Effect of Chronic Valproic Acid Use on Anterior Cerebral Blood Flow of Children with Idiopathic Generalized Epilepsy

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Abstract

Objective: Cerebral blood flow has been blamed as a factor in the negative effect of antiepileptic drugs on neurocognition. This study aimed to investigate whether valproic acid (VPA), used for the treatment of idiopathic generalized epilepsy (IGE), causes a change in cerebral blood flow in children.

Methods: Included in this study were 33 children who were receiving VPA for IGE and 34 age-matched controls. Doppler and spectral measurements in common carotid artery (CCA), left and right internal CA (ICA) and external CA (ECA), anterior cerebral artery (ACA) and middle cerebral artery (MCA) were performed and the maximum velocity (VM), end-diastolic velocity (EDV), resistive index (RI), pulsatility index (PI) and flow rate (FR) were calculated.

Results: The mean age of drug and control groups were 9.33 ± 2.11, and 9.74 ± 2 years, respectively. Follow-up of patients was 17.7±3.2 months. The period of VPA treatment was 17.4±3.4 months. No statistically significant differences were found between control and VPA group for the VM, EDV, RI, PI, and FR values obtained from the bilateral ICA, ACA, and MCA.

Conclusions: The results showed that VPA in therapeutic doses did not affect anterior cerebral blood flow. However according to result, it is still difficult to conclude that neurocognitive deterioration is not observed in patients receiving VPA.

Keywords: valproic acid, cerebral blood flow, pediatric epilepsy, antiepileptic drug.

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INTRODUCTION

Cognitive and behavioral disorders often accompany childhood epilepsies. Cognitive deterioration, such as memory deficits, mental slowdown, and attention deficits, are frequently observed. The etiology of epilepsy, seizures type, underlying cerebral pathology, and antiepileptic drugs have been blamed for this coexistence. Adverse effects of antiepileptic drugs on cognitive functions are a well-known entity. However, it is difficult to make

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an exact estimate of the rate of drug-related effect on cognitive function due to the different reasons mentioned above. Even though blood levels of antiepileptic drugs are kept within the therapeutic range, attention, memory, and psychomotor functions are negatively affected [1,2]. Negative effects on attention, concentration and memory have been more frequently observed with phenobarbital (PB) when compared to other older antiepileptic drugs, such as valproic acid (VPA), carbamazepine (CBZ), and phenytoin (PHT) [3-5]. Additionally, the decrease effect of PB on cerebral blood flow and glucose metabolism rate has been reported as more prominent than the effects of the others [6-9]. Therefore, it was thought that antiepileptic drugs exert their adverse effects on cognitive functions through decreasing cerebral blood flow and the glucose metabolic rate.

VPA is a commonly used antiepileptic drug with a broad-spectrum of anticonvulsant activity. It is primarily preferred as a first-line treatment for tonic-clonic, absence, and myoclonic seizures. Additionally, it is also used for bipolar disorder treatment and migraine prophylaxes. Although there are sufficient data about the cognitive effects of VPA, literature studies evaluating the effect of VPA on cerebral blood flow and glucose metabolic rate are very limited. Moreover, these studies were mostly conducted on adult epilepsy patients or healthy adult volunteers [8-10]. The current study aimed to elucidate the effects of VPA on the cerebral blood flow of pediatric epilepsy patients.

MATERIALS AND METHODS

Children who were followed-up at the Pediatric Neurology Clinic of the Ondokuz Mayis University for idiopathic generalized epilepsy (IGE) and receiving VPA were included in the study, while children who were followed-up for non-migraine headaches were included in the control group, after obtaining local ethics committee approval. Written informed consent was obtained from the parents or legal guardians of the children and patients included. Inclusion criteria were accepted as being 6 and 12 years of age, the absence of anemia and high blood pressure, being on VPA monotherapy for at least 12 months, VPA blood level in the therapeutic range (50–100 mg/dL), being seizure-free for at least 3 months, and having a normal electroencephalogram recorded in this period. We tried to divide the VPA group into 2 subgroups according to VPA blood level as group Ia (50-75mg/dL) and group Ib (75-100mg/dL). Due to group Ia consisted of only 4 children, we could not make any comparison between the subgroups.

Inclusion criteria for the control group were having no headache episodes for at least 10 days. Carotid Doppler examination was performed using a Toshiba Aplio device (Tokyo, Japan). The examination was initiated using a 12-MHz linear probe for the bilateral morphological examination of the common carotid artery (CCA), internal CA (ICA), and external CA (ECA), which was followed by the evaluation of at least 3 waves obtained automatically or manually from the Doppler, and spectral examinations from the first two centimeters of the ICA. The maximum velocity (VM), end-diastolic velocity (EDV), resistive index (RI), and pulsatility index (PI) in addition to the flow calculated on the vascular lumen section were recorded. Transcranial Doppler examination was performed using the same device with a 2-MHz probe from the temporal window. The circle of Willis was identified using color Doppler, and spectral measurements were performed on the anterior cerebral artery (ACA) and middle cerebral artery (MCA). Maximum velocity, EDV, RI, and PI, in addition to flow rate (FR) calculated on the vascular lumen from the spectral graphics were recorded. The spectral measurements performed on the anterior and middle cerebral arteries were repeated three times and their average was taken. Although the posterior circulation has additionally an effect on neurocognitive functions, unfortunately we did not perform the measurements of posterior circulation.

