MODERN PHARMACOTHERAPY METHODS FOR GENERALIZED EPILEPSY FORMS

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Abstract: Epilepsy is a chronic polyetiological disease, manifested by repeated unprovoked convulsive or other seizures, loss of consciousness and accompanied by changes in personality. Among the forms of epilepsy, one of the most common and dangerous forms are generalized seizures. In recent years, the concept of generalized epilepsy has undergone significant changes: focal features have been identified with generalized epilepsy and typical features of idiopathic generalized epilepsy with focal epilepsy. The incidence of epilepsy is 50-70 per 100,000 population, the prevalence is 5-10 per 1000 people. It is believed that 1 seizure and more in life endure about 5% of the population. The prevalence of epilepsy among children is high and ranges from 0.3% to 2% in various age populations (0.7-1.0% on average). The basic principles of treatment of epilepsy: individuality of treatment; continuity and duration of treatment; the complexity of treatment (etiologial, pathogenetic and symptomatic); continuity of treatment.

Key words: epilepsy; seizures; rational polytherapy; antiepileptic drugs; ionotropic AMPA receptors.

INTRODUCTION

Epilepsy is chronic multiple etiologic disease, manifested by repeated unprovoked convulsive or other seizures, loss of consciousness and accompanied by changes in personality [1]. Among the forms of epilepsy, one of the most common and dangerous forms are generalized seizures [2]. In recent years, the concept of generalized epilepsy has undergone significant changes: focal features have been identified with generalized epilepsy and typical features of idiopathic generalized epilepsy with focal epilepsy. The urgency lies in the fact that the proximity of these forms is also confirmed by genetic studies, when, with a single genetic disorder,
diverse focal and generalized phenotypes are observed in different members of the same family. This naturally required the search for new anticonvulsants for the successful treatment of various forms of epilepsy, including generalized ones, contributing to an improvement in the quality of life.

**Purpose:** to analyze according to literary data modern methods of pharmacotherapy for generalized forms of epilepsy.

**MATERIALS AND METHODS**

Analysis of data on the incidence of epilepsy among the adult population of Tashkent from 2011 to 2017. Using the data on the number of primary patients as a percentage, we can observe the maximum growth by 2016, and the beginning of the decline by 2017. Using the data of diagnoses that were first established, we can observe a wave-like change in the data, with maximum values in 2015, a tendency to decline in 2016-2017.

**RESULTS AND ITS DISCUSSION**

The incidence of epilepsy is 70-90 per 100,000 populations; the prevalence is 7-12 per 1000 people. It is believed that 1 seizure and more in life endure about 5% of the population. The prevalence of epilepsy among children is high and ranges from 0.3% to 2% in various age populations (0.7-1.0% on average) [3]. Generalized seizures are seizures, the initial clinical and electrophysiological manifestations of which indicate the involvement in the pathological process of both hemispheres of the brain. In the overwhelming majority of cases, generalized epileptic seizures are characterized by loss of consciousness. Typical and atypical absences, clonic, tonic, clonic-tonic and atonic seizures, as well as myoclonia are referred to generalized seizures [4].

The basic principles of treatment of epilepsy: individuality of treatment; continuity and duration of treatment; the complexity of treatment (etiological, pathogenetic and symptomatic); continuity of treatment [5]. It is necessary to begin treatment with monotherapy; treatment begins with a small dose and gradually increase it until the cessation of seizures or signs of overdose. With insufficient clinical effect of treatment, the diagnosis is clarified, the regularity of the drug intake (compliance) is checked, as well as the achievement of the maximum tolerated dose. As a rule, in 70% of patients, correctly selected monotherapy provides adequate control of seizures [5, 6]. Only in cases of ineffectiveness of properly selected monotherapy (after at least two consecutive attempts to use drugs in monotherapy mode) is it possible to use rational polytherapy (these are first choice drugs that are considered adequate for a particular type of epileptic seizures). In its conduct should follow certain rules. Rational polytherapy is based on the concepts of pharmacodynamics, i.e. drug interactions with a neuronal substrate at the level of neuronal membranes and synaptic formations, which determine its specific therapeutic effect or side effects.
It is theoretically inappropriate to combine drugs with the same predominant mechanism of action, it is advisable to use drugs with complementary properties [7]. With the continuation of seizures on the background of monotherapy, it is advisable timely appointment of the second drug. With good clinical effect, the abolition of the first drug is possible. Long-term treatment with two drugs is carried out exclusively when it is impossible to conduct adequate monotherapy. Treatment with three drugs is advisable only if treatment with two adequate drugs is ineffective.

If the form of epilepsy is not precisely established, treatment begins with the drug with the widest spectrum of action is Depakine-chrono, Depakinechronosphere [8]. With success and drug remission for 2-5 years, the question of the gradual withdrawal of the drug may be raised. With the ineffectiveness of valproate, they clarify the form of epilepsy and select a more specific drug. Valproates are broad-spectrum drugs, i.e. they have high clinical efficacy in various forms of epileptic seizures [9]. At the same time, their maximum effect is manifested when exposed to generalized tonic-clonic seizures and absences. The most commonly used derivatives of valproic acid for the treatment of epilepsy are the following: sodium valproate (depakine, depakine-chrono), valproic acid (conculex), calcium salt of valproic acid (convulsofine).

