Assessment of Topiramate VS Valproate Effects on Serum Lipid Profile in Young Adults with Epilepsy : A Retrospective Study

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ABSTRACT

Aims : to assess and compare lipid profile indices (serum total cholesterol TC, triglycerides TG, low density lipoprotein cholesterol LDL-c, high density lipoprotein cholesterol HDL-c, and atherogenic index AI) in epileptic patients receiving valproate and topiramate monotherapy for at least six months, taking dosage and length of treatment into account, in comparison to healthy controls.

Methods: This study, which took place between the first of December 2012 and the 30th of April 2013, used a retrospective, cross-sectional, case series design.

The study involved 78 epileptic patients who had been separated into two groups.37 epileptic patients in group one were receiving TPM alone, while 41 epileptic patients were receiving VPA monotherapy. 40 healthy people of equal age and sex were used as controls in this investigation. Both patients and controls had fasting blood samples drawn for the assessment of serum lipid parameters.

Results : We observed statistically significant lower serum TC levels at a dose level of 200 mg TPM with a significant lower levels of TC,TG and HDL-c levels among patients receiving VPA at dose greater than 400mg /day .

There were no statistically significant differences in the lipid profiles of the two groups of epileptic patients.

Conclusions : In epileptic patients the use of TPM at a dose of 200mg /day was associated with significant decrease in TC with no changes in other lipid profile parameters while the use of VPA at a dose greater than 400 mg /day was associated with a significant decrease in TC, TG and HDL-c.

Keywords: Epilepsy , Antiepileptic drugs , Topiramate , Valproate , Lipid profile .

تقييم تأثير التوبراميت مقابل الفالبروات على مؤشر الدهون في مرضى الصرع : دراسة بتأثير رجعي

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الخلاصة

الأهداف: تقييم ومقارنة مؤشرات الدهون (الكوليسترول الكلي في الدم TC ، الشحوم الثلاثية TG ، البروتين الدهني منخفض الكثافة LDL-c ، البروتين الدهني عالي الكثافة HDL- c ومؤشر التصلب AI) في مرضى الصرع الذين يستخدمون عقارفالبروات (VPA)مقابل توبيراميت (TPM)) لمدة ٦ أشهر على الأقل مع مراعاة الجرعة ومدة العلاج ، مقارنة بالضوابط الصحية.

الطرق: تم اعتماد تصميم سلسلة الحالة بأثر رجعي ، لهذه الدراسة التي أجريت في الفترة من ١ ديسمبر ٢٠١٢ إلى ٣٠ أبريل ٢٠١٣.

اشتملت الدراسة على ثمانية وسبعين مريضاً مصاباً بالصرع مقسمين إلى مجموعتين ، المجموعة الأولى تضمنت ٣٧ مريضاً مصاباً بالصرع خضعوا للعلاج الأحادي TPM ، أما المجموعة الثانية فقد اشتملت على ٤١ مريضاً مصاباً بالصرع خضعوا للعلاج الأحادي VPA.تشتمل الدراسة أيضا ٤٠ شخص سليم بنفس العمر والجنس كمجموعات ضابطة. تم أخذ عينات دم الصيام من كل من المرضى والضابطة ومعايرة مؤشرات الدهون في الدم.

النتائج: لاحظنا انخفاض مستويات TC في مصل الدم بشكل معتد به إحصائيًا عند مستوى جرعة ٢٠٠ ملغم TPM مع مستويات أقل بكثير من مستويات TC و TG و HDL-c بين المرضى الذين يتلقون VPA بجرعة أكبر من ٤٠٠ ملغم/ يوم. لوحظ عدم وجود فرق ملاحظ بين مجموعتي مرضى الصرع فيما يتعلق بملف الدهون.

الاستنتاجات: في مرضى الصرع ، ارتبط استخدام TPM بجرعة ٢٠٠ ملغم / يوم بانخفاض كبير في TC مع عدم وجود تغييرات في مؤشرات ملف الدهون الأخرى بينما ارتبط استخدام VPA بجرعة أكبر من ٤٠٠ ملغ / يوم مع انخفاض كبير. انخفاض في TC و TG و HDL-c.

الكلمات المفتاحية : الصرع ، ادوية الصرع ، التوبراميت ، الفالبرويت ، مؤشرات الدهون .

INTRODUCTION

Epilepsy is a common neurological condition defined by clinical seizures brought on by electrical disruption in the brain, which may be idiopathic or symptomatic. More than 50 million people worldwide are believed to have epilepsy, according to the World Health Organization (WHO) [1]. Epilepsy is typically treated with medicines, and surgery is rarely used. Anti-epileptic medications (AEDs) are commonly used for a number of diseases , such as epilepsy, migraine, and psychiatric problems. Patients with epilepsy frequently need to take AEDs for the rest of their lives [2]. Both valproate and topiramate are among the common AEDs used in the treatment of epilepsy [3]. Cardiovascular disease (CVD) risk is elevated in those with epilepsy. There is no clear definition of the precise processes of this relationship. AEDs' influence on people with epilepsy's risk of developing CVD is still debatable [4].

