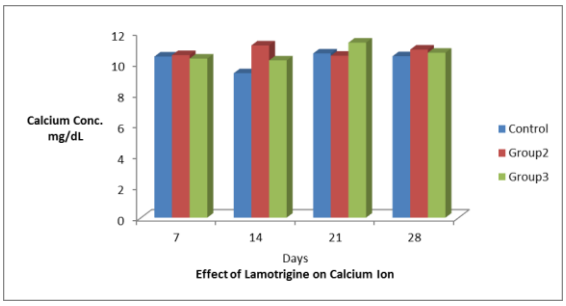

Figure (2): Effect of lamotrigine on serum calcium ion level after 7, 14, 21 and 28 days in female rat treated with 3.5mg, 7.14mg and control group.

Potassium ion level increased significantly in group 2 and 3 in day 14 and a significant decrease in day 28 with the nonsignificant change at day 21.fig. (3).

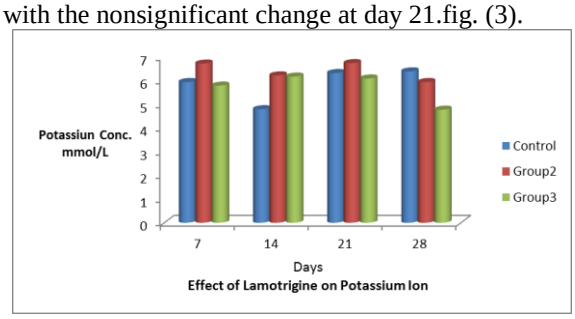

Figure (3): Effect of lamotrigine on serum potassium ion level after 7, 14, 21 and 28 days in female rat treated with 3.5mg, 7.14mg, and control group.

According to sodium ion level, there was a nonsignificant increase in group 2 and 3 in days 14, 21 and 28, a significant decrease in day 7. Fig. (4).

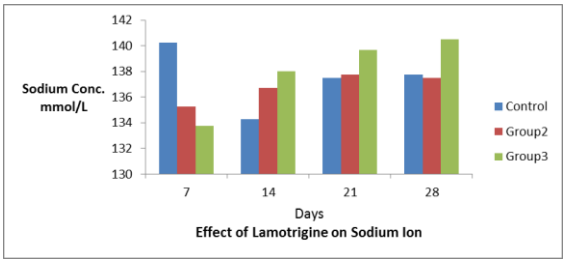

Figure (4): Effect of lamotrigine on serum sodium ion level after 7, 14, 21 and 28 days in female rat treated with 3.5mg, 7.14mg, and control group.

Fig. (5) showed chloride ion level in group 2 and 3 which non-significant in days 7,21and 28 and a significant increase in group3 in day 14.

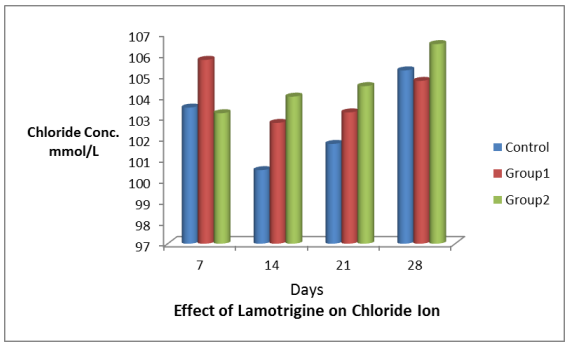

Figure (5): Effect of lamotrigine on serum chloride ion level after 7, 14, 21 and 28 days in female rat treated with 3.5mg, 7.14mg, and control group.

Discussion

Antiepileptic drugs (AEDs) prescribed as typical treatment and are widely used for not only epilepsy, bipolar disorder, and chronic pain but also for a diversity of nonepileptic conditions [18]. One out of three antiepileptic drugs users used these drugs for epilepsy [19]. A huge number of AEDs are obtainable. Since 1990, 16 new or second-generation AEDs have been recorded, and lamotrigine is one of them [20]. Lamotrigine after oral administration is quickly and completely absorbed from the gastrointestinal tract with Tmax values of 2.2 hours. Food does not affect the bioavailability of lamotrigine and the pharmacokinetics are dose relative [21]. By glucuronidation, N-2 glucuronide is considered as a major metabolite of Lamotrigine [22].