Statistical analyses

Data analyses were performed by using IBM SPSS for Windows, 22.0 (Armonk, NY, USA). Whether the distribution of the continuous variables was normal or not was determined using the Kolmogorov Smirnov test. The Levene test was used for evaluation of the homogeneity of the variances. Unless specified otherwise, the continuous data were presented as the mean ± SD for normally distributed data, and median (range) for skewed distributions. Statistical analysis differences in the normally distributed variables between two independent

groups were compared using the student t test, while the Mann-Whitney U test was applied for comparisons of the non-normally distributed data. A P value <0.05 was considered statistically significant.

RESULTS

Enrolled in this study were 33 children (18 females, 15 males) with a mean age of 9.33 ± 2.11 years who met the inclusion criteria. The control group consisted of 34 children (17 females, 17 males) with a mean age of 9.74 ± 2 years. The patients had only generalized tonic/clonic and/or generalized tonic seizures. Follow-up duration with the diagnosis of epilepsy was 17.7±3.2 months. The period of VPA monotherapy was 17.4±3.4 months. No statistically significant differences were found between control and VPA group for the VM, EDV, RI, and PI values obtained from the bilateral internal carotid arteries (P > 0.05). In the ACA and MCA of right hemisphere, the VM and EDV values of the control group were higher than those in the VPA group. The decrease in velocity of VPA group was insignificant (P > 0.05). On the contrary, the PI and RI values of the ACA and MCA in the control group were lower than those in the VPA group. The differences were non-significant (P > 0.05). The VM and EDV values of the left ACA in the VPA group and left MCA in the control group were higher than in the control and VPA groups, respectively. No statistically significant differences were observed in the velocity changes of ACA and MCA of left hemisphere (P > 0.05). The differences in the PI and RI values of both the ACA and MCA of left hemisphere were non-significant when the VPA group was compared with the control group (P > 0.05). The differences in FR values of bilateral ACA and MCA were non-significant between VPA and control group (P > 0.05) (Table 1). The majority of children in VPA group had VPA blood level between 75-100mg/dL. Therefore we could not make any statistically analysis to reveal the effect of VPA blood level on cerebral blood flow.

DISCUSSION

Epileptic patients have an increased risk for impaired cognitive function. Structural lesions causing epilepsy, genetic predisposition, seizures (early onset, frequency, epileptic encephalopathies), psychosocial factors, and especially the adverse effects of antiepileptic drugs, are the factors increasing this risk [1,2]. The negative effects of antiepileptic drugs on cognitive function have been widely researched and numerous studies have been performed on this subject concerning older antiepileptic drugs [3-5,11]. PB has a well-known negative effect on cognitive function in childhood. In a randomized placebo-controlled study conducted on children with febrile seizures, PB was shown to cause memory and concentration problems [12]. Another study investigated children who were given PB or VPA following febrile seizures and revealed behavioral problems and lower neuropsychometric evaluation scores in children who were given PB [3]. CBZ, VPA, and PHT have similar effects on cognitive function.

Table 1. Velocity (cm/s) and index data in valproic acid and control group

		ACA			MCA		
		VPA group (n:33) (mean±SD)	Control group (n:34) (mean±SD)	P-value	VPA group (n:33) (mean±SD)	Control group (n:34) (mean±SD)	P-value
Right	VM	83.12±33.11	85.21±24.76	> 0.05	130.14±22.83	139.13±24.95	> 0.05
	EDV	38.08±13.64	39.56±11.32	> 0.05	56.95±11.03	60.91±11.80	> 0.05
	PI	0.78±0.11	0.76±0.12	> 0.05	0.87±0.12	0.84±0.12	> 0.05
	RI	0.53±0.04	0.52±0.05	> 0.05	0.56±0.04	0.55±0.05	> 0.05
Left	VM	89.46±40.16	87.12±26.24	> 0.05	141.04±33.91	154.30±30.60	> 0.05
	EDV	43.07±19.68	41.26±10.47	> 0.05	61.21±15.67	68.84±14.21	> 0.05
	PI	0.75±0.10	0.79±0.30	> 0.05	0.86±0.10	0.83±0.13	> 0.05
	RI	0.51±0.04	0.50±0.04	> 0.05	0.56±0.03	0.55±0.05	> 0.05

ACA: Anterior cerebral artery, MCA: Middle cerebral artery, VM: Maximum velocity, EDV: End-diastolic velocity, PI: Pulsatility index, RI: Resistive index.

