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NEW POSSIBILITIES OF PHARMACOTHERAPY FOR PATIENTS WITH REFRACTORY EPILEPSY

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ABSTRACT

The aim of the work was to study the efficacy and tolerability of perampanel in 52 patients with drug-resistant focal epilepsy. Materials and methods. The average age of patients was 28.92±14.02 years; men – 56%; disease duration more than 10 years – 69.2%; symptomatic epilepsy – 76.9%; with frontal – 46.2% and temporal – 44.2% localization of the epileptic focus. Most patients (71.2%) were prescribed perampanel after three previous lines of therapy. The initial frequency of all types of seizures was 127.29±82.29 per month; secondarily generalized – 6.72±1.90 per month.

Keywords: Pharmacoresistant focal, partial epilepsy, perampanel, efficacy, tolerability.

INTRODUCTION

It can be safely stated that epileptology is currently a very dynamic science, as evidenced by the achievements of recent years: another proposal for the classification of epilepsies (updated every 5-10 years); formulation of the provision on epileptic encephalopathy - a breakthrough in understanding the epileptic process; description of new clinical syndromes; study of the epidemiology and genetics of epilepsy; pharmacogenetic studies; creation of new antiepileptic drugs (AEDs) by targeted synthesis (lamotrigine, topiramate, levetiracetam, pregabalin, oxcarbazepine, lacosamide, perempanel, zonisamide, eslicarbazepine, rufinamide); introduction into widespread practice of vagus stimulators, etc. [1].

MATERIALS AND METHODS

Knowledge of the principles of epilepsy therapy [2], organization of the treatment process at the modern level allow achieving a significant effect: the percentage of remissions reaches 65-75. However, the level of drug-resistant cases decreases insignificantly, and constant visits of this group of patients to an epileptologist can create a false impression of the weak effectiveness of disease therapy. At the same time, it is currently well known that the frequency of drug-resistant cases of epilepsy does not exceed 25-30%. Among the causes of drug resistance, significant ones are structural abnormalities of the brain structure (hippocampal sclerosis, focal cortical dysplasia, etc.), pathological neuroplasticity, autoimmune brain damage, pharmacodynamic variability of genes of receptors for AEDs, ion channels of neurons, drug transporters, etc. To explain drug resistance, the theory of the target, multidrug resistance, neural network and synthetic, combining all the previous ones, are used [3]. Diagnosis of drug-resistant epilepsy is extremely important, since patients with drug-resistant epilepsy are candidates for non-drug correction methods (including epilepsy surgery, vagus nerve stimulation), and drug-resistant epilepsy itself significantly reduces the

adaptation and socialization of patients. Formulating the diagnosis of drug-resistant epilepsy suggests other tactical approaches to treating the disease:

- use of AEDs with different mechanisms of action (the so-called pharmacodynamic synergism);
- use of AEDs with multiple mechanisms of action;
- prescription of so-called non-metabolizable AEDs;
- return to a previously effective treatment regimen;
- use of periodic change of AEDs (in case of their effectiveness in the past, but with subsequent development of tolerance);

– testing the effectiveness of new AEDs; - use of drugs from other groups.

RESULTS AND DISCUSSION

The study included patients with drug-resistant focal epilepsy using PER as an additional antiepileptic drug (AED). The study was designed as a multicenter retrospective study. Epileptologists from different cities, many of whom participated in international clinical studies 304, 306, 307 [7], filled out a specially designed questionnaire that included data on the types of epileptic seizures; their frequency; form of epilepsy; duration of the disease; previous therapy; reasons for changing therapy; current AED regimen with dosages; individual PER titration regimen; efficacy; PER dose; tolerability of combination therapy; assessment of general health and comments from the specialist who filled out the questionnaire. The analysis included all the material presented by the co-authors, regardless of age restrictions (the drug is approved for use starting from the age of 12 years). A total of 52 patients were included in the study.

After the introduction of PER into the treatment regimen, already within the first month there was a reliable decrease in the frequency of all types of seizures to 52.06±29.26 per month (Sign test, p=0.00001), and secondary generalized seizures – to 3.71±1.71 (Sign test, p=0.00001) per month. After the second month of taking the drug, the frequency of seizures decreased further: to 30.43±12.35 seizures per month without differentiation by seizure types (Sign test, p=0.003); to 2.64±1.18 secondary generalized seizures (Sign test, p=0.04). Subsequently, up to 12 months after the start of treatment, a decrease in the frequency of seizures was noted, but it was insignificant (see Fig. 1). When analyzing the effectiveness of PER for 6 months. observations, it was possible to achieve complete cessation of all types of seizures in 8% of the sample n=52 and cessation of secondary generalized seizures in 31% of the sample n=36.

