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Article

The Frequency and Structure of Adverse Drug Reactions in the Pharmacotherapy of Epilepsy

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Abstract: The problem of the safety of antiepileptic therapy due to the duration of treatment and the need for regular intake of antiepileptic drugs (AEDs) is extremely significant. Adverse reactions (ADRs) may outweigh any positive effect of therapy associated with seizure reduction. The purpose of the study: to analyze the frequency and structure of ADRs of AEDs. Materials and Methods: The work was carried out within the framework of comprehensive research on the topic No. 210-16 "Epidemiological, genetic and neurophysiological aspects of diseases of the nervous system (central, peripheral and vegetative) and preventive medicine" (registration number 0120.0807480). Results: The frequency of ADRs against the background of third-generation AEDs was not inferior to that against the background of receiving second-generation AEDs, while the structure of ADRs was different: third-generation AEDs had a higher incidence of ADRs from the central nervous system, including a worsening of the course of epilepsy. The ratio of the chances of valproic acid accumulation with the achievement of toxic concentration in the blood and the development of undesirable side effects in poor metabolizers (carriers of the polymorphism of CYP2C9*2 or CYP2C9*3) the gene encoding the cytochrome P450 isoenzyme 2C9 of the liver is 5.94 and 4.27, respectively. Conclusion: A personalized approach to ensuring the safety of valproic acid preparations based on taking into account the carriage of polymorphisms of the *CYP2C9* gene allows to reduce the incidence of ADRs in patients receiving valproic acid preparations from 59.28% to 10.78%. The introduction of a personalized approach to the administration of valproates to patients suffering from epilepsy in the Krasnoyarsk Territory did not lead to an increase in direct costs.

Keywords: *bipolar affective disorder; pharmacogenetic testing; treatment; safety*

1. Introduction

The problem of the safety of antiepileptic therapy due to the duration of treatment and the need for regular intake of antiepileptic drugs (AEDs) is extremely significant [1]. Adverse drug reactions (ADRs) can overshadow any positive effect of therapy associated with seizure reduction [2, 3]. HP can reduce the patient's quality of life, and sometimes cause serious social (for example, family breakdown) and new medical (depression, anorexia nervosa, etc.) problems and, accordingly, lead to additional financial costs associated

with ineffective treatment, the development of complications and the need to prescribe other medications or methods of therapy for both the treatment of the underlying disease and the correction of ADRs [4, 5]

. The metabolism of AEDs can be influenced by polymorphism of the genes *CYP2C9*, *CYP2C19*, *CYP3A4* of the liver cytochrome P450 isoenzymes [6]. However, a personalized approach to the prevention of HP in patients with epilepsy, taking into account individual pharmacogenetic characteristics, has been implemented only in certain regions of the Russia [7, 8]. Valproic acid (VPA) and its derivatives have been widely used as an antiepileptic agent for more than half a century. The advantage of VPA is the breadth of therapeutic action, the absence of an inducing effect on the activity of liver enzymes, and the possibility of using in patients of various age categories. Among the restrictions on the use of VPA, women of childbearing age require special attention due to the risk of developing a teratogenic effect [9].

Information on the actual incidence of AEDs-induced ADRs is necessary to assess the benefit-risk ratio and make decisions on tactics for further use of AEDs in clinical practice. Studies on the role of polymorphisms of genes encoding liver CYP450 isoenzymes involved in VPA metabolism have shown that the main isoenzyme is *CYP2C9* [10]. The frequency of occurrence of slow metabolizers according to CYP2C9 is variable and depends on the patient's ethnicity [11, 12, 13]. Taking into account the multinational composition of the population of the Krasnoyarsk Territory, it is necessary to study the regional features of the occurrence of polymorphic allelic variants of genes responsible for the metabolism of PEP, their effect on the incidence of HP in order to develop personalized therapeutic strategies that take into account the individual characteristics of the patient and optimize approaches to pharmacotherapy of epilepsy.

2. Purpose

The purpose of the study: to analyze the frequency and structure of ADRs of antiepileptic drugs (AEDs).

3. Materials and Methods

The study was conducted on the basis of the Department of General and Clinical Pharmacology of the Medical Institute of the Federal State Educational Institution of the Peoples' Friendship University of Russia, on the basis of the Department of Pharmacology with courses in Clinical Pharmacology, Pharmaceutical Technology and Postgraduate Education and the Department of Medical Genetics and Clinical Neurophysiology of the Institute of Postgraduate Education - The Neurological Center of Epileptology, Neurogenetics and Brain Research of the University Clinic (NC UC) of the V. F. Voino-Yasenetsky State Medical University of the Ministry of Health of the Russian Federation.

