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Selective neuronal potassium channel opener (SNEPCO) flupirtine in treatment-resistant epilepsy comorbid depression in adults

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Abstract

Objective: Despite the presence of more than 20 antiepileptic drugs, in 30% of patients with epilepsy the control of seizures is not achieved. The study was to investigate the efficacy of flupirtine, anticonvulsant drug with a new mechanism of action, in the form of activation of potassium channels.

Methods: A total of 100 patients with pharmacoresistent epilepsy in adults and non-psychotic depression, associated with this disease, were included in the study. The dynamics of the frequency of seizures and the intensity of depressive disorders was studied by using the Hamilton Scale.

Results: In 60 % of cases treated with flupirtine therapeutic remission was achieved with cessation of seizures, in the rest observations marked reduction of seizures was noticed. At the same time a decrease of the severity of depression was registered.

Significance: Flupirtine is an effective drug in the treatment of pharmacoresistent epilepsy in adults with non-psychotic depressive disorder.

Introduction

Epidemiological studies show that epilepsy is one of the most common neurological diseases with certain mental disorders. All over the world, approximately 50 million people suffer from epilepsy. Recurrent seizures are associated with a number of harmful effects. Seizure-related deaths can account for up to 40% of all deaths in patients with chronic epilepsy. The rate of sudden death, which accounts for 7-17% of deaths among patients with epilepsy, is estimated to be 27 times higher in patients with seizures than those who do not have seizures [1]. The incidence of epilepsy in the European countries and the United States is about 40-70 cases per 100,000 population, while in developing countries the incidence is much higher. It is interesting that the incidence of epilepsy in men, especially in old and senile age, is higher than that of women [2].

Epilepsy is one of the most common neuropsychiatric diseases. In the adapted version of the ICD-10 revision (put in place by order No. 170 of the Ministry of Health of the Russian Federation of May 27, 1997) in class VI, diseases of the nervous system-disorders related to epilepsy are provided for only 15 headings (G40 Epilepsy-G40.0- G40.9; G41 Epileptic status - G41.0- G41.9). In class V, mental and behavioral disorders associated with epilepsy are treated in a 17 rubric. In other words, the number of mental and behavioral disorders associated with epilepsy is greater than that of neurological. Therefore, we consider it expedient to consider epilepsy as a neuropsychic disorder.

Proceeding from the above, the search for anticonvulsants with a new mechanism of action remains a relevant and promising direction of research, both in neurology and in psychiatry.

The purpose of this work was to study the possibility of using flupirtine (cadadolone) - SNEPCO (Selective Neuronal Potassium Channel Opener) - in the therapy of resistant epilepsy and a nonpsychotic depressive disorder in adults associated with it.

Materials and methods of research

In accordance with the Helsinki Declaration of the World Medical Association "Recommendations for doctors engaged in biomedical research involving people", adopted by the 18th World Medical Assembly (Finland, 1964, revised in Japan in 1975, Italy - 1983, Hong Kong - 1989, the South African Republic - 1996, Edinburgh - 2000); The Constitution of the Republic of Azerbaijan, the Law "On Psychiatric Assistance" (adopted on 12.06.2001, with amendments and additions - 11.11.2011, Decisions of the Cabinet of Ministers of the Republic of Azerbaijan No. 83, dated April 30, 2010 "On Approval of the Rules for Conducting Scientific, Preclinical and Clinical studies of medicines "are established:

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- The conditions of the conducted researches corresponded to the generally accepted norms of morality, the requirements of ethical and legal norms, as well as the rights, interests and personal dignity of the participants of the studies were observed;
- Conducted research is adequate to the topic of research work;
- There is no risk for the subject of research;
- Participants in the study were informed about the goals, methods, expected benefits of the study and associated with risk and inconvenience in the study;
- The subject's informed consent about participation in the research was received;

The decision of the Ethical Committee at the Azerbaijan Psychiatric Association on the article of NA. Aliev, Z.N. Aliev "Selective Neuronal Potassium Channel Opener flupirtine (SNEPCO) in treatment-resistant epilepsy in adults" submitted for publication in psychiatric journals: in connection with compliance with its legislative requirements and regulatory documents is to approve the article by N.A. Aliyev, Z.N. Aliev "Selective Neuronal Potassium Channel Opener flupirtine (SNEPCO) in treatment-resistant epilepsy in adults"

The criteria for epilepsy resistance were determined according to Kwan P. B. and Brodie M.J. [3]:

- Lack of effectiveness from the first used drug makes the doctor think about the resistant nature of epilepsy. It does not matter which anticonvulsant was used.
- The lack of effect from the second variant of mono therapy makes the diagnosis of resistance almost absolute.
- Impossibility of achieving a stable remission for seizures with the use of two well endured and correctly selected modes of AED (in mono or poly therapy mode).