The intermediate results obtained in the present study indicate high prospects for the use of PER in epilepsy. In the group with drug-resistant focal epilepsy, a complete absence of seizures was achieved in 8% (n=4) for a period of 6 months, and secondary generalized seizures (SGSS) were observed in 31% (in 11 of 36 patients with SGSS). In the present study, the seizure freedom rates were almost identical to those published previously: remission of all types of seizures for a period of 1 year was achieved in 5.3% [1], and according to the results of the study by B. J. Steinhoff et al. (2014), seizures were not recorded in 14% [2], and the maximum effect of PER in relation to SGSS was also confirmed.

In the open phase of the study by G. L. Krauss et al. (2014) in focal epilepsy, by the end of the second year of using perampanel as an additional therapy, a reduction in the frequency of

primary generalized tonic-clonic seizures by more than 90% was achieved [4]. Perampanel was effective in the treatment of primary generalized tonic-clonic seizures: during the period of maintenance therapy (from the 23rd to the 159th week of the study), it was possible to achieve freedom from generalized seizures in 30% of cases [5]. The median effective daily dose of PER in this study was 6 mg, which is close to the previously published 7.7 mg (4-15 mg) [4]. A specially conducted analysis did not allow us to identify the most effective combination with PER, since the drug showed its therapeutic properties regardless of the concomitant AED. PER was discontinued in only four cases (7.7%) due to the development of AE (lethargy (n=2), decreased appetite (n=1), drowsiness (n=1)). As can be seen from the nature of the AE, they were not life-threatening, so it can be assumed that the true factors that led to the discontinuation of PER were the high cost of the drug, the patient's uncertainty about its effectiveness, or the unwillingness to further select therapy.

The present study confirmed the good tolerability of PER: AEs were registered in only 30.1% of observations (n=16). The only AE, such as aggression, was observed in 11.5% (n=6), all other AEs were detected with a frequency of less than 10%, among which the most frequent were drowsiness (9.6%), gait unsteadiness (5.8%), tearfulness (5.8%). In general, the percentage of AEs in this study was lower than in previously published studies, probably due to the fact that there was no strict protocol, and when minimal signs of AEs appeared, the doctor immediately took the necessary actions: explained to the patient about the need to take the drug at night, in some cases the PER dose was temporarily reduced, or even a regimen of taking PER every other day was prescribed for several days. Aggression, observed in every tenth patient, was transient, arose at a daily dose of 8 mg, and in none of the cases did it require discontinuation of PER for its correction. In the overwhelming majority of cases, it regressed when the daily dose was reduced to 6 mg. Previously conducted studies recorded aggression as an AE during the use of PER mainly in adolescents [4], in contrast to the results obtained in the Russian Federation - only one patient out of six was an adolescent (possibly due to the small number of adolescents in the sample). This subgroup was characterized by the presence of symptomatic epilepsy with frontal or temporal lobe localization of the epileptic focus and the absence of a connection with the use of a specific AED. Five out of six patients with aggression were taking VK as part of polytherapy, however, such psychiatric side effects as depression, psychosis, irritability/emotional lability are not typical for patients taking VK [5]. Given the high percentage of this AE, it is recommended to purposefully collect anamnesis about the presence of mental/behavioral problems in the patient in the past and pay increased attention to them: actively monitor possible manifestations of aggression.

In general, patients rated the use of PER as part of complex therapy very positively: 73% reported an improvement in quality of life, while 15.4% reported no changes. In the questionnaires they filled out, epilepsy patients noted an improvement in mood, a sense of well-being, and a surge of energy. Patients did not note the effect of PER on cognitive functions, which is consistent with the results of the study by K. J. Meador et al. (2016), which showed a minimal effect of PER on cognitive functions compared to placebo [3].

CONCLUSION

Thus, PER proved to be effective in the treatment of resistant forms of focal epilepsy, reducing the seizure frequency by an average of 76% by the second month of treatment. The drug exerted its therapeutic effect in all types of partial seizures, with maximum effectiveness in VGSP. Along with a good clinical effect, PER demonstrated a quite satisfactory and predictable safety profile. It is known that combination therapy is usually used in case of pharmacoresistance, and accordingly the risk of developing AEs potentially increases, especially neurotoxicity with a similar mechanism of action of AEDs. The use in this situation of the latest AEDs, the mechanisms of which are qualitatively different from those used previously, allows for individualization of pharmacotherapy and has high prospects for use in special groups of patients (by age, gender, concomitant somatic pathology, etc.). The use of PER in real clinical practice has shown that after a dose of 4 mg, its effectiveness should be assessed, and further titration can be carried out slower by two or more times. The present study has shown that in a situation where the physician is free to choose the dose and titration rate, the effectiveness of PER was comparable with previously published study results, and tolerability was significantly better. The average dose of PER for adult patients was only 6 mg. In summary, it can be safely stated that perampanel is an additional therapy drug for the treatment of drug-resistant epilepsy with high effectiveness and good tolerability.

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