The study was carried out within the framework of comprehensive research on the topic No. 210-16 "Epidemiological, genetic and neurophysiological aspects of diseases of the nervous system (central, peripheral and vegetative) and preventive medicine" (registration number 0120.0807480).

To achieve the goal and solve the tasks set, the following were studied: the database of the NC CC for 2010-2016, containing information on 1,169 patients suffering from

epilepsy; 359 outpatient records of patients observed in the NC CC with a diagnosis of epilepsy taking antiepileptic drugs; the results of the study of single nucleotide variants of the *CYP2C9* gene (CYP2C9*1, CYP2C9*2, CYP2C9*3) in 326 patients with epilepsy, including 167 samples for the study of the association of HP with the carrier of CYP2C9*2 and CYP2C9*3 polymorphisms among patients observed at the neurological center of epileptology, Neurogenetics and brain research at the University Clinic; 159 samples for the study of the frequency of carrier in various ethnic groups (Russians, Yakuts, Tuvinians).

Therapeutic drug monitoring (TDM) of the VPA level in plasma was carried out on the basis of the Central Research Laboratory KrasSMU, in the Laboratory of Research Institute of Medical Problems of the North (Krasnoyarsk), the Laboratory "Invitro" (Krasnoyarsk). The level of VPA was determined by high-performance liquid chromatography. The value of the reference value of the VPA level in the plasma was 50-100 micrograms /ml.

Genetic studies were conducted on the basis of the Interdepartmental Laboratory of Medical Genetics of the Department of Medical Genetics and Clinical Neurophysiology of V. F. Voino-Yasenetsky State Medical University. Polymorphisms of the *CYP2C9* gene localized on chromosome 10q24.1-24.3 and encoding the liver cytochrome P450 isoenzyme 2C9 were studied by polymerase chain reaction (PCR) in real time: wild type CYP2C9*1; variative (minor) types CYP2C9*2 (R144C, c.430 C > T) and CYP2C9*3 (I359L, c.1075 A > C). According to the results of the genetic test, the type of metabolism of AEDs was clarified: CYP2C9*1/*1 – extensive metabolizer (EM); heterozygous CYP2C9 genotypes*1/*2 , CYP2C9*1/*3 – intermediate metabolizer (IM), homozygous CYP2C9 genotypes*2/*2 , CYP2C9*3/*3 and the compound heterozygous genotype CYP2C9*2/*3 – a poor metabolizer (PM).

Statistical processing of the obtained results was carried out using the Statistica v.6.1 statistical software package (Stat Soft, USA). To compare and evaluate the revealed differences, the nonparametric Pearson Chi-squared criterion ($\chi 2$) with the pairwise comparison procedure (Marascuilo) was used.The differences were regarded as statistically significant at a significance level of $p < 0.05$.

3. Results

3.1. Incidence of Adverse Drug Reactions

The incidence of AEDs-induced ADRs varied from 24.5% to 50%. A comparison of the incidence of ADRs of various AEDs with valproates did not reveal a statistically significant difference, with the exception of carbamazepine. When using carbamazepine, the incidence of AEDs is statistically significantly lower compared to valproates: 25.9% and 40.32%, respectively ($p < 0.05$). A comparison of the incidence of ADRs of various AEDs with carbamazepine did not reveal a statistically significant safety advantage of other peptides, and the incidence of ADRs of topiramate was statistically significantly higher (43.64% and 25.9%, respectively; $p < 0.05$).

3.1.1. Valproates

The incidence of ADRs was, in general, 40.32%. The ADRs belonged to type A in 98.97% of cases, to type B – 1.03%. In one case, type D ADRs was registered – a congenital malformation in a child born to a mother taking VPA during pregnancy. The causal relationship between the use of VPA and the development of ADRs was assessed as "probable" (208/275; 75.63%), "possible" (52/275; 18.92%), "definite" (15/275; 5.45%).

The highest incidence was found for ADRs from the gastrointestinal tract. The structure of ADRs from the central nervous system (CNS): encephalopathy (36/682; 5.28%), aggravation of seizures (35/682; 5.13 %), cognitive impairment (22/682; 3.23%), drowsiness

(10/682; 1.47%), tremor of the hands (51/682; 7.48%), ADRs from the psycho-emotional sphere - irritability, aggression, disobedience (12/682; 1.76 %) and emotional disorders, depression (9/682; 1.32%).