We examined 20 patients with primary generalized idiopathic epilepsy (JIE) and "nonpsychotic depressive disorder due to epilepsy (F06.362)". Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan from January 2012 to January 2014 for 18 months.

The severity of depression in patients was determined by both the ICD-10 criteria and the Hamilton scale. All examined patients had resistance to antiepileptic therapy. Before the application of the katadolon forte, patients took standard antiepileptic and antidepressant drugs (depakin-chrono 1000 mg/day, lamotrigine 150 mg/day, levitracetam 3000 mg/day, Citalopram 20 mg/day). The katadol forte was taken in the first 14 days 200 mg twice a day, then 400 mg in the morning and in the evening. All patients suffered from primary - generalized idiopathic epilepsy (JIE). Epileptic seizures were in the form of primary generalized tonic-clonic seizures. Attacks of epilepsy were observed daily. Characteristics of patients with JIE are presented in Table 1. Statistical processing of the obtained data was carried out by the Wilcoxon test (comparisons of observations before and after treatment) [4].

In determining the concept of treatment-resistant epilepsy, existing basic literature was taken into account [5,6].

According to the instructions for the medical use of the katadolone (flupirtine), it refers to the clinical and pharmacological group - the non-opioid analgesic of the central action.

Table 1. Characteristics of patients with JIE

Indicators	Quantity
Number of patients	100
Sex, men / women	50/50
The average age (16-45)	31.5±5.3 years
The duration of the disease	10.0±2.2 years
Non-working	70
Disabled persons	30
Frequency of attacks	Often

The classification of clinical and pharmacological groups is based on the therapeutic effect. Pharmacological action: Selective Neuronal Potassium Channel Opener. By its pharmacological effects, the drug is a non-opioid analgesic of central action that does not cause addiction and habituation, in addition, it has a miorelaxing and neuroprotective effect. The action of flupirtine is based on the activation of potential-independent potassium channels, which leads to the stabilization of the membrane potential of the neuron. The effect on the current of potassium ions is mediated by the effect of the drug on the regulatory G protein system. In therapeutic concentrations, flupirtine does not link to α1, α2-adrenoreceptors, serotonin 5HT1, 5HT2 receptors, dopamine, benzodiazepine, opioid, central m-and n-cholinergic receptors.

The central effect of flupirtine is based on 4 main effects [7].

Analgesic action. Flupirtine was introduced as an alternative analgesic to opioids and NSAIDs. Subsequently, multiple other actions such as muscle relaxation and neuroprotective activity were identified.

Muscle relaxant action. The muscle relaxation is due to inhibition of both mono- and polysynaptic reflexes.

Neuroprotective action. Apoptosis, a programmed cell death, is caused by increased intracellular Ca^{++} levels, mitochondrial dysfunction, cell membrane disruption, and finally, nucleolysis. *In vitro* studies with primary cortical neurons from rat embryos have shown that lead acetate, prions like PrPsc, HIV coat protein gp120, and β amyloid peptide will cause apoptotic cell death.

Antiparkinson action. Flupirtine has an NMDA receptor antagonistic action and hence it was studied for its Antiparkinson effect as an adjuvant to L-3, 4-dihydroxyphenylalanine (L-DOPA).

The analgesic effect is based both on indirect antagonism to NMDA receptors and on the modulation of pain mechanisms associated with the effect on GABA -ergic systems. Flupirtine in therapeutic doses activates (opens) the potential of non-dependent potassium channels, which leads to stabilization of the membrane potential of the nerve cell. This inhibits the activity of NMDA receptors and, as a consequence, blockade of neuronal ion channels of calcium. Due to the developing inhibition of neuron excitation in response to nociceptive stimulation, inhibition of nociceptive activation, an analgesic effect is realized. This inhibits the growth of the neuronal response to repeated painful incentives. This action prevents the increase of pain and its transition to a chronic form, and with the existing chronic pain syndrome leads to a decrease in its intensity. The modulating effect of flupirtine on the perception of pain through the descending noradrenergic system was also established.

