EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 6
62-65
Year: 2020

A NEW APPROACH TO GABA MIMETICS

Musaeva D. M.*

Candidate of Medical Sciences, Bukhara State Medical Institute.

***Corresponding Author: Musaeva D. M.**
Candidate of Medical Sciences, Bukhara State Medical Institute.

Article Received on 31/03/2020 **Article Revised on 21/04/2020** **Article Accepted on 12/05/2020**

ABSTRACT
Annotation. In experiments on white rats of the Vistar line, the effect of GABA-mimetics on the duration of sleep caused by the test drug etaminal sodium in acute toxic hepatitis was studied. It has been established that in animals with acute toxic hepatitis, the duration of sleep of sodium etaminal is prolonged in comparison with healthy individuals. Experimental therapy with GABA - mimetics: aminalon and phenobarbital - led to a significant elimination of the disturbed pharmacodynamics of the test drug sodium etaminal compared to untreated animals, which indicated a hepatoprotective effect of GABA mimetics

KEYWORDS: GABA-mimetics, acute toxic hepatitis, hepatoprotector, pharmacodynamics of sodium etaminal.

Relevance

The development of rational methods of drug treatment of metabolic disorders in liver diseases, as well as their pharmacological correction is an urgent problem.

It is considered established that pathologies of the hepatobiliary system are one of the important modulators of pharmacodynamics and pharmacinetics of drugs. In order to increase the effectiveness of pharmacotherapy, the doctor needs to know the specifics of the action of drugs in specific conditions.

Drugs that affect the processes of neuroplasticity of the Central nervous system occupy one of the leading places in the treatment of nervous diseases, mental disorders and vascular diseases of the brain.[1] Traditionally, angioneurology uses a number of drugs that affect plastic, neurotransmitter, neuroprotective and integrative processes in the brain. Among them, a special place is occupied by nootropic drugs.[3] Nootropics are not accidentally called drugs of the XXI century, emphasizing their prospects. For example, in the United States, nootropics (along with antidepressants) are currently the most intensively developing group of drugs in neuropharmacology. This is due to their unique clinical and pharmacological capabilities, which differ significantly from other neuro - and psychotropic drugs. They are characterized by a metabolic and neurotrophic effect, which causes the processes of improving redox reactions, reducing the aggressive action of lipid peroxidation products(POL), and a positive effect on neurotransmission.[2,10] In addition, these drugs have a vasoactive and mild antiplatelet effect-they reduce platelet aggregation, reduce the adhesion of red blood cells to the surface of the endothelium, and reduce blood viscosity. Due to these properties, a group of nootropic drugs is often called neurometabolic cerebroprotectors, which indicates a common property for drugs in this group — to stimulate metabolic processes in the nervous tissue, optimizing the level of metabolism.[4,8]

The group of medicines, which consists of nootropic drugs, is developing very dynamically both in Uzbekistan and abroad. Leading pharmaceutical companies in various countries are engaged in the development of new drugs. Evaluation of the Yearbook Pharmaprojects, in various stages of research, clinical studies and market introduction is 132 nootropic drugs, of which 79 are in the stage of preclinical studies, 34 — at different stages of clinical studies and 19 at the stage of registration and market penetration.[9]

The result of this practice is often completely unjustified polypragmasia, especially common in the elderly and senile age, i.e. when it is most undesirable. It is not uncommon to simultaneously prescribe to one patient up to 5-10 or more drugs of different groups with different mechanisms of action, which has a number of negative consequences: an increase in the number of side effects and uncontrolled treatment, the potentiation of known side effects of individual drugs and the occurrence of unexpected complications, difficulties in selecting the dose regime for the doctor and in observing this regime for the patient, a significant increase in the cost of the treatment process and.[4,6]

Aminalon being a g-Aminobutyric acid (GABA) is a biogenic substance. It is contained in the Central nervous

system and takes part in neurotransmitter and metabolic processes in the brain. When using GABA for therapeutic purposes in the presence of cerebral pathology, it was found that it improves the dynamics of nervous processes in the brain, thinking, memory, and has a mild psychostimulating effect. As a drug, aminalon has found use mainly in geriatric practice and in the treatment of children with mental retardation.[13]

Phenobarbital is usually considered as a sleeping aid. One of the main properties of phenobarbital is its ability to cause "induction" of enzymes and increase the activity of the monooxygenase enzyme system of the liver, which should be taken into account when simultaneously using it with other drugs, the effect of which may be weakened.[7]

Particular attention is drawn to the position of the liver – the main pharmacometabolizing organ in such a situation, since such an unreasonable use of several neurotropic agents leads to a violation of both the pharmacodynamics and pharmacokinetics of drugs.[6,11,14] Liver damage can significantly affect the biotransformation of drugs, since many drugs in the body are metabolized in the liver.[5,12,15] In diseases of the liver itself, this polypragmasia attracts special attention, which has not yet been sufficiently studied.

