EFFECTS OF TOPIRAMATE VS VALPROATE ON SERUM LEPTIN AND LIPID PEROXIDATION IN EPILEPTIC PATIENTS

Imad A-J Thanoon and Noor N.D Al-Hafith

ABSTRACT

Aims: To assess and compare the body mass index (BMI), serum leptin, and lipid peroxidation represented by serum malondialdehyde (MDA) levels in epileptic patients on valproate (VPA) and topiramate (TPM) monotherapy for at least 6 months taking in consideration dosage and duration of therapy, in comparison to healthy controls.

Methods: A cross-sectional, case-series study design was adopted, for this study, which was conducted from December 1st, 2012 to April 30th, 2013. Seventy-eight epileptic patients were included in the study divided into 2 groups. Group one included 37 epileptic patients on TPM monotherapy and group two included 41 epileptic patients on VPA monotherapy. Included in this study also 40 age and sex matched healthy subjects as a control groups. Fasting blood samples were taken from both the patients and controls and assay of serum leptin, Lipid. Body mass index were calculated using special equation.

Results: By comparison, of epileptic patients with controls, there was a highly significant difference in serum MDA levels in patients on TPM monotherapy, with a highly significant difference in BMI and serum MDA levels in epileptic patients on VPA monotherapy.

Non-significant differences were noted between both groups of epileptic patients with regard of the measured parameters.

Conclusions: In epileptic patients, VPA therapy was associated with a significantly higher BMI in comparison to healthy controls. Both antiepileptic drugs was associated with raised oxidative stress as indicated by the significantly elevated MDA levels on comparison to healthy controls. Both antiepileptic drugs affects lipid profile parameters at different levels with insignificant effects on serum leptin level.

Keywords: Epilepsy, Valproate, Topiramate, Malondialdehyde, Leptin, Lipid profile, Body mass index.

INTRODUCTION

Epilepsy is a chronic neurological disorder that requires long term treatment [21]. Antiepileptic drugs were the initial treatment modality for the vast majority of patients with epilepsy [11]. Topiramate and valporate are among the antiepileptic drugs commonly used in epilepsy [1]. Both weight gain and weight loss have been associated with the use of antiepileptic drugs [3]. There is growing evidence that leptin in addition to its role in regulating energy balance has a wide spread action in the control nervous system. In the hippocampus leptin is a potent regulator of neuronal excitability as it has the ability to inhibit epileptic form like activity [15]. The pro oxidant/antioxidant balance in epilepsy is not only modelated by seizures perse, but also by antiepileptic drugs [9]. Effects of old and new antiepileptic drugs on reactive oxygen species production in controversial [22]. The aims of this study were to assess and compare, the body mass index (BMI), serum leptin, and the lipid peroxidation represented by serum malondialdehyde (MDA) in epileptic patients in VPA or TPM monotherapy for at least 6 months in comparison to healthy control.

PATIENTS AND METHODS

The study was conducted at Al-Zahrawi Private Hospital in Mosul- Iraq, from December 1st 2012 to April 30th 2013,a cross sectional, case series study design was adopted. The Scientific Research Committee at the College of Medicine, University of Mosul, and the local Health Committee and Ethics committee at Nineveh Health Directorate in Mosul- Iraq approved the protocol of this study.
Out of 86 epileptic patients received, only 78 were included in this study. They were divided into 2 groups as follows:

Group 1: included 37 epileptic patients (22 males and 15 females) there ages ranged between 17 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 between 17 and 39 years, on VPA monotherapy for at least 6 months in doses ranged between 200 and1000mg/d.
The control group included 40 apparently healthy volunteers (25 males and 15 females) with an age ranged between 18 and 47 years.
Epileptic patients receiving other drugs, those with other neurological, renal hepatic, cardiac or endocrinal diseases were excluded from the study, so as smokers and pregnant or lactating women.
A 5ml venous blood samples were taken from both the patients and controls and assay of serum leptin (by ELISA techniques), serum MDA (using thiobarbituric acid assay method) [4].
BMI were calculated according to special equation

\[
\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}
\] [18]

The data obtained in the current study were analyzed using Statistical Package for Social Sciences version 17 (SPSS).

**RESULTS**

**The study population**

The characteristics of the subjects under study (epileptic patients and control) are given in table 1 and 2.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Topiramate Mean±SD</th>
<th>Valproate Mean±SD</th>
<th>Control Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>22.65±2.27</td>
<td>23.43±2.27</td>
<td>22.35±1.82</td>
<td>0.06</td>
</tr>
<tr>
<td>MDA</td>
<td>1.14±0.21</td>
<td>1.20±0.17</td>
<td>1.01±0.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Leptin</td>
<td>8.79±4.71</td>
<td>10.31±5.42</td>
<td>8.17±4.56</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Analysis was performed by the use of ANOVA test

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>17-47</td>
<td>24.48±6.43</td>
</tr>
<tr>
<td>Valproate</td>
<td>17-39</td>
<td>24.70±5.51</td>
</tr>
<tr>
<td>Control</td>
<td>18-47</td>
<td>25.07±5.91</td>
</tr>
</tbody>
</table>

Analysis was performed by the use of ANOVA test

**Effect of TPM and VPA on Studied Parameters**

By comparison of the parameters under study between epileptic patients on TPM and the control, there was a significant difference (P<0.01) in the levels of serum MDA. (Table 3)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Topiramate Mean±SD</th>
<th>Control Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>22.65±2.27</td>
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<td>0.5</td>
</tr>
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<td>Leptin</td>
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<td>8.17±4.56</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Analysis were performed by independent two samples student t-test