The mechanism of action of valproate is associated with GABA-ergic inhibition and increased postsynaptic inhibition, as well as blockade of T-type N- and Ca-channels. Depakine is well absorbed. Its bioavailability exceeds 90%. The maximum drug accumulates in the plasma for 2-4 hours. At the same time, it is noticed that the absorption of valproates when taken after a meal, especially after abundant fatty foods, somewhat slows down. Depakine is 70-90% bound to plasma proteins. The half-life is 8-20 hours. The frequency of intake 1-3 times a day (depending on the form of release of the drug). The time to reach a stable concentration is 5-7 days. Therapeutic blood concentration corresponds to 50-150 µg / ml. The average daily dose is 20-30 mg / kg of body weight. The advantage of valproate compared with other traditional antiepileptic drugs (AED) is their less pronounced effect on cognitive function. Against the background of treatment with valproates, patients retain their mental performance, professional activity, and the learning performance of children does not deteriorate. Studies of the Committee on Drugs at the American Pediatric Academy also confirm the absence of the negative effect of valproates used in moderate therapeutic doses on cognitive function and school performance. Possible dose-related side effects include drowsiness, nystagmus, dizziness, ataxia, tremor, headache, hallucinations, weight gain or loss, increased or decreased appetite, hair loss, menstrual disorders (oligo- or amenorrhea).
Most of these symptoms regress when the dose of valproate is reduced. An interesting fact is that weight gain most often occurs if treatment with valproate begins before the age of 20 years than after this age, regardless of the duration of treatment. Valproate can inhibit blood formation, causing thrombocytopenia, leukopenia, inhibit platelet aggregation, contributing to increased bleeding. In this regard, valproate with anticoagulants or acetylsalicylic acid should be carefully prescribed. Non-dependent side effects are extremely rare. These include effects that develop acutely and in a few weeks or months from the start of treatment. Symptoms of acute and chronic intoxication include myasthenia, hypo- or areflexia, miosis, cardiovascular and respiratory disorders, brain swelling, metabolic acidosis, hypernatremia, confusion, and coma. The treatment is aimed at eliminating hypovolemia. Naloxone can be used to relieve the depressive effect of valproate on the nervous system [3, 10].

Perampanel (Faykompa, OOO "Eisai") is the newest antiepileptic drug, registered for use in additional therapy in patients 12 years and older with focal and secondary-generalized seizures. Perampanel was licensed in the USA and European countries in 2012 [4, 11]; registered in 2013 and in 2014 entered the pharmaceutical market in Russia. Perampanel has a fundamentally different mechanism of anti-epileptic action, different from other AEF: through noncompetitive inhibition of ionotropic AMPA receptors (a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) glutamate (the main excitatory neurotransmitter in the central nervous system (CNS) a) the drug causes a decrease in neuronal excitability. Perampanel is a potent, highly selective, noncompetitive inhibitor of the ionotropic AMPA receptors of the neuronal postsynaptic membranes at the neocortex and hippocampal levels [11]. According to many authors, perampanel is the first AEP with a specific effect on glutamate metabolism (glutamate-mediated excitation in the central nervous system), the effectiveness and tolerability of which in resistant focal seizures have been proven in phase III clinical studies [4].

To date, a number of observational studies have been conducted in which the use of perampanel in clinical practice as an additional drug for the treatment of patients with refractory partial epilepsy has been studied. The findings suggest that perampanel is effective and well tolerated, including in patients with resistant epilepsy and concomitant diseases. The main adverse effects of the use of perampanel include drowsiness and dizziness, less often ataxia, aggression, nausea and irritability. Tolerability is best in patients receiving 1 or 2 baseline AEDs [11].

In generalized seizures - primary generalized tonic-clonic, absences (especially in combination with generalized seizures in the framework of syndromes of idiopathic generalized epilepsy), myoclonic - valproate are the drugs of choice; carbamazepines and phenytoin are contraindicated.
for absans and myoclonic seizures [5]. For simple absences, valproate or ethosuximide are the drugs of choice. Atypical absansy, atonic and tonic seizures are often resistant to treatment. In individual cases, one of the following drugs may be effective: phenytoin, valproate, lamotrigine, clonazepam, ethosuximide, phenobarbital, acetazolamide, and glucocorticoids, or a combination of the two. In myoclonic seizures, sodium valproate is the drug of choice; clonazepam and lamotrigine are also used. With insufficient efficacy or poor tolerability of traditional AEDs, new anticonvulsants are used (for example, lamotrigine or topiramate).

The abolition of AED should be gradual, taking into account the form of epilepsy and its prognosis, the possibility of resuming seizures, the individual and age characteristics of the patient (both medical and social factors should be taken into account). Abolition of antiepileptic therapy is carried out, as a rule, not less than 2-3 years after the complete cessation of seizures (up to 5 years is also recommended), under the control of EEG data [9].

CONCLUSIONS

The modern approach makes it preferable to choose a drug with a wide spectrum of action (which helps with any types of seizures and epilepsy forms), taking into account its effectiveness, dose rate titration, dosage form, side effects and cost. Among the drugs with a wide spectrum of action (valproate - VPA, levetiracetam, lamotrigine, topiramate) as the first choice for the initial treatment of generalized epilepsy, the original forms of the HPA with controlled release of the active substance - DepakineChrono and DepakineChronosphere are priorities. Thus, valproatics are currently the most used and effective antiepileptic drugs in the treatment of epilepsy, and on the basis of the data presented in the literature, perampanel is the most modern and promising drug for the treatment of partial and secondary-generalized seizures with high efficacy and favorable tolerability.

References: