The Effect of Treatment With Antiepileptic Drugs (Carbamazepine, Valproic Acid, Topiramate, And Their Combination) On Lipid Profile, C-Reactive Protein, And Renal Function in Iraqi Epileptic Patients

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Abstract

This study was designed to evaluate the effect of treatment with antiepileptic drugs carbamazepine, valproic acid, topiramate, and their combination on lipid profile, C-reactive protein, and renal functions (urea & creatinine) in Iraqi epileptic patients. Ninety epileptic patients were participated in this study and their age ranged from (1-45) years. Seventy patients were previously diagnosed with epilepsy and received antiepileptic drugs for at least six months before this study (retrospective groups). The remaining patients were newly diagnosed with epilepsy (prospective groups). Twenty healthy subjects were selected to be a normal group for the purpose of comparison. The result showed an elevation in lipid profile after three months of treatment and this elevation was significant in serum total cholesterol, HDL-c, and LDL-c in retrospective groups and only significant for HDL-c in prospective groups. A clinically significant elevation in the level of CRP was observed in one patient and in seven patients after treatment with topiramate and combination therapy respectively. No significant differences were observed in renal function tests among the groups after treatment. In conclusion, the long term antiepileptic treatment increased the risk of atherosclerosis without significantly affecting renal functions.

Key word: antiepileptic drugs, lipid profile, CRP, renal function.

الخلاصة

ان الهدف من هذه الدراسة هو لتقييم تأثير الأدوية المضادة للصرع كاربامازبين ، حمض فالبرويك، توبيراميت، والجمع بين اثنين منهم على مستويات الدهون المختلفة ، البروتين النشط (س)، ووظائف الكلى في المرضى العراقيين المصابين بالصرع. تم اختيار تسعين مصابا بالصرع ليساهموا فعليا في هذه الدراسة ، تتراوح اعمارهم من (1-45) سنة. سبعون من هؤلاء المرضى تم تشخيصهم من قبل بالصرع وتلقوا الأدوية المضادة للصرع ما لا يقل عن ستة أشهر قبل هذه الدراسة (مجموعات الأثر الرجعي). اما المرضى المتبقين فتم تشخ يصهم حديثا بالصرع ولم يتلقوا أي نوع من الادوية المضادة للصرع قبل هذه الدراسة (مجموعات المحتملين). عشرون شخصا من الأصحاء تم اختيارهم لغرض المقارنة. لوحظ إرتفاع في مستوى الدهون المختلفة بعد ثلاثة اشهر من العلاج وهذا الارتفاع كان كبيرا في مصل الكولسترول الكلي ، الكولسترول العالي الكثافة، والكولسترول القليل الكثافة في مجموعات الأثر الرجعي والكولسترول العالي الكثافة فقط في مجموعات المحتملين، كما ولوحظ وجود ارتفاعا سريريا كبيرا في مستوى البروتين النشط (س) في احد المرضى وسبعة مرضى بعد العلاج باستعمال توبيراميت والع لاج المركب على التوالي . لم تلاحظ أي فروق ذات دلالة إحصائية في اختبارات وظائف الكلى بين المجموعات بعد العلاج . خلصت الدراسة إلى أن استعمال الادوية المضادة للصرع لفترة طويلة تزيد من خطر تصلب الشرايين دون أن تؤثر بشكل كبير على وظائف والكلى.

Introduction

Epilepsy is a disorder that is best viewed as a symptom of disturbed electrical activity in the brain, which may be caused by a wide variety of etiologies. It is a collection of many different types of seizures that vary widely in severity, appearance, cause, consequence, and management [(1)]. It is a chronic dynamic medical problem that often required long-term antiepileptic drugs (AEDs) [(2)]. Of note is that seizures in many patients do not remit despite appropriate medication, and lifelong AEDs therapy is usually required for those with refractory epilepsy. This practice poses a medical dilemma because prolonged AEDs therapy is often associated with a wide range of chronic adverse effects, including metabolic and endocrine disturbances, behavioral or psychiatric problems, idiosyncratic reactions, negative cognitive effects, and drug interactions [(3)]. Biochemical properties and empiric evidence suggest that some AEDs may have chronic metabolic effects. In particular, there is growing support for the idea that some treatments for epilepsy are associated with changes in vascular risk markers, prompting us to reevaluate epidemiologic data linking epilepsy to vascular disease and to review the current literature on the relationship between commonly used AEDs and markers of increased vascular risk [(4)]. Although serum chemistry and urinalysis are often performed in patients with epilepsy receiving AEDs in order to detect serum concentrations of AEDs, and occasional hepatorenal toxicity, the results are usually normal. This led to doubts as to whether urinalysis is reliable in detecting early renal changes, and whether or not it should be a routine examination in these patients [(5)]. This study was designed to evaluate the effect of treatment with AEDs carbamazepine, valproic acid, topiramate, and their combination on lipid profile, C-reactive protein, and renal functions (urea & creatinine) in Iraqi epileptic patients.