3.1.2. Carbamazepine

The ADRs were registered in 25.9% of cases. The ADRs belonged to type A in 96.41% of cases, to type B – 3.59%. The causal relationship between carbamazepine intake and the development of ADRs was assessed as "probable" (26/65; 40%), "possible" (342/65; 52.31%), "definite" (5/65; 7.69%).

The ADRs from the CNS was registered with the highest frequency.

3.1.3. Oxcarbazepine

The incidence of ADRs was 27.78%. The ADRs belonged to type A in 95.41% of cases, and to type B – 4.59%. The causal relationship between oxcarbazepine intake and the development of ADRs was assessed as "probable" (29/30; 96.7%), "possible" (1/30; 3.3%). There was no statistically significant difference between the incidence of ADRs against the background of oxcarbazepine and oxcarbazepine use ($p > 0.05$).

At the same time, a comparison of the ADRs structure of carbamazepine and oxcarbazepine revealed a statistically significant decrease in the development of ataxia against the background of the use of oxcarbazepine ($p < 0.05$). On the contrary, the frequency of aggravation of epileptic seizures was statistically significantly higher against the background of the use of oxcarbazepine ($p < 0.05$).

3.1.4. Topiramate

In general, the frequency of ADRs registration was 43.64%. The ADRs belonged to type A in 98.18% of cases, to type B – 1.82%. The causal relationship between the use of to-piramate and the development of ADRs was assessed as "probable" (63/72; 87.5%), "possible" (9/72; 12.5%). The CNS ADRs were most frequently recorded: cognitive impairment (14/165; 8.48%), seizure aggravation, encephalopathy and temporal lobe syndrome were registered with the same frequency (6/165; 3.64% each), dizziness (2/165; 1.21%). From the psycho–emotional sphere, ADRs were registered in 6.67% of patients: emotional disorders and depression (8/165; 4.85%), irritability, aggression and disobedience (3/165; 1.82%).

3.1.5. Levetiracetam

The frequency of ADRs registration was 36.91%. The ADRs were classified as type A in 100% of cases. The causal relationship between levetiracetam intake and the development of ADRs was assessed as "probable" (46/55; 83.64%), "possible" (7/55; 12.73%), "definite" (2/55; 3.63%). In the structure of HP, the most frequently recorded CNS disorders are: aggravation of seizures (21/149; 14.09 %), hyperexcitability (11/149; 7.38%), drowsiness (6/149; 4.03%), visual hallucinations (3/149; 2.01 %), cognitive impairment (2/149; 1.34%). From the psycho-emotional sphere, the ADRs were registered in 12.75% of patients: irritability and aggression (16/149; 10.74%), emotional disorders and depression (3/149; 2.01%).

3.1.6. Lamotrigine

An analysis of information on 85 patients receiving lamotrigine showed that ADRs were registered in 21 patients (24.71%). The ADRs belonged to type A in 88.24% of cases, to type B – 11.76%. The causal relationship between lamotrigine intake and the

development of ADRs was assessed as "probable" (18/21; 85.71%), "possible" (3/21; 14.29%). Skin ADRs is most often registered (11.76%).

3.1.7. Lacosamide

The number of patients receiving lacosamide in the study sample was small, only 16 people. Of these, the development of ADRs was registered in 8 patients, which is 50%. Cardiac arrhythmias in the form of sinus bradyarrhythmia and aggravation of seizures occurred with the same frequency (2/16; 12.5%). Dyspepsia, hypotension, hypotension and diplopia were registered in one case each (1/16; 6.25%). The causal relationship between lacosamide intake and ADRs development was assessed as "probable" in all cases (8/8; 100%).

So, an assessment of the effect of AEDs on various organs and systems showed that obesity and ADRs from the gastrointestinal tract were statistically significantly more likely to develop when taking valproates ($p < 0.05$). Skin rash ("dermatitis") is most often reported when taking lamotrigine (10/85; 11.76%) ($p < 0.05$). Cognitive disorders were statistically significantly more often registered against the background of topiramate intake (14/165; 8.48%) ($p < 0.05$). Psycho-emotional ADRs were statistically significantly more often reported in patients receiving levetiracetam (30/149; 20.13%) ($p < 0.05$).

Thus, obesity, alopecia and gastrointestinal disorders prevailed in the structure of VPA-induced ADRs, and cognitive and psycho-emotional disorders prevailed in the structure of AEDs in the third generation.

