Effects of Carbamazepine on blood pressure, serum glucose concentration, lipid profile and prevalence of metabolic syndrome in epileptic patients

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Abstract

To investigate the effects of carbamazepine on serum glucose concentrations, lipid profile, blood pressure and prevalence of metabolic syndrome in epileptic patients. Seventy epileptic patients involved in this study. They have primary generalized and partial seizures with duration of treatment with carbamazepine of 11.5±8.37 years. Another 100 apparently healthy individuals were also participated in the study as a control group. Ten ml of venous blood samples were taken from each patient and control after 14 hours fasting. The obtained serum was separated and used for the estimation of glucose concentration, total cholesterol, triglycerides and HDL-cholesterol by using special Kits. LDL-cholesterol was determined by Friedewald equation. Metabolic syndrome was determined according to ATP III criteria for the diagnosis of metabolic syndrome. The patients and controls were matched regarding age and sex. Weight, BMI and waist circumference were statistically not different between patients and controls. Comparison between the measured variables shows significant elevations of the lipid parameters in the patient group as compared with the control group. Non significant differences obtained between serum glucose concentrations and significant low values of BP were obtained in the patient group as compared with the controls. The number of patients and control having metabolic syndrome according to ATP II diagnostic criteria for metabolic syndrome were 4 and 3, respectively. The difference is not significant. This study demonstrated that carbamazepine have no effects on serum glucose concentrations, but have elevating effects on lipid parameters and reducing effects on BP. It has no effects on the prevalence of metabolic syndrome in the epileptic patients.

Key Words: Epilepsy, carbamazepine, glucose, lipids, BP, metabolic syndrome.

Introduction

Epilepsy is a disorder of the brain that is characterized by an enduring predisposition to generate seizures and by its neurobiological, cognitive, psychological and social consequences (1). It affects people in every country throughout the world and characterized by a tendency to recurrent seizures and is defined by two or more unprovoked seizures (2). About 50 million people worldwide have epilepsy and nearly 90% of epilepsy occurs in developing countries. People with epilepsy and their families can suffer from stigma and discrimination in many parts of the world (3). In 1912, phenobarbitone was found to be an effective seizure suppressant. In 1938, phenytoin was introduced as another treatment for epilepsy (4). Carbamazepine was introduced in 1953, and was one of the first antiepileptic drugs developed by a pharmaceutical company (Geigy). Valproate was licensed in the United States in 1976 for the treatment of absence seizures (5). Drugs such as felbamate, gabapentin, lamotrigine, oxcarbazepine, topiramate, and rufinamide have been introduced to the American market. Each of these drugs contains unique properties, whether in its mechanism of action, pharmacokinetics, or side-effect profile (5). Carbamazepine is a first-line drug in the treatment of most forms of epilepsy and also the drug of first choice in trigeminal neuralgia. Furthermore, it is now frequently used in bipolar depression. Most oral formulations of carbamazepine are well absorbed with high bioavailability. Carbamazepine is metabolised in the liver by oxidation before excretion in the urine. A major metabolite is carbamazepine-10,11-epoxide which is further metabolized by hydration before excretion. Metabolism of carbamazepine is comparable in children and adults. The best anticonvulsant effect seems to be obtained at plasma concentrations of 15 to 40 mmol/L and a similar optimal plasma concentration range was found in a controlled study in trigeminal neuralgia. During treatment with carbamazepine the plasma concentrations of this metabolite are usually 10 to 50% of those of the parent drug (6). The use of anticonvulsant agents were accompanied with many metabolic changes. Several cross-sectional studies have demonstrated that patients treated with phenobarbital, phenytoin, or carbamazepine have elevated total cholesterol levels compared with normal controls (7, 8). Kim and Lee (9) reported that 41% of epileptic women treated with valproic acid have metabolic syndrome. Antiepileptic drugs may be associated with either increases or reductions in body weight (10). Body mass index increased and HDL-cholesterol decreased in patients on VPA monotherapy compared with Carbamazepine (9). Total-cholesterol, HDL-cholesterol and LDL-C serum levels were high in children receiving carbamazepine or phenobarbitone and low in those treated with valproic acid (11). The present study was designed to estimate serum glucose concentration, lipid profile, and blood pressure, and prevalence of metabolic syndrome in a number of epileptic patients treated with carbamazepine monotherapy.