Subjects & Methods

a) Patients

This study was carried out at Tikrit teaching hospital from November 2011 until June 2012. Ninety patients completed the courses of the study successfully. Seventy patients were previously diagnosed with epilepsy and received AEDs for at least six months before this study (retrospective groups) and these patients had poorly controlled epilepsy. Their age ranged from 1 - 45 years (mean ± SEM = 18.85 ± 1.25), of them 32 (45.71%) patients were male and 38 (54.28%) patients were female. The remaining patients were newly diagnosed with epilepsy and did not receive any AED before this study (prospective groups). Their age ranged from 2 - 32 years (14.95 ± 2.11), of them 9 (45%) patients were male and 11 (55%) patients were female. The previously diagnosed patients were recruited into the following retrospective groups:

Group 1: Includes 20 epileptic patients tested at baseline and after three months of treatment with carbamazepine (at dose 431.57 ± 16.75 mg/day) (mean ± SEM).

Group 2: Includes 20 epileptic patients tested at baseline and after three months of treatment with valproic acid (at dose 492.10 ± 35.01 mg/day).

Group 3: Includes 10 epileptic patients tested at baseline and after three months of treatment with topiramate (at dose 57.50 ± 7.49 mg/day).

Group 4: Includes 20 epileptic patients tested at baseline and after three months of treatment with combination therapy as following:

i. Sixteen patients receiving carbamazepine and topiramate (at dose 787.5 ± 67.00 mg/day and 73.43 ± 12.80 mg/day respectively).
ii. Two patients receiving carbamazepine and valproic acid (at dose 600.00 ± 199.99 mg/day and 800.0 ± 0.0 mg/day respectively).

iii. Two patients receiving valproic acid and topiramate (at dose 800.00 ± 0.0 mg/day and 50.0 ± 0.0 mg/day respectively).

The newly diagnosed patients were recruited into the following prospective groups:

Group 1: Includes 10 epileptic patients tested at baseline and after three months of treatment with carbamazepine (at dose 400 ± 29.81 mg/day) (mean ± SEM).

Group 2: Includes 10 epileptic patients tested at baseline and after three months of treatment with valproic acid (at dose 430 ± 29.99 mg/day).

b) Healthy Subjects

Twenty subjects who were apparently healthy selected for the purpose of comparison. These subjects were selected from the medical staff and some relative volunteers, of them 9 were male (45%) and 11 were female (55%). Their ages were ranged from 1 – 45 years (19.55 ± 4.50).

c) Exclusion Criteria:

- Diabetic patients.
- Hypertensive patients.
- Patients with IHD, CHF, arrhythmias, or dyslipidemia.
- Renal impaired patients.
- Patients with thyroid dysfunction.
- Pregnancy, whether confirmed or suspected.

d) Sample Collection And Preparation

Six milliliters of venous blood sample were drawn from each patient in the morning at 8:30 – 9:30 AM after an overnight fasting by vein puncture, before starting drug treatment (as baseline sample) and then after 3 months of treatment. Serum was used for the measurement of total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), C-reactive protein (CRP), urea, and creatinine. One blood sample was drawn from each healthy subject. Lipid profile, urea, and creatinine were measured in serum by colorimetric method using the kit from Biolabo, (France) for lipid profile, Biomérieux, (France) for urea, and Randox, (UK) for creatinine. All the assays were performed on spectrophotometer; whereas, CRP was measured serologically using CRP latex test kit from Plasmatec, (UK).

e) Statistical Analysis

All data were expressed as mean ± standard error means (SEM). Statistical analyses were carried out using paired t-test and analysis of variance (ANOVA) to compare between mean values of parameters. P value < 0.05 was considered statistically significant. Descriptive analysis was carried out by Microsoft Office Excel 2007 software.

Results

Effect Of Treatment With Carbamazepine, Valproic Acid, Topiramate, And Combination Therapy On Lipid Profile:

i. Retrospective Groups

- ***Serum Total Cholesterol (TC):***

Table (1) showed the serum TC in retrospective groups at baseline and after three months of treatment. Serum TC values after three months of treatment in all the groups were significantly higher ($p<0.05$) than these values at baseline level. These values in patients receiving carbamazepine, topiramate, and combination therapy for three months showed a significant increase when compared with healthy subject's values; whereas, no significant increase ($p>0.05$) was observed in the those values in patients treated with valproic acid for three months when compared with the healthy subject's values. At baseline, only the patients receiving carbamazepine showed a significant difference in the serum TC values when compared with the values of healthy subjects; whereas, no significant changes were seen in the other groups. There were no significant differences among the groups at baseline and after three months treatment. The percent increase between the baseline values of serum TC and after three months values were ranged from 4.28% to 10.17%.

