



Effect of antiepileptic drug (valproic acid) on children growth



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KEYWORDS

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Abstract *Background:* Epilepsy often requires long-term antiepileptic drug therapy. Antiepileptic drugs are potentially an effective treatment for patients with epilepsy. Poor adherence is, however, very common in patients experiencing side-effects due to AEDs.

The aim of this study: The aim of this study was to evaluate the effects of AED monotherapy by VPA on alterations in serum calcium levels and statural growth and body mass index in pediatric patients newly diagnosed with epilepsy.

Patients and methods: The present study included 25 children, newly diagnosed with epilepsy and maintained on VPA monotherapy for at least one year. The serum levels of patients taking VPA were routinely monitored. Another 25 children with a history of simple febrile convulsions were included as a control group. All patients and controls were selected from Al-Azhar University hospital (new Damietta) during the period from June 2011 to June 2012. The main screening assessments included seizure frequency, vital signs, physical and neurologic examinations, medical history, and standard clinical laboratory tests (e.g., CBC, BUN, SGPT, SGOT); all these parameters were estimated at the start of the study, at 6 and 12 months. Weight and height measurements were recorded at the start of the study and at 6 and 12 months of continuous treatment of valproic acid. In addition serum calcium and glucose levels were obtained at the same time.

Results: There was no significant difference between study and control groups at basal time regarding height, weight or BMI. On the other hand, there was a significant increase of weight and BMI and a decrease of height centiles at 6 months and 1 year; and as regards serum glucose, there was no significant difference between study and control group at basal time, while there was a significant increase in the study group in the control group at 6 months and 1 year. On the other hand, there was no significant difference between cases and controls as regards serum calcium at any time.

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Conclusion: Childhood and adolescence are crucial periods in which to attain peak bone mass, and it is a crucial period for growth in general; and most patients with epilepsy are diagnosed and treated in this period, therefore, AEDs, and especially VPA, should be used with caution in pediatric patients with epilepsy.

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Introduction

According to WHO, epilepsy is one of the most common neurological disorders affecting approximately 50 million people.³² Epilepsy can be defined as a chronic condition characterized by recurrent clinical events or epileptic seizures, which occur in the absence of a metabolic or toxic disease or fever.⁸ Epilepsy often requires long-term antiepileptic drug (AED) therapy. Antiepileptic drugs (AEDs) are potentially an effective treatment for patients with epilepsy. Treatment failure and poor adherence are, however, very common in patients experiencing side-effects due to AEDs. In approximately 25% of the patients, side-effects lead to treatment discontinuation.^{21,27} Valproic acid is effective in treatment of all types of epilepsy. It is among the most widely used antiepileptic drugs in clinical practice.⁶

In human long bones, the growth plate is made up of chondrocytes at different stages of differentiation, and is divided histologically into three distinct zones: resting, proliferative, and hypertrophic.²⁸ Longitudinal bone growth is achieved through the action of chondrocytes in the proliferative and proliferative zones of the growth plate.²³ Bone provided systemic and local hormones, calcium and other chemicals, to maintain the intra- and extracellular mineral pools and can work with osteoblasts, osteocytes, and extracellular matrix proteins to mineralize osteoid.²² Calcium is an important element for normal epiphyseal growth plate development, and changes in extracellular calcium affect the function of chondrocytes.²⁴ Proliferation of epiphyseal growth plates results from complex interactions between hormones and growth factors, which may directly or indirectly affect the serum levels of calcium and the condition of those cells, leading to final stature.

Although some studies suggest that patients with epilepsy treated with AEDs have an increased risk of fractures, low bone mineral density (BMD), and abnormalities in bone metabolism, skeletal diseases associated with long-term AED treatment are seriously unrecognized.^{19,26}

Evidence suggests that patients with epilepsy are predisposed to bone problems and fractures. However, one meta-analysis concluded that the deficit in bone mineral density was too small to explain the increase in the risk of fractures in patients with epilepsy.³¹ Bone abnormalities such as short stature, abnormal dentition, rickets, and osteomalacia have been reported to be linked to the use of AEDs.¹⁰

Weight gain is a well-known adverse effect of VPA treatment, occurring in 40% of children.⁴ Weight gain is the most common reason for patients to discontinue VPA treatment.³⁰

In one study, 38% of VPA-treated patients gained more than 10% of their body weight compared with 8% of patients treated with lamotrigine.³ Further, weight gain associated with VPA seems to be appetite-related and not metabolic.⁷

Aim of the work

The aim of this study was to evaluate the effects of AED monotherapy by VPA on alterations in serum calcium levels and statural growth and body mass index in pediatric patients newly diagnosed with epilepsy.

Patients and methods

The present study included 25 children, newly diagnosed with epilepsy and maintained on VPA monotherapy for at least one year (starting dose 20 mg/kg/day, maintenance dose 20–40 mg/kg). The serum levels of patients taking VPA were routinely monitored, and the levels kept within the therapeutic range (50–100 µg/mL). Another 25 children with a history of simple febrile convulsions were included as a control group. All patients and controls were selected from Al-Azhar University hospital during the period from June 2011 till June 2012 from Pediatrics, Neurology and Emergency departments. An informed consent was obtained from the guardian to participate in the study and the study protocol was approved by the local ethics committee. Epileptic children were classified according to the International League Against Epilepsy (ILAE) Commission on Classification and Terminology 2005,¹ into generalized and focal epilepsy.

Inclusion criteria

- (1) Epilepsy patients using Valproic Acid Monotherapy for at least 1 year.
- (2) Age 2–14 years.
- (3) Either sex.

Exclusion criteria

- (1) A history of taking medications that affect bone metabolism (e.g., steroids, diuretics, vitamin D, calcium supplements, bisphosphonates, or calcitonin);
- (2) Any endocrine or medical disorders (e.g., hypothyroidism or renal diseases);
- (3) A history of nutritional deficiency;
- (4) Limitations in ambulation or daily physical activity;
- (5) Any progressive neurological disorders other than epilepsy; and
- (6) Clinical/biochemical evidence of rickets or growth retardation.

The main screening assessments included seizure frequency, vital signs, physical and neurologic examinations, medical history, and standard clinical laboratory tests (e.g., CBC, BUN,

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