Research Paper

Comparative Study on the Effect and Influence of Sodium Valproate and Perampanel on Nerve Damage and Cognitive Function in Epilepsy

HAIHUA CHEN AND LIAN FENG*

Department of Pediatrics, Shaoxing Central Hospital, Shaoxing, Zhejiang 312030, China

Chen *et al.*: Role of Sodium Valproate and Perampanelin in Epilepsy

This study compared the efficacy of sodium valproate and perampanel in the treatment of children with epilepsy and their effects on nerve damage and cognitive function. 68 individuals were divided into group A and group B, each with 34 individuals. On the basis of rehabilitation training, group A received sodium valproate treatment, while group B received perampanel treatment. By comparing the duration of epileptic seizures, seizure frequency, blood drug concentration, therapeutic effect, nerve damage and cognitive function, and incidence of adverse drug effects both the groups, impact of the two drugs on the children were evaluated. After medication, the duration and frequency of seizures in the two groups were lower than those before medication, but the duration and frequency of seizures in the sodium valproate group were lower ($p<0.05$). The blood concentration of group A was lower than that of group B ($p<0.05$) and there was no significant difference in treatment effect between both the groups ($p>0.05$). The medication of the two groups had an effect on the nerve injury and cognitive function of the children, and there was no significant difference in comparison ($p>0.05$). There was no significant difference in the incidence of drug adverse events between the two groups ($p>0.05$). Both sodium valproate and perampanel have a good curative effect on children with epilepsy, and the drug safety is high. Further, both the drugs effect on the nerve damage and cognitive function of children, but sodium valproate seems to be more effective and is worth recommending for medication.

Key words: Sodium valproate, perampanel, epilepsy, gamma-aminobutyric acid, glutamate

Pediatric epilepsy is a common nervous system disease, mainly manifested in a series of symptoms such as recurrent disturbance of consciousness, limb twitching, eye movement, and lip chewing. Its pathogenesis is complex, and it is widely believed that epilepsy in children may involve multiple factors such as neuronal electrophysiology and neurotransmitter regulation[1]. In terms of neuronal activity, seizures in children with epilepsy may be associated with abnormal neuronal discharges. In general, neurons maintain the mutual balance of neuronal networks through the alternating regulation of excitatory and inhibitory signals. However, neurons in children with epilepsy may have abnormalities such as hyperexcitability and inhibitory deficits, which will lead to abnormal discharge of neurons and eventually trigger epileptic seizures. Neurotransmitters are likely involved in the regulation of seizures. As a very important inhibitory neurotransmitter, Gamma-Aminobutyric Acid (γ-GABA) can inhibit the excitability of neurons[2]. Glutamate, as an excitatory neurotransmitter, can increase the excitability of neurons. When an epileptic seizure occurs, the interaction between GABA and glutamate and other neurotransmitters is out of balance, and the abnormal neuronal discharges will occur, leading to epileptic seizures. Drug therapy is one of the main treatments used for epilepsy in children. The commonly used drugs mainly include phenytoin, sodium valproate, flumazenil, perampanel, and lamotrigine. The treatment of these drugs for children with epilepsy mainly relies on increasing the inhibitory effect of GABA and reducing the excitability of glutamate, so as to prevent the abnormal discharge of nerves. The choice of drugs should be adjusted individually according to the child's age, type of epilepsy, and frequency of seizures. In this study, sodium valproate and perampanel were selected as different medications.

***Address for correspondence**
E-mail: LianFengSX@163.com

A number of studies have confirmed the efficacy and safety of sodium valproate in the treatment of epilepsy in children[3]. Sodium valproate, is a carboxylic acid antiepileptic drug, which mainly increases the GABA receptor response on the neuronal cell membrane and inhibits excessive neuronal excitation, so as to achieve the effect of inhibiting epileptic seizures[4]. Sodium valproate is mainly used in 3 types of epilepsy, namely transient loss of consciousness epilepsy, partial epilepsy and generalized tonic-clonic epilepsy. These types are very common in children with epilepsy, and long-term use of sodium valproate is required to control epileptic seizures. Perampanel, also known as carbamazepine, is an antiepileptic drug, which is mainly used to control epileptic seizures. It is a sodium ion channel modulator, which can inhibit the excitability of neurons and achieve the purpose of reducing the frequency and severity of epileptic seizures. It is important to note that regular therapeutic drug monitoring is essential for drugs like sodium valproate or perampanel. Studies have shown that both sodium valproate and perampanel have certain side effects, mainly including dizziness, drowsiness, and nausea[5]. Therefore, while studying the two drugs for the treatment of epilepsy in children, it is equally important to pay close attention to the adverse reactions of the drugs.

