Epilepsy & Behavior 78 (2018) 68–72

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Influence of valproate on language functions in children with epilepsy

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ARTICLE INFO

Article history:
Received 20 August 2017
Revised 21 October 2017
Accepted 26 October 2017
Available online xxxx

Keywords:
Epilepsy
Valproate
Language function test

ABSTRACT

The aim of the current study was to assess the influences of valproate (VPA) on the language functions in newly diagnosed pediatric patients with epilepsy. We reviewed medical records of 53 newly diagnosed patients with epilepsy, who were being treated with VPA monotherapy (n = 53; 22 male patients and 31 female patients). The subjects underwent standardized language tests, at least twice, before and after the initiation of VPA. The standardized language tests used were *The Test of Language Problem Solving Abilities*, a Korean version of *The Expressive/Receptive Language Function Test*, and the *Urimal Test of Articulation and Phonology*. Since all the patients analyzed spoke Korean as their first language, we used Korean language tests to reduce the bias within the data. All the language parameters of the *Test of Language Problem Solving Abilities* slightly improved after the initiation of VPA in the 53 pediatric patients with epilepsy (mean age: 11.6 ± 3.2 years), but only "prediction" was statistically significant (determining cause, 14.9 ± 5.1 to 15.5 ± 4.3; making inference, 16.1 ± 5.8 to 16.9 ± 5.6; prediction, 11.1 ± 4.9 to 11.9 ± 4.2; total score of TOPS, 42.0 ± 14.4 to 44.2 ± 12.5). The patients treated with VPA also exhibited a small extension in mean length of utterance in words (MLU-w) when responding, but this was not statistically significant (determining cause, 5.4 ± 2.0 to 5.7 ± 1.6; making inference, 5.8 ± 2.2 to 6.0 ± 1.8; prediction, 5.9 ± 2.5 to 5.9 ± 2.1; total, 5.7 ± 2.1 to 5.9 ± 1.7). The administration of VPA led to a slight, but not statistically significant, improvement in the receptive language function (range: 144.7 ± 41.1 to 148.2 ± 39.7). Finally, there were no statistically significant changes in the percentage of articulation performance after taking VPA. Therefore, our data suggested that VPA did not have negative impact on the language function, but rather slightly improved problem-solving abilities.

1. Introduction

Patients with epilepsy, which is a well-known disorder, may have cognitive impairments, including deficits in the language functions. Language impairment in patients with epilepsy are associated with the type of epilepsy, age of onset, duration of epilepsy, frequency of seizures, and antiepileptic drugs (AEDs) [1–3].

Although AEDs are the treatment of choice for epilepsy, some of them are well known to aggravate language function [4–8]. The adverse effects of AEDs on cognitive function depend on the number of drugs, type, dosage, and duration [9–12]. Severe linguistic adverse effects are one of the reasons AEDs are frequently discontinued [13,14]. Therefore, when prescribing AED treatment, physicians should carefully observe the patient's cognitive ability and language development, especially in the pediatric age group.

New AEDs, with fewer adverse drug reactions such as neuropsychological, gastrointestinal, dermatological, hematological, and other effects were developed in the last few decades [15]. However, given their effectiveness and cost-benefit, classic AEDs are still used for epilepsy.

Valproate (VPA) is one of the classic AEDs, which is widely used to treat generalized and focal epilepsy. It increases the level of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), in the brain, and enhances the action of GABA at the postsynaptic receptor [16,17]. Several authors reported that VPA is associated with various adverse effects, such as nausea, headache, prolonged bleeding time, thrombocytopenia, tremor, alopecia, asthenia, infection, somnolence, and hepatic toxicity [18–21]. However, VPA is known to have little adverse effect on cognitive function, including language function, when compared with other classical AEDs, such as phenobarbital (PB), phenytoin, and carbamazepine. Donati et al. [22] reported that VPA, carbamazepine, and oxcarbazepine monotherapy, prescribed to newly diagnosed children and adolescents with focal seizures, had no impact on their cognitive function. Further, Sun et al. [23] reported that VPA and topiramate monotherapy had little impact on cognitive function. However, Masur et al. [24] reported that VPA worsened attention compared with ethosuximide and lamotrigine in children with newly

Abbreviations: AEDs, antiepileptic drugs; MLU-w, mean length of utterance in words; PB, phenobarbital; REVT, Receptive & Expressive vocabulary test; SD, standard deviation; TOPS, Test of Language Problem Solving Abilities; U-TAP, Urimal test of articulation and phonology, Urimal means Korean language; VPA, valproate.

