Effects of Sodium Valproate, Oxcarbazepine, and Levetiracetam on Developmental Domains in Children with Epilepsy Assessed by the Chinese Version of the Griffiths Mental Development Scales (Post-print)

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Abstract

Background Epilepsy is a chronic paroxysmal brain disease with relatively high incidence that can severely impact patients' quality of life. Therefore, timely treatment to control epileptic seizures is particularly important. Numerous studies have shown that antiepileptic drugs have an impact on cognition, but research specifically on their effects on different functional domains in children is limited.

Objective To investigate the effects of valproate (VPA), oxcarbazepine (OXC), and levetiracetam (LEV) on the development of different functional domains in children with focal epilepsy using the Chinese version of the Griffiths Mental Development Scales (GDS-C).

Methods A total of 83 children with focal epileptic seizures who presented to the pediatric neurology outpatient clinic and ward of the Third Affiliated Hospital of Zhengzhou University for the first time between January 2021 and April 2022 were selected as the experimental group and divided into VPA group (n=27), OXC group (n=28), and LEV group (n=28) using the random number table method. Thirty healthy children who underwent physical examination during the same period served as the control group. Clinical efficacy was evaluated based on seizure frequency, changes in interictal epileptiform discharges (IEA) on EEG before treatment and after 6 months of treatment were recorded, and the developmental quotient of different functional domains in the participating children was assessed using the Chinese version of the Griffiths Mental Development Scales (GDS-C).

Results The total effective rates of clinical efficacy in the VPA, OXC, and LEV groups were 92.3%, 89.3%, and 92.9%, respectively, with no statistically significant difference among the three groups (2=0.418, P=1.000). The total effective rates of interictal epileptiform discharges on EEG in the VPA, OXC, and LEV groups were 88.5%, 57.1%, and 89.3%, respectively, with a statistically significant difference among the three groups (2=11.152, P=0.004); the total effective rate in the OXC group was lower than that in the VPA and LEV groups (P<0.05). Before treatment, there were statistically significant differences in the developmental quotients across all dimensions among the four groups of children (P<0.05); the developmental quotients across all dimensions in the three epilepsy groups were lower than those in the control group (P<0.05). After treatment, there were statistically significant differences in the developmental quotients of motor, personal-social, hand-eye coordination, and performance dimensions among the VPA, OXC, and LEV groups (P<0.05); the developmental quotients of motor and personal-social dimensions in the LEV group were higher than those in the VPA group (P<0.05); the developmental quotients of personal-social, hand-eye coordination, and performance dimensions in the LEV group were higher than those in the OXC group (P<0.05); there were no statistically significant differences in the developmental quotients of language and practical reasoning dimensions among the three groups (P>0.05). Compared with baseline, the developmental quotients of personal-social and practical reasoning dimensions in the VPA group decreased (P<0.05); the developmental quotients of personal-social, language, hand-eye coordination, performance, and practical reasoning dimensions in the LEV group increased (P<0.05).

Conclusion VPA, OXC, and LEV all have good therapeutic effects on focal epilepsy in children, with comparable efficacy among the three; regarding the improvement of interictal epileptiform discharges on EEG, OXC is inferior to VPA and LEV; VPA may have adverse effects on the personal-social and practical reasoning dimensions in children, OXC has minimal impact, and LEV may have certain improving effects on the personal-social, language, hand-eye coordination, performance, and practical reasoning dimensions in children.

Full Text

Abstract

Background
Epilepsy is a chronic episodic brain disorder with high incidence that can seriously affect patients' quality of life. Timely treatment to control seizures is therefore particularly important. Numerous studies have demonstrated that antiepileptic drugs affect cognition, but few have investigated their specific impact on different functional domains in pediatric patients.

Objective
To explore the effects of sodium valproate (VPA), oxcarbazepine (OXC), and levetiracetam (LEV) on the development of different functional domains in chil-

dren with focal epilepsy using the Griffiths Development Scales-Chinese Edition (GDS-C).

Methods
Eighty-three children with focal epilepsy who presented for the first time to the pediatric neurology outpatient clinic and ward of the Third Affiliated Hospital of Zhengzhou University between January 2021 and April 2022 were selected as the trial group. They were randomly divided into VPA (n=27), OXC (n=28), and LEV (n=28) groups using a random number table method. Thirty healthy children undergoing physical examination during the same period served as the control group. Clinical efficacy was evaluated based on seizure frequency, and changes in electroencephalographic interictal epileptiform activity (IEA) were recorded before treatment and after 6 months of treatment. The GDS-C was used to assess developmental quotients across different functional domains in the children.

