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Weight gain in children on oxcarbazepine monotherapy

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ABSTRACT

Background: Studies of the effect of oxcarbazepine (OXC) on body growth of children with epilepsy are rare and their results are controversial. To the contrary, many studies have shown significant weight gain following valproate (VPA) treatment.
Purpose: To prospectively evaluate the effect of OXC monotherapy on growth patterns of children with epilepsy and compare it with the effect of VPA monotherapy.
Method: Fifty-nine otherwise healthy children, aged 3.7–15.9 years, with primary generalized, partial or partial with secondary generalization seizure disorder, were included in the study. Twenty six children were placed on OXC and thirty three on VPA monotherapy. Body weight (BW), height and body mass index (BMI) as well as their standard deviation scores (SDS), were evaluated prior to as well as 8 months post initiation of OXC or VPA therapy.
Results: Eight months post OXC-treatment, BW, SDS-BW, BMI and SDS-BMI increased significantly. The increase was similar to that observed in the VPA group. An additional 15.4% of children in the OXC group and 21.2% in the VPA group became overweight or obese. The effect of both OXC and VPA therapy on linear growth did not reach statistical significance.
Conclusion: Similarly to VPA, OXC monotherapy resulted in a significant weight gain in children with epilepsy. Careful monitoring for excess weight gain along with counseling on adapting a healthy lifestyle should be offered to children on OXC therapy.

1. Introduction

Oxcarbazepine (OXC) is a new generation antiepileptic drug in wide use as single-agent or combination treatment for partial seizure disorders in patients older than 4 years. OXC is a structural derivative of carbamazepine (CBZ), a dihydro-ketone analogue, with a similar mechanism of action. It is a prodrug activated to eslicarbazepine in the liver. OXC's metabolism is much less dependent on cytochrome P-450 liver enzymes than CBZ, resulting in fewer side effects (Bang and Goa 2003; Chung and Eiland 2008).

Weight gain is a well-known adverse effect of many antiepileptic drugs such as valproic acid (VPA), an old and broad-spectrum antiepileptic which is effective against many types of seizures in childhood (Hamed et al., 2009; Rauchenzauner et al., 2010; Verrotti et al., 2011; Cansu et al., 2011b). Studies on the growth patterns of children on OXC therapy are limited with contradictory results. Some investigators failed to reveal changes in their patients' weight (Cansu et al., 2011a), whereas others showed significant weight gain (Nam and Kim, 2006). With regards to height, in contrast to other studies (Mikkonen et al., 2005; Cansu et al., 2011a; Lee et al., 2013), a recent study showed a positive effect of OXC on growth velocity (Cansu et al., 2012). On the other hand, epilepsy itself is known to affect growth as it has been shown to halt height velocity and increase body weight (El-Khayat et al., 2010; Hamed, 2007).

Weight gain along with the known adverse effects of antiepileptic drugs on several other cardiovascular risk factors such as insulin, lipids and homocysteine levels may provoke endothelial dysfunction and premature atherosclerosis (Tokgoz et al., 2012; Mikkonen et al., 2005; Sonmez et al., 2006; Chuang et al., 2012;

Abbreviations: OXC, oxcarbazepine; VPA, valproate; CMZ, carbamazepine; SDS, standard deviation scores; BMI, Body Mass Index.

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Attilakos et al., 2006; Hamed et al., 2007; Voudris et al., 2006). Therefore close monitoring of weight combined with dietary and lifestyle counseling could be of paramount importance in children receiving antiepileptic treatment.

The main aim of this study was the prospective evaluation of growth patterns in children on OXC monotherapy.

2. Study population and methods

Fifty-nine children and adolescents (29 males) with primary seizure disorder recruited from a hospital-based Pediatric Neurology outpatient clinic were included in the study. All children had normal motor and mental development, average activity levels and did not have co-morbid conditions. Upon enrollment there were no children on antiepileptic therapy, other medications or special diets. Written informed consent was obtained from guardians prior to enrollment. The conduction of the study conformed to clinical research ethics according to the Declaration of Helsinki.

Exclusion criteria were discontinuation, non-compliance, alteration or addition of an adjunctive agent to initial treatment and parental desire to discontinue participation in the study. Only three children were excluded during the study (3 out of 62 children, participation rate 95%).

The patients included in the study were assigned to two groups according to antiepileptic therapy. The selection of treatment was performed by the pediatric neurologist based on the type of seizures and electroencephalogram (EEG) findings. Twenty six patients (15 males) were placed on OXC monotherapy and were compared to 33 patients (14 males) who were placed on VPA monotherapy.