Patients and Methods

Seventy epileptic patients involved in this study. They were 33.4±13.09 years in age. They have primary generalized and partial seizures with duration of treatment with carbamazepine of 11.5±8.37 years. Another 100 apparently healthy individuals were also participated in the study as a control group. They were 32.49±11.9 years in age. This study was performed

during the period from 1/ 12/ 2011 to 1/ 6/ 2012 in General A-Haweja Hospital in Kirkuk City. The protocol of the study had approved by regional research committees of the college of medicine including the scientific committee of the department of pharmacology and higher education committee. The design of the study is case control study. Inclusion criteria including epileptic patients already on therapy with carbamazepine for a period not less than 6 months. Exclusion criteria including patients with a history of hepatic, renal or cardiac disease. Patients with diabetes mellitus or any other diseases that may affect the outcome of the study. Patients on other epileptic drugs or taking any other drug that may affect the results of the study. Ten ml of venous blood samples were taken from each patient and control after 14 hours fasting. The serum was separated and used for the estimation of glucose concentration and lipids. Serum glucose concentrations were estimated by a colorimetric method using a kit supplied by BIOCON (Germany). Total cholesterol and HDL-cholesterol were determined by an enzymatic method using kits supplied by BIOLABO (France). Serum triglyceride concentrations were measured by enzymatic method using a kit supplied by BIOMERIEUX (France). LDL-cholesterol was determined by Friedewald equation (12). Metabolic syndrome was determined according to ATP III criteria for the diagnosis of metabolic syndrome (13). The diagnosis was made when 3 of 5 of the following criteria were present: waist circumferences: men > 102 cm, women > 88 cm, triglycerides ≥ 150 mg/dl, HDL-cholesterol: men < 40 mg/dl, women < 50 mg/ dl, BP ≥ 130 systolic/ 85 mmHg diastolic and FBS ≥ 110 mg/ dl. Statistical Methods: Anova t-test was used to compare between patients and control groups. χ^2 test for comparison between the number of variables which are in accordance to ATP III diagnosis of MS in the patient and the control groups and to compare between gender of the 2 groups and between the prevalence of metabolic syndrome in the 2 groups. Unpaired t-test was used to compare between variables of the patients and control groups. Data considered significant at P value ≤ 0.05.

Results

Table 1 show the patients and control characteristics. The patients and controls were matched regarding age and sex. Weight, BMI and waist circumference were statistically not different between patients and controls. Comparison between the measured variables showed significant elevations of the lipid parameters, and lower BP in the patient group as compared with the control group. Non significant differences obtained between serum glucose concentrations (Table 2).

Table 3 shows the number of patients having markers of metabolic syndrome. The number of patients and control having metabolic syndrome according to ATP II diagnostic criteria for metabolic syndrome was present in table 4. No statistical difference was found between the 2 groups.

Table (1):- Patients and control characteristics.

Variables	Carbamazepine N=70	Control N=100	P-value
Age(year)	33.40±13.09	32.49±11.80	NS
Weight (Kg)	70.50±13.12	70.11±12.86	NS
BMI (Kg/m^2)	25.63±4.26	25.62±4.49	NS
Waist circumference (cm)	87.11±13.20	86.55±11.17	NS
Duration of treatment (years)	11.50±8.37	-	
Gender Male Female	 44 (62.9%) 26 (37.1%)	 64 (64.0%) 36 (36.0%)	NS

Table (2):- Comparison between variables of the patients and control groups.

Variables	Carbamazepine N=70	Control N=100	P-value
Glucose (mg/dl)	95.59±11.30	92.79±8.09	NS
Cholesterol (mg/dl)	194.34±44.72	159.27±30.58	Sig
Triglyceride (mg/dl)	138.63±72.55	105.95±45.05	Sig
HDL (mg/dl)	54.77±13.96	47.81±9.95	Sig
LDL (mg/dl)	111.85±37.39	90.26±27.36	Sig
Systolic BP (mmHg)	113.50±9.29	120.15±4.89	Sig
Diastolic BP (mmHg)	75.50±5.96	79.40±15.29	Sig

Table (3):- Show the number of variables which are in accordance to ATP III diagnosis of MS in the patient and the control groups.

Metabolic syndrome criteria	Carbamazepine	Control	P-value
	No. (%)	No. (%)	
Waist circumf(cm) Negative Positive	 53 (75.7%) 17 (24.3%)	 83 (83.0%) 17 (17.0%)	NS
Glucose (mg/dl) Negative Positive	 63 (90.0%) 7 (10.0%)	 99 (99.0%) 1 (1.0%)	Sig
Triglyceride (mg/dl) Negative Positive	 49 (70.0%) 21 (30.0%)	 86 (86.0%) 14 (14.0%)	Sig
HDL (mg/dl) Negative Positive	 57 (81.4%) 13 (18.6%)	 64 (64.0%) 36 (36.0%)	Sig

Blood Pressure (mmHg) Negative Positive	 69(98.6%) 1(1.4%)	 100(100%) 0(0%)	-

Table (4):- Number of patients with MS in each group

Metabolic syndrome	Carbamazepine No. (%)	Control No. (%)	P-value
Negative	66 (94.3%)	97 (97.0%)	NS
Positive	4 (5.7%)	3 (3.0%)	