MATERIALS AND METHODS

General data:

The research data has been derived from 68 children suffering with epilepsy who were admitted to Shaoxing Central Hospital from January 2021 to December 2022. They were divided into group A and group B on the basis of odd and even number classification, with 34 cases in each group. There was no significant difference in the basic information between the two groups ($p>0.05$) (Table 1).

Inclusion criteria:

Children who were diagnosed with epilepsy symptoms by the hospital; children with <12 y age; children among whom the Electroencephalogram (EEG) showed abnormal discharge and family members or guardians who knew the purpose of this study and those who signed the informed consent were included in the study.

Exclusion criteria:

Children above >12 y age; children who are allergic to sodium valproate or perampanel; children whose intestinal dysfunction is not conducive to drug absorption; children with mental disorders and children with poor medication compliance were excluded from the study.

Medication method:

All the children were subjected to rehabilitation training. Rehabilitation training mainly includes acupuncture, physical therapy, and brain function training.

Children in group A were treated with sodium valproate on the basis of rehabilitation training. The initial medication method included administration of daily dose is 10 mg/kg of sodium valproate oral liquid, orally divided into 3 doses (produced by Zhejiang Yuanda Pharmaceutical Co., Ltd., Approval number 202009011 with 10 ml×20 sticks/box of specification). From the 3rd w, the daily dose is 30 mg/kg, 3 times every day. The total duration of medication is 3 mo.

Similarly children in group B were given perampanel medication on the basis of rehabilitation training, where the total duration of medication is 3 mo. Medication method included administration of perampanel oral liquid (produced by North China Pharmaceutical Group Preparation Co., Ltd., Approval number 20051001 with 0.2 g/piece of specification). The dosage varied depending on the age. So the initial dose was 1 mg/day for children under 20 kg and from the 3rd w, the daily dose is 2 mg, orally divided into 2 doses. Similarly, for children of (20-40) kg weight, the initial dose is 2 mg daily and from the 3rd w the daily dose was 4 mg, orally in two divided doses. For children >40 kg, the initial dose is 4 mg, and the daily dose was 8 mg, from the 3rd w. During the medication period, indicators such as child's liver function, blood drug concentration and renal function were tested every month to ensure the safety of the drug.

Observation indicators:

Seizure assessment: It refers to the duration and frequency of epileptic seizures, which were recorded before and after 1st and 3rd mo of the medication. Longer seizure duration indicates higher seizure frequency, indicating worsened effect of the drug.

Blood concentration: The blood drug concentration of the two groups of children was detected after the end of 1st and 3rd mo of medication. In this study, the higher the blood drug concentration, the poorer is drug metabolism and excretion ability, denoting poor drug effect.

Drug efficacy: Drug efficacy was evaluated using different grades namely, control rate, significantly effective, effective and invalid. Control rate indicated no epilepsy occurred within 3 mo after medication, and EEG showed normal. Significantly effective implied that the frequency of epileptic seizures in children has been reduced by >75 % compared with that before the medicine, and the EEG showed that the frequency of epileptiform discharges has been reduced by >50 % after 3 mo of drug administration. The drug efficacy was considered to be effective, when the frequency of seizures in children was reduced by 50 %-75 % compared with before taking the medicine, and the EEG showed that the frequency of epileptiform discharges is reduced by 25 %-50 % after 3 mo of drug administration. Finally, if none of the above mentioned symptoms or no response towards medication was observed then it was considered as invalid.

Total effective rate=control rate+marked rate+effective rate

Neurological impairment: The neurological impairment was evaluated by the Consciousness Seizure Scale (CSS), where higher score, indicated more severe neurological impairment.

