Evaluate the effects of long-term valproic acid treatment on metabolic profiles in newly diagnosed or untreated female epileptic patients: A prospective study

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ABSTRACT

Purpose: Excessive weight gain associated with sodium valproate (VPA) may predispose patients with epilepsy to other health problems such as insulin resistance. We prospectively evaluated the long-term impact of VPA monotherapy compared with lamotrigine (LTG) monotherapy on anthropometric and metabolic parameters in women with epilepsy. Our primary objective is to understand the underlying mechanism responsible for VPA-induced obesity.

Methods: Sixty-six female patients with newly diagnosed or untreated epilepsy were included in the study. Thirty-four patients with VPA and thirty-two patients with LTG were treated for a period of one year in our center. Anthropometric and clinical data were collected at 5 time points: before, at 6th week, 3rd month, 6th month, 9th month and 12th month (last visit). Biochemical and hormonal data were collected 2 time points: before and last visit.

Results: Subjects in the VPA group had significantly higher body weight than LTG-treated subjects (64.88 ± 3.25 vs. 58.28 ± 2.43, $P < 0.001$). HOMA-IR level was significantly increased (2.76 vs. 1.35, $P < 0.05$), and adiponectin levels were significantly lower in the VPA group (3.46 vs. 6.22, $P < 0.05$). Triglycerides levels were significantly increased (118 vs. 96, $P < 0.05$), and HDL-C levels were significantly lower in the VPA group. Both the VPA-treated group and the LTG-treated group showed no significant difference in term of total cholesterol, LDL-C, fasting blood glucose and serum leptin levels.

Conclusions: Based on the findings of this study, we proposed that VPA induced hypoadiponectinemia which correlates significantly with insulin resistance. These two factors may be responsible for weight gain, possible by stimulating appetite. Valproic acid appears to be use cautiously in obese females with epilepsy.

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1. Introduction

Sodium valproate (VPA) and lamotrigine (LTG) are the broad-spectrum anticonvulsants drugs used in both generalized and partial seizures. Weight gain is a well-known adverse effect of VPA treatment occurring in up to 71% of exposed patients, although typically the rate is around 10% [1]. Weight gain is the most common reason for patients to discontinue VPA treatment [2–4]. In a study, 38% of VPA-treated patients gained more than 10% of their body weight compared with 8% of patients treated with LTG [5].

Further, weight gain associated with VPA seems to be appetite-related and not metabolic [6]. However, the real pathogenic mechanisms underlying VPA-induced weight increase is remain unclear. Reports in epileptic populations have shown that VPA is associated with hyperinsulinaemia, both in conjunction with and independent from changes in weight [7–9]. Various ideas regarding mechanisms behind the link between VPA-induced weight gain and insulin resistance (IR) have been suggested. The observation of hyperinsulinaemia in the lean patients taking VPA suggesting the role of factors others than excess adiposity in the pathogenesis of IR [8]. The adipocytokines such as leptin and adiponectin which are derived from adipose tissue could be involved in impairing insulin signaling and reduce GLUT4 gene expression.

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The purpose of this study was to examine the changes in body weight and several biochemical and endocrine parameters in female epileptic patients receiving either VPA or LTG monotherapy. Secondary outcome was to explore the relation between adipocytokines and insulin resistance among VPA-treated patients.

2. Methods

2.1. Subjects

The present study was conducted at the department of Neurology, M.S. Ramaiah Memorial hospital, Bangalore, India, with the approval of local Ethics committee. Informed consent was obtained from all the subjects. All subjects gave consent to use non-hormonal contraception throughout the study and for at least 3 weeks after the last dose of study drug. The type of epilepsy was classified according to the recommendations of the International League Against Epilepsy (ILAE) [10].

2.1.1. Subjects in the patient groups

The study was conducted in 66 newly diagnosed or untreated female epileptic patients. In untreated epileptic patients up to 2 weeks of treatment with any AED other than VPA or LTG is allowed prior to enrollment in the study. During the first two weeks, if a patient entered the study on an antiepileptic drug other than VPA or LTG, it should be tapered off within two weeks after the initiation of treatment with study drug. After this time period, only benzodiazepines may be used acutely (up to 24 h) for management of breakthrough seizures. Patients between the ages of 12 and 40 years were recruited into the study from October 2004 to May 2006. Brain magnetic resonance imaging or computed tomographic scans were interpreted as normal.

