The Pharmaceutical and Chemical Journal, 2021, 8(1):146-150

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

A New Approach to GABA Mimetics

Sharipova O.Z., Musaeva D.M., Sharipova R.G.

Bukhara State Medical Institute
Department of Pharmacology and Clinical Pharmacology

Abstract 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

Introduction

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 features of the action of drugs in specific conditions.

Drugs affecting 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, a number of drugs are used in angioneurology that affect plastic, neurotransmitter , neuroprotective and integrative processes in the brain. Among them a special place is occupied by drugs nootropnogo series [3]. It is no accident that nootropics are called drugs of the 21st century, emphasizing their prospects. For example, in the United States, nootropics (together with antidepressants) are currently the most rapidly developing group of drugs in neuropharmacology. This is due to their unique clinical and pharmacological capabilities, which are significantly different from other drugs of the neuro - and psychotropic type of action. They are characterized by metabolic and neurotrophic effects, which cause the improvement of redox reactions, a decrease in the aggressive action of lipid peroxidation products (LPO), 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 erythrocytes to the endothelial surface, and reduce blood viscosity. Due to these properties, the group of nootropic drugs is often called neurometabolic cerebroprotectors , which indicates a common property for drugs of this group - to stimulate metabolic processes in the nervous tissue, optimizing the level of metabolism [4, 8].

The group of drugs, which are nootropic drugs, is developing very dynamically both in Uzbekistan and abroad. Traveling pharmaceutical companies in various countries are engaged in the development of new drugs. According yearbook Pharmaprojects , at various stages of research, clinical study and introduction on the

market is tsya 132 nootropic drug s , 79 - at the stage of preclinical study, 34 - at various stages of clinical study, and 19 - at the stage of registration and introduction on the market [9] .

The result of this practice is often completely unjustified polypharmacy, especially common in old and senile age, i.e. when it is most undesirable. There are frequent cases of simultaneous prescription of up to 5-10 or more drugs of various groups with different mechanisms of action to one patient, which results in a number of negative aspects: an increase in the number of side effects and uncontrollable treatment, potentiation of the known side effects of certain drugs and the occurrence of unexpected complications, difficulties in selection of the dose regimen for the doctor and in compliance with this regimen for the patient, a significant increase in the cost of the treatment process [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 found application mainly in geriatric practice and in the treatment of children with mental retardation [13].

Phenobarbital is commonly considered as a hypnotic. One of the main properties of phenobarbital is its ability to cause "induction" of enzymes and enhance the activity of the monooxygenase enzyme system of the liver, which should be taken into account when it is used simultaneously with other drugs, the effect of which may be weakened in this case [7].

Particular attention is drawn to the position of the liver - the main farmakometaboliziruyuschego body in such a situation, since such unwarranted use several neurotropic cFe dstv straight ivodit to disruption as the pharmacodynamics and pharmacokinetics of drugs [6, 11, 1 4]. Liver injury is very sushestvenno can affect biotransformation of drugs because many drugs into the body e metabolized in the liver [5, 12, 15]. In diseases of the liver itself, such polypharmacy attracts special attention, which has not yet been sufficiently studied.

Based on the foregoing p spruce of this study was a comparative study of the impact of aminolone and Phenobarbital on the duration of sleep caused by the test drug - etaminalom sodium in toxic liver injury.

Materials and research methods

The experiments were carried out on 60 sexually 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 change of light and darkness. The experiments were carried out in accordance with the "Rules for Conducting Work with the Use of Experimental Animals", as well as the rules adopted by the European Convention for the Protection of Vertebrate Animals used for Experimental Research or for Other Scientific Purposes (ET S No. 123) Strasbourg, 18.03.1986. The studies were carried out at room temperature 20–22 ^{0}C. Models of acute toxic hepatitis (OTH) were used: carbon tetrachloride and heliotrin in the experiment. Two series of experiments were carried out [12]. In each series, experiments were carried out in 5 groups of animals, 6 animals each. The first group consisted of healthy animals, while the animals of the other groups reproduced acute tetrachlomethane hepatitis by intragastric administration for four days of a 50% oil solution prepared in CCl_4 olive oil at a dose of 1.25 ml / kg [14]. Control animals were injected with olive oil in the same 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 injected with water for injection [6]. A day after the last injection of hepatotoxins, one group received orally 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 distilled water in a similar volume. All investigated drugs were injected intragastrically using a probe with a metal olive for six days, once a day. In 24 hours after the last injection of drugs in all groups of animals, the pharmacodynamics of sodium etaminal was determined. This test was carried out as follows: a freshly prepared aqueous solution of sodium ethaminal was injected intraperitoneally at a dose of 40 mg / kg [5, 7]. The pharmacological activity of the test barbiturate was judged by the duration of the stay of the rats in the "lateral" position after the administration of the drug, as well as by the absence of the "overturning" reflex, and was expressed in minutes.

The results of the experimental studies were processed statistically using the standard Stat Plus 2009 software package according to the well-known methods of variation statistics with an assessment of the significance of indicators (M ± m) and the differences of the considered samples by Student's t -test. The difference was taken as significant at a probability level of 95% or more (p <0.05).