Anti-epileptic medications induced changes to the serum lipid profile may have long-term negative effects on patients in the form of severe cardiovascular or cerebral events. The production of arterial plaque is accelerated by an increase in serum cholesterol, particularly LDL cholesterol. As most epileptic patients are young adults, an early and rapid beginning of atherosclerosis in them would have a detrimental effect on their cardiovascular health as they age [2]. Thus, it may be helpful to evaluate changes in serum lipid levels after antiepileptic medication in order to select the medicine that is the safest and prevent cardiovascular events later in life [5].

PATIENTS AND METHODS

- Retrospective, case-series, and cross-sectional study designs were used in this study.
- The study was carried out at Al-Zahrawi private hospital from 1 December 2012 to 30 April 2013.
- Study participants: There are 118 participants in this study, including 40 healthy volunteers and 78 epileptic patients. Two groups of 78 patients with epilepsy were formed:

Group 1 : included 37 epileptic patients (22 males and 15 females)there ages ranged between17 and 47 years ,on TPM monotherapy for at least 6 months in a daily dose ranged between 50-200mg.

Group 2 : included 41 epileptic patients (25 males and 16 females)there ages ranged from 17 to 39 ,on VPA monotherapy for at least 6 months in doses ranged between 200-1000mg /day .

- Blood samples will be taken from both the study participants and the controls. After an overnight fast, a qualified lab technician will collect 5 ml of venous blood under sterile conditions using a disposable syringe. The sample will then be tested for TC, HDL-C, LDL-C, and TG.
- Young adult patients between the ages of 17 and 47 (both sexes) who have been using antiepileptic medications for at least six months are eligible for inclusion.
- Patients with secondary epilepsy, those with other neurological or mental disorders, those with other hereditary or medical conditions are also excluded. Patients with acute illnesses, malignancies, or other difficulties, pregnant women on antiepileptic medications, Patients using more than one antiepileptic drug as well as those receiving hypolipidemic medications.
- All information will be gathered from each patient using a questionnaire, and results will then be analyzed using (SPSS).
- Ethical Considerations: Both cases and controls will be asked for informed, written permission after the study's specifics and value have been explained to them. The ethical committee at the College of Medicine at the University of Mosul, as well as the local health committee and ethics committee at the Nineveh Health Directorate in Mosul, Iraq, will also provide their approval.

RESULTS

Effects of Topiramate Versus Valproate on Lipid Profile Indices

By comparison of the parameters under study between both two epileptic groups and the control ,there was insignificant difference regarding lipid profile indices between both groups and control (Table 1).

Table 1 :comparison of the studied parameters between both epileptic group on TPM and epileptic group on VPA and the control

Parameters	Topiramate Mean ± SD	Valproate Mean ± SD	Control Mean ± SD	p-value
TC (mmol/l)	4.83±0.95	4.63±0.96	4.79±0.86	0.5
TG (mmol/l)	2.92±0.92	2.64 ±1.00	2.86±0.95	0.3
HDL-c(mmol/l)	1.68±0.37	1.77±0.42	1.71±0.38	0.5
LDL-c(mmol/l)	1.81±0.71	1.65±0.71	1.78±0.68	0.5
AI	2.94±0.58	2.69±0.57	2.87±0.53	0.1

Analysis was performed by the use of ANOVA test

Effects of Dose of TPM And VPA on The Studied Parameters

a. Topiramate

The mean serum level of TC significantly decreased (p 0.01) at dose of 200 mg /day ,with insignificant difference in the other parameters (Table 2).

Table 2:Effect of TPM dose on the study parameter

Parameters	50 mg N=22 Mean ± SD	100mg N=11 Mean ± SD	200mg N=4 Mean ± SD	p-value
TC (mmol/l)	5.18±1.03	4.39±0.57	4.11±0.38	0.01
TG (mmol/l)	3.12±0.86	2.73±0.97	2.35±0.94	0.2
HDL-c(mmol/l)	1.74±0.35	1.65±0.38	1.43±0.44	0.3
LDL-c(mmol/l)	2.01±0.78	1.49±0.47	1.60±0.50	0.1
AI	3.04±0.65	2.73±0.42	2.98±0.53	0.3

ANOVA test was used for analysis.

b.Valproate

The mean serum level of TC was reduced significantly (p0.02);

TG (p<0.02);and HDL-c (p<0.0001) at VPA doses greater than 400mg /day(Table 3).

Table 3: Effect of VPA dose on the study parameters

Parameters	≤400mg N=27 Mean ± SD	>400mg N=14 Mean ± SD	p-value
TC (mmol/l)	4.95±1.00	4.01±0.47	0.002
TG (mmol/l)	2.97±1.01	1.99±0.60	0.002
HDL-c(mmol/l)	1.95±0.39	1.44±0.25	<0.0001
LDL-c(mmol/l)	1.64±0.83	1.67±0.45	0.9
AI	2.60±0.61	2.85±0.456	0.2

Analysis was performed by the use of independent two samples unpaired t-test.