- ***Serum Triglycerides (TG):***

Table (2) showed the serum TG in retrospective groups at baseline and after three months of treatment. The values of TG after three months of treatment were not significantly higher than those values at the baseline level. Also, these values were not significantly different from the values of healthy subjects. The values of TG at baseline in patients treated with carbamazepine, valproic acid, or combination therapy did not show significant differences when compared with the healthy subjects' values. However, these values in patients treated with topiramate showed a significant reduction as compared with the values of healthy subjects. There were no significant differences among the groups after three months of treatment. However, the values of TG in patients receiving topiramate at baseline level showed a significant difference when compared with those values obtained from patients treated with combination therapy. The percent increase between the baseline values of TG and after three months values were ranged from 0.96% to 10.11%.

- ***Serum High Density Lipoprotein-cholesterol (HDL-c):***

Table (3) showed the serum HDL-c in retrospective groups at baseline and after three months of treatment. The values of HDL-c after three months of treatment were significantly higher than the baseline values. Meanwhile, patients treated with carbamazepine, topiramate, or combination therapy showed a significant increase in HDL-c values when compared with the healthy subjects' values. There was no significant increase in these values in patients treated with the valproic acid for three months as compared with healthy subject values. At baseline, the values of HDL-c in patients receiving carbamazepine, topiramate, or combination therapy showed significant increases when compared with the healthy subjects' values; whereas, there was no significant change in these values in patients treated with valproic acid. There were no significant differences among the groups at the baseline and after three months of treatment. The percent increase between the baseline values of HDL-c and after three months values were ranged from 5.82% to 16.66%.

- ***Serum Low Density Lipoprotein-cholesterol (LDL-c):***

Table (4) showed the serum LDL-c in retrospective groups at baseline and after three months of treatment. The values of LDL-c after three months of treatment in all groups were significantly higher than the baseline values. These values in patients treated with carbamazepine, topiramate, or combination therapy were also significantly higher than the values of healthy subjects. No significant difference was showed between LDL-c values in patients treated with valproic acid for three months and the healthy subjects' values. There were no significant changes in the values of LDL-c in all groups at baseline level when compared with the values of healthy subjects. Among the groups, there were no significant differences at the baseline and after three months of treatment. The percent increase between the baseline values of LDL-c and after three months values were ranged from 4.52% to 13.11%.

ii. Prospective Groups

- ***Serum Total Cholesterol (TC):***

Table (5) showed the serum TC in prospective groups at baseline and after three months of treatment. The values of serum TC after three months of treatment were not significantly changed from those values at baseline in both groups. However, these values in patients receiving carbamazepine at baseline and after three months were significantly higher than the healthy subjects' values; whereas no significant changes in those values were observed in patients treated with valproic acid at baseline and after three months of therapy. Between the groups, there were no significant differences at the baseline and after three months of

treatment. The percent increase between the baseline values of TC and after three months values was 10.82% for carbamazepine and 3.03% for valproic acid.

- ***Serum Triglycerides (TG):***

Table (6) showed the serum TG in prospective groups at baseline and after three months of treatment. The values of TG after three months of treatment were not significantly changed when compared with those values at baseline level in both groups. Also, these values at baseline and after three months of treatment were not significantly differed from the values of healthy subjects. Between the groups, there were no significant differences at the baseline and after three months of treatment. The percent increase between the baseline values of TG and after three months values was 2.08% for carbamazepine and 5.43% for valproic acid.

- ***Serum High Density Lipoprotein-cholesterol (HDL-c):***

Table (7) showed the serum HDL-c in prospective groups at baseline and after three months of treatment. There were significant increases in HDL-c values in both groups after three months of treatment when compared with that of baseline and healthy subject's values. However, these values at baseline in both groups were not significantly differed from those of healthy subjects. Between the groups, there were no significant differences at the baseline and after three months of treatment. The percent increase between the baseline values of HDL-c and after three months values was 30.43% for carbamazepine and 12.24% for valproic acid.

- ***Serum Low Density Lipoprotein-cholesterol (LDL-c):***

Table (8) showed the serum LDL-c in prospective groups at baseline and after three months of treatment. The values of LDL-c in both groups after three months of treatment were not significantly differed from those values at baseline level. However, these values at baseline and after three months of treatment in patients receiving carbamazepine were significantly higher than the values of the healthy subjects. On the other hand, these values at baseline and after three months of treatment in patients receiving valproic acid were not significantly higher than those of healthy subjects. Between the groups, there were no significant differences at the baseline and after three months of treatment. The percent increase between the baseline values of LDL-c and after three months values was 4.48% for carbamazepine and 5.83% for valproic acid.

a) Effect Of Treatment With Carbamazepine, Valproic Acid, Topiramate, And Combination Therapy On C-Reactive Protein:

i. Retrospective Groups

Table (9) showed the serum CRP in retrospective groups at baseline and after three months of treatment. The results of CRP at baseline for all patients were negative. After three months of treatment, these results were still negative in all patients except one patient receiving topiramate showed a positive CRP result. While in combination therapy's group, two patients showed a positive CRP result at baseline level and eighteen patients showed a negative result. After three months of treatment with combination therapy, the number of patients with a positive CRP result increased to seven and thirteen patients still had a negative result. All these seven patients were received a combination therapy consisting of carbamazepine and topiramate.