Based on the above, the purpose of this work was to compare the effect of aminolone and phenobarbital on the duration of sleep caused by the test drug-sodium etaminal in toxic liver damage.

Research materials and methods

The experiments were performed on 60 Mature male rats with an initial weight of 155-175 g. the Animals were kept in standard vivarium conditions with free access to food and water, natural changes of light and darkness. The experiments were carried out in accordance with the "Rules for conducting work using experimental animals", as well as the rules adopted by the European Convention for the protection of vertebrates used for experimental research or for other scientific purposes (ETS No. 123) Strasbourg, 18.03.1986. Studies were conducted at room temperature of 20-220C. Models of acute toxic hepatitis (ATH) were used: carbon tetrachloride and heliotrin in the experiment. Two series of experiments were conducted.[12] In each series, experiments were conducted in 5 groups of animals with 6 animals in each group. The first group consisted of healthy animals, and the animals of the other groups reproduced acute Tetrachloromethane hepatitis by intragastric administration for four days of 50% oil solution prepared with olive oil CCl4, at a dose of 1.25 ml/kg.[14] Control animals were injected with olive oil in a similar volume. Acute heliotrin hepatitis was reproduced by a single subcutaneous injection of a freshly prepared solution of heliotrin at a dose of 160 mg / kg subcutaneously, and control animals were given water for injection.[6] A day after the last administration of hepatotoxins, one group received inside aminolone at a dose of 50 mg / kg, the second-100 mg/kg, the other phenobarbital-50 mg/kg, and the untreated group of rats received a similar volume of distilled water. All the studied drugs were administered intragastrically using a probe with a metal olive for six days once a day. In 24 hours after the last administration of drugs in all groups of animals, the pharmacodynamics of sodium etaminal was determined. This test was performed as follows: a freshly prepared aqueous solution of sodium etaminal was administered intraperitoneal at a dose of 40 mg/kg.[5,7] The pharmacological activity of the tested barbiturate was judged by the duration of the rats 'stay in the "side" position after administration of the drug, as well as by the absence of the "turning over" reflex and expressed in minutes.

The results of experimental studies were processed statistically using the standard software package Stat Plus 2009 using well-known methods of variation statistics with an assessment of the significance of indicators (M±m) and differences in the samples under consideration according to the student's t-criterion. The difference was assumed to be reliable at a probability level of 95% or more ($p<0.05$).

RESEARCH RESULT

As shown by the results of experimental studies, in rats with acute toxic hepatitis caused by carbon tetrachloride, there is a significant (by 138.3%) prolongation of the duration of sleep induced by sodium etaminal (Fig. 1).

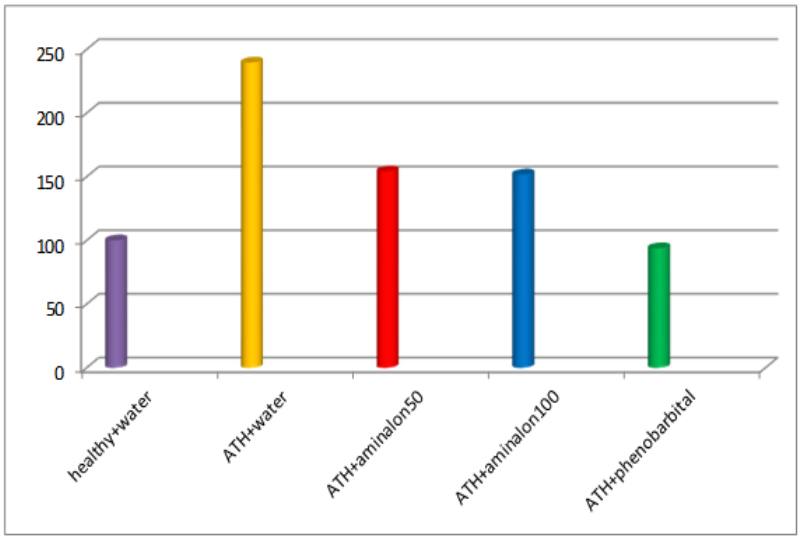

Figure 1: Duration of etaminal sleep in rats with acute toxic hepatitis, reproduced by the introduction of carbon tetrachloride.