Results
The total clinical effective rates were 92.3% for the VPA group, 89.3% for the OXC group, and 92.9% for the LEV group, with no statistically significant difference among the three groups (^{2}=0.418, P=1.000). The total EEG IEA effective rates were 88.5% for the VPA group, 57.1% for the OXC group, and 89.3% for the LEV group, showing a statistically significant difference (^{2}=11.152, P=0.004). The OXC group's EEG IEA effective rate was lower than that of both the VPA and LEV groups (P<0.05). Before treatment, significant differences existed among the four groups in developmental quotients across all dimensions (P<0.05), with all three epilepsy groups scoring lower than the control group (P<0.05). After treatment, significant differences were observed among the three drug groups in motor, personal-social, hand-eye coordination, and performance dimensions (P<0.05). The LEV group showed higher developmental quotients than the VPA group in motor and personal-social dimensions (P<0.05), and higher than the OXC group in personal-social, hand-eye coordination, and performance dimensions (P<0.05). No significant differences were found among the three groups in language or practical reasoning dimensions (P>0.05). Compared with baseline, the VPA group showed decreased developmental quotients in personal-social and practical reasoning dimensions (P<0.05), while the LEV group demonstrated increased developmental quotients in personal-social, language, hand-eye coordination, performance, and practical reasoning dimensions (P<0.05).

Conclusion
VPA, OXC, and LEV all demonstrate good therapeutic efficacy for focal epilepsy in children, with equivalent effectiveness among the three agents. Regarding improvement in EEG IEA, OXC is inferior to VPA and LEV. VPA may adversely affect personal-social and practical reasoning dimensions, OXC has minimal impact, while LEV may have beneficial effects on personal-social, language, hand-eye coordination, performance, and practical reasoning dimensions.

Keywords

Epilepsy; Focal epilepsy; Sodium valproate; Oxcarbazepine; Levetiracetam; Griffiths Development Scales-Chinese Edition; Functional domains

Introduction

Epilepsy is one of the most common and important seizure disorders in pediatric neurology, characterized as a chronic brain disease with a persistent tendency toward epileptogenesis. Epidemiological data indicate that there are currently over 70 million epilepsy patients worldwide, with nearly 10 million in China, and approximately 600,000 new cases annually [1-2]. Sixty percent of these patients develop epilepsy during childhood. Antiepileptic drugs (AEDs) represent the most important and fundamental treatment for epilepsy and are the first-line therapeutic option. However, numerous clinical studies have shown that AEDs can cause damage to the psychological, nervous, gastrointestinal, and hematological systems in children with newly diagnosed epilepsy. Most current research focuses on evaluating overall cognitive function levels in children with epilepsy, with few studies examining the impact on specific functional domains. This study aims to use the Griffiths Development Scales-Chinese Edition (GDS-C) to assess changes in developmental quotients across different functional domains in children with epilepsy before and after treatment with sodium valproate (VPA), oxcarbazepine (OXC), and levetiracetam (LEV), and to analyze the differential effects of these AEDs on various functional domains to provide evidence for clinical drug selection in pediatric epilepsy.

Methods

Study Participants

We selected 83 children with focal epilepsy who presented for the first time to the pediatric neurology outpatient clinic and ward of the Third Affiliated Hospital of Zhengzhou University between January 2021 and April 2022 as the trial group. Using a random number table method, participants were divided into VPA (n=27), OXC (n=28), and LEV (n=28) groups. Thirty healthy children undergoing physical examination at our hospital during the same period served as the control group. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University (approval number: 2022-088-01), and informed consent was obtained from all participants' guardians and from the participants themselves when appropriate.

Inclusion criteria for the trial group: (1) Met the International League Against Epilepsy 2017 classification criteria for epileptic seizures [3] and were diagnosed through clinical and electroencephalographic examination; (2) Aged 2-6 years; (3) No prior treatment with other AEDs; (4) Received monotherapy during the study period.