Effects of Duration of Therapy of TPM and VPA on the Serum Lipid

a. Topiramate

There was a insignificant effect of duration of therapy with TPM on the study parameters (Table 4) .

Table 4:Effect of duration of therapy with TPM on the study parameters

Parameters	6 months N=8 Mean ± SD	12 months N=11 Mean ± SD	>12 months N=18 Mean ± SD	p-value
TC (mmol/l)	4.66±0.52	4.80±1.09	4.93±1.04	0.8
TG (mmol/l)	2.85±0.69	3.01±0.95	3.02±0.99	0.5
HDL-c(mmol/l)	1.71±0.32	1.71±0.41	1.65±0.38	0.8
LDL-c(mmol/l)	1.76±0.39	1.70±0.94	1.90±0.68	0.7
AI	2.76±0.39	2.88±0.71	3.05±0.57	0.4

Analysis was performed by the use of ANOVA test

b.Valproate

There was insignificant effect of duration of therapy with VPA on the parameters under the study (Table 5).

Table 5 :Effect duration of therapy with VPA on the study parameters

Parameters	6 months N=10 Mean ± SD	12 months N=16 Mean ± SD	>12 months N=15 Mean ± SD	p-value
TC (mmol/l)	4.94±0.96	4.54±0.95	4.52±1.00	0.5
TG (mmol/l)	2.98±0.97	2.51±0.97	2.54±1.07	0.4
HDL-c(mmol/l)	1.94±0.47	1.75±0.42	1.69±0.38	0.3
LDL-c(mmol/l)	1.64±0.94	1.64±0.64	1.67±0.67	0.9
AI	2.66±0.70	2.66±0.55	2.73±0.55	0.9

Analysis was performed by the use of ANOVA test

DISCUSSION

The goal of the current study was to determine how common antiepileptic medications affected the lipid profile variables TC, TG, HDL-c, LDL-c, and AI. It is yet unclear how AEDs affect patients with epilepsy's risk for CVD [4]. This study revealed significant decrease in the TC level in the patients receiving TPM at the level of 200mg /day. This is consistent with Li's [6] and Verrotti's [7] findings that weight reduction during TPM treatment is linked to differences in blood sugar, insulin, and cholesterol levels. Franzoni [8] examined the impact of TPM on the levels of lipids and lipoproteins in children taking TPM monotherapy and found a small decline in TC, TG, and HDL-c. These variations occur within the average range. In premenopausal women with epilepsy, Genc [9] studied the effect of TPM monotherapy and discovered reductions in body mass index, waist circumference, serum HDL-c, and modestly decreased TC levels. TPM stands out from other AEDs in part because of its tendency to lower body weight [7]. According to Mintzer [10], losing weight could somewhat lower serum cholesterol levels.

Patients receiving VPA at doses more than 400 mg/day experienced a significant decrease in blood TC, TG, and HDL-c. Our results are consistent with Katski [4] who demonstrated that VPA-treated patients have lower TC, LDL-c and HDL-c levels compared with subjects without epilepsy; TG concentrations were either lower or higher than controls. A study done by Manimekalai [11] on pediatric epileptic patients to demonstrate the difference between conventional and newer AEDs on lipid profile parameters found that AEDs that activate the cytochrome P enzyme(CYP), such as oxcarbazepine and phenytoin , are closely linked to elevated levels of TC, LDL-c, HDL-c, and TG ,while levetiracetam and valproate exhibited no discernible change, TC, LDL-C, HDL-C, and TG . The different biotransformation pathways of these medications, which include phenytoin, phenobarbital, and carbamazepine as CYP-450 enzyme inducers and valproic acid as a CYP-450 enzyme inhibitor, may account for the differences in lipid profiles amongst AED groups [12]. Increase the CYP-450 system's activity, which is necessary for the manufacture of serum cholesterol. Valproic acid, on the other hand, is an inhibitor and can lower serum cholesterol because of this [13].

Another study by Aziz [14] to estimate the effects of duration of VPA on lipid concluded that use of VPA for more than 12 months decreases the level of total cholesterol. A metanalysis study on epileptic children receiving valproate for along term concluded that VPA therapy causes a decrease in the levels of TC and LDL-c [15]. Conversely Zuberi [16] reported that patients with epilepsy taking carbamazepine or VPA have altered vascular risk factors that could result in atherosclerosis, whereas those taking lamotrigine have less of a change in their lipid profiles. Treatment with AEDs also raises body mass index and body weight. Therefore lipid profile and body weight monitoring is required to identify and manage any major change. When treating patients, the drug selection should also be taken into account.

The current study also demonstrated insignificant difference regarding lipid profile between epileptic patients receiving TPM and those receiving VPA.

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