All children were examined prior to the initiation of OXC or VPA therapy and 8 months later. None of them changed Tanner stage within these 8 months. Moreover, physical activity levels and dietary habits were similar between the two groups and stable for each individual patient during the study period. Body weight and height were measured on accurate medical scale and stadiometer (SECA). The International Obesity Task Force (IOTF) standards were applied. Body mass index (BMI) was calculated by the ratio of weight to height (body weight in kg/height in m^2). Based on age- and sex-specific cutoff points of BMI on the percentile curves of an international reference population, children were classified as normal BMI, overweight and obese (Cole et al., 2000). In addition, a standardized age- and sex-specific growth reference was used to calculate height-for-age, weight-for-age and body-mass-index-for-age standard deviation scores (SDS) (https://web.emmes.com/study/ped/resourcehttps://web.emmes.com/study/ped/resource).

An EEG was performed at diagnosis and follow-up. Seizures were classified according to the report of the International League Against Epilepsy (ILAE) Commission on Classification and Terminology 2005–2009 (Epilepsia 2010). Twenty-eight children had generalized and thirty-one partial or partial evolving to a bilateral, convulsive seizure. All patients evaluated by brain MRI had normal findings.

2.1. Statistical analysis

All statistical analyses and data management were performed using STATA for Windows v 8.5, (StataCorp, Texas, USA, 2006). Data are expressed as Mean ± SD, median, range. Time differences of variables were calculated (deltas). Subgroup data within each group were compared using non parametric Wilcoxon paired test. Deltas of OXC group were compared with deltas of VPA group using non parametric Mann-Whitney U test (independent samples). Association between numerical variables was assessed with non parametric Spearman's rho coefficient. $P < 0.05$ was considered statistically significant.

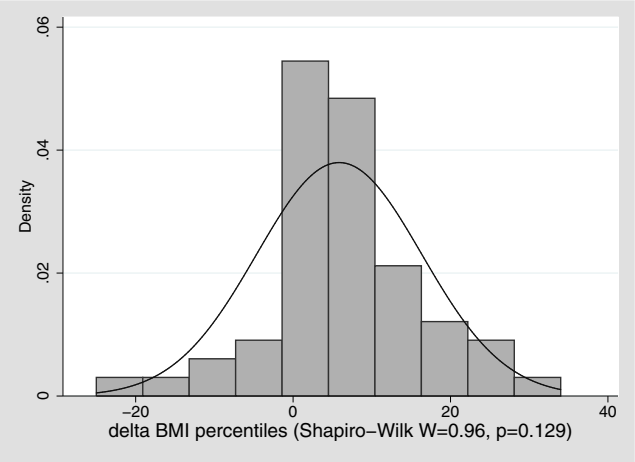

Fig. 1. Delta BMI percentile distribution. Graphically there is normality approximation, which was confirmed statistically (Shapiro-Wilk W = 0.96, p = 0.129).

3. Results

The mean age of the children and adolescents included in the study was 8. 9 (SD: 2.9) years and the median 8.9 years (range: 3.7–15.9 years). The mean age of male and female subjects was not statistically different ($p = 0.38$). Moreover, the mean age of children placed on OXC did not yield statistically significant difference from those placed on VPA ($p = 0.23$). Additionally, the mean age between children with generalized and partial or partial evolving to a bilateral convulsive seizure did not differ significantly ($p = 0.15$).

The effect of OXC on the SDS of body weight, height and BMI in comparison with the effect of VPA is shown in Table 1. A significant increase of weight-SDS and BMI-SDS was observed in the OXC group, similar to that observed in the VPA group.

Specifically, eight months post treatment, body weight and BMI increased significantly in OXC group and the percentage of overweight/obese children climbed from 23% to 38.5%, an increase of 15.4%. In the VPA group an increase of 21.2% was observed. In addition, following treatment with either OXC or VPA, a significant number of children with normal pre-treatment BMI were found to have increased post-treatment BMI by 1–3 percentiles.

Although not statistically significant, a reduction in height-SDS was observed in children under OXC therapy (Table 1). Fourteen out of 26 children on OXC had a decelerated growth rate. The effect of OXC on height did not differ significantly from that of VPA (Table 1).

No statistically significant gender differences were found in both groups. The differences (Δ-deltas) of BMI-SDS pre-treatment and 8 months post-treatment for every child were calculated. The distribution of those differences was evaluated graphically and seemed to approach normal distribution (Fig. 1). The differences of the distribution of the BMI percentiles pre- and post-treatment for both groups are shown in Fig. 2.

4. Discussion

In the present study, the use of OXC for eight months resulted in a significant increase in body weight and BMI proportional to that observed at the eight month of VPA monotherapy. To the opposite, OXC as well as VPA monotherapy had no significant effect on height growth rate.

A number of antiepileptic medications have known adverse effects on children's growth patterns (Rättyä et al., 1999; Kothare and Kaleyias, 2007; Hamed, 2015). On the other hand, epilepsy itself can cause growth alterations and weight gain (Hamed, 2007; Hamed et al., 2009; Mikkonen et al., 2005). The use of VPA in