Myorelaxing action. Antispastic action on muscles is associated with blocking the transmission of excitation to motoneurons and intermediate neurons, leading to the removal of muscle tension. This flupirtine effect is manifested in many chronic diseases, accompanied by painful muscular spasms (musculoskeletal pain in the neck and back, arthropathy, tension headaches, fibromyalgia).

Neuroprotective action. Neuroprotective properties of the drug cause the protection of nerve structures from the toxic effect of high concentrations of intracellular calcium ions, which is associated with its ability to cause blockade of neuronal ionic calcium channels and reduce the intracellular current of calcium ions.

In our studies we used catalolon forte 400 mg in pills. The examined patients were diagnosed with "Nonpsychotic depressive disorder in connection with epilepsy (F06.362)". It is known that one of the clinical predictors of epilepsy resistance is associated with psychiatric disorders.

Results

As can be seen from Table 2, during the observation period of 18 months the absence of seizures out of 100 patients was achieved in 50 patients, while 10 had a decrease in the frequency of seizures, but the therapy was not effective in 40 patients.

The data obtained by us in connection with a small number of patients and a short period of observation (18 months) should be considered preliminary. The next stage of the work will be carried out on a large number of patients and longer duration of observation, with a placebo-controlled, double-blind method. Contraindications in our patients were following: patients with history of hypersensitivity to flupirtine, hepatic encephalopathy, cholestasis, myasthenia gravis, chronic alcoholism, primary biliary cirrhosis, and liver disease. The adverse effects of fluprutin were determined by spontaneous complaints of patients. In our study adverse effects-dizziness (7%), drowsiness (3%), pruritis (3%), dry mouth and gastric fullness (2%), nausea, and muscle tremor (1%) were observed. All these effects were dose dependent. We did not observe other side effects in our patients, such as heart burn, vomiting, disturbed sleep pattern, sedation, headache, fatigue, and mood elevation.

Discussion

Currently in the world, this disease affects more than 50 million people. Despite the fact that there are more than 20 drugs for the treatment of epilepsy in 30% of patients it is impossible to control paroxysms. Therefore, the search for new drugs for the therapy of epilepsy remains topical. Development of antiepileptic drugs is mainly carried out in several directions: 1) exposure to ion channels of an electrically excitable membrane; 2) the effect on the concentration of neurotransmitters in the neuron and the synaptic cleft (primarily on the neurotransmitter amino acids - glutamine and γ-aminobutyric acid (GABA), 3) the change in the synaptic protein involved in the release of neurotransmitters. For example, it is well known that the action of phenythionine and carbamazepine is associated with the blockade of the sodium channels of the excitable membrane, phenobarbital, benzodiazepines, tiagabine, and vigobatrin affect the GABA system (the first two drugs act on GABA receptors, the third on GABA transport and finally the latter on GABA transaminase). Valproate and ethosuksamid block the calculous channels of the excitable membrane. Levetiracetam, and brivaracetam through synaptic protein increase the secretion of neurotransmitters.

Table 2. Indicators beginning and end of the study

Indicators	Beginning of the study	End of the study
The Hamilton scale	20.5±0.5 19-22 points - Severe degree of depressive episode	10.5±0.5* 8-13 – Easy Depression episode
Diagnosis of depression in ICD-10	Depressive episode of severe degree without psychotic symptoms (F32.2)	Depressive episode of mild degree (F32.0)
Frequency of seizures:		
Remission		50
Rare		10
Average Frequency		3
Frequent	100	37

* * Wilcoxon's test is W = 80; P = 0.022 (the changes are statistically significant)

Thus, the treatment of resistant epilepsy remains one of the most important problems of modern epileptology. On the other hand, treatment-resistant epilepsy is often accompanied by mental disorders. Among them, especially depression should be noted.

In medicine, it has long been known that people suffering from epilepsy, in addition to having seizures, also find other symptoms. Around 400 BC, Hippocrates observed that "melancholy usually becomes epileptics and epileptics become melancholic" [8,9]. Some authors indicates that depression deserves special attention due to its high frequency (10-30% of patients) and the risk of suicide occurring among epileptic patients is much more frequent than the average among population [10,11]. Further, the author believes that in addition to changes in the mood as a result of primary epileptic brain dysfunction, negative social stigmatization plays an important role in the development of depression, which leads to restrictions on education, occupation, social contacts, spending of free time.