ii. Prospective Groups

Table (10) showed the serum CRP in prospective groups at baseline and after three months of treatment. All patients in both groups at baseline level showed a negative CRP result. These results remained negative after three months of treatment with either carbamazepine or valproic acid.

b) Effect Of Treatment With Carbamazepine, Valproic Acid,

Topiramate, And Combination Therapy On Renal Function:

i. Retrospective Groups

- ***Serum Urea:***

Table (11) showed the serum urea in retrospective groups at baseline and after three months of treatment. The values of serum urea after three months of treatment in all groups were not significantly differed from those at the baseline level. Also, these values at baseline and after three months of treatment were not significantly differed from the values of healthy subjects. Among the groups, there were no significant differences at the baseline and after three months of treatment. The percent increase between the baseline values of urea and after three months values were ranged from 0.30% to 5.41%.

- ***Serum Creatinine:***

Table (12) showed the serum creatinine in retrospective groups at baseline and after three months of treatment. The values of serum creatinine after three months of treatment were not significantly differed from those at baseline in all the groups except the group of patients that received combination therapy that showed a significant increase when compared with baseline values. These values after three months of treatment with carbamazepine or valproic acid therapy were significantly lower than the values of healthy subjects; whereas these values in patients treated with topiramate or with combination therapy were not significantly lower than the values of the healthy subjects. The values of serum creatinine in all groups at baseline were significantly lower than the values of healthy subjects. There were no significant differences among the groups at the baseline level. However, serum creatinine values in patients treated with combination therapy for three months showed a significant difference when compared with the group of patients receiving carbamazepine or valproic acid. The percent increase between the baseline values of creatinine and after three months values were ranged from 11.76% to 17.14%.

ii. Prospective Groups

- ***Serum Urea:***

Table (13) showed the serum urea in prospective groups at baseline and after three months of treatment. There were no significant changes in serum urea values after three months of treatment with carbamazepine or valproic acid as compared with healthy subjects' and the baseline values. Also, baseline values of serum urea in both groups were not significantly different from the values of healthy subjects. Between the groups, there were no significant differences at the baseline and after three months of treatment. The percent increase between the baseline values of urea and after three months values was 4.03% for carbamazepine and 2.44% for valproic acid.

- ***Serum Creatinine:***

Table (14) showed the serum creatinine in prospective groups at baseline and after three months of treatment. The values of serum creatinine in both groups after three months of treatment were not significantly different from those at baseline. These values at baseline and after three months of treatment in both groups were significantly lower than the values of healthy subjects. Between the groups, there were no significant differences at the baseline and after three months of treatment. The percent increase between the baseline values of creatinine and after three months values was 10.16% for carbamazepine and 14.06% for valproic acid.

Table (1):- Serum total cholesterol in retrospective groups at baseline and after three months of treatment.

Retrospective groups	Number of patients	SERUM TOTAL CHOLESTEROL (mmol/L)		
		Baseline	After 3 months	% change
Healthy subjects	20	3.57 ± 0.15	----------	----------
Carbamazepine	20	3.97 ± 0.14 b	4.33 ± 0.20 *a	9.06%
Valproic acid	20	3.73 ± 0.14	3.89 ± 0.19 *	4.28%
Topiramate	10	3.85 ± 0.19	4.18 ± 0.23 *a	8.57%
Combination therapy	20	3.93 ± 0.16	4.33 ± 0.21 *a	10.17%

Each value represents the mean ± standard error of mean.
* $P < 0.05$ significant difference between baseline and after 3 months values.
a $P < 0.05$ significant difference between healthy subjects and after 3 months values.
b $P < 0.05$ significant difference between healthy subjects and baseline values.

Table (2):- Serum triglycerides in retrospective groups at baseline and after three months of treatment.

Retrospective groups	Number of patients	SERUM TRIGLYCERIDES (mmol/L)		
		Baseline	After 3 months	% change
Healthy subjects	20	1.04 ± 0.075	----------	----------
Carbamazepine	20	0.92 ± 0.054	0.99 ± 0.039	7.60%
Valproic acid	20	1.04 ± 0.10	1.05 ± 0.044	0.96%
Topiramate	10	0.89 ± 0.091 bc	0.98 ± 0.079	10.11%
Combination therapy	20	1.07 ± 0.080	1.10 ± 0.092	2.80%

Each value represents the mean ± standard error of mean.
b $P < 0.05$ significant difference between healthy subjects and baseline values.
c $P < 0.05$ significant difference between different drug types.

Table (3):- Serum HDL-c in retrospective groups at baseline and after three months of treatment.