While by comparison of the parameter under study, between epileptic patients on VPA and the control, there are a significant difference in the BMI (P < 0.02) and serum MDA levels (P < 0.001). (Table 4).
Table 4. Comparison of studied parameters between epileptic under VPA and the control

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Valproate Mean±SD</th>
<th>Control Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>23.43±2.27</td>
<td>22.35±1.82</td>
<td>0.02</td>
</tr>
<tr>
<td>MDA</td>
<td>1.20±0.17</td>
<td>1.01±0.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Leptin</td>
<td>10.31±5.42</td>
<td>8.17±4.56</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Analysis were performed by independent two samples student t-test

By comparing the parameter under study between the two groups of epileptic patients, there was no significant difference between both groups. (Table 5).

Table 5. Comparing the studied parameters under study between both groups of epileptic patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Topiramate Mean±SD</th>
<th>Valproate Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>22.65±2.27</td>
<td>23.43±2.27</td>
<td>0.1</td>
</tr>
<tr>
<td>MDA</td>
<td>1.14±0.21</td>
<td>1.20±0.17</td>
<td>0.1</td>
</tr>
<tr>
<td>Leptin</td>
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<td>0.1</td>
</tr>
</tbody>
</table>

Analysis were performed by independent two samples student t-test

DISCUSSION

This study showed a significantly lower BMI in epileptic patients receiving TPM monotherapy in comparison to their matched control. This is in agreement with the results of studies on Ben-Menachem [2] and [25]. Animal studies suggested that TPM reduces food intake acutely and increases metabolic rate, by significantly influencing brain and peripheral levels of hormones and peptides [8]. Human studies suggested the role of reduced caloric intake, hormonal involvement and changes in glucose and lipid metabolism [31]. This study also revealed a significantly higher BMI in epileptic patients receiving VPA in comparison to healthy controls. Many studies have incriminated VPA as a cause of weight gain among treated men and women with epilepsy [13]. Dinesen [7], reported a weight gain of at least 4 kg in 57% of adult epileptic patients treated with VPA. Novak [23], reported a greater BMI in more than one fourth of their epileptic patients at the start of VPA and more than one third after a 20 months follow up period. The precise mechanism underlying the VPA associated weight gain remain unclear. It is most likely multifactorial because control of food intake and energy expenditure is complex and is regulated at peripheral and central levels [14]. Possible mechanisms include the effect of VPA on the hypothalamus, VPA – induced hyperinsulinemia and insulin resistance, genetic factors, the interaction between VPA induced hyperleptinemia and leptin resistance [30]. The current study also demonstrated insignificant differences in serum leptin level between epileptic patients on TPM and their matched controls. This is in agreement with the study of [28]. They reported no significant differences in serum leptin levels before and after TPM treatment. Theisen [29] also reported no evidence of direct causal involvement of leptin in TPM related weight loss.

Li, [19], suggested that there was no significant differences in leptin level before and after TPM therapy and that the change in leptin would not be the key mechanism for weight loss after TPM therapy. In the same line with our results Genc [10] reported that TPM therapy had no effect on serum leptin level. While Husam [16] reported a reduction in serum leptin level after 6 months of TPM treatment and Ben-Menachem [2] concluded that leptin levels were significantly reduced during TPM therapy and the greater the weight loss, the greater the reduction in serum leptin levels with regard VPA therapy, this study also revealed insignificant differences in serum leptin between epileptic patients on VPA and the controls. This is in agreement with the results of Pylvanen [26], who suggested that serum leptin level did not differ between epileptic patients on VPA and the controls. They also reported that serum leptin levels did not differ between obese patients on VPA and obese controls or between the lean patients on VPA and the lean controls.

In this study, the higher BMI seen in patients on VPA (compared with the control group) did not reach the level of obesity (BMI in the VPA group< 25kg/m^2) and this may explain why there was no significant increase in serum leptin levels in such patients. This hypothesis supported by previous studies done by Verritte [32, 33]. They reported a significant increase in serum leptin levels in epileptic patients who become obese during VPA monotherapy, while VPA – treated patients who remained lean did not show any significant change in their serum leptin levels. Conversely Hamed [14] reported increased serum leptin-levels among patients treated with VPA and not in untreated group, those treated with carbamazepine, lamotrigine or a polytherapy with VPA and lamotrigine. This study also reported a significant differences in the serum MDA levels between epileptic patients on TPM or VPA monotherapy and the controls.
These results were in line with that of Cardile [5], Pavone and Cardile [24]. Both reported that TPM increased the oxidative stress (OS) represented as MDA level. In contrast Kubera [17], reported that TPM plays an antioxidant role and it reduces lipid peroxidation in the piriform cortex of rats. Liu [20], Hamed [12], reported that epileptic patients treated with phenytoin, carbamazepine and VPA have increased MDA levels. Yis [34], also reported that there was a raise in lipid peroxidation in epileptic patients during VPA therapy. While Cengiz [6], reported lower MDA levels in patients receiving VPA in comparison to healthy controls. Accumulating evidence suggests that antiepileptic drugs (AEDs) induce or exacerbate OS in epileptic patients. One possible mechanism related to OS induced by AEDs is that these drugs metabolized to reactive epoxide intermediates which can covalently bind to biomolecules and then induce structural and functional impairments [27].

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