CSS includes 8 dimensions which includes level of consciousness, gaze function, facial paralysis, language, upper limb muscle strength, hand muscle strength, lower limb muscle strength and walking ability. The total score is 45 points, which is divided into mild (0~15) points, moderate (16~30) points and severe (31~45) points.

Cognitive function assessment: Cognitive function was assessed by using Wechsler Children's Intelligence Scale (WISC), in which higher scores indicate better cognitive functioning ability.

Incidence of adverse drug reactions: Adverse drug reactions are divided into serious adverse drug reactions and general adverse drug reactions. Serious adverse drug reactions mainly include pancreatitis, anaphylactic shock, cardiovascular system disorder, airway obstruction, atelectasis, bronchospasm, leukopenia, thrombocytopenia, abnormal liver function, renal function impairment, visual impairment and hearing impairment, etc. General adverse reactions of drugs mainly include nausea, vomiting, diarrhea, dizziness, fatigue, anxiety, depression, insomnia, lethargy, itching and rashes, etc. The incidence of serious adverse drug reactions and general adverse drug reactions were compared between the two groups.

Statistical analysis:

The data and the information included in this study were analyzed by statistical software Statistical Package of Social Sciences (SPSS) version, 22.0. T test or Chi-square (χ^2) test was performed and $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Epileptic seizures were compared between both the groups after medication. Before the medication, two indices of epileptic seizures in the two groups were almost the same ($p>0.05$). Table 2 compared the indicators of epileptic seizures between both the groups after the end of 1st and 3rd mo of medication, in which group A showed better results than group B ($p<0.05$).

TABLE 1: COMPARISON OF BASIC INFORMATION OF PATIENTS IN THE TWO GROUPS ($\bar{x}\pm s$)

Group	n (men/women)	Age	Course of disease (y)	Type of epilepsy (number of patients)		
				Focal onset	Generalized seizures	Seizure type unknown
A	18/16	5.28±1.52	2.12±0.37	12	13	9
B	17/17	5.29±1.51	2.13±0.36	13	14	7
χ^2	0.082	0.043	0.046	0.098	0.092	0.112
p	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

TABLE 2: COMPARISON OF EPILEPTIC SEIZURES IN CHILDREN BEFORE AND AFTER MEDICATION IN THE TWO GROUPS (x̄±s)

Group	n	Duration (min/time)			Seizure frequency (times/month)		
		Before medication	After 1 mo of medication	After 3 mo of medication	Before medication	After 1 mo of medication	After 3 mo of medication
A	34	4.78±1.13	1.29±0.21	1.36±0.23	3.22±0.26	1.42±0.22	1.48±0.23
B	34	4.77±1.12	1.39±0.23	1.51±0.24	3.21±0.26	1.52±0.23	1.61±0.24
t		0.098	1.085	1.126	0.092	1.124	1.237
p		>0.05	<0.05	<0.05	>0.05	<0.05	<0.05

Blood drug concentration was compared between both the groups. The blood drug concentration in group A was significantly lower than that in group B after the end of 1st and 3rd mo of medication ($p<0.05$) (Table 3).

Drug efficacy between the groups after 3 mo of medication was observed. The total effective rates of drug treatment in groups A and B were 94.12 % and 91.18 %, respectively, and there was no significant difference between the two groups ($p>0.05$) (Table 4).

Nerve damage before and after treatment between both the groups was observed and by the end of the 1st and 3rd mo of medication, the CSS scores of children in group A were lower than those in group B, but there was no significant difference between the two groups ($p>0.05$) (Table 5).

Similarly, the cognitive function before and after medication was compared. There are three dimensions of cognitive function, operational Intelligence Quotient (IQ); language IQ and total IQ. By comparing the scores of the three dimensions before and after the medication, there was no significant difference observed between both the groups ($p>0.05$) (Table 6).

Adverse drug reactions were also compared between both the groups. Children in group A and group B had no serious adverse drug reactions, and there were 5 patients of general adverse drug reactions in group A and 6 patients in group B. There was no significant difference between the two groups ($p>0.05$) (Table 7).