Exclusion criteria: (1) Non-epileptic seizures such as pseudoseizures; (2) Intracranial space-occupying lesions or vascular malformations indicated by cranial CT or MRI; (3) Severe dysfunction of heart, lung, liver, kidney, or other vital organs; (4) Inability to take medication as scheduled; (5) Severe psychological disorders.

Assessment Procedures

The GDS-C was used to evaluate developmental quotients across different functional domains in children with epilepsy. The GDS-C, revised from the 2006 British Isles edition [6], completed Chinese normative research revision in seven regions (Beijing, Shanghai, Hong Kong, Zhengzhou, Tianjin, Xi'an, and Kunming) between 2009-2013. It is applicable for developmental assessment of Chinese children aged 0-8 years, has relevant intellectual property rights, and demonstrates good reliability, validity, and theoretical foundation. This scale evaluates children's psychoneurodevelopment across six dimensions: motor, personal-social, language, hand-eye coordination, performance, and practical reasoning, and has been widely used in China to assess development across different functional domains [developmental quotient = (developmental age equivalent / actual age) × 100; normal development: $ $85 points, borderline: 70-84 points, developmental delay: <70 points].

All assessments were conducted by professionally trained and certified personnel in a dedicated evaluation room with appropriate conditions (quiet, clean, well-ventilated, suitable temperature and humidity). Each child was tested individually in good condition with family accompaniment. All participants were followed for more than six months, with accurate recording of general information, medication type and dosage, and GDS-C assessment data.

Evaluation Criteria

Clinical efficacy was evaluated based on monthly seizure frequency before and after treatment: (1) Controlled: complete seizure freedom; (2) Improved: 50-99% reduction in seizure frequency; (3) Ineffective: <50% reduction in seizure frequency. Total effective rate = [(controlled + improved) / total number of cases] × 100% [4].

EEG IEA assessment was used to evaluate electroencephalographic improvement: (1) Controlled: complete disappearance of IEA; (2) Improved: 25-99% reduction in IEA; (3) Ineffective: <25% reduction in IEA. Total effective rate = [(controlled + improved) / total number of cases] × 100% [5].

Statistical Analysis

Data normality was first examined. Normally distributed continuous data were expressed as ($\bar{x}\pm s$). Comparisons among multiple groups were performed using one-way ANOVA, pairwise comparisons using LSD-t test, and within-group comparisons before and after treatment using paired t-test. Categorical data were

expressed as percentages and analyzed using ^{2} test. P<0.05 was considered statistically significant.

Results

Participant Characteristics

Among the 83 children with focal epilepsy, there were 43 males and 40 females, with a mean age of (41.8$±$10.7) months. No statistically significant differences were found among the three drug groups in age, gender, disease duration, or seizure frequency (P>0.05) .

Clinical Efficacy

After treatment, the total clinical effective rates were 92.6% for the VPA group, 89.3% for the OXC group, and 92.9% for the LEV group, with no statistically significant difference among the three groups (^{2}=0.418, P=1.000) .

EEG Interictal Epileptiform Activity

After treatment, the total EEG IEA effective rates were 88.9% for the VPA group, 57.1% for the OXC group, and 89.3% for the LEV group, showing a statistically significant difference among the three groups (^{2}=11.152, P=0.004). The OXC group's EEG IEA effective rate was significantly lower than that of both the VPA and LEV groups (P<0.05) .

Developmental Quotients Across Functional Domains

Before treatment, significant differences existed among the four groups in developmental quotients across all dimensions (P<0.05). All three epilepsy groups had lower developmental quotients than the control group (P<0.05), though no significant differences were found among the three epilepsy groups themselves (P>0.05) .

After treatment, significant differences were observed among the three drug groups in motor, personal-social, hand-eye coordination, and performance dimensions (P<0.05). The LEV group demonstrated higher developmental quotients than the VPA group in motor and personal-social dimensions (P<0.05), and higher than the OXC group in personal-social, hand-eye coordination, and performance dimensions (P<0.05). No significant differences were found among the three groups in language or practical reasoning dimensions (P>0.05) .

Compared with baseline, the VPA group showed decreased developmental quotients in personal-social and practical reasoning dimensions (P<0.05). The LEV group showed increased developmental quotients in personal-social, language, hand-eye coordination, performance, and practical reasoning dimensions (P<0.05). No significant differences were found in other dimensions before and after treatment within each group (P>0.05) .