In healthy volunteers, the elimination half-time is 32.8 hours [21]. The present study showed significant in hematological parameters especially in hemoglobin concentration, packed cell volume and white blood cell count in group 2 and 3 in days 7 and 28, this result is in agreement with Adeneye *et.al.* 2006 [23] who noted that, the blood considered as an appropriate medium of transport for numerous drugs in the human body and for that matter components of red blood cells, white blood cells, haemoglobin, and platelets are exposed to notable concentrations of toxic compounds, as damage and demolition of the blood cells which are harmful to the normal functioning of the body.

About 1-3 million blood cells (erythrocytes, leucocytes, and platelets) produced in a healthy adult and this value could be changed in abnormal physiological or pathological condition [24]. The normal ranges of haematological parameters and blood formation rate were affected by these drugs which including cytotoxic agents [25]. LTG does not change the weights of many organs or laboratory measures such as complete blood count and biochemical parameters [26].

In healthy volunteers, using lower doses of lamotrigine (25mg/day) may be hard to measure in clinical laboratory method; while high doses cause

serious adverse events [12]. Serum AST, ALT, urea, and creatinine were altered and the value of some of them were significant and others were not. A significant increase of liver enzymes ALT & AST was observed at the end of 21 days of treatment with lamotrigine in adult male Wistar rats after picrotoxin treatment -induced convulsions [27]. Many studies recorded that most antiepileptic drugs could cause hepatotoxicity, LTG caused a temporary elevation of liver enzymes without appearing symptoms or signs of hepatic dysfunction to hepatotoxicity [28].

Serum AST and ALT are good index of liver function and increasing of these enzymes can be used as biomarkers to previse the possible toxicity of lamotrigine drug [29]. These enzymes play an important role in different metabolic routes [30]. Level of AST and ALT increased significantly in the group treated with lamotrigine which showed the lamotrigine effect on liver function and often suggests the presence of liver problems [31]. While Fayad and Choueiri ,2000 [32] reported that the discontinuous use of LTG does not affect liver function and liver enzymes. In spite of using lamotrigine or any medical does, dietary choline deficiency and physical exercise may cause elevation of liver enzymes [33].

Ali *et.al.*2003 [34] revealed that acute treatment with any dose of LTG (1.3, 2.6 and 5.2 mg/kg) does not affect many biochemical parameters, and chronic treatment (21 days) with all doses of LTG did not exhibit any hepatotoxic activity. Second-generation antiepileptic drugs cause less induction of liver enzymes in comparison to the first generation antiepileptic drugs [35]. In this study (fig.1), showed level of estradiol after 28 days of treatment with lamotrigine changed significantly when compared with control group, this result is similar with [(36] which proved that, healthy female patients took lamotrigine and the combined oral contraceptive, individually or as co-therapy for 130 days, recorded slight effect of lamotrigine on estradiol level. Lamotrigine drug reduces estradiol level [37]. While [11] found that, healthy rats treated with lamotrigine for different period caused a significant increase in the level of estradiol.

Lamotrigine is considered traditional sodium channel–blocking antiepileptic drugs, is confirmed its therapeutic effects by reacting with sodium channels [38]. A large reduction of the high-voltage-activated calcium currents produced by lamotrigine and slight use-dependent inhibition of the sodium conductance [39]. Sodium inward current, voltage-gated–calcium currents and the transient potassium outward current affected by lamotrigine drug may cause potent mechanisms to inhibit pathological irritation in epilepsy and a possible advantage in treating disturbances in bipolar disorder [40].

Conclusion

Treating of female albino rats with two doses of lamotrigine drug for 28 days have a significant effect on altering the level of most hematological, biochemical parameters, ions, and estradiol level included in this study, Further studies are necessary to investigate the high doses and long-term effect of this drug on healthy and epileptic rats.

References

[1] Biale, M.(2012). Why are antiepileptic drugs used for nonepileptic conditions? *Epilepsia*, **53(7)**:26–33.

[2] Leppik, I.E. (1994). Antiepileptic drugs in development: prospects for the near future. *Epilepsia*, **35 (4)**: 29-40.

[3] Leach, M.J.; Harden, C.M. and Millar, A.A. (1986). Pharmacological studies of lamotrigine, a novel potential antiepileptic drug, II: Neurochemical studies on the mechanisms of action. *Epilepsia*, **27 (5)**: 490-497.

[4]Pellock, J.M. (1997). Lamotrigine. *Journal of Child Neurol*ogy, **12(1)**: S1-S1

[5] Cohen, A.F. et al. (1987). Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. *Clinical Pharmacology & Ther*apeutic, **42(5)**: 535–541.

[6] EURAP Study Group. (2006). Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Neurology*, **66(3)**: 354–360.