Retrospective groups	Number of patients	SERUM HDL-c (mmol/L)		
		Baseline	After 3 months	% change
Healthy subjects	20	0.98 ± 0.047	----------	----------
Carbamazepine	20	1.09 ± 0.023 b	1.20 ± 0.050 *a	10.09%
Valproic acid	20	1.03 ± 0.056	1.09 ± 0.067 *	5.82%
Topiramate	10	1.08 ± 0.049 b	1.26 ± 0.12 *a	16.66%
Combination therapy	20	1.11 ± 0.062 b	1.26 ± 0.066 *a	13.51%

Each value represents the mean ± standard error of mean.
* $P < 0.05$ significant difference between baseline and after 3 months values.
a $P < 0.05$ significant difference between healthy subjects and after 3 months values.
b $P < 0.05$ significant difference between healthy subjects and baseline values.

Table (4):- Serum LDL-c in retrospective groups at baseline and after three months of treatment.

Retrospective groups	Number of patients	SERUM LDL-c (mmol/L)		
		Baseline	After 3 months	% change
Healthy subjects	20	2.10 ± 0.13	----------	----------
Carbamazepine	20	2.44 ± 0.16	2.76 ± 0.23 *a	13.11%
Valproic acid	20	2.21 ± 0.12	2.31 ± 0.15 *	4.52%
Topiramate	10	2.31 ± 0.14	2.49 ± 0.21 *a	7.79%
Combination therapy	20	2.32 ± 0.20	2.50 ± 0.22 *a	7.75%

Each value represents the mean ± standard error of mean.
* $P < 0.05$ significant difference between baseline and after 3 months values.
a $P < 0.05$ significant difference between healthy subjects and after 3 months values.

Table (5):- Serum total cholesterol in prospective groups at baseline and after three months of treatment.

Prospective groups	Number of patients	SERUM TOTAL CHOLESTEROL (mmol/L)		
		Baseline	After 3 months	% change
Healthy subjects	20	3.57 ± 0.15	----------	----------
Carbamazepine	10	4.25 ± 0.20 b	4.71 ± 0.34 a	10.82%
Valproic acid	10	3.95 ± 0.31	4.07 ± 0.30	3.03%

Each value represents the mean ± standard error of mean.
a P < 0.05 significant difference between healthy subjects and after 3 months values.
b P < 0.05 significant difference between healthy subjects and baseline values.

Table (6):- Serum triglycerides in prospective groups at baseline and after three months of treatment.

Prospective groups	Number of patients	SERUM TRIGLYCERIDE (mmol/L)		
		Baseline	After 3 months	% change
Healthy subjects	20	1.04 ± 0.075	----------	----------
Carbamazepine	10	0.96 ± 0.15	0.98 ± 0.079	2.08%
Valproic acid	10	0.92 ± 0.051	0.97 ± 0.16	5.43%

Each value represents the mean ± standard error of mean.

Table (7):- Serum HDL-c in prospective groups at baseline and after three months of treatment.

Prospective groups	Number of patients	SERUM HDL-c (mmol/L)		
		Baseline	After 3 months	% change
Healthy subjects	20	0.98 ± 0.047	----------	----------
Carbamazepine	10	0.92 ± 0.085	1.20 ± 0.050 *a	30.43%
Valproic acid	10	0.98 ± 0.024	1.10 ± 0.026 *a	12.24%

Each value represents the mean ± standard error of mean.
* P < 0.05 significant difference between baseline and after 3 months values.
a P < 0.05 significant difference between healthy subjects and after 3 months values.

Table (8):- Serum LDL-c in prospective groups at baseline and after three months of treatment.

Prospective groups	Number of patients	SERUM LDL-c (mmol/L)		
		Baseline	After 3 months	% change
Healthy subjects	20	2.10 ± 0.13	----------	----------
Carbamazepine	10	2.90 ± 0.23 b	3.03 ± 0.33 a	4.48%
Valproic acid	10	2.40 ± 0.38	2.54 ± 0.29	5.83%

Each value represents the mean ± standard error of mean.
a $P < 0.05$ significant difference between healthy subjects and after 3 months values.
b $P < 0.05$ significant difference between healthy subjects and baseline values.

Table (9):- Serum CRP in retrospective groups at baseline and after three months of treatment. The data were expressed as number (n) and percentage (%).

Retrospective groups	Number of patients	SERUM CRP		
			Baseline	After 3 months
Healthy subjects	20	Positive	0 (0%)	----------
		Negative	20 (100%)	----------
Carbamazepine	20	Positive	0 (0%)	0 (0%)
		Negative	20 (100%)	20 (100%)
Valproic acid	20	Positive	0 (0%)	0 (0%)
		Negative	20 (100%)	20 (100%)
Topiramate	10	Positive	0 (0%)	1 (10%)
		Negative	10 (100%)	9 (90%)
Combination therapy	20	Positive	2 (10%)	7 (35%)
		Negative	18 (90%)	13 (65%)

Table (10):- Serum CRP in prospective groups at baseline and after three months of treatment. The data were expressed as number (n) and percentage (%).