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https://doi.org/10.1016/j.yebeh.2017.10.039
1525-5050/

diagnosed childhood absence epilepsy. Therefore, despite the majority of studies showing that VPA does not adversely affect cognitive function, the impact on cognitive function is still controversial.

We evaluated the language problem-solving abilities, and receptive and expressive vocabulary in newly diagnosed pediatric patients undergoing VPA monotherapy for the reaffirmation of the safety profile, in relation to language development.

2. Material and methods

2.1. Patients

A total of 71 newly diagnosed pediatric patients with epilepsy in the Department of Pediatrics of Chonbuk National University Hospital were recruited for the current study. All patients started treatment with VPA alone, which they maintained, until at least the second set of language tests was performed. We performed standardized tests on these patients, which covered all important aspects of speech and language processing. Initial language data were collected right before the VPA treatment was initiated. VPA monotherapy was then maintained for at least 1 month until the second set of tests was performed. The follow-up data, which were collected, were then compared and evaluated against the initial data.

Of the 71 patients who were recruited for this study, 18 patients had to be excluded for the following reasons: a test interval of over 12 months (7 patients), lack of data (9 patients), and overly abnormal result between initial and follow-up tests (2 patients). Thus, a total of 53 patients were included in the current study. A comparative analysis was also conducted with a control group of 50 school-aged children residing in the same province, with no medical or treatment history, which could have affected their language function.

2.2. Methods

The current study is a retrospective chart review of prospectively collected data, including the type of epilepsy, demographic findings, and the result of the language function test.

The VPA therapy was initiated at a dose of 10 mg/kg/day (maximum dose: 250 mg/day), which was then slowly titrated up to 30 mg/kg/day, as required, over 1–2 weeks (maximum daily dose: 1000 mg/day). The language function of the experimental cohort was assessed using three kinds of Korean language tests, at time points before initiating VPA treatment, and after the titration of the medication. The interval of first to second test was within 2–12 months (average period: 3.9 months). There was no recurring epileptic seizure between tests. However, after the second language test, only 1 patient had recurring epileptic seizure, which led to change from VPA to other AEDs.

2.3. Language tests

2.3.1. Test of Language Problem Solving Abilities (TOPS) and the mean length of the utterance of words (MLU-w)

The TOPS is a test that measures metalinguistic skills of transforming logical thinking to language during the ages within 5–12 years. The patients answered each question presented in the illustrations below (Fig. 1, Table 1). The illustrations, which were used in the current study, were developed by the Seoul Community Rehabilitation Center, Republic of Korea [25]. The test contained 17 illustrations, which were divided into three groups, i.e., determining cause, and making inference, and prediction. The “determining cause” category consisted of 18 questions, including “Why” questions. The “making inference” category consisted of 20 questions related to “How” questions. The “prediction” category consisted of 12 questions, like “How do you know?” and “What happens?” (Table 1). The answers of pediatric patients were recorded and documented during the time of testing. Scores ranging from 0 to 2 were assigned, depending on the response to each category. Scores were defined as raw scores, mean scores, and total scores for each category.

Fig. 1. Test of language problem solving.

The length of articulation for each answer of the TOPS was measured using the MLU-w, which defined a mean score of the length of articulation obtained by adding all the words in the answer and then dividing them by the number of sentences included in the answer (Table 1).

2.3.2. Receptive & Expressive vocabulary test (REVT)

The REVT measures receptive and expressive vocabulary development, from the age of 2 years to adulthood. The REVT was developed by the Korean Journal of Communication Disorders. During the receptive skill test, participants were asked to select one of four pictures corresponding to the target vocabulary; during the expressive skill test, participants had to express vocabulary to the presented pictures (Fig. 2A, B).

2.3.3. Urimal test of articulation and phonology, Urimal means Korean language (U-TAP)

The U-TAP is a standardized tool that is used to evaluate the patient's articulation ability, in correlation to their age. The test identifies the weak points of phonation. The test can test children aged 2–12 years. The tester presents a certain picture to the children and leads them to make a sentence, which includes a targeted phoneme. The target phonemes include 19 consonants and 10 vowels. The accuracy is calculated by dividing the number of incorrect phonemes by the total number of phonemes, and is expressed as the correct percentage.

2.4. Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 21.0 for windows. An independent *t*-test was used to compare the differences between the subject and control groups. Paired *t*-tests were used to compare the differences before and after VPA monotherapy. All values were expressed as mean ± standard deviation (SD). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient characteristics

The mean age of the patient cohort was 11.6 ± 3.2 years (male:female patients = 22:31). During this study, the patients did not change the type of drug they were taking, nor did they add other AEDs. They also completed all follow-up language tests during the study period. In the study cohort, 46 patients had generalized seizures, including 13 patients with epilepsy with generalized tonic–clonic seizure alone, 12 patients with childhood absence seizure, 14 patients with juvenile absence seizure, and seven patients with juvenile myoclonic

Table 1
Examples of the Language Problem Solving test and the mean length of utterance in words in the subject group.

	Question	Pre-VPA	On-VPA
Determining cause	친구가 왜 놀랄까요 (Why was she surprised?)	금붕어 때문에 (Because of fish)	애기/가/어항/을/들고/있어요[a] (The child is holding a fishbowl)
Making inference	아이가 어항을 떨어뜨린다면 어떻게 될까요 (What would happen if she drops the fishbowl?)	다쳐요 (Fish may get hurt)	유리가 깨져서 물고기가 나와요 (The glass may break and the fish will come out)
Prediction	아이가 어항을 갖지 못하게 하려면 어떻게 했어야 하나요? (What should you do to keep her from reaching a fishbowl)	높은 곳에다가 올려놔요 (Keep the fish bowl high)	높은 곳에다 올려놨어야 했어요 (We should have kept the fish bowl high)

[a] Example of length of utterance in words; six words are included in this sentence.

epilepsy. The study cohort also included six patients with focal-impaired awareness seizure and one patient with focal to bilateral tonic–clonic seizure. The etiology of focal epilepsy is unknown. During VPA monotherapy, none of the patients experienced recurring epileptic seizure. The medication was changed for one patient who experienced recurrence of epileptic seizure after the second language test. There were no significant adverse effects that might lead to discontinuation during treatment. The mean dose of VPA when patients were tested is 20 mg/kg/day. Thirty-four patients took the maximum dose of 1000 mg/day. The mean dose of VPA taken by nonmaximum dose patients was 19.6 mg/kg/day. The mean age and the maximum dose of VPA according to seizure type are described in Table 2.

The mean age of the control group was 11.0 ± 3.8 years, which was 7 months lesser than that of the patient group. Although the patient group showed slightly higher scores on the TOPS and REVT, in comparison to the control group, these differences were not statistically significant. Further, the total MLU-w score was slightly higher for the control group than the patient group; however, this too was not statistically significant.

3.2. The TOPS

The highest score in the "determining cause" category was 36. The mean score before the VPA treatment was 14.9 ± 5.1, while it was 15.5 ± 4.3 after the VPA treatment. This difference was not statistically significant (Table 3; $P > 0.05$). The mean score decreased in 22 of 53 patients (41.5%) after the VPA treatment, while 5 (9.4%) and 26 (49.1%) patients had the same score and an increased mean score, respectively.

The highest score in the "making inference" category was 40. The mean scores before and after the VPA treatment were 16.1 ± 5.8 and 16.9 ± 5.6, respectively; the difference was not statistically significant (Table 3; $P > 0.05$). After the VPA treatment, 16 of 53 patients (30.2%) had a decreased mean score. In comparison, five patients (9.4%) had the same score, and 32 patients (60.4%) had an increased mean score.

The highest score in the "prediction" category was 24. The mean score before the VPA treatment was 11.1 ± 4.9, while it was 11.9 ± 4.2 after the VPA treatment; the difference was only statistically significant in subclassification of TOPs (Table 3; $P < 0.05$). After the VPA treatment, 28 of 53 patients (52.8%) had increased mean scores, while 9 patients (17.0%) had the same scores as before, and 16 patients (30.2%) had decreased mean scores.