These antiepileptic drugs have fewer effects on cognitive function when compared to PB, and especially VPA has a minimal effect. A study comparing CBZ and VPA in 63 school children with new diagnosis of epilepsy found no significant differences between the control, which consisted of 47 age-matched children, and the drug groups with regards to cognitive function at 12 months of treatment [13]. In another study where VPA, CBZ, and PHT were compared, children receiving VPA and PHT were found to have better memory scores at 6 and 12 months of treatment [14]. In a similar another study, which evaluated the neurocognitive measurements of 73 children who were given PB, CBZ, or VPA monotherapy, there were no significant differences between the CBZ and VPA groups in the pretreatment period or at 6 and 12 months after antiepileptic drug (AED) treatment [15]. A study that investigated coordination, memory, concentration, and mental performance in children with epilepsy in the pretreatment and treatment period (at 6 and 12 months of treatment) periods, reported a minimal effect in the CBZ and VPA group [16]. As a result of these studies, it can be said that the negative effect of VPA on cognitive function is minimal in children and independent of serum VPA levels. Although neuropsychometric evaluation was not conducted in our study, the parents and teachers did not report a discernible deterioration in cognitive function.

The negative effect of antiepileptics on cognitive function is correlated with their effects on the cerebral glucose metabolism rate and cerebral blood flow. PB has the most pronounced slowing effect on the cerebral glucose metabolism rate among antiepileptic drugs and has a detrimental effect on attention, concentration, and memory [3-6]. On the other hand, the neurocognitive effects of VPA, CBZ, and PHT are barely noticeable, since these drugs exert a negligible effect on cerebral metabolism when compared to PB [7-10]. Although the cognitive adverse effects of antiepileptics have been correlated with cerebral blood flow and metabolic rate, the number of studies investigating the relationship between antiepileptic usage, cerebral metabolism rate, and blood flow in children is limited. Futagi et al. investigated the effect of VPA, CBZ, and PB on cerebral blood flow in 45 pediatric patients by calculating the flow in the ICA. Average maximal blood flow velocity and maximal EDV in the ICA were measured in 30 (10 VPA, 10 CBZ, and 10 PB) of the patients. Similar measurements were performed on 15 patients during and following the termination of PB treatment. While CBZ caused a statistically significant slowing, VPA caused a non-significant drop in the maximal blood flow velocity. Similarly, PB caused slowing, but it was not statistically significant. In the PB group, which consisted of 15 children, a significant increase in the maximal EDV was recorded following the termination of PB treatment [10]. Gaillard et al.[9] examined the effects of VPA on 10 healthy adult volunteers. A statistically significant global decrease in cerebral glucose metabolism and cerebral blood flow was detected, especially in the cerebellum, thalamus, and superotemporal and superofrontal regions, as a result of VPA treatment. Additionally, the positive correlation between the cerebral blood flow and decrease in glucose metabolism rates was underlined. When evaluated together with previous studies, the effect of VPA on velocities was similar to those of CBZ and PTH, but minimal if compared to PB. Another study investigated the effects of VPA and CBZ mono and dual therapy on cerebral glucose metabolism in epileptic patients and found that combined therapy lowered the metabolic rate more than monotherapy in a synergistic manner [8]. The longer duration of therapy seemed to be another important factor for this effect, in addition to polytherapy [5-9].

Different theories have been proposed concerning the relationship between the cerebral blood flow, cerebral glucose metabolism rate, and neurocognitive effect. Polytherapy has a more profound effect on the metabolic rate when compared to monotherapy, and thus, has more neurocognitive adverse effects [5-9]. Additionally, neurocognitive adverse effects are more common with antiepileptic drugs, which act via gamma-aminobutyric acid (GABA) receptors (PB, benzodiazepines, etc.). PHT and CBZ exert their antiepileptic effects through sodium channel inhibition. This mechanism of action causes a lower effect on the cerebral glucose metabolic rate when compared to PB. As expected, PHT causes mild/moderate cognitive effects, while CBZ causes milder effects. Although VPA increases cerebral GABA levels, its main antiepileptic activity is through voltage-dependent Na channels. As such, it has a minimal effect on the cerebral glucose metabolic rate and cognitive function [9,17]. On the other hand, the effects of vigabatrin, which acts through GABA transaminase and significantly increases cerebral

GABA levels, on cerebral glucose metabolism rate is similar to those of VPA, CBZ, and PHT. Thus, it can be said that antiepileptics, which act through GABA receptors (PB, benzodiazepines) rather than increasing endogenous GABA levels, have more profound effects on the cerebral glucose metabolic rate [18].

There are two important limitations of this study. The lack of neurocognitive evaluation of the patients and posterior circulation measurements were limitations.

In conclusion, we did not observe any significant effects of VPA on the anterior cerebral blood flow of children with the diagnosis of IGE. Due to the limitations, it may be difficult to conclude that chronic VPA treatment does not increase the risk of neurocognitive impairment. The studies including posterior circulation and/or neurocognitive evaluation are needed to give information about the relationship between antiepileptic drug and neurocognition.

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