Experimental therapy with aminolone leads to a distinct reduction in sleep duration compared to the values of untreated animals. At the same time, increasing the dose of the drug twice did not lead to an increase in the marked effect. In contrast, phenobarbital at a dose of 50 mg / kg shortens the duration of sleep of sodium etaminal to the value of healthy rats. Consequently, the GABA-mimetic agents aminalon and phenobarbital clearly eliminate violations of the pharmacodynamics of sodium etaminal in conditions of acute toxic hepatitis.

While phenobarbital significantly exceeds aminalon in their activity. As is known, phenobarbital is a classic inducer of the monooxygenase enzyme system, so the decrease in sleep duration caused by sodium etaminal is the result of increased biotransformation of this barbiturate. Aminolone, increasing the energy potential of cells, stimulates biosynthetic processes in the brain, probably, this effect of the drug is also manifested in hepatocytes[4], which is why the biotransformation of the studied test drug-sodium etaminal in this pathology in rats is enhanced.

The heliotrin model of acute toxic hepatitis in experimental animals is considered to be the most adequate reproduction of viral hepatitis occurring in humans. Based on this, the study of GABA mimetics in acute heliotrin hepatitis was of great interest (Fig. 2).

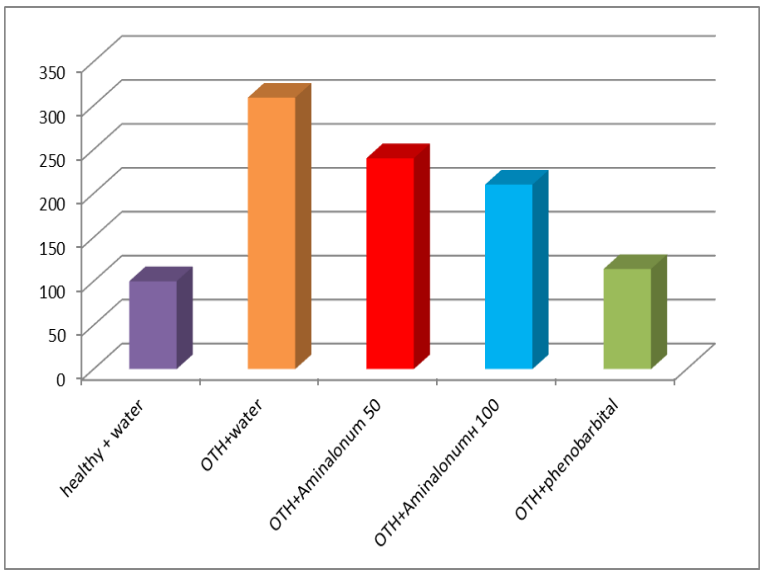

Figure 2: Duration of etaminal sleep in rats with acute heliotrin hepatitis.

As can be seen from these tables, in rats with acute heliotrinovym hepatitis, sodium etaminal causes sleep exceeding in duration by almost two times, than in rats with fat dystrophy caused by carbon tetrachloride. It is noteworthy that in this series of experiments, GABA-mimetic drugs have a corrective effect on the disturbed pharmacodynamics of sodium etaminal. Thus, aminalon at a dose of 50 mg / kg reduces the duration of sleep by

22.0%, and at a dose of 100 mg/kg - by 32.0%, while phenobarbital – by 62.8%, respectively, compared with untreated groups of animals. It can be seen that GABA-mimetic agents have a unidirectional effect on the disturbed pharmacodynamics of sodium etaminal in heliotrin hepatitis.

It can be assumed that GABA mimetics have a protective effect that increases energy metabolism and plasticity in the brain tissue, and similarly affect hepatocytes, which contributes to the restoration of impaired liver functions.