According to various authors, depressive disorder in epilepsy occurs from 22% to 58% of patients [12]. Moreover, in the literature there are data on the relationship between epilepsy and depression, the treatment of this combined pathology, their molecular basis, etc. [13-18]. In 2015, World Health Organization (WHO) adopted a resolution on epilepsy. As known from this document, Russia was the co-sponsor of this resolution [19]. Practical physicians should individualize the concept of "resolution of epilepsy". As criteria for the resolution of epilepsy the working group defined the attainment of a certain age in patients with age-dependent epileptic syndrome, or the absence of epileptic seizures for 10 years in patients who did not take anticonvulsants for more than 5 years [20].

The available up-to-date literature data indicate an increase in the membrane conductivity for K + ions (i.e., activation-opening of the potassium channels) causes neuronal hyperpolarization and, in most cases, reduces the frequency of neuronal excitation, exerting a strong inhibitory effect on the excitability of neurons. Potassium channels control the membrane potential of rest and, therefore, play an important role in regulating the excitability of neurons. In turn, it leads to the cessation of convulsive paroxysms. These data served the basis for the present study [21-24].

The role of potassium channels in the management of epileptic processes was pointed out by Lavreskaya E.F**.** [25]. The dreams of a far-sighted Russian scientist are now becoming real. In order to understand the outstanding merits of this author, we consider it important to include several extracts from her monograph. She wrote: "It is necessary to emphasize several important points relating to those functions in which a special role belongs to the potassium channels

1. The main function of potassium channels is the catalysis of the transfer of potassium ions through the membrane, which ensures the existence of a difference in electrical potentials between the inner and outer sides of the membrane in all living cells. The fulfillment of this functional role is ensured by the high conductivity and high selectivity of these channels.

2. In addition to this potential-forming role, potassium channels participate in the process of depolarization of the membrane of electro excitable cells, accelerating repolarization and as if returning the potential to a resting level. In rare cases, membrane depolarization can occur due to a decrease in potassium permeability.

3. All the mentioned above determines the special role played by the change in the potassium permeability of the membrane providing many physiological processes, in particular, excitation in nerve and muscle cells, the creation of rhythms in neuronal and cardiac pacemakers, the secretion of hormones by glandular cells and mediators by nerve endings, certain types of reception (For example, light), memory processes and many others, not fully clarified yet.

4. The multiplicity of the channels regulating the potassium conductivity of the membrane indicates a special plasticity of this membrane function. The variety of potassium channels is reflected in various sensitivity to pharmacological agents, blockers. This opens important prospects for the selective impact on various components of potassium conductivity and, thus, on the processes in which they participate."

After decades, foreign researchers began writing about this. For example, it was found that the potassium channel activator-flupritin was more effective than phenobarbital and diazepam, when the seizures in rats were caused by the introduction of kainate and flurotil in the postnatal days [26].

We will not analyze problems concerning algorithms for mono- and polytherapy in clinical epileptology, as they are described in detail in review articles [27,28].

The generalization of the data of this work on the use of the katalodol forte - Selective Neuronal Potassium Channel Opener flupirtine (SNEPCO) in the therapy of treatment-resistant epilepsy and associated nonpsychotic depressive disorder in adults, indicate a high therapeutic effect in primary generalized idiopathic epilepsy. Side effects from the reception of the katadol forte were not noted. Clinicians are well aware of the fact that patients with epilepsy badly endure muscle tension, on the other hand, they also react painfully to pronounced muscle weakness. In this regard, it should be noted that analgesic, miorelaxing and neuroprotective effect of the katadolon forte positively affect the quality of life of patients.

The results of our research have some limitations. Firstly, limitations in the study were not included in control group. Secondly, limitations were connected with small number of samples for investigation. The third limitation was connected with absence of placebo-controlled, double-blind method.

Conclusions

Flupirtine is an effective drug in the treatment of pharmacoresistent epilepsy in adults with non-psychotic depressive disorder. The present findings emphasize the importance of flupirtine is an effective drug in the treatment of pharmacoresistent epilepsy comorbid depression in adults with non-psychotic depressive disorder. Thus, it can be concluded that in epilepsy, concomitant depressive disorders need special consideration within the framework of a comprehensive diagnostic and therapeutic approach to treatment.

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Author disclosure

Authors declare that the manuscript is submitted on behalf of all authors. None of the material in this manuscript have been published previously in any form and none of the material is currently under consideration for publication elsewhere other than noted in the cover letter to the editor. Authors declare to have any financial and personal relationship with other people or organizations that could inappropriately influence this work. All authors contributed to and have approved the final manuscript. Conflict of interest: none.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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There is no conflict of interest

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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