Urine pregnancy test was done on all patients at the time of screening. Any positive result was not eligible for study. Those who were followed up for fewer than 3 months or who discontinued drug treatment within 3 months of initiation, were excluded. Other exclusion criteria were breast feeding, body mass index (BMI) > 30 kg/m^2, any history suggestive of clinically significant impairment of renal/hepatic dysfunction and currant abuse of alcohol or other substances. Other screening assessments included seizure frequency, vital signs, physical and neurological examinations and medical history.

2.2. Study protocol

It was an open label randomized comparative prospective study. Patients were randomly allotted into two groups, with 34 patients in VPA group and 32 patients in LTG group. All patients in both groups should received respective drugs as monotherapy for at least one year. All patients were followed for one year from time of inclusion. The intelligence levels were similar in both groups. Neither the behavior nor the cognitive therapies were implemented on our patients either before or during the study period.

2.2.1. Dosage and dosing

All patients in LTG group were initiated with LTG 25 mg once a day for 1st two weeks then 50 mg once a day for another 2 weeks followed by maintenance dose 200 mg twice a day. On the basis of clinical response the dose of LTG was titrated according to the dosing schedule to a maximum of 550 mg/day. If a decision was made to discontinue LTG therapy, a step-wise reduction of dose over at least 3 weeks was recommended. For all patients randomized to VPA group were received VPA in a dose of 750 mg/day for the first week and escalating to 1000 mg/day in next week. Target maintenance dose for VPA was 1000–2000 mg/day.

2.2.2. Initial screening examinations

The patients with epilepsy who met the inclusion criteria mentioned above were clinically and physically examined by two neurologists, and interviewed by the first author. Anthropometric data such as weight, height were measured. All the patients were evaluated at inclusion, at the end of 6th week, at the end of 3rd month, sixth month, ninth month and 12th month. During each visit all the patients underwent complete neurological examination, review of medical history, adverse events or reactions, compliance, concomitant medications were checked.

2.2.3. Collection of anthropometric and clinical data

Age, gender, BMI, seizure type, duration of illness, age at onset, dose of drug utilized, response to antiepileptic therapy, and family history were recorded clearly in a designed form. The height was measured to the nearest 0.1 cm with the wall-mounted statiometer. The weight was measured to the nearest 0.1 kg on electronic scale. Body mass index (BMI) was calculated by using quetelet's index [weight (kg)/height (m^2)]. Patients with BMI 18.0–22.9 kg/m^2 were considered as normal weight, BMI 23.0–24.9 kg/m^2 were categorized as being overweight and those with ≥25 kg/m^2 as obese [11]. At the end of study, we categorized the patients according to their respective BMI (baseline vs. last visit at 12th month) in the both groups.

2.2.4. Collection of biochemical parameters

Blood samples were collected following 12hr overnight fast. The following parameters were measured using commercially available radioimmunoassay kits: fasting insulin, fasting glucose, adiponectin, leptin and lipid profiles at the time of inclusion and at the end of study (12th month). Serum lipid profiles were estimated using an automated analyser (advia 1800 analyser, Siemens, Germany). Serum insulin were estimated by Advia Centaur CP (Siemens diagnostics) insulin immunoassay with sensitivity of 0.5 mIU/L and assay range is 0.5–300 mIU/L. Intra-assay and interassay coefficients of variation were 2.4% and 1.8% respectively. Serum leptin and adiponectin were estimated using commercially available ELISA kits (Ani Biotech Orgenium laboratories, Finland). The glucose oxidase peroxidase method was used for measurements of plasma glucose (Siemens advia 1800). The insulin resistance was estimated using the homeostasis model assessment for insulin resistance (HOMA-IR); fasting insulin (mIU/L) × fasting glucose (mg/dl)/405 [12]. Insulin resistance is defined as level of HOMA-IR greater than 2.5 [13]. At the end of study, all of the VPA-treated patients were further classified into two cohorts (HOMA-IR > 2.5 vs. HOMA-IR ≤ 2.5)

2.3. Statistical analysis

SPSS 11.0 software was used for analysis of data, with two-tailed, significant level at $P < 0.05$. Data is expressed as mean ± SD for quantitative parametric measures in addition to median (range) for quantitative nonparametric measures and both number and percentage for categorized data. Student's t-test was used for comparison between two independent mean groups for parametric data. Wilcoxon Rank Sum test and Mann–Whitney U test for nonparametric data. Correlation analyses were conducted using Spearman or Pearson correlation coefficients depending once again, on the distribution of the variables.

3. Results

The basic characteristics of the study population are depicted in Tables 1 and 2. The study profile is outlined in Fig. 1. The mean weight was significantly higher in VPA-treated patients than in LTG-treated patients ($P < 0.001$) (Fig. 2). The gained in weight in