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Original Article

Evaluation of Appetite-Stimulating Hormones in Prepubertal Children With Epilepsy During Topiramate Treatment

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ABSTRACT

We investigated the mechanism of topiramate-related appetite loss and exposed its relationship to body weight, body mass index, body fat index, and serum insulin, lipid, leptin, neuropeptide-Y, cortisol, ghrelin, and adiponectin levels. Twenty children with epilepsy were evaluated at baseline and months 3 and 6 of treatment. Their body fat index, leptin, and neuropeptide-Y levels significantly decreased at month 3, whereas significant decreases occurred in body weight, body mass index, body fat index, neuropeptide-Y, cholesterol, and cortisol levels of patients at month 6 compared with baseline. Weight loss during topiramate treatment was attributed to loss of appetite and reduced food intake caused by reductions in neuropeptide-Y. To the best of our knowledge, this study is the first to describe reductions in neuropeptide-Y with topiramate use in humans.

Introduction

Topiramate is a new-generation antiepileptic drug with a distinct efficacy and side-effects profile attributable to its unique structure [1,2]. In contrast with other antiepileptic drugs, topiramate is likely to cause loss of appetite and weight because of certain metabolic changes. Topiramate-related loss of appetite has been attributed to topiramate-related changes in appetite-stimulating (neuropeptide-Y, ghrelin, galanine, and noradrenalin) and appetite-suppressing (leptin, insulin, adiponectin, corticotropin-releasing hormone, and serotonin) hormones, or to topiramate-related changes in the thermogenic mechanism [3-5].

The present study investigated the mechanism of topiramate-related loss of appetite, and exposed its relationship with the variables already mentioned in prepubertal children with epilepsy for whom topiramate treatment was planned. For this purpose, body weight, length, body mass index, body fat index, and serum cholesterol, triglyceride, high-density lipoprotein and low-density-lipoprotein cholesterol, insulin, cortisol, leptin, insulin-like growth factor 1, insulin-like growth factor-binding protein, neuropeptide-Y, ghrelin, and adiponectin levels were measured at baseline, and at months 3 and 6 of treatment.

Materials and Methods

Twenty prepubertal children between ages 6 and 12 years who presented at the Pediatric Neurology Outpatient Clinic of Mersin University School of Medicine, and who were scheduled to receive topiramate treatment for epilepsy, were included in the study. Patients presented at the outpatient clinic with a history of at least two unprovoked seizures, and were diagnosed with epilepsy based on detailed anamnesis with physical and neurologic examination, as well as electroencephalography and cerebral imaging. Topiramate treatment was initiated at a dose of 1 mg/kg/day in two doses, and was gradually (2 mg/kg/day for each week) increased up to a dose of 7 mg/kg/day.

This study was performed in accordance with the current version of the Declaration of Helsinki and the laws and regulations of the Ethics Committee at Mersin University. Ethics committee approval for this study was also obtained from General Directorate of Pharmaceuticals and Pharmacy at the Ministry of Health in the Republic of Turkey. Parents of patients signed an informed consent form.

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The study included patients with generalized or localization-related idiopathic epilepsy according to the 1989 classification of the International League Against Epilepsy [6]. Patients with febrile convulsions and thyroid, hepatic, or renal disease and those using drugs that influenced appetite or seizure control were excluded from the study. Body fat and body mass indices of the patients were calculated by a dietician, using standard devices at baseline and at months 3 and 6 of treatment. Body mass and body fat indices were measured with a Tanita Body Composition Analyzer (Tanita, Arlington Heights, IL).

Venous blood samples for the analysis of cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, insulin, cortisol, leptin, insulin-like growth factor 1, insulin-like growth factor-binding protein, neuropeptide-Y, ghrelin, and adiponectin levels were collected from patients on the morning after an 8-hour fast at baseline and at months 3 and 6 of treatment, and were analyzed in the Biochemistry and Clinical Biochemistry Laboratory of our hospital. Baseline values of patients were compared with those measured at months 3 and 6 of treatment.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 13 (SPSS, Inc., Chicago, IL). Descriptive statistics are presented as means ± standard deviations. The Wilcoxon matched-pairs test was used to compare repeated measures. Correlations between body mass index, body fat index, and other parameters were evaluated by the Pearson correlation test. $P < 0.05$ was considered significant.

Results

The mean age of patients was 8.45 ± 2.3 years. Mean body weight, length, body mass index, body fat index, and insulin, cholesterol, high-density lipoprotein, leptin, neuropeptide-Y, and cortisol levels of patients at baseline and at 3 and 6 months of therapy are presented in Table 1. No significant difference was evident between baseline and month 3 and 6 values of triglyceride, low-density lipoprotein, ghrelin, adiponectin, insulin-like growth factor 1, and insulin-like growth factor-binding protein.

Although no significant difference was evident between the baseline and 3-month body weight and body mass index values ($P > 0.05$), a significant reduction was observed at month 6 compared with baseline ($P < 0.05$). In addition, a positive correlation was also evident between baseline, month 3, and month 6 body mass index and leptin levels ($P < 0.05$). Moreover, a significant increase was observed in the lengths of patients at months 3 and 6 of treatment compared with baseline values ($P < 0.05$). Body fat index values of patients significantly decreased at months 3 and 6 of treatment, compared with those at baseline ($P < 0.05$). Moreover, body fat index values of patients were significantly lower at month 6 than at month 3 ($P < 0.05$; Table 1).

Although no significant difference was evident between baseline and 3-month cortisol values of patients ($P > 0.05$), a significant reduction was observed at month 6 compared with baseline ($P < 0.05$). Neuropeptide-Y values of patients significantly decreased at 3 and 6 months of treatment, compared with baseline ($P < 0.05$), and no significant difference was evident between months 3 and 6 (Table 1).

A significant decrease was observed in low-density lipoprotein levels at month 6 of treatment, compared with those at baseline and month 3 ($P < 0.05$). A positive correlation was evident between the 6-month body mass index and low-density lipoprotein levels ($P < 0.05$, $r = 0.045$).

Discussion

Loss of appetite and weight comprise common side effects of topiramate treatment and limit use of the drug. Many factors and mediators play a role in the topiramate-related loss of appetite and unintended weight loss [3]. Only a few studies in the literature illuminate the pathogenesis of topiramate-related loss of appetite and weight in children [3-5,7-10]. The present study aimed to explore the mechanism of topiramate-related loss of appetite and weight loss, and to expose the association of this mechanism with body weight, body mass index, body fat index, and insulin, cholesterol, triglyceride, high-density-lipoprotein, low-density-lipoprotein, neuropeptide-Y, cortisol, ghrelin, adiponectin, insulin-like growth factor 1, and insulin-like growth factor-binding protein levels.

In this study, with respect to baseline values, body weight and body mass index decreased at month 6 of treatment, whereas body fat index decreased at both 3 and 6 months. Similar to findings in the present study, Klein et al. reported reductions in body weight, body mass index, and body fat index [7]. Another study reported that

Table 1. Findings of physical examinations and laboratory parameters of patients at baseline and at months 3 and 6 of treatment

	Baseline (n = 20)	Month 3 (n = 20)	Month 6 (n = 20)	*P*1	*P*2	*P*3
Body weight (kg)	26.86 ± 9.4	26.35 ± 9.2	26.38 ± 9.55	>0.05	0.038	>0.05
Length (cm)	125.80 ± 18.72	127.40 ± 19.27	128.55 ± 19.82	0.007	0.001	0.007
BMI (kg/m^2)	16.17 ± 2.10	15.86 ± 2.07	15.38 ± 1.92	>0.05	0.003	0.004
Body fat index	11.74 ± 5.42	9.97 ± 5.89	8.46 ± 5.17	0.014	0.001	0.001
Insulin (μU/mL)	6.64 ± 4.47	9.91 ± 8.04	7.65 ± 5.57	0.03	>0.05	>0.05
Cholesterol (mg/dL)	144.3 ± 17.0	139.9 ± 12.8	134.0 ± 12.9	>0.05	0.006	>0.05
HDL (mg/dL)	51.6 ± 13.3	49.2 ± 10.4	46.5 ± 9.8	>0.05	0.04	>0.05
Leptin (ng/mL)	0.91 ± 0.83	0.79 ± 0.11	1.02 ± 0.18	0.004	>0.05	>0.05
NPY (ng/mL)	55.65 ± 14.3	43.75 ± 16.1	45.35 ± 12.9	0.017	0.021	>0.05
Cortisol (μg/dL)	399.5 ± 176.0	343.5 ± 140.1	293.7 ± 136.7	>0.05	0.025	>0.05

Abbreviations:
BMI = Body mass index
HDL = High-density lipoprotein
NPY = Neuropeptide-Y
*P*1 = Significant difference between values at baseline and month 3
*P*2 = Significant difference between values at baseline and month 6
*P*3 = Significant difference between values at month 3 and month 6

topiramate-related weight loss and decreases in body mass index and body fat index values were dose-independent [8]. In the present study, we did not evaluate dose-related effects, but treated all patients with a standard dose (7 mg/kg/day).