Research Results

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%) lengthening of the duration of sleep induced by sodium etaminal (Fig. 1).

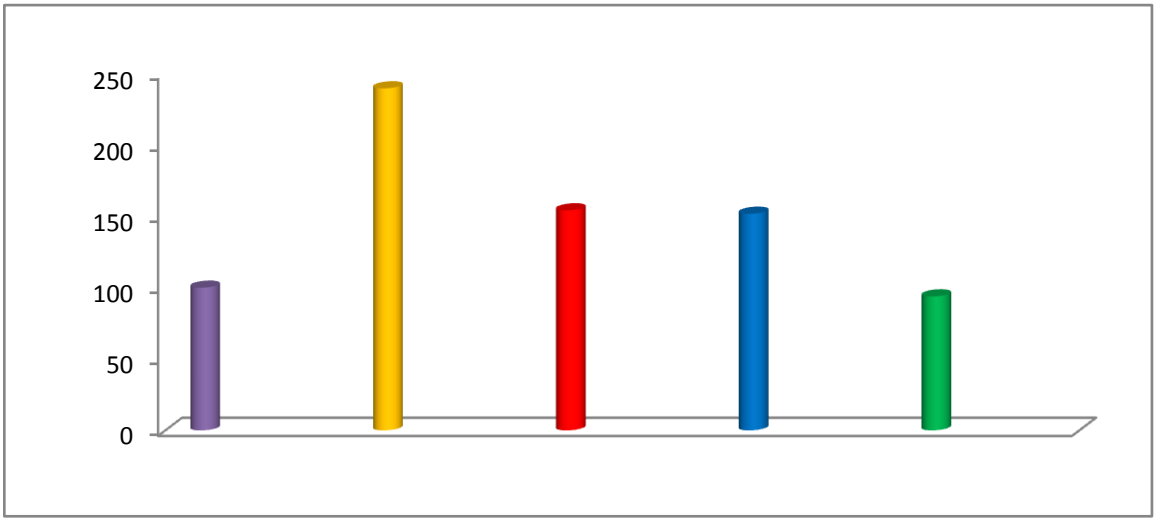

Figure 1: The duration of etaminal sleep in rats with acute toxic hepatitis, reproduced by the administration of carbon tetrachloride

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

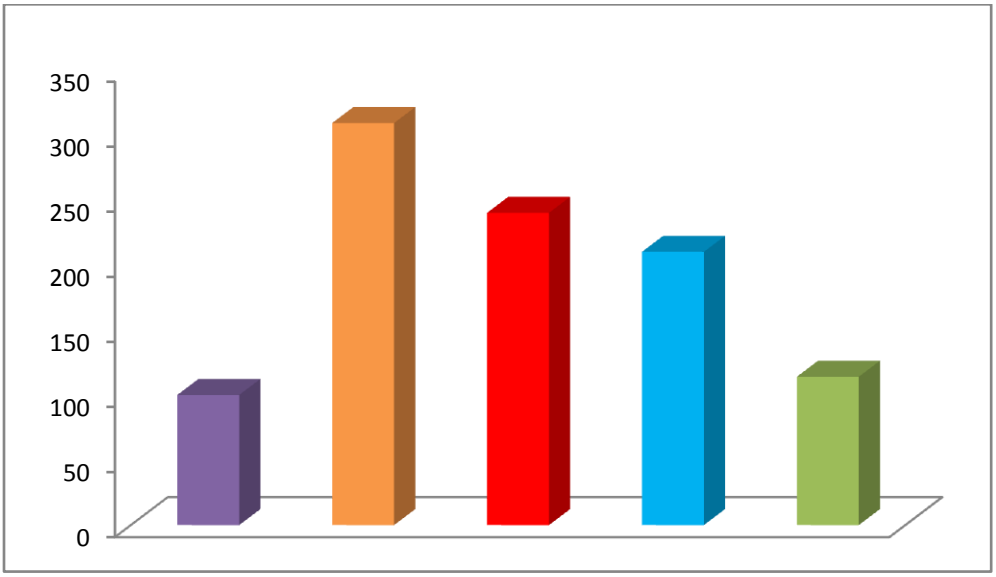

Figure 2: Duration of etaminal sleep in rats with acute heliotrin hepatitis

At the same time, phenobarbital is noticeably superior to aminolone in its activity. As you know, phenobarbital is a classical inducer of the monooxygenase enzyme system, therefore, the decrease in the duration of sleep caused by sodium etaminal is the result of increased biotransformation of this barbiturate. Aminolone, enhancing the energy potential of cells, stimulates biosynthetic processes in the brain, probably, such an action of the drug is also manifested in hepatocytes [4], in connection with which the biotransformation of the studied test drug, sodium etaminal, is enhanced in this pathology in rats.

The heliotrin model of acute toxic hepatitis in experimental animals is considered to be the most adequate reproduction of viral hepatitis that occurs in humans. Proceeding from this, it was of great interest to study GABA-mimetics in conditions of acute heliotrin hepatitis (Fig. 2).

