Seizure (2007) **16**, 226—232

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SEIZURE

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Valproate, weight gain and carbohydrate craving: A gender study

Firas El-Khatib [a], Markus Rauchenzauner [b], Monika Lechleitner [c], Fritz Hoppichler [d], Anis Naser [a], Markus Waldmann [a], Eugen Trinka [a], Iris Unterberger [a], Gerhard Bauer [a], Gerhard J. Luef [a,*]

[a] *Department of Neurology, Medical University Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria*
[b] *Department of Paediatrics, Medical University Innsbruck, Austria*
[c] *Department of Internal Medicine, Medical University Innsbruck, Austria*
[d] *Special Institute for Preventive Cardiology and Nutrition, Salzburg, Austria*

Received 3 December 2004; received in revised form 8 September 2006; accepted 11 December 2006

KEYWORDS
Valproate;
Weight gain;
Leptin;
Carbohydrate craving

Summary

Purpose: To compare the incidence and magnitude of weight gain associated with valproic acid (VPA) monotherapy in male and female epilepsy patients and to determine possible gender-specific differences in frequency of carbohydrate craving, body-composition, glucose homeostasis and lipid metabolism.
Methods: Epilepsy patients on VPA monotherapy were consecutively recruited at the outpatient clinic of the Department of Neurology, Innsbruck Medical University. Weight gain during VPA-therapy, frequency of carbohydrate craving and physical exercise, sociopsychological problems and family history for diabetes were obtained from all patients. Clinical data also comprised body-impedance analysis, body mass index and waist-to-hip ratio. Morning fasting blood samples were drawn to determine serum leptin, glucose and lipid concentrations, as well as insulin, C-reactive protein and TNF-α.
Results: One hundred and six patients (55 women) were enrolled in the study. Significant weight gain was seen during VPA-therapy in both genders (each $p < 0.001$) with women experiencing increment of weight more frequently and more pronounced than did men. Analyses of patients who gained weight during VPA-therapy revealed significantly higher serum leptin concentrations in women than in men ($p < 0.001$). Women also revealed significantly higher high-density lipoprotein-cholesterol and lower triglyceride concentrations than men ($p = 0.004$ and 0.014, respectively). Frequency of carbohydrate craving was 25.8% in women and 14.3% in men. More women tried to lose or control weight through diet than did men (22.6%

* Corresponding author. Tel.: +43 512 504 23877; fax: +43 512 504 24260.
E-mail address: gerhard.luef@uibk.ac.at (G.J. Luef).

1059-1311/$ — see front matter
doi:10.1016/j.seizure.2006.12.009

versus 7.1%). Moreover, weight gain as a sociopsychological problem was more numerous in women than in men.
Conclusion: Women are more prone to gain weight during VPA therapy though higher frequency of diet and sociopsychological burden than men, which might possibly be related to leptin-resitance and a higher frequency of carbohydrate craving.

Introduction

Valproic acid (VPA) has a broad spectrum of anticonvulsant activity, being at present the antiepileptic drug (AED) of choice for all forms of generalized epilepsy and has become established worldwide as one of the most widely prescribed AEDs.[1,2] However, weight gain as the most common side-effect of VPA[3–5] limits its use in clinical practice more often than do other possible idiosyncratic side-effects and high rates of teratogenicity. VPA-related weight gain was found to be frequent in women with epilepsy, increasing the possibility for metabolic disturbances.[4] Verrotti et al. reported the development of obesity in 37% of female patients with epilepsy after 1 year of treatment with VPA.[6] Weight gain due to VPA treatment is usually observed during the first 3 months of therapy,[7–11] reaching its maximum after 6 months.[3,4,12,13]

Consequences of VPA-associated weight gain are the risk for developing non-alcoholic fatty liver disease (NAFLD)[14] and insulin resistance (IR).[4,15,16] Furthermore, it is well established that weight gain and obesity are associated with an increase in patients' cardiovascular risk[17] and increased noncompliance or therapy interruption.[12,13,18]

Up to now, attempts to determine factors responsible for VPA-induced weight gain failed.[19] Several mechanisms have been proposed: (i) ineffective leptin action despite high leptin levels,[6,20,21] (ii) hyperinsulinemia resulting from increased secretion of β-cells[22] and (iii) increased consumption of food and energy-rich drinks due to increased appetite (e.g. carbohydrate craving) and modified thirst.[3,13]

VPA treatment in humans is known to increase the serum level of two hormones, leptin[6,20,21] and insulin,[23] produced by adipose tissue and the pancreatic islet cells,[22] respectively. One of the physiologic roles of leptin is an appetite-reducing feedback signal.[24] In humans, serum leptin and insulin concentrations are associated with the amount of adipose tissue and are higher in obese than in lean people.[25,26] In epilepsy patients, higher serum leptin as well as insulin concentrations in overweight females compared to males[15] have been demonstrated.

To date, the etiology of VPA-induced weight gain is considered to be multi-factorial since weight is the output of energy homeostasis controlled by many organs that produce and secrete a variety of appetite-regulating peptides and cytokines that act within the hypothalamus.[27]

The aims of this study were to elucidate possible effects of gender on the magnitude of VPA-associated weight gain, carbohydrate craving and disturbances in body-composition, glucose and lipid homeostasis.

Methods

One hundred and twenty patients (61 women and 59 age matched men) were consecutively recruited from our outpatient clinic, presenting with either partial or generalized epilepsy treated with VPA monotherapy for at least 6 months. None of the patients had any other regular medication in addition to VPA. Patients with a mental handicap, with a history of psychogenic seizures and/or concomitant diseases possibly contributing to weight gain were excluded.

All patients underwent standardized questionnaire about family history of diabetes, the magnitude of weight gain under VPA therapy, eating habits, especially carbohydrate craving, sociopsychological burden of weight gain and physical exercise at the time of investigation. Each patient was measured for weight, height, hips and waist using a wall-mounted stadiometer, a tape measure and a calibrated weight scale, respectively, with subjects wearing underwear only.

Body-impedance analysis and fasting blood samples were obtained in all patients fulfilling the inclusion criteria between 8 and 10 in the morning. Each sample of whole blood was centrifuged to obtain serum, which was immediately frozen at −80 °C within 1 h after sampling, and stored in aliquots until the assays were run. Additionally, baseline anthropometric data from 1 day before VPA treatment was obtained from the patients' record (''initial weight'').

Body impedance as an expression of body fat portion was measured with a body fat monitor (OMRON BF 302), which measures the percentage and total amount of fat in kilograms contained in the human body. It analyses the electrical resistance of