[7] Garnett, W.R. (1997). Lamotrigine: pharmacokinetics. *Journal of Child Neurol*ogy, **12(1)**: S10–15.

[8] Doig, M.V. and Clare, R.A. (1991). Use of thermospray liquid chromatography - mass spectrometry to aid in the identification of urinary metabolites of a novel antiepileptic drug, lamotrigine. *Journal of Chromatography*, **554(1-2)**: 181–189.

[9] Pickrell, W.O. et al. (2014). Trends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010. Seizure, **23(1)**:77–80.

[10] Abu-rish, E.Y.; Elhayek, Sh. Y.; Mohamed, Y.S.; Hamad, I. and Bustanji, Y. (2017). Evaluation of immunomodulatory effects of lamotrigine in BALB/c mice. *Acta Pharmaceutica*, **67(4)**: 543–555

[11] Al-taee, A.A. (2016). Histological and Biochemical Study of Female Albino Rats (Rattus rattus) Treated with Lamotrigine**.** *International Journal of PharmTechRes*earch**,9(9)**: 321-329.

[12] Perez-Lloret, S.L.; De Mena,O.F.; Pieczanski,P.; and Moncalvo. J.R. (2012). Bioequivalence of Lamotrigine 50-mg Tablets in Healthy Male Volunteers: A Randomized, Single-Dose,2-Period, 2-Sequence Crossover Study. *Arzneimittelforschung*, **62(10)**:470-476.

[13] Milosheska, D. et al. (2016). Pharmacokinetics of lamotrigine and its metabolite N-2-glucuronide: Influence of polymorphism of UDP-glucuronosyltransferases and drug transporters. *British Journal of Clinical Pharmacology***, 82(2)**:399-411

[14] Roste, L.S.et al.(2003). Gonadal morphology and sex hormones in male and female Wistar rats after long-term lamotrigine treatment. *Seizure*,**12(8)**: 621–627.
[15] Sidhu J, Job S, Singh S, and Philipson R.(2006). The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *British Journal of Clinical Pharmacology*, **61(2)**:191–199.
[16] Shin, J.W.; Seol, I.C. and Son, C.G. (2010) Interpretation of Animal Dose and Human Equivalent Dose for Drug Development. *The Journal of Korean Oriental Medicine*.**31(3)**: 1-7.
[17] Peter, A. and Kellie, B. (2012). SPSS statistics: a practical guide version 20. Cengage learning, Australia.
[18] Landmark, C.J. (2008). Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* .**22(1)**:27–47.
[19] Hamer, H.M, et al. (2012). Prevalence, utilization, and costs of antiepileptic drugs for epilepsy in Germany – a nationwide population-based study in children and adults. *Journal of Neurology*, **259(11)**:2376–2384.
[20] Hsieh, L.P, and Huang, C.Y.(2011). Trends in the use of antiepileptic drugs in Taiwan from 2003 to 2007: a population-based national health insurance study. *Epilepsy Research* **,96(1-2)**:81–88.
[21] Biton, V. (2006). Pharmacokinetics, toxicology and safety of lamotrigine in epilepsy. *Expert Opinion Drug Metabolism Toxicology*, **2(6)**: 1009 – 1018.
[22] Sinz, M. W, and Remmel, R. P.(1991). Isolation and characterization of a novel quaternary ammonium-linked glucuronide of lamotrigine. *Drug Metabolism Disposition*,**19(1)**: 149 – 153.
[23] Adeneye, A. A.; Ajagbonna, O. P.; Adeleke, T. I. and Bello, S.O. (2006). Preliminary toxicity and phytochemical studies of the stem bark aqueous extract of Musanga cecropioides in rats. *Journal of Ethnopharmacology*, **105(3)**:374–379.
[24] Guyton, A. C. and Hall, J. E. (2000). Textbook of Medical Physiology. 10th edn., Philadelphia: Saunders: p 421
[25] Zuk, A.; Targosz-Korecka, M. and Szymonski, M. (2011). Effect of selected drugs used in asthma treatment on morphology and elastic properties of red blood cells.International .*Journal of Nanomedicine***. 6**: 249–257.
[26] Betts, T. (1992). Clinical uses of lamotrigine. *Seizure***. 1(1)**:3-6
[27] Shams El Dine, S.M. (2014). Possible effects of lamotrigine on liver of Wistar rats exposed to chemoconvulsion and Chronic Restraint model. *American Journal of Psychiatry and Neuroscience*. **2(4)**: 50-55.
[28] Ziegler D. et al. (2009). Neuropathic pain in diabetes, prediabetes and normal glucose tolerance: the MONICA/KORA Augsburg Surveys S2 and S3. *Pain Medicine*. **10(2)**: 393-400
[29] Day, A.; Mayne, P. and Mayne, P.D. (1994). Clinical Chemistry in Diagnosis and Treatment. 6th edn. London: Ahodder Arnold Publication:
[30] Johnston, D.E. (1999). Special considerations in interpreting liver function tests. *American Family Physician* . **59(8)**:2223-2230.
[31] Meldrum, B.S. (1994). Lamotrigine a novel approach. *Seizure*. **3 (SupplA)**: 41-45.
[32] Fayad, M., Choueiri, R. and Mikati, M. (2000). Potential hepatotoxicity of lamotrigine. *Pediatric Neurology*. **22(1)**: 49-52.
[33] Paul, T. Giboney, M.D. (2005). Mildly elevated liver transaminase levels in the Asymptomatic Patient. *American Family Physician*. **71(6)**:1105-1110.
[34] Ali, A. et al.(2003). Lamotrigine is not hepatoxic in mice. *Indian Journal of Pharmacology*. **35(4)**: 248-249.
[35] McAuley, J.W. and Anderson, G.D. (2002). Treatment of epilepsy in women of reproductive age, pharmacokinetic considerations. *Clinical Pharmacokinetic*. **41(8)**:559–579.
[36] Sidhu, J; Job, S.; Singh, S. and Philipson, R. (2006). The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *British Journal of Clinical Pharmacology*. **61(2)**: 191–199.
[37] Reimers, A. (2014) New antiepileptic drugs and women. *Seizure* **23(8)**: 585-591.
[38] Niespodziany I, Leclère N, Vandenplas C, Foerch P, and Wolff, C.(2013). Comparative study of lacosamide and classical sodium channel blocking antiepileptic drugs on sodium channel slow inactivation. *Journal of Neuroscience Research.* **91(3)**:436–443.
[39] Stefani, A.; Spadoni,F. and. Bernardi, G.(1997). Differential Inhibition by Riluzole, Lamotrigine, and Phenytoin of Sodium and Calcium Currents in Cortical Neurons: Implications for Neuroprotective Strategies. *Experimental Neurology*.**147(1)**:115-122.
[40] Grunze, H.; von Wegerer, J.; Greene, R.W. and Walden, J. (1998). Modulation of Calcium and Potassium Currents by Lamotrigine. *Neuropsychobiology*. **38(3)**: 131–138.

دراسة بعض المعايير الدموية والكيموحيوية في انثى الجرذان البيض المعاملة بعقار اللاموترجين

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الملخص

صممت هذه التجربة لتقيم تأثير عقار اللاموترجين المضاد للصرع على بعض المعايير الدموية والكيموحيوية في أنثى الجرذان البيض. استخدمت ثمانية واربعون جرذا قسمت الى ثلاثة مجاميع (كل مجموعة =16 جرذ) , المجموعة الاولى استخدمت كمجموعة تحكم والمجموعة الثانية والثالثة تم تجريعهم يوميا عن طريق الفم ب 3.57 ملغم/كلغم و7.14ملغم/كلغم

وزن الجسم على التوالي ولمدة 28,21,14,7 يوما وكل المجاميع تغذت على العلف القياسي. أظهرت النتائج ان هناك تغير معنوي في العوامل الدموية في المجموعة الثانية والثالثة مقارنة بمجموعة التحكم في جميع الفترات الزمنية عدا معدل تركيز خضاب الدم. حصل تغير معنوي في مستوى انزيما ت الكبد ومستوى اليوريا والكرياتينين في مصل الدم ومستوى عنصر الكالسيوم والبوتاسيوم والصوديوم والكلورايد في المجموعتين الثانية والثالثة , تغير وزن الاعضاء في المجموعة الثانية والثالثة عند مقارنتهم بمجموعة التحكم خلال 28,21,14,7 يوما. ارتفع مستوى هرمون الاستراديول في المجموعة الثالثة في اليوم السابع والرابع عشر والحادي والعشرون وانخفضت في اليوم الثامن والعشرون عند مقارنته بالمجموعة الثانية ومجموعة التحكم. تستنتج من هذه الدراسة ان معاملة الجرذان بجرعتي عقار اللاموترجين ولمدة 28 يوما بشكل عام له تأثير على العوامل المدروسة في هذا البحث.