Discussion

Epilepsy is the most common neurological disease in children, characterized as a chronic brain disorder caused by abnormal, excessive, and synchronized neuronal discharges, with transient, recurrent, and episodic features. Long-term frequent, recurrent, or severe seizures can lead to brain cell hypoxia, structural brain damage, and even persistent neuropsychiatric disorders, making prompt seizure control particularly important. AEDs represent the most crucial means of controlling seizures. With appropriate drug selection and dosing, over 50% of children can achieve seizure freedom with monotherapy. However, due to different mechanisms of action, various AEDs have different adverse effects. VPA, OXC, and LEV are first-line drugs for focal epilepsy, with mechanisms of action involving increased GABA levels for VPA [7-8], blockade of voltage-dependent sodium channels for OXC [9], and binding to synaptic vesicle protein 2A (SV2A) for LEV [10-11], respectively. Therefore, these three drugs may have differential effects on development across functional domains in children with focal epilepsy.

This study used the GDS-C to compare developmental quotients across different functional domains before and after treatment. Before treatment, children with epilepsy had significantly different developmental quotients across all dimensions compared with the control group, though still within the normal reference range, indicating that recurrent seizures can affect normal development. The mechanism may involve abnormal excessive neuronal discharges during seizures causing brain neuronal dysfunction, apoptosis, and necrosis, thereby affecting children's psychobehavioral development. The language domain showed more pronounced deficits, possibly because language functional areas are widely distributed in the brain and thus more vulnerable to damage. Additionally, recurrent seizures often cause psychological problems in children, who may be reluctant to communicate with others, potentially leading to further decline in language function [12].

VPA, as a broad-spectrum AED, has incompletely understood mechanisms of action that likely involve multiple pathways to achieve seizure control. Findings regarding VPA's effects on cognitive function in children with epilepsy are inconsistent. Some studies have found no significant differences in verbal IQ (VIQ), performance IQ (PIQ), or full-scale IQ (FIQ) in children with epilepsy treated with VPA, suggesting no cognitive impairment [13]. Animal experimental studies have shown that VPA can inhibit hippocampal cell apoptosis, antagonize hippocampal neuronal damage, and improve learning and memory in rats, suggesting potential beneficial effects on cognitive dysfunction [14]. However, other reports indicate that VPA may cause some cognitive impairment in children with epilepsy [15-18]. Our results showed that after 6 months of VPA treatment, children's developmental quotients in personal-social and practical reasoning dimensions decreased compared with baseline, possibly related to VPA's effects on the balance between inhibitory and excitatory neurotransmitters in the brain.

Compared with baseline, the LEV group showed increased developmental quotients in personal-social, language, hand-eye coordination, performance, and practical reasoning dimensions. The mechanism primarily involves LEV's high-affinity binding to SV2A in the brain, increasing GABA release and reducing abnormal neuronal discharges, thereby promoting development across functional domains in children with epilepsy [19-20]. The OXC group showed no significant differences in developmental quotients across functional domains before and after treatment. After treatment, the LEV group demonstrated higher developmental quotients than the VPA group in motor and personal-social dimensions, and higher than the OXC group in personal-social, hand-eye coordination, and performance dimensions. These findings suggest that LEV may have beneficial effects on development across functional domains in children with epilepsy compared with VPA and OXC.

This study compared the efficacy of VPA, OXC, and LEV in treating focal epilepsy. All three monotherapies showed high total effective rates with no statistically significant differences, confirming that VPA, OXC, and LEV are all effective for short-term control of seizure frequency in focal epilepsy, with equivalent efficacy. VPA and LEV showed more significant suppression of IEA, consistent with previous reports [21-24]. Notably, in the OXC group, one case (3.57%) showed increased EEG epileptiform discharges after treatment, consistent with a previous adult epilepsy study [25].

In summary, the GDS-C can be used to assess development across functional domains in children with epilepsy. VPA, OXC, and LEV all demonstrate good therapeutic efficacy for focal epilepsy in children with equivalent effectiveness. Regarding EEG improvement, OXC is inferior to VPA and LEV. In terms of effects on development across functional domains, VPA may have adverse effects, OXC has minimal impact, and LEV may have beneficial effects. Therefore, in the pharmacological management of children with focal epilepsy, drug selection should be tailored to individual patient characteristics to achieve not only seizure control but also improved developmental outcomes.

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