Prospective groups	Number of patients	SERUM CRP		
			Baseline	After 3 months
Healthy subjects	20	Positive	0 (0%)	----------
		Negative	20 (100%)	----------
Carbamazepine	10	Positive	0 (0%)	0 (0%)
		Negative	10 (100%)	10 (100%)
Valproic acid	10	Positive	0 (0%)	0 (0%)
		Negative	10 (100%)	10 (100%)

Table (11):- Serum urea in retrospective groups at baseline and after three months of treatment.

Retrospective groups	Number of patients	SERUM UREA (mg/dl)		
		Baseline	After 3 months	% change
Healthy subjects	20	26.79 ± 1.17	----------	----------
Carbamazepine	20	24.17 ± 1.22	25.48 ± 0.77	5.41%
Valproic acid	20	26.50 ± 1.50	26.70 ± 0.75	0.75%
Topiramate	10	26.62 ± 1.72	26.70 ± 1.06	0.30%
Combination therapy	20	24.62 ± 1.05	25.69 ± 0.73	4.34%

Each value represents the mean ± standard error of mean.

Table (12):- Serum creatinine in retrospective groups at baseline and after three months of treatment.

Retrospective groups	Number of patients	SERUM CREATININE (mg/dl)		
		Baseline	After 3 months	% change
Healthy subjects	20	0.85 ± 0.031	----------	----------
Carbamazepine	20	0.64 ± 0.036 b	0.73 ± 0.049 a	14.06%
Valproic acid	20	0.63 ± 0.058 b	0.73 ± 0.051 a	15.87%
Topiramate	10	0.68 ± 0.058 b	0.76 ± 0.066	11.76%
Combination therapy	20	0.70 ± 0.041 b	0.82 ± 0.040 *c	17.14%

Each value represents the mean ± standard error of mean.
* $P < 0.05$ significant difference between baseline and after 3 months values.
a $P < 0.05$ significant difference between healthy subjects and after 3 months values.
b $P < 0.05$ significant difference between healthy subjects and baseline values.
c $P < 0.05$ significant difference between different drug types.

Table (13):- Serum urea in prospective groups at baseline and after three months of treatment.

Prospective groups	Number of patients	SERUM UREA (mg/dl)		
		Baseline	After 3 months	% change
Healthy subjects	20	26.79 ± 1.17	----------	----------
Carbamazepine	10	24.53 ± 0.91	25.52 ± 1.14	4.03%
Valproic acid	10	25.81 ± 1.03	26.44 ± 1.02	2.44%

Each value represents the mean ± standard error of mean.

Table (14):- Serum creatinine in prospective groups at baseline and after three months of treatment.

Prospective groups	Number of patients	SERUM CREATININE (mg/dl)		
		Baseline	After 3 months	% change
Healthy subjects	20	0.85 ± 0.044	----------	----------
Carbamazepine	10	0.59 ± 0.042 b	0.65 ± 0.081 a	10.16%
Valproic acid	10	0.64 ± 0.034 b	0.73 ± 0.078 a	14.06%

Each value represents the mean ± standard error of mean.
a $P < 0.05$ significant difference between healthy subjects and after 3 months values.
b $P < 0.05$ significant difference between healthy subjects and baseline values.

Discussion

Effect on lipid profile

The effects of treatment with AEDs carbamazepine, valproic acid, topiramate, and their combination on lipid profile were tested in this study; however, changes in serum lipids caused by antiepileptic treatment have often been discussed controversially [(6)] and the data regarding the effects of AEDs on lipid profile are limited, especially for the newer AEDs [(7)].

As shown in table (1), there was a significant elevation in the values of TC in all retrospective groups after three months of treatment when compared with baseline values. Whereas the data in table (5) showed that the values of TC in prospective groups showed a non significant elevation after treatment in both groups. The enzyme inducing agents increase the activity of the hepatic cytochrome P450 system, which is involved in synthesis of serum cholesterol. Animal data show that a particular enzyme, CYP51A1, catalyzes the conversion of lanosterol into cholesterol intermediates [(8)].When these intermediates build up through inhibition of the enzyme, they in turn inhibit the rate-limiting step of cholesterol synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), and slow the synthesis of cholesterol. It follows that induction of CYP51A1 should therefore increase cholesterol production through metabolism of these intermediates and reduced feedback inhibition. While the pathway has not been explicitly studied in humans to our knowledge, this mechanism engenders some predictions regarding the effects of certain AEDs in patients [(9)]. In table (2), the values of TG in all retrospective groups showed a non significant elevation after three months of treatment, and the data in table (6) also showed a non significant elevation in the values of TG in prospective groups after treatment. The mechanism by which AEDs increase serum TG levels remains unclear [(10)]. In table (3), the data showed that the values of HDL-c in all retrospective groups after three months of treatment were significantly elevated when compared with baseline values, and the data in tables (7) also showed a significant elevation in the values of HDL-c in all prospective groups after treatment. Liver enzyme induction by AEDs might cause an increase in HDL - c by an increased synthesis of apolipoprotein A, the main HDL lipoprotein particle. Increased apolipoprotein A levels due to decreased catabolism might contribute to increased HDL serum concentrations, but increased