It is estimated that 60 % of epilepsy patients in China develop in early childhood which determines the pathogenesis of epilepsy in children, and the incidence rate in young children is assessed to be 0.151 %[6]. The etiology of epilepsy is relatively complex, generally believed to include internal and external causes[7]. Internal causes mainly include congenital abnormalities and chromosomal diseases of the central nervous system, as well as diffused atrophy of the cerebral cortex caused by degenerative changes of brain cells generally affected by various congenital factors, like, epileptic seizures caused by lobar atrophy. Likewise, external causes include brain acquired diseases, such as traumatic brain injury, cerebrovascular disease, etc. Alcoholism and drug poisoning caused by epilepsy are also considered as toxic diseases. The pathogenesis of epilepsy in children has not been fully clarified, but the conclusion that epilepsy is caused by abnormal neuronal discharge has widely been accepted[8]. It is generally believed that the emergence of neuronal electrophysiological activity is due to the difference in the distribution of ions inside and outside the neurons and the movement across the membrane[9]. Therefore, the abnormal discharge of epileptic neurons is caused by the abnormal transmembrane movement of ions. There is also a large amount of Potassium (K^+) flowing outwards and Calcium (Ca^{2+}) flowing inwards in the paroxysmal depolarization movement in EEG, and there are abnormal movements of Sodium (Na^+) and Chlorine (Cl^-). Generally speaking, the operation of normal electrophysiological activities depends on the normal structure, function of neurons, the receptors and carriers on the surface of nerve cell membranes are expressed normally[10]. From this point of view, the occurrence of epilepsy is mainly a process involving multiple neurobiology. Studies have shown that abnormalities of astrocytes, cortical developmental disorders, abnormalities of glutamate and its receptors, abnormalities of neurotrophic factors, and changes in immunology may lead to the occurrence of epilepsy[11].

TABLE 3: COMPARISON OF BLOOD DRUG CONCENTRATION BETWEEN THE TWO GROUPS (x̄±s, μg/ml)

Group	n	After 1 mo of medication	After 3 mo of medication
A	34	8.54±1.28	2.18±0.93
B	34	14.36±2.27	6.72±1.14
t		2.136	4.728
p		<0.05	<0.05

TABLE 4: COMPARISON OF EFFECTIVE RATES OF DRUG TREATMENT BETWEEN THE TWO GROUPS (x̄±s, NUMBER OF PATIENTS)

Group	n	Control	Significantly effective	Effective	Invalid	Total effective rate
A	34	12	8	12	2	94.12 %
B	34	10	8	13	3	91.18 %
χ^2						0.785
p						>0.05

TABLE 5: COMPARISON OF CSS SCORES BEFORE AND AFTER TREATMENT IN THE TWO GROUPS (x̄±s, POINTS)

Group	n	Before medication	After 1 mo of medication	After 3 mo of medication
A	34	15.29±1.36	8.29±0.82	7.18±0.78
B	34	15.31±1.37	8.76±0.91	7.42±0.81
t		0.096	0.319	0.286
p		>0.05	>0.05	>0.05

TABLE 6: COMPARISON OF COGNITIVE FUNCTION BEFORE AND AFTER TREATMENT IN THE TWO GROUPS (x̄±s, POINTS)

Group	n	Operational IQ		Verbal IQ		Total IQ	
		Before medication	After medication	Before medication	After medication	Before medication	After medication
A	34	89.28±2.17	99.18±2.36	91.37±2.34	101.32±2.15	92.35±2.41	100.52±2.91
B	34	89.31±2.19	98.24±2.29	91.26±2.31	100.08±2.11	92.36±2.41	99.89±2.88
t		0.102	0.187	0.098	0.179	0.099	0.167
p		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

TABLE 7: COMPARISON OF ADVERSE DRUG REACTIONS (x̄±s, NUMBER OF PATIENTS)

Group	n	Serious adverse drug reaction	General adverse drug reactions	Total incidence (%)
A	34	0	5 (14.71)	14.71
B	34	0	6 (17.65)	17.65
χ^2				0.913
p				>0.05

The pharmacological mechanism of sodium valproate in the treatment of epilepsy in children was explored. Sodium valproate belongs to a carboxylic acid antiepileptic drug, and its pharmacological mechanism is mainly closely related to GABA. As a core neurotransmitter,