The mean total score of TOPs, which has a maximum score of 100, before the VPA treatment was 42.0 ± 14.4. This increased to 44.2 ± 12.5 after the VPA treatment. The difference was statistically significant (Table 3; $P < 0.05$). After the VPA treatment, 32 of 53 patients (60.4%) exhibited an increased mean score. In comparison, 19 patients (35.8%) had decreased mean score, while the score remained unchanged in 2 (3.8%) patients.

3.3. The MLU-w in TOPS

The total MLU-w during the test increased from 5.7 ± 2.1 to 5.9 ± 1.7 after the VPA treatment, but this difference was not statistically significant ($P > 0.05$). The difference in mean from the MLU-w for the "determining cause" category of questions, before and after VPA treatment, was not statistically significant, despite the increase from 5.4 ± 2.0 to 5.7 ± 1.6 ($P > 0.05$). The MLU-w for the "making inference" category of questions before and after VPA treatment was 5.8 ± 2.2 and 6.0 ± 1.8, respectively. However, this difference was not statistically significant ($P > 0.05$). The MLU-w for the "prediction" category of questions did not change (from 5.9 ± 2.5 to 5.9 ± 2.1) after the VPA treatment. Again, however, this difference was not statistically significant ($P > 0.05$).

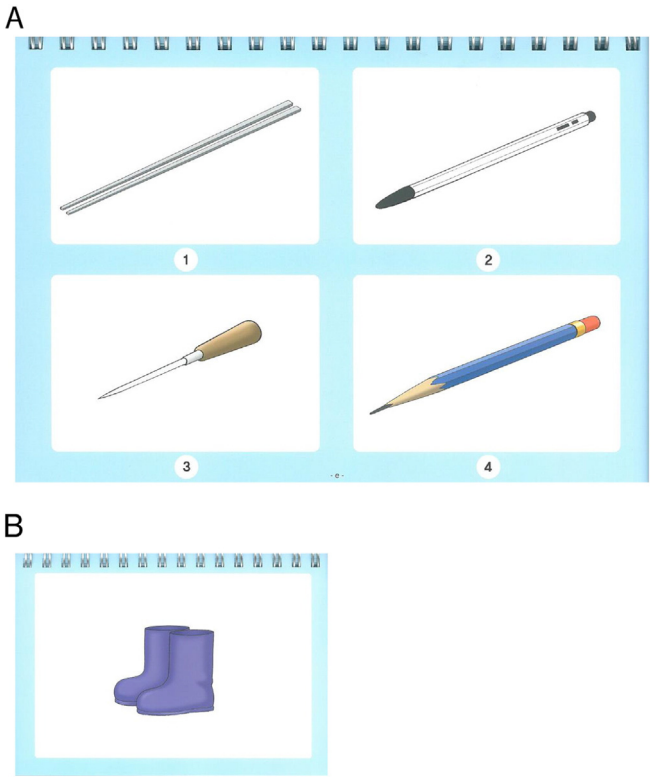

Fig. 2. A) Receptive vocabulary test. B) Expressive vocabulary test.

Table 2
Mean age and maximum dose of valproate (VPA) according to epilepsy clinical variables.

Seizure type	Subtype	Number	Mean age (years)	Maximum dose of VPA (mg/kg/day)
Generalized epilepsy	Juvenile absence epilepsy	14	12.8	19.3
	Childhood absence epilepsy	12	7.8	23.9
	Generalized tonic–clonic seizure alone	13	13.1	18.0
	Juvenile myoclonic epilepsy	7	13.5	21.0
Focal epilepsy	Focal impaired awareness seizure	6	10.8	17.1
	Focal to bilateral tonic–clonic seizure	1	14.3	18.9

Table 3
Changes in the Test of Language Problem Solving Abilities scores after valproate (VPA) treatment.

Category	Pre-VPA	On-VPA	Control
Determining cause	14.9	15.5	14.5
Making inference	16.1	16.9	14.9
Prediction	11.1	11.9*	11.3
Total score	42.0	44.2*	40.8

* $P < 0.05$, statistically significant difference between groups.

3.4. The REVT

In the Receptive Vocabulary Test, the age equivalency before the VPA treatment was 144.7 ± 41.1 months, which increased to 148.2 ± 39.7 months; this increase was statistically significant ($P < 0.05$). However, the age equivalency was only increased by 3.5 months, whereas, the mean test interval was 3.9 months. So, the receptive language function was not increased up to normal development after initiation of VPA. Among the 53 patients who were observed, 11 patients did not perform expressive vocabulary test because they were tested before the development of expressive vocabulary. They were instead evaluated using the Peabody picture vocabulary test, which is the previous version of REVT. A total of 34 (81%) patients exhibited improvement in expressive skill. The mean age before the VPA treatment was 10.7 ± 2.9 years, which increased to 11.5 ± 2.9 years after the treatment; this increase was statically significant ($P < 0.05$).

3.5. The U-TAP

The accuracy of the articulation before VPA treatment was 99.65%, which increased to 99.78% after VPA treatment. The accuracy of the articulation in the control group was 99.86%. The average U-TAP scores before and after treatment were nearly the same, and thus, could not be statistically analyzed.

4. Discussion

Cognitive dysfunction frequently occurs in patients with epilepsy, with an incidence that varies from 30% to 65% [2,26,27] especially in focal epilepsy and benign rolandic epilepsy.

There are some known factors that may influence cognitive function, such as underlying neuropathology, structural brain abnormality, epileptic discharges, AEDs, and other numerous psychosocial issues, including public attitudes and self-esteem [28]. However, recently, as the genetic cause of idiopathic-generalized epilepsies, such as childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy is becoming known, a relationship between genetically determined epilepsy and cognitive dysfunction has been suggested [29,30].

Focusing on AEDs, PB and phenytoin showed most significant adverse effects on thinking. In several studies, PB monotherapy is considered to have more cognitive adverse effects, compared with VPA or carbamazepine [4,6]. Topiramate has also have been thought to have more cognitive adverse effects than other AEDs [10,31]. Compared with other AEDs, fewer cognitive adverse effects have been reported with VPA; further, the cognitive problems, such as slower cognitive processing and memory performance, which were reported, were minimal and not significant [27,32].

In many studies, the cognitive adverse effects of AEDs were known to be reversible, but since the school age is the most important period for learning and extension of language use, clinicians should not overlook the cognitive adverse effects of AED's during this period. Caplan et al. [33] reported that as patients with epilepsy became older, they had more language impairment and wider linguistic deficits. Basic syntactic and semantic skills are developed by the age of 5 years, but the skills progressively develop and accelerate during adolescence, with an increase in syntactic complexity, advanced use of grammar and vocabulary, as well as abstraction. Further, it is also supported by the growth in thought, cognitive flexibility, and integration of knowledge [33].

Locke [34] suggested that the critical period for acquiring vocabulary and word utterance is within 2–3 years of age, when analytical computation begins to be activated. If there is a failure to acquire words and in word utterance, following an analytical mechanism, further extension of the linguistic thinking process is also inhibited [34]. Therefore, language tests should be performed not only on children with epilepsy taking AEDs, who are above the ages of 2–5 years, but also those under 2 years, so that language development can be carefully monitored. However, since young children cannot perform language tests adequately, the selection of AEDs with little linguistic adverse effect should be considered.

In the current study, VPA had no significant adverse effects on language. When testing language problem-solving abilities, subtle improvements were seen in “prediction” category. So, we concluded that VPA had no adverse effect on linguistic thinking and problem-solving abilities. In MLU-w, there were no significant differences before and after medication. The VPA did not shorten the length of sentence. In test of REVT, there were no definite improvements or aggravation of receiving, recalling, and expression of words. As a result, we concluded that since VPA has no adverse effects on language development we can safely use it to treat epilepsy in pediatric patients. We also recommend considering VPA as a first AED, to treat patients with epilepsy, who have a delay in language development and as an alternative drug for patients who have suffered an adverse effect on language due to other AEDs.

There are some limitations in the current study that need to be noted. We only analyzed the initial language test and the first follow-up within 12 months. Therefore, this study cannot comment on the long-term effect of VPA and clinical progression of patients over 12 months. Further, there are some ambiguous medical records that cannot be rechecked, given the retrospective nature of this study. Finally, the small number of patients in the sample is also one of the limitations of the current study. Thus, we hope to continue our research, and have planned an additional study, including a larger number of patients, with accurate data and evaluation of the reversibility of impaired language problem solving skills limited to an aggravation group after the continuation of VPA monotherapy.

Conflicts of interest

None.

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