As seen from the tables, in rats with acute geliotrinovym hepatitis etaminal sodium causes sleep superior in duration than almost twice than in rats with steatosis induced by carbon tetrachloride. It is noteworthy that in this series of experiments, GABA-mimetic drugs have a corrective effect on the impaired pharmacodynamics of sodium etaminal. Thus, aminalon at a dose of 50 mg / kg reduces sleep duration by 22.0%, and at a dose of 100 mg / kg - by 32.0%, at the same time phenobarbital - by 62.8%, respectively, compared with untreated groups of animals. It is seen that GABA-mimetic agents have unidirectional effect on impaired pharmacodynamics etaminal sodium at geliotrinovom hepatitis.

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

Conclusions

And converging the foregoing it can be said that n USAGE GABA-mimetics amid toxic liver injury leads to faster pharmacodynamic test preparation and that indicates the positive effect of GABA-mimetic s in broken steps biotransformation , restoring them when toxic liver injury. 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 of drug therapy for various clinical syndromes and diseases. The optimal choice of the drug is facilitated by the doctor's correct understanding of pharmacokinetics and pharmacodynamics , which is necessary to determine a rational single and daily dose of the drug used.

References

[1]. Anichkov S.B. Neuropharmacology L., Medicine, 1982.-384 p.

[2]. Balabekova M.K. Experimental study of the corrective effect of ruvimin on the course of aseptic inflammation in experimental rats // International Journal of Applied and Fundamental Research. - 2014. - No. 3 - P. 14-15

[3]. Gromova, O.A. Neurometabolic pharmacotherapy / O.A. Gromova 2000. 53 p.

[4]. D. Giustarini, I. Dalla-Donn, D. Tsikas, R. Rossi. Oxidative stress and human diseases: origin, relationship, measurement, mechanisms and biomarkers. Crit Rev Clin Lab Sci, 46 (2009), p. 241 – 281.

[5]. D.M. Musaeva, B. Sh. Samadov, G.S. Ochilova. Hepatoprotective effect of phenobarbital in experimental toxic hepatitis // Materials of the international scientific-practical conference “Likas - people. Suchasni problemi farmakoterapiї i priznachennya likarskih zasobiv". 2020. T. 1. S. 341-344.

[6]. D. M. Musaeva, F. By. Klichova, G. With. Ochilova. The effect of GABA mimetics on the pharmacodynamics of sodium etaminal in experimental toxic hepatitis . - Scientific journal, No. 8 (31). 2018. p. 44-46

[7]. Musaeva D.M., G.S. Ochilova, A.K. Ochilov, O. Yu. Omonov. Influence of GABA-mimetics on the pharmacodynamics of the test drug - sodium etaminal in experimental toxic hepatitis // Proceedings of the VI International Scientific Conference "Prospects for the Development of Biology, Medicine and Pharmacy". Shymkent. 2018, S. 76-77.

[8]. H. Kerem Alzubi , Zuhair A. Hassan Omar F. Habur , Fadia A. Mayyas Omar H. Al Yacoub, Salim A. Banihani , Mahmoud A. Alomari , Nasr NS Alrabadi , vitamin E modifying high fat diet and Induced Decrease in Seizure Threshold in Rats: The Role of Oxidative Stress, Physiology and Behavior, Vol. 206, 2019.

[9]. Kovaleva E.L. The search for substances with nootropic properties among GABA derivatives // In the book: Pharmacology and clinical use of neuroactive amino acids and their analogues., Volgograd. 1985. P. 146

[10]. Kotova, O. V. Pantogam - an active against stress and fatigue / O. V. Kotova, I. A. Sablina // New pharmacy. 2010. - No. 9. - S. 22-23.

[11]. Laura Moran Blanco, Nuria Lopes- Alcantara, Olga Estevez, Pierluigi Ramadori, J. Christophe. Vrook Iris Asensio, Javier Vaquero , Rafael Banares , Julia Nevzorova , Francisco Javier Cubero , damage FRI-089 - Genetic Hepat hepatitis depending on Nrf2, when Experimental Toxic Liver Damage, Journal of Hepatology , Volume 70, Issue 1, Supplement, 2019, pages e423-e424.

[12]. Mavlanov Sh.R., RakhmanovA. 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. p. 114-116.

[13]. Titova, N.V. Modern view of nootropic therapy / N.V. Titova // Neurology. Psychiatry. 2007. T. 15, No. 24. S. 1846-1850.

[14]. Khakimov Z.Z., Rakhmanov A.Kh., Ulmasov M.A. et al. Peculiarities of nonspecific inhibition of cyclooxygenase by voltaren in acute toxic hepatitis // Dokl. Acad. Sciences of the Republic of Uzbekistan. 2015. №3. p. 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.

[16]. Abdullayeva M.A., Abdurakhmonov M.M. Congenital risk factors in uzbek population with nonspecific aortoarteriitis// European science review. Austria. - 2018. - № 11-12. - P. 51-53.