synthesis of apolipoprotein A might also be an explanation of these findings [11]. Increased apolipoprotein A levels have been documented in patients treated with carbamazepine [12]. Alteration of apolipoprotein A metabolism could, therefore, be a possible mechanism in the increase of HDL-c levels. The data in table (4) showed a significant elevation in the values of LDL-c in all retrospective groups after three months of treatment when compared with baseline values. Whereas the data in tables (8) showed that the values of LDL-c in prospective groups showed a non significant elevation after treatment. Studies in persons treated with enzyme-inducing AEDs documented an enormous increase of the activity of the cholesterol synthesis rate limiting enzyme HMG-CoA reductase. Thus an increase in LDL levels might (in part) be explained by this mechanism [13]. Thus, the AEDs may influence blood lipids because of their effects on the cytochrome P450 (CYP450) enzyme system, which is found mainly in the liver and is important in the metabolism of many drugs. The AEDs also influence TC, HDL-c, LDL-c, and TG levels. As suggested by some studies, AEDs that induce the activity of CYP450 enzymes are most likely to affect blood lipid levels [7]. In this study, the lowest elevation in lipid profile was observed in group treated with valproic acid when compared with other groups. This is probably due to the fact that valproic acid is an inhibitor of certain CYP and uridine diphosphate (UDP) glucuronyl-transferase [7] which is a hepatic enzyme responsible for the conjugation and usually results in the production of pharmacologically inactive and less lipid-soluble metabolites, which are often excreted in the urine or in the bile [14]. Whereas carbamazepine is a potent inducer of liver microsomal enzymes [15], thereby significantly altering the metabolism of lipids. Although topiramate is a relatively weak inducer of CYP450 [16], it was shown to produce a significant elevation in lipid profile in this study. This is probably due to the fact that these patients were previously received AEDs other than topiramate before this study and were decided to switch to topiramate because of both lack of tolerability and lack of efficacy. Mintzer *et al.* (2012) reported that conversion from inducers (carbamazepine) to topiramate resulted in a -35 mg/dl decline in total cholesterol ($p=0.033$), with significant decreases in all cholesterol fractions, triglycerides, and LDL particle concentration ($p\leq0.03$ for all); however, alterations in cholesterol fractions remained significant when compared to those seen in normal controls and the effect is dose dependent and low-dose topiramate appears not to induce the enzymes involved in cholesterol synthesis [17]. A significant elevation in TC, HDL-c, and LDL-c was produced by combination therapy in this study and this may be due to the additive effect of both agents on lipid profile; however, these elevations are not significantly different from those produced by carbamazepine or topiramate. The results also indicated that the short duration of treatment with AEDs (i.e. three months as in prospective groups) did not produce a significant elevation in lipid profile (except HDL-c), and longer period may be required to produce such effect.

The risk of atherosclerosis has been the main point of discussion about the effect of AEDs on lipid profile. High serum TC, LDL-c, and TG levels are considered risk factors for development of atherosclerosis and coronary heart disease whereas HDL-c is acknowledged protective against these diseases [7,18-20]. Atherosclerosis is the descriptive term for thickened and hardened lesions of the medium and large muscular and elastic arteries. These lesions are lipid rich and occur within the intima, although the media and adventitia may also be involved [21]. The question of the association between the use of AEDs and the incidence of cardiovascular diseases is interesting. According to one report, the incidence of ischemic heart disease was

significantly increased in persons with epilepsy. There is clear evidence linking abnormalities in lipid and lipoprotein levels to premature atherosclerosis [22]. It is noteworthy that there are case reports of atherosclerosis following carbamazepine therapy [23]. The results gained in this study are in agreement with the results of the other studies. Anju *et.al.* (2005) were prospectively studied the effect of carbamazepine therapy on lipid profile. They reported that mean TC, LDL-c and HDL-c were significantly raised in patients, whereas the values of mean VLDL-c and TG were not significantly different from those of healthy subjects [24]. Eiris et al. (2000) reported no significant changes in lipid profile associated with valproic acid treatment [25].