GABA can play a key inhibitory role in the central nervous system. GABA receptors can be classified into $GABA_A$ and $GABA_B$, among which sodium valproate mainly relies on $GABA_A$ receptors to function. Specifically, $GABA_A$ receptor acts as an ion channel receptor, and its activation facilitates the entry of Cl^- ions into neurons, thereby reducing the concentration difference between intracellular and intracellular ions, and supercharging the resting membrane potential of neurons, eventually reaching The purpose of inhibiting the degree of neuronal excitability. Sodium valproate increases the activation of $GABA_A$ receptors, so that its ability to inhibit neurons has been enhanced, thereby achieving the purpose of controlling epilepsy. In addition, sodium valproate also has a reuptake effect on GABA transmitters. The specific pharmacological mechanism is that in neurons, after the $GABA_A$ receptor is activated, GABA molecules will be quickly engaged into the presynaptic neurons, so that the concentration of the synaptic cleft increases rapidly, and the effect of GABA is enhanced. Additionally, sodium valproate can also regulate the channel of calcium ions by inhibitory effect. Calcium ion channels are one of the key sources of neuronal excitation, and the entry of calcium ions can make neurons more excited. Sodium valproate inhibits the activity of L-type calcium ion channels, allowing less Ca^{2+} ions to enter neurons, thereby inhibiting neuronal excitation. Sodium valproate can also inhibit the activity of N-type calcium channel to achieve the purpose of inhibiting neuron excitation. This mechanism is of great help in some complex epilepsy. Sodium valproate can also regulate sodium ion channels. As another key source of neuronal excitation, Na^+ ion channels can also cause the degree of neuronal excitation. Sodium valproate can quickly inhibit the activity of sodium ion channels, allowing a smaller amount of Na^+ ions to enter neurons, thereby inhibiting the excitation of neurons. This mechanism can play a very good role in myoclonic epilepsy and tonic epilepsy. In short, the core of the pharmacological mechanism of sodium valproate is the inhibition of GABA, reuptake of GABA, and the mediation of Ca^{2+} and Na^+ channels. They work together to inhibit the excitability of neurons and achieve the drug effect of controlling epileptic seizures.

Pharmacological mechanism of perampanel in the treatment of epilepsy in children was studied. As a 3rd generation antiepileptic drug, perampanel is an ionic receptor antagonist on postsynaptic neurons. It relies on non-competitive binding to Alpha (α)-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid (AMPA) receptors to inhibit excessive neurotransmission induced by glutamate. In order to achieve antiepileptic effect, this mechanism will not be replaced by glutamate due to the continuous increase in the level of glutamate, and can maintain the long-acting effect of antagonizing AMPA receptors, thereby prolonging the action time of the drug. Perampanel belongs to the benzodiazepine class of antiepileptic drugs, and its main effect is achieved through neuromodulation. It relies on regulating the activity of burst neurons to inhibit abnormal discharge of neurons and reduce epileptic seizures. Perampanel can also block Ca^{2+}, Na^+, K^+ ions and other channels. By blocking ion channels, the potential changes of neurons and neurotransmission are affected, thereby playing an anti-epileptic effect. Likewise, perampanel enables GABA receptor activation to function. In this way, the excitability of neurons can be suppressed, and the abnormal discharge of neurons can be reduced, thereby reducing the possibility of epileptic seizures. In addition, perampanel also exerts the drug effect through the mechanism of anti-oxidation. When a seizure occurs, the metabolic activity of neurons is significantly increased, which leads to an acceleration of intracellular oxidative stress. However, perampanel can reduce the damage of oxidative stress by relying on its antioxidant effect, so as to protect the function and structure of neurons, and indirectly plays an anti-epileptic effect. In summary, the pharmacological mechanism of perampanel in the treatment of epilepsy in children is relatively complex, involving glutamate receptor antagonism, neuromodulation, ion channel blockade, GABA receptor stimulation or anti-oxidation and other aspects. These multi-dimensional drug effects finally achieve the efficacy of anti-epileptic drugs.