The aggravation of epileptic seizures was registered in 93 patients, which accounted for 7.96% of the total number of analyzed cases. At the same time, seizure aggravation was statistically significantly more common in children than in adults - 13.77% versus 5.9%, respectively ($p < 0.05$), which is an alarming phenomenon from a clinical point of view. On the one hand, an increase in seizures in children can lead to speech and psychomotor regression. On the other hand, an increase in seizures is a common reason for the unjustified appointment of additional AEDs or an increase in the dose of previously taken AEDs.

Against the background of taking second-generation AEDs, the frequency of aggregation was low and did not significantly differ among patients taking VPA (5.28%) compared with patients taking carbamazepine (3.19%), ($p > 0.05$). The frequency of aggravation against the background of topiramate and lamotrigine intake (4.24% and 3.53%, respectively) was the lowest in the group of generation III AEDs and did not statistically differ from the frequency of aggravation against the background of VPA intake ($p > 0.05$). The highest frequency of aggravation was revealed against the background of taking AEDs of the third generation – levetiracetam and oxcarbazepine (15.44% and 12.04%, respectively), which is statistically significantly higher than that against the background of taking VPA (5.28%) ($p < 0.05$).

The analysis of the AEDs safety and frequency of ADRs development did not reveal a significant advantage of the III generation AEDs compared to the II generation AEDs. Significant differences are observed in the structure of the identified ADRs. Compared with the second-generation AEDs, the third-generation AEDs are most characterized by ADRs from the psycho-emotional sphere (aggressiveness, depression, hyperexcitability). The aggravation of epileptic seizures is possible against the background of taking AEDs of any generation, however, the incidence of hypertension against the background of taking levetiracetam and oxcarbazepine is statistically significantly higher than when taking VPA.

3.2. Pharmacogenetic Study

Homozygous CYP2C9 genotype*1/*1 was dominated in all groups, while it was more common among Yakuts (88.9%) and Tuvans (81.3%) compared with Russians (62.5%). Heterozygous CYP2C9*1 /*2 and CYP2C9*1/*3 genotypes in Russians were 17.5% and 15.0%, respectively; and in Yakuts (7.4% and 3.7%) and Tuvinians (6.2% and 12.5%), respectively Homozygous carriage of the CYP2C9*2 allele was detected only in the group of Russians with a percentage ratio of 2.5%, and homozygous carriage of the CYP2C9*3 allele was not registered in any of the studied ethnic groups. Compound heterozygote CYP2C9*2 /*3 genotype was found only among Russians with a frequency of 2.5%.

Ethnic peculiarities in the frequency of ONV of the *CYP2C9* gene associated with a slowdown in AEDs liver metabolism in the population of the regions of Eastern and Northeastern Siberia can be explained by several reasons, including genetic drift, natural selection, and adaptation of the population to local environmental conditions Wednesday. The main reasons for the low prevalence of ONV CYP2C9*2 and CYP2C9*3 in the Yakut ethnic group among patients with epilepsy include the relative transport isolation of regions and the formation of regional genetic isolates, especially in hard-to-reach areas of this republic.

The results obtained indicate that the dosing of a number of AEDs for the treatment of epilepsy and drugs for the treatment of comorbid and concomitant diseases in this category of patients should be carried out from the perspective of personalized medicine and taking into account the ethnic aspect. For example, the administration of valproates, diphenine and other AEDs with the hepatic pathway of metabolism with the participation of the CYP2C9 isoenzyme in the Russian ethnic group of patients with epilepsy in one of the largest regions of the Russian Federation, the Krasnoyarsk Territory, should be carried out most carefully and carefully, taking into account the higher frequency of "poor metabolizers", due to the fact that According to the 2010 census, persons of Russian nationality make up 88.07% (the absolute majority) of the population of the Krasnoyarsk Territory.

5. Conclusion

The frequency of ADRs against the background of third-generation AEDs was not inferior to that against the background of receiving second-generation AEDs, while the structure of ADRs was different: third-generation AEDs had a higher incidence of ADRs from the central nervous system, including a worsening of the course of epilepsy. The ratio of the chances of VPA accumulation with the achievement of toxic concentration in the blood and the development of undesirable side effects in poor metabolizers - carriers of the polymorphism of CYP2C9*2 or CYP2C9*3 - is 5.94 and 4.27, respectively. A personalized approach to ensuring the safety of valproic acid preparations based on taking into account the carriage of polymorphisms of the *CYP2C9* gene allows to reduce the incidence of ADRs in patients receiving VPA from 59.28% to 10.78%.

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