Discussion

The present study revealed a non significant difference between weight, BMI, and waist circumference of the patient and control group, indicating that carbamazepine therapy had no effects on these variables of obesity. These results were in agreement with results of many previous studies. Verity *et al* (14) reported that the most important adverse effects of valproic acid is weight gain while carbamazepine did not cause weight gain. Also, Uludag *et al.* (15) reported that carbamazepine therapy does not affect significantly BMI, leptin and insulin. The author concluded that carbamazepine is a relatively low risky antiepileptic drug in terms of obesity. Lipid parameters including total cholesterol, LDL-cholesterol, triglycerides and HDL-cholesterol were significantly increased in the carbamazepine group as compared to control group. These results were in agreement with the results of many studies which also revealed an increased lipid parameter after therapy with carbamazepine. Bramswig *et al* (16) reported that during treatment with carbamazepine significant increases in total cholesterol, LDL-cholesterol, and in triglycerides, but not in HDL-cholesterol, were observed. In another study, serum total cholesterol and high-density lipoprotein cholesterol concentrations increased after 2 months of treatment with carbamazepine and remained high after 1 and 5 years (17). Compared with controls, patients on carbamazepine showed significant higher total-cholesterol, HDL-cholesterol, and LDL-cholesterol and none significantly higher triglyceride values (7).

The mechanism responsible for carbamazepine effects on lipid parameter may be due to that carbamazepine like other enzyme inducing antiepileptic agents increase the activity of the hepatic cytochrome P450 system, which is involved in synthesis of serum cholesterol (18). Accordingly, enzyme inducing antiepileptic drugs would be expected to increase synthesis of cholesterol which appeared as high levels of cholesterol while enzyme inhibiting antiepileptics would decrease synthesis of cholesterol as appeared by low levels of cholesterol (7, 19). Switching from inducing agents carbamazepine and phenytoin, to the non inducing lamotrigine and levetiracetam demonstrated a decline in total cholesterol averaging 26 mg/ dl after 6 weeks (20). The present study revealed no significant difference between serum glucose concentration of carbamazepine group and control group indicating a non effect of

carbamazepine on glucose metabolism. Review of the literature revealed no articles concerned with this subject. The results demonstrated neutral effects of carbamazepine on serum glucose concentration. A significant difference in blood pressure between carbamazepine group and control group was found in the present study. Review of literature revealed a very limited data concerning the effects of carbamazepine on blood pressure. Marini *et al* (21) reported that hypertension or hypotension were rarely been documented in patients with either therapeutic or toxic blood levels of carbamazepine. A 20-year-old epileptic patient developed hypertension during CBZ treatment, without any demonstrable etiological factor. After CBZ discontinuation, a gradual normalization of blood pressure values was observed. The authors discuss the possible role of ADH in the production of this infrequent side effect (22). In another study seventy-two adult and pediatric patients with serum carbamazepine concentrations greater than 12 micrograms/ mL demonstrate hypotension in the adult patients (23).

The mechanism by which carbamazepine produce blood pressure reduction in the present study may be due to that carbamazepine has a tricyclic molecular structure, which strongly resembles a tricyclic and is shown to have some antidepressant properties (24-25). Tricyclic antidepressants were found to reduce blood pressure. Oguara *et al* (26) reported that systolic blood pressure fell and the reduction lasted longer in the elderly than in the young after dothiepin and amitriptyline. Amitriptyline injected into rats produced hypotension (27). Due to their structural similarity, carbamazepine may shared the hypotensive effects of amitriptyline reported in the above 2 articles. In the present study, carbamazepine produce no significant difference with the control group regarding metabolic syndrome, indicating that carbamazepine does not contribute to the occurrence of metabolic syndrome in the epileptic syndrome. These results were in agreement with the results of many previous articles which also reported that carbamazepine therapy caused no metabolic syndrome in the epileptic patients. Mania et al (28) compared the prevalence of metabolic syndrome in patients treated with valproic acid, carbamazepine and controls. He found that metabolic syndrome is relatively frequent in VPA-treated patients group (45%) compared with CBZ group and controls (15.4% and 27.3% respectively). Kim and Lee demonstrated that Metabolic syndrome was more frequently associated with VPA-treated patients (41.7%) than CBZ (5.3%), lamotrigine (0%), or topiramate group (0%) (9).

In conclusion

This study demonstrated that carbamazepine have no effects on serum glucose concentrations, but have elevating effects on lipid parameters and reducing effects on BP. It has no effects on the prevalence of metabolic syndrome in the epileptic patients.

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