Further, the efficacy and safety evaluation of the two drugs was studied. The core of the evaluation of epilepsy drugs in children is efficacy and safety. Studies have shown that the efficacy of monotherapy of sodium valproate in children with epilepsy is related to multiple factors such as the age, type of seizure, and frequency of seizures[12]. It is effective in the treatment of partial epilepsy in children,

but less effective in the treatment of generalized epilepsy. Moreover, lower the frequency of epileptic seizures, better is the drug effect of sodium valproate. Some scholars have pointed out that the combination of sodium valproate and lamotrigine has an obvious effect, and the reason may be that the combined drug can inhibit the abnormal discharge of neurons. Half-life of triazine has been prolonged, the blood concentration of the drug has been increased, and the efficacy of the drug has been improved[13]. Wang *et al.*[14] pointed out that high doses of sodium valproate can better control epileptic discharges and improve cognitive function in children. But Wang *et al.*[15] research results are different, which may be related to the different characteristics of the cases. The research results of Wang *et al.*[16] and others showed that different doses of sodium valproate had different adverse reactions to epileptic children of different ages, and children in younger age groups were more prone to adverse drug reactions, such as dizziness and vomiting[16]. This shows that the dose of sodium valproate should be strictly controlled for the children of young age. Sodium valproate, as an antiepileptic drug, has some side effects. Common side effects include visual impairment, dizziness, nausea, vomiting, drowsiness and so on. A study found that about 10 % of children with epilepsy who received sodium valproate had side effects of visual impairment[17]. The visual impairment mainly manifests as blurring, double images, visual hallucinations and so on. And as the dose of sodium valproate increases, the incidence of visual impairment also increases. Studies have pointed out that when the side effects of visual impairment occur when sodium valproate is used, the symptoms often do not last for a long time[18]. Therefore, when the side effect of visual impairment occurs, a reduction in the dosage of the drug should be considered. At the same time, dizziness, nausea, vomiting, drowsiness and other side effects may also occur. Some researchers pointed out that these side effects are generally mild, and these symptoms can often be relieved by reducing the dose or using other drugs[19].

Clinical studies have shown that when perampanel is used in combination with enzyme-inducing antiepileptic drugs in children with epilepsy, the response rate of perampanel is not significantly different from that of other antiepileptic drugs[20]. Some researchers pointed out that perampanel is often the main drug in the treatment of epilepsy in children[21]. Many studies have confirmed that perampanel has good efficacy and tolerability[22]. A follow-up study pointed out that the pharmacokinetics, efficacy, drug safety and tolerability of perampanel in children with epilepsy aged (2-12) y within 52 w, the drug efficacy and safety of perampanel where all performed well[23]. Some researchers pointed out that perampanel has a certain effect on some special refractory epilepsy, although its effect is not universal, but it can bring hope to patients[24]. Common adverse drug reactions of perampanel include drowsiness, dizziness, nausea, aggressive behavior, and decreased appetite. Studies have pointed out that young children are prone to lethargy, and older children are prone to mental problems. While some researchers pointed out that when a child develops rash and fever, the primary consideration should be to rule out drug eruption with eosinophilia and systemic symptoms. In this case, the mortality rate is high, and rescue measures should be taken as soon as possible[25]. However, this adverse reaction rarely occurs clinically. Although perampanel has certain side effects, the incidence rate is still very low, and most of the adverse reactions can be relieved by reducing the drug dose or adding other drugs. When using perampanel in younger children, close attention should be paid to its drug reaction, and the dosage should be adjusted in time.

In this study, the two drugs have good therapeutic effects, and sodium valproate has lower effects on the duration of epileptic seizures, seizure frequency, and blood drug concentration in children. Both drugs are relatively safe and have certain effects on the neurological damage and cognitive function of the children. It can be seen that after the 1st and 3rd mo of the medication, the blood drug concentration of the children and the nerve damage score is constantly decreasing, and the cognitive function score is constantly increasing. This shows that as the time elapses after the end of the medication, while the blood concentration of the drug on the children is decreasing, the impact on the children's nerve damage and cognitive function are also gradually decreasing. The blood concentration research in this study is not deep enough; follow-up research should be extended in this manner.

Conflict of interests:

The authors declared no conflict of interest.

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