Effect on c-reactive protein

CRP, a pentameric protein produced by the liver, has emerged as the "golden marker" for inflammation. It has been evaluated in many phases of coronary disease and has proven to be a reliable predictor of cardiovascular risk [26]. CRP may directly promote atherosclerosis and endothelial inflammation by attenuating the release of nitric oxide (NO), a key molecule in the endothelium that plays a pivotal role in the maintenance of vascular tone [27]. Qualitative measurements of CRP were performed in this study (with either a positive or a negative result). The positive results predict a clinically significant elevation in CRP level in human serum (equal or more than 6 mg/l, which is considered the lowest concentration of clinical significance). As shown in tables (9 & 10), carbamazepine and valproic acid had no clinically significant effects on CRP in patients in retrospective and prospective groups using these drugs individually as both drugs showed a 100% negative results at baseline and after three months of treatment. But the results showed a clinically significant elevation in the level of CRP in one patient and in seven patients after three months of treatment with topiramate and combination therapy respectively. These seven patients were receiving combination therapy consisting of carbamazepine and topiramate and this may be due to the additive effect of both medications on the level of CRP as it has been found that agents induce CYP450 enzymes system elevate CRP, and that this effect are reversible upon deinduction [17]. As mentioned previously, carbamazepine is a potent enzyme inducer, and topiramate is a relatively weak inducer of CYP450, whereas valproic acid is an inhibitor of certain CYP and uridine diphosphate (UDP) glucuronyl-transferase. Tan *et al.*(2009) reported that CRP was elevated in a population on mixed AEDs, compared with normal controls [3]. In addition to that, the duration of treatment also has a significant effect on CRP. Chuang YC. *et al.* (2012) reported that patients with epilepsy who were receiving long term mono-therapy with carbamazepine or valproic acid exhibited altered circulatory markers of vascular risk (including CRP) that may contribute to the acceleration of the atherosclerotic process, which is significantly associated with the duration of AED mono-therapy [28]. The CRP findings gained in current study are in agreement with the following studies. In a study conducted by Ahmet G. and Serap K. (2009), 29 patients using valproic acid (Group I), and 21 patients using carbamazepine (Group II) for one year aged 1.5-15 years and 35 healthy children (Group III) were included. They did not report a significant change in CRP in both groups as compared with healthy group (the values of CRP were 5.0 mg/l in first group, 6.4 mg/l in second group, and 6.3 mg/l in healthy group) [29]. Mintzer S. *et al.* (2012) found that conversion of epileptic patients from carbamazepine or phynetoin to topiramate resulted in a decrease of over 50% in serum CRP ($p<0.001$) after six weeks from conversion but this alteration in CRP remained

significant when compared to those seen in normal controls [17]. Yuen AW. *et al.* (2010) tried to measure CRP in 50 people with refractory epilepsy to estimate the potential effect of valproic acid use on this marker. Multiple regression analysis showed that valproic acid use was associated with 55% lower mean CRP concentrations when compared with patients receiving other AEDs [30].

Effect on renal function

From the results in this study, and as shown in tables (11 & 13), serum urea levels in patients in both retrospective and prospective groups were not significantly different from those values of healthy subjects at baseline. Elevations in serum urea concentrations resulted from the treatment in retrospective and prospective groups for three months were also not significant indicating that treatment with these drugs for the mentioned period had no significant effect on serum urea concentrations. Serum creatinine concentrations in patients treated with above mentioned drugs for three months in both retrospective and prospective groups were lower than those concentrations of normal healthy subjects at baseline as shown in tables (12 & 14). However, these drugs increased creatinine levels from its baseline values but the effect still not significant except for patients treated with combination therapy that may usually be due to the complex and additive effects associated with its use. It is obvious that AEDs used in this study had no significant harmful effects on renal function within the time period of this study. However, and on the basis of several clinical trials, it has been accepted that after a long duration of treatment (many years), AEDs may cause changes in renal function. Proximal tubular renal syndrome caused by valproic acid has been reported, acute interstitial nephritis has been observed after the administration of valproic acid and carbamazepine, and acute renal failure has been described as a consequence of carbamazepine [5]. The results gained in this study are in agreement with other studies as shown below. Nadia A. *et al.* (2003) performed a retrospective analysis on139 epileptic patients received carbamazepine and 183 received valproic acid. Creatinine clearance estimated as a marker of renal function. They found that 120 patients treated with carbamazepine and 152 patients treated with valproic acid had normal renal function (normal creatinine clearance), whereas only 10 and 15 patients respectively had reduced renal function. The remaining showed no clear effect [31]. Subash V. *et al.* (2011) found that the overall blood urea mean was statistically not significant in 30 epileptic children receiving valproic acid for six months as compared with blood urea values from 56 healthy subjects (28.15 mg/dl for patients and 30.01 mg/dl for the healthy subjects) [32]. Zhang L. *et al.* (2011) reported that the addition of topiramate to other AEDs resulted with no clinically significant changes in laboratory finding of renal function tests [33]. Although topiramate has weak carbonic anhydrase activity in vitro, with a reported incidence of renal calculi in 1.5% of patients treated [34,35], there were no reports of nephrolithiasis in the present study.

Conclusion

- AEDs increase levels of lipids through the induction of cytochrome P450 enzyme system that increase the risk of atherosclerosis and long period may be required to produce such effect. So serum lipid profiles should be carefully monitored in patients receiving enzymes inducing antiepileptic drugs.
- AEDs can cause a clinically significant elevation in CRP level in human serum through the induction of cytochrome P450 enzyme system that also increases the risk of atherosclerosis;

however, high risk is associated with combination therapy and with long term of treatment.

- AEDs used in this study have no significant harmful effects on renal function in both retrospective and prospective groups within the time period of this study.

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