CONCLUSIONS

Based on the above, we can say that the use of GABA-mimetics against the background of toxic liver damage leads to an acceleration of the pharmacodynamics of the test drug, which indicates a positive effect of GABA-mimetics on the disturbed stages of biotransformation, restoring them in case of toxic liver damage. Thus, GABA-mimetic drugs due to various mechanisms of therapeutic action can affect not only neurological pathology, but also the state of the main internal organs.

Understanding the mechanism of action of drugs on the body expands the range of possibilities for drug therapy of various clinical syndromes and diseases. The optimal choice of the drug contributes to the correct understanding of the doctor's pharmacokinetics and pharmacodynamics, which is necessary to determine the rational single and daily dose of the drug used.

LIST OF REFERENCES

1. Anichkov C. B. Neuropharmacology L., Medicine, 1982; 384c.
2. Balabekova M. K. Experimental study rubymine corrective influence on the course of aseptic inflammation in experimental rats //International journal of applied and fundamental research, 2014; 3: 14-15.
3. Gromova, O. A. Neurometabolic pharmacotherapy / O. A. Gromova. - M., 2000; 53.
4. D. Giustarini, I. Gave-Donne, D. Tsikas, R. Rossi. Oxidative stress and human diseases: origin, relationship, measurement, mechanisms and biomarkers. Crit Rev Clin Lab Sci., 2009; 46: 241-281.
5. D. M. Musayeva, B. Sh. Samadov, G. S. Ochilova. Hepatoprotective effect of phenobarbital in experimental toxic hepatitis // Materials of the international scientific and practical conference " Medicine to man. Modern problems of pharmacotherapy and prescription of medicines", 2020; 1: 341-344.
6. D. M. Musayeva, F. K. Klicheva, G. S. Ochilova. Effect of GABA mimetics on the pharmacodynamics of sodium etaminal in experimental toxic hepatitis. - Scientific journal, 2018; 8(31): 44-46.
7. Musayeva D. M., G. S. Ochilova, A. K. Ochilov, O. Yu. Omonov. Effect of GABA mimetics on the pharmacodynamics of the test drug – sodium etaminal in experimental toxic hepatitis // Materials of the VI international scientific conference "Prospects for the development of biology, medicine and pharmacy". Shymkent, 2018; 76-77.
8. Karem H. Alzoubi, Zuhair A. Hasan, Omar F. khabur, Fadia A. Mayas, Omar N. al Yaqub, Salim A. Banihani, Mahmud A. Alomari, Nasr N. S. Alrabadi, vitamin E modifying a high-fat diet. induced reduction of the seizure threshold in rats: the role of oxidative stress, physiology and behavior, 2019; 206.
9. Kovaleva E. L. Search for substances with nootropic properties among GABA derivatives / / in the book: Pharmacology and clinical application of neuroactive amino acids and their analogues, Volgograd, 1985; 146
10. Kotova, O. V. Pantogam-active against stress and fatigue / O. V. Kotova, I. A. Sablina // New pharmacy, 2010; 9: 22-23.
11. Laura Morano Blanco, Nuria Lopez-Alcantara, Olga Estevez, Pierluigi Ramadori, Christophe J. Vrouk, iris Asensio, Javier Vaquero, Rafael Banares, Julia Nevzorova, Francisco Javier Cubero, Damage FRI-089-Genetic Hepatic hepatitis depending on Nrf2, in experimental toxic liver damage, Journal of Hepatology, volume 70, issue 1, Appendix, 2019; e423-e424.
12. Mavlanov sh. R., Rakhmanov A. Kh. Study of the effect of dry extract from medicinal plants on the biliary function of the liver in experimental heliotrin hepatitis //Medical journal of Uzbekistan, 2015; 2: 114-116.
13. Titova, N. V. Modern view on nootropic therapy / N. V. Titova // Neurology. Psychiatry, 2007; 15(24): 1846-1850.
14. Khakimov Z. Z., Rakhmanov A. Kh., Ulmasov M. A. and others. Features of non-specific inhibition of cyclooxygenase by voltaren in acute toxic hepatitis / / Dokl. Acad. Nauk Gruz, 2015; 3: 90-93.
15. Xiaohua D., Jin Z., Hui W. et al. Effect of Yajieshaba, a preparation of Dai indigenous medicine, on enhanced liver detoxication // J. Tradit. Chinese medicine, 2015; 35(2): 197-205.