Previous studies indicated that weight loss is associated with changes in glucose, insulin, and cholesterol levels [3,5,11,12]. Similarly to our findings, Narula et al. reported a decrease in serum fasting blood glucose, high-density lipoprotein, triglyceride, and total cholesterol levels in patients receiving topiramate [13]. Moreover, the increase in insulin levels observed at month 3 of treatment may have prevented the weight loss in our study. However, the mechanism of topiramate-related reductions in body weight, body mass index, and body fat index remains unclear. Therefore, a slow reduction in insulin level during the course of treatment may constitute a response to preserve body weight. Moreover, Liang et al. reported that topiramate reduces fasting glucose levels and enhances insulin sensitivity, and they also reported that these effects were not related to food intake and weight loss [11].

Leptin is an adipose tissue-secreted hormone that plays an important role in the regulation of body weight and food intake [3-5]. Various studies reported that topiramate reduces leptin levels [10,13,14]. Husum et al. determined a reduction in leptin levels at month 6 of topiramate treatment [14]. However, Genc et al. detected no change in leptin levels in patients with epilepsy receiving topiramate [4]. Lalonde et al. suggested that the metabolic effects of topiramate were neither inhibited nor potentialized by leptin [15]. In the present study, leptin levels significantly decreased at month 3 of treatment compared with baseline levels ($P < 0.05$). However, no significant difference was evident between baseline and 6-month leptin levels. On the other hand, a significant positive correlation was observed between body mass index and leptin levels at all periods during treatment ($P < 0.05$). Moreover, the present study demonstrated a reduction in body fat index values at month 3 of topiramate treatment. Because fat tissue comprises one of the main sites of leptin synthesis, the reduction in leptin levels at month 3 of treatment may be associated with the reduction in body fat index. Moreover, according to Li et al., adiponectin levels increased at month 6 of topiramate treatment without a change in leptin levels [5]. In our study, no significant change was observed in adiponectin levels at any period.

Ghrelin may be affected by the more severe weight loss that would result from longer uses of topiramate [16]. An absence of significant changes in ghrelin was considered attributable to a limited follow-up period. Large-scale studies with longer follow-up periods may provide explicit information on this issue. Moreover, the absence of significant changes in insulin-like growth factor 1 and insulin-like growth factor-binding protein levels with topiramate treatment was consistent with the finding that normal growth continued in our patients.

Neuropeptide-Y is a strong appetite-stimulating pancreatic protein polypeptide [17]. Husum et al. reported that topiramate led to a reduction in neuropeptide-Y and galanin levels in rat hippocampus [14]. In our study, neuropeptide-Y levels significantly decreased at months 3 and 6, and cortisol levels decreased at month 6, compared with values at baseline ($P < 0.05$). A reduction in cortisol levels may be associated with the decreased stimulation of corticotropin-releasing hormone because of decreased neuropeptide-Y levels. Based on the results of the present study, weight loss during topiramate treatment may be associated with loss of appetite and decreased food intake, which were secondary to the decrease in neuropeptide-Y levels. On the other hand, Richard et al. [10] suggested that topiramate-related weight loss occurred secondary to energy consumption, whereas Astrup et al. [18], Ben-Menachem et al. [19], and Bray et al. [8] suggested that it was associated with increases in body temperature.

To the best of our knowledge, the present study was the first to investigate concomitant changes in serum neuropeptide-Y, ghrelin, cortisol, insulin-like growth factor 1, and insulin-like growth factor-binding protein levels during topiramate treatment in humans. The present study demonstrated that body weight, body mass index, body fat index, and neuropeptide-Y levels significantly decreased with topiramate treatment. Based on the results of the present study, weight loss during topiramate treatment may be associated with a loss of appetite and decreased food intake, secondary to decreases in neuropeptide-Y levels. To the best of our knowledge, the decrease in cortisol and neuropeptide-Y levels during topiramate treatment was first demonstrated in the present study. On the other hand, although the pathogenesis of topiramate-related loss of appetite and weight remains unclear, comprehensive and long-term studies with larger case groups may contribute to the understanding of this pathogenesis.

This study was performed at the Mersin University School of Medicine, and its results were previously presented at the Thirteenth Ulusal Cocuk Noroloji Kongresi in Turkey. The authors received financial support for research from the Department of Scientific Research at Mersin University.

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