

⇒ Research Article



Comparison of the Effects of Sodium Valproate and Carbamazepine on Renal Function in Children With Epilepsy

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Abstract

Background: Renal disorders have been observed with the long-term treatment of some antiepileptic drugs (AEDs). We aimed to compare the effects of carbamazepine (CBZ) and valproate (VPA) on renal function in children with epilepsy.

Methods: This quasi-experimental study included children with epilepsy aged 2 months to 14 years who had persistently been receiving CBZ or VLP monotherapy for more than 6 months and were referred to Bandar Abbas Children's Hospital, Bandar Abbas, Iran, 2019-2020. Demographic features, including age and sex, as well as family history of epilepsy, disease duration, and duration of treatment were recorded for each patient. Random blood and urine samples, along with 24-hour urine samples were collected from all the participants. Blood urea nitrogen (BUN), sodium, alkaline phosphatase (ALP), and pH were measured in blood samples. Glucose, protein, sodium, potassium, phosphorus, and creatinine were estimated in 24-hour urine samples. N-acetyl-beta-D-glucosaminidase (NAG) and pH were assessed in random urine samples.

Results: Of the 80 children in this study with a mean age of 7.43 ± 3.22 years, 58 (72.5%) were males. Children in both groups were comparable in terms of age, sex, family history of epilepsy, and disease and treatment duration. The urine NAG level was significantly higher in the VPA group compared to the CBZ group ($P=0.010$). Further, 24-hour urine protein and glucose levels were significantly higher in the VPA group. As for blood parameters, except for sodium ($P=0.034$), ALP ($P<0.001$), and pH ($P=0.006$) which were significantly higher in the CBZ group, other parameters were significantly higher in the VPA group.

Conclusion: Overall, CBZ appears to be safer than VPA regarding its effects on renal function in children treated for epilepsy.

Keywords: Epilepsy, Renal function, Carbamazepine, Valproate

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Background

With a prevalence of 8.2-12.9 per 1000 individuals in the general population, epilepsy is regarded as one of the most common neurological disorders (1). Life-long treatment with antiepileptic drugs (AEDs) is required in approximately 37-55% of patients (1). Metabolic, endocrine, cognitive, behavioral, and vascular complications can occur with long-term AED treatment (2-4). AEDs may also have adverse effects on the kidney (5). Interstitial nephritis, acute renal injury, renal tubular acidosis, and nephrolithiasis have been reported as the uncommon side effects of some AEDs (1, 6, 7).

Carbamazepine (CBZ) and valproate (VPA) are two common AEDs for the treatment of epilepsy in adults

and children. Fanconi syndrome has been reported as an adverse effect of VPA in children with epilepsy (8-11). Furthermore, renal dysfunction at a subclinical level has been observed in children with epilepsy treated with CBZ or VPA, either alone or in combination with other AEDs (12-14). According to in vitro experiments, oxidative stress, fibrosis, and inflammation appear to be the pathological processes by which VPA damages renal tissues. However, the exact mechanisms by which AEDs might cause kidney injury are still unknown (15, 16).

Objectives

This study aimed to compare the renal effects of CBZ with VPA in children with epilepsy, reflected in urine

pH, N-acetyl-beta-D-glucosaminidase (NAG), glucose, and protein, blood pH, serum alkaline phosphatase (ALP), and blood urea nitrogen (BUN), as well as serum and urine sodium, potassium, calcium, phosphorus, and creatinine.

Methods

Participants

The current quasi-experimental study included children with epilepsy referred to Bandar Abbas Children's Hospital, Bandar Abbas, Iran from March 21, 2019, to March 20, 2020. The inclusion criteria were being in the age range of 2 months to 14 years and having received CBZ or VLP monotherapy for more than 6 months. On the other hand, children with intermittent drug use and underlying kidney or hematologic diseases were excluded from the study. The sample size was calculated as at least 40 patients in each group based on $\alpha=0.05$ and $\beta=0.2$.

Study Design

Demographic features such as age and sex, as well as family history of epilepsy, disease duration, and duration of treatment with either CBZ or VLP were recorded for each patient. Random urine and blood samples, along with 24-hour urine samples were collected from all the participants. BUN, sodium, ALP, and pH were measured in blood samples. Additionally, glucose, protein, sodium, potassium, phosphorus, and creatinine were assessed in 24-hour urine samples. Finally, NAG and pH were estimated in random urine samples.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) software (version 26.0, Armonk, NY: IBM Corp.) was used for data analysis. Means and standard deviations, as well as frequencies and percentages, were applied for describing continuous and categorical variables, respectively. The chi-square test was employed to compare categorical variables between the CBZ and VPA groups. Based on the results of the Kolmogorov-Smirnov normality test, an independent *t* test was used to compare continuous variables between groups. *P* values ≤ 0.05 were considered statistically significant.

Results

Of the 80 children included in this study, 40 (50%) and 40 (50%) were in the CBZ group and 40 (50%) in the VPA group. Their mean age was 7.43 ± 3.22 years. Moreover, 58 (72.5%) and 22 (27.5%) children were male and female, respectively. Table 1 compares the general characteristics of the patients between the CBZ and VPA groups. Patients in both groups were comparable in terms of age ($P=0.126$), sex ($P=0.105$), family history of epilepsy ($P=0.622$), disease duration ($P=0.717$), and duration of treatment ($P=0.847$).

The urine NAG level was significantly higher in the

VPA group in comparison to the CBZ group ($P=0.010$). Similarly, 24-hour urine protein and glucose levels were significantly higher in the VPA group ($P=0.001$ for both). However, the 24-hour urine creatinine level was significantly higher in the CBZ group ($P<0.001$). Other urine parameters, including sodium, potassium, calcium, phosphorus, and pH did not significantly differ between groups (Table 2).

As for blood parameters, except for sodium ($P=0.034$), ALP ($P<0.001$), and pH ($P=0.006$) which were significantly higher in the CBZ group, other parameters were significantly higher in the VPA group. It is noteworthy that calcium levels were comparable between groups ($P=0.335$, Table 3).

Discussion

In the current study, significantly higher urine NAG levels were found after using VPA when compared to CBZ. NAG is a lysosomal enzyme originating from proximal tubules. Due to its high molecular weight, NAG cannot be filtered through the glomerular basal membrane; therefore, its increased urinary excretion shows renal tubular cell breakdown, indicating proximal tubular dysfunction (17). Similar to our results, Mazaheri et al reported a higher NAG/creatinine index with VPA in comparison to CBZ, yet without a statistically significant difference (12). Havali et al also concluded that urine NAG levels were significantly higher in the VPA group compared to controls, while the difference between the CBZ group and controls was not statistically significant (14). The findings of these studies and those of ours demonstrate a higher renal tubular damage with VPA. Nevertheless, it should be noted that the duration of treatment, drug blood levels, and the baseline status of tubular function might have been different in these studies, leading to significant findings in our study and nonsignificant results in the studies of Mazaheri et al and Havali et al (12, 14). Contrary to our results, Endo et al found a significantly higher α_1 -microglobulin (another indicator of renal tubular dysfunction) excretion with CBZ monotherapy rather than VPA monotherapy (18). This can be justified by the difference in the sample size, along with the higher age of patients in the study by Endo et al, and potentially the various doses of drugs taken by the participants in either study.

Another finding of the present study was that serum creatinine was significantly higher in the VPA group in comparison to the CBZ group. Not many studies have compared the effects of these drugs on serum creatinine levels. Nonetheless, serum creatinine levels were almost similar in the CBZ and VPA groups of the study by Havali et al, with nonsignificant differences between both groups and controls (14). Although we found significantly higher serum creatinine levels in the VPA group, the mean creatinine was still within normal limits in both groups. This represents the potentially unremarkable effect of

Table 1. General Characteristics of the Study Population

Variables	Total (n=80)	VPA (n=40)	CBZ (n=26)	P Value
Sex, No. (%)				
Male	58 (72.5)	32 (80.0)	26 (65.0)	0.105 ^a
Female	22 (27.5)	8 (20.0)	14 (35.0)	
Age (y), mean ±SD	7.43 ±3.22	6.90 ±2.92	7.97 ±3.44	0.126 ^b
Family history of epilepsy, No. (%)	12 (15.0)	6 (15.0)	6 (15.0)	0.622 ^a
Disease duration (months), mean ±SD	34.65 ±11.00	34.20 ±11.22	35.10 ±10.91	0.717 ^b
Duration of treatment (months), mean ±SD	24.85 ±9.18	25.05 ±10.34	24.65 ±7.97	0.847 ^b

Note. N: Number; SD: Standard deviation; CBZ: Carbamazepine; VPA: Valproate.

^aAnalyzed by Chi-square test. ^bAnalyzed by an independent *t* test.

Table 2. Comparison of Urine Parameters Between CBZ and VPA Groups

Variables	Total (n=80)	VPA (n=40)	CBZ (n=40)	P Value ^a
NAG (ng/mL) mean ±SD	10.09 ±6.58	13.07 ±6.83	7.10 ±4.76	0.010
Na (mEq/day) mean ±SD	170.35 ±44.26	197.77 ±43.28	160.92 ±43.73	0.056
K (mEq/day) mean ±SD	61.11 ±17.76	59.82 ±8.39	62.40 ±23.90	0.532
Ca (mg/day) mean ±SD	138.40 ±7.07	139.82 ±7.62	136.97 ±6.26	0.072
P (mg/day) mean ±SD	426.31 ±82.61	413.75 ±84.18	438.87 ±80.09	0.175
Cr (mg/day) mean ±SD	924.67 ±190.18	842.72 ±174.89	1006.62 ±170.01	<0.001
Protein (mg/day) mean ±SD	72.10 ±24.30	80.67 ±28.38	63.52 ±15.49	0.001
Glucose (mg/day) mean ±SD	68.30 ±7.96	69.60 ±6.94	67.00 ±8.77	0.001
pH mean ±SD	5.48 ±0.02	5.48 ±0.02	5.47 ±0.02	0.232

Note. N: Number; SD: Standard deviation; CBZ: Carbamazepine; VPA: Valproate; NAG: N-acetyl-beta-D-glucosaminidase; Na: Sodium; K: Potassium; Ca: Calcium; P: Phosphorus; Cr: Creatinine.

^aAnalyzed by an independent *t* test.

Table 3. Comparison of Blood Parameters Between CBZ and VPA Groups

Variables	Total (n=80)	VPA (n=40)	CBZ (n=40)	P Value ^a
Na (mEq/L) mean ±SD	138.78 ±6.51	137.22 ±1.71	140.35 ±8.83	0.034
K (mEq/L) mean ±SD	4.18 ±0.32	4.28 ±0.34	4.09 ±0.26	0.005
Ca (mg/dL) mean ±SD	9.46 ±0.25	9.43 ±0.26	9.43 ±0.23	0.335
P (mg/dL) mean ±SD	5.26 ±0.66	5.41 ±0.67	5.00 ±0.59	0.005
Cr (mg/dL) mean ±SD	0.55 ±0.07	0.56 ±0.08	0.53 ±0.06	0.048
BUN (mg/dL) mean ±SD	12.24 ±2.71	12.97 ±2.31	11.51 ±2.91	0.015
ALP (IU/L) mean ±SD	223.97 ±6.51	199.77 ±36.23	248.17 ±71.93	<0.001
pH mean ±SD	7.38 ±0.02	7.37 ±0.02	7.39 ±0.20	0.006

Note. No: Number; SD: Standard deviation; CBZ: Carbamazepine; VPA: Valproate; Na: Sodium; K: Potassium; Ca: Calcium; P: Phosphorus; Cr: Creatinine; BUN: Blood urea nitrogen; ALP: Alkaline phosphatase.

^aAnalyzed by an independent *t* test.

long-term VPA treatment in children without underlying kidney dysfunction; however, it appears that VPA should be administered with more caution compared to CBZ when concurrent kidney diseases are present.

The findings of the current study confirmed significantly higher serum phosphorus levels in patients taking VPA compared to those receiving CBZ, while Nicolaidou et al demonstrated no difference between patients taking these drugs and the general population with respect to serum phosphorus levels (19). Mean serum phosphorus levels were within the reference range of serum phosphorus for children in both groups. Most probably results similar to those of Nicolaidou et al would have been obtained by

comparing the two groups of our study with a control group taking none of these drugs.

In the current study, a significantly higher urinary excretion of creatinine was observed in the CBZ group, while the 24-hour urine protein and glucose levels were significantly higher in the VPA group. Despite significant differences, these findings bear no clinical significance due to the values being within normal limits in both groups.

A significantly higher serum ALP level was further found with CBZ compared to VPA. To the best of our knowledge, no previous studies have compared ALP levels between pediatric or even adult patients taking CBZ or VPA. An increase in serum ALP could occur as a result of

mineral bone disorder secondary to hyperparathyroidism in chronic kidney disease (CKD); nevertheless, because of the rare possibility of CKD development due to CBZ or VPA based on serum creatinine levels, the significantly higher ALP level in the CBZ group of our study might more potentially be due to the hepatotoxicity of CBZ which has been documented in animal studies (20). Another plausible reason for the elevation of serum ALP in patients taking AEDs can be lower vitamin D levels, leading to the release of ALP from the bones; however, neither VPA nor CBZ appear to significantly affect vitamin D levels in pediatric patients with epilepsy (21, 22).

The primary strength of the current study was that patients in the CBZ and VPA groups were homogenous in terms of age, sex, family history of epilepsy, disease duration, and duration of treatment. Of these factors, the duration of the disease and duration of treatment are of higher importance since they can interfere with the results.

On the other hand, one limitation of the present study was that we did not have a baseline evaluation of kidney function in these patients, which is before the initiation of treatment. Another limitation was that blood drug concentrations were not determined in this study. This could have influenced the results since patients were under treatment with different doses, with higher doses probably having more effects on renal function.

Conclusion

In conclusion, CBZ appears to be safer than VPA for the treatment of childhood epilepsy in terms of adverse effects on renal function. This is of utmost importance when VPA is prescribed for children with underlying kidney diseases. The results of the current study should be confirmed by future studies, especially if implementing a different design such as a clinical trial.

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Author's contribution

Conceptualization and study validation: ME. Study supervision: AM. Implementation: EH. Data analysis and interpretation: GZ. Writing and reviewing: ME. All the authors have read and approved the manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interests

The authors declare that they have no competing interests.

Ethics approval

The study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1394.202) and it complies with the statements of the Declaration of Helsinki. Written informed consent was obtained

from the parents/guardians of all patients.

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