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ARGININE GLUTAMATE - DAILY DEPENDENCE OF HEPATOPROTECTIVE ACTIVITY

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Abstract

Glutargin" was first introduced into clinical practice in 1996, but widespread therapeutic use began after 2003, when the clinical efficacy of the drug was confirmed in practice.

Summarizing the results of the analysis of the daily dependence of hepatoprotective activity of arginine glutamate on prooxidant-antioxidant imbalance, the course of metabolic, excretory and detoxification processes in acute paracetamol hepatitis established periods of the day when the drug is most pronounced hepatitis. It was found that the most significant positive changes in prooxidant-antioxidant imbalance with glutargine were observed under conditions of its use against the background of night and day simulations of hepatitis, which is confirmed by the most pronounced increase in reduced glutathione (18-32%) and decrease in thiobarbituric acid %). It was investigated that in the night and day periods under the action of arginine glutamate the most pronounced daily decrease in the activity of cytolysis markers was observed, while in the morning and evening only the tendency to decrease was registered. It was found that the most pronounced tendency to normalize the glycogen content of arginine glutamate was observed against the background of modeling hepatitis at night. It was investigated that under the influence of arginine glutamate an increase in urea content by 10-34% was observed in all study periods of the day.

Thus, based on the chronopharmacological preclinical study of the daily dependence of hepatoprotective properties of arginine glutamate, the most pronounced effect of the drug on the integrated effect on the study of the system and the exchange for its use at night and day

Keywords: *arginine glutamate, hepatoprotective activity, circadian rhythm*

Introduction

In order to study the chronopharmacological activity of arginine glutamate, a domestic preparation based on amino acids "Glutargin" was selected (tablets 250 mg № 30 Health Pharmaceutical Company) [1, 2].

"Glutargin" was first introduced into clinical practice in 1996, but widespread therapeutic use began after 2003, when the clinical efficacy of the drug was confirmed in practice [3, 4]. The relevance of this drug is primarily due to amino acids involved in the detoxification of ammonia [5]. Significant increase in ammonia levels in the blood occurs in many diseases characterized by liver damage (severe viral hepatitis, acute alcoholic hepatitis, cirrhosis of the liver of various origins) and hepato-renal failure (severe jaundice, hepatoparosis, acute various pathological conditions and mushroom poisoning) [6, 7]. It should be noted the important fact that the hepatoprotective effect of arginine glutamate persists in the presence of intrahepatic cholestasis, while most known hepatoprotectors in these conditions do not have a therapeutic effect [8, 9, 10, 11].

There is also a pronounced nootropic effect of arginine glutamate and the ability to eliminate the phenomena of dystrophy in the following categories of patients: liquidators of the Chernobyl nuclear power plant accident with vegetative-vascular dystonia on the background of sluggish hypercholesterolemia; patients with preclinical forms of alcohol abuse and patients with post-infectious asthenia after transmission of viral hepatitis [12, 13, 14, 15]. In the above patients, clinical improvement was registered with long-term oral administration of arginine glutamate in relatively small doses: 0.25 g 3-4 times a day for 1 month, then 0.25 g glutarine 2-3 times a day for 1.5 -2 months.

The combination of antioxidant, membrane stabilizing, detoxifying, nootropic activity of arginine glutamate and the possibility of its use in the presence of severe intrahepatic cholestasis is the basis for the inclusion of arginine glutamate as an adjunct therapy in the treatment of malignancies cervical cancer, gastric cancer with liver metastases, the effect of the drug in tumors of different localization is being studied [16, 17]. Positive results of practical use of glutargine became the basis of its frequent use for the treatment of pathology of the hepatobiliary tract. All of the above confirms the versatility of the pharmacological activity of glutargin, and the establishment of a chronoportrate of this drug will significantly optimize its rational use in clinical practice.

Materials and Methods

Experimental chronopharmacological study of arginine glutamate activity was carried out in three stages. At the first stage of our research, the circadian activity of rat liver functions under physiological conditions was studied. The second stage is devoted to the study of the peculiarities of desynchronoses of circadian rhythms of rat liver function under conditions of acute chronodetermined paracetamol hepatitis (HCDPG). Evaluation of the circadianian dependence of the severity of hepatoprotective activity of arginine glutamate on the background of acute toxic hepatitis simulated in four different periods of the day was performed in the third stage of experimental studies.

Acute toxic hepatitis in rats of both sexes was simulated by administration of paracetamol at a dose of 1000 mg/kg of rat as a suspension in a 2 % starch gel solution. The studied model of hepatitis was reproduced in chronodetermined mode, ie, the toxic dose of paracetamol was administered to rats at fixed hours and periods of the day: 09.00 (morning), 15.00 (day), 21.00 (evening), and 03.00 (night), so the model is interpreted as acute chronodetermined paracetamol-induced hepatitis (ACPH). The study drug "Glutargin" was used intragastrically at a dose of 135 mg/kg and administered in a therapeutic-prophylactic regimen 1 hour before the use of paracetamol and 2 hours after its administration. In animals of the control pathology groups, blood sampling and liver isolation for further studies were performed 24 hours after administration of paracetamol.

Serum was obtained from whole blood according to conventional methods. In all experimental groups of rats of intact control, control pathology and groups of animals injected with drugs in the serum were determined: the activity of ALAT and ASAT using the Reitman-Frenkel reaction; the content of total bilirubin by caffeine reagent by the Yendrashik method; cholesterol content - enzymatically, according to the concentration of quinonymine

formed, which is proportional to the content of this lipid; ALP activity - kinetically by the rate of n-nitrophenol formation, which is directly proportional to the activity of the enzyme. Determination of the studied indicators was performed using standard kits by SPE "Philisit-Diagnostics" (Ukraine), LLC "SpineLab" (Ukraine).

Indicators that reflect the prooxidantantioxidant balance of the body: the content of TBA-AP, GSH, SOD, and catalase activity and glycogen as an indicator of carbohydrate metabolism were determined in the liver homogenate. TBA reactants were determined by the method, to determine GSH used a modification of G. L. Ellman's method, catalase activity was determined by the amount of hydrogen peroxide decomposed per unit time, and the activity of SOD was determined degree autooxidation.

Analysis of circadian rhythms based on the values of the studied indicators in the morning, day, evening, and night periods allows to objectively assess the state of circadian rhythms, and the choice of 09.00, 15.00, 21.00, and 03.00 hours for the study is based on average hours in the morning, day, evening and night, respectively. The analysis of the obtained experimental data was performed using the following chronobiological nomenclature: acrophase (AF) - time of day when the maximum value of the studied indicator is registered; bathyphase (B) - time of day when the value of the studied indicator is minimal; mesor (M) - the average value of the studied indicator during the day; amplitude (A) - the maximum deviation of the studied indicator in two directions from the mesor. Mesor and amplitude were determined using Cosinor-Analisis 2.4 for Excel 2000/XP software

Statistical processing of the obtained results was performed using the program "Statistica 8.0". The nonparametric Mann-Whitney test was used. When comparing the statistics was to take the significance level p <0,05 was taken.

Chronopharmacological study was conducted in the spring season (March) on famel rats weighing 220-250 g in compliance with all bioethical standards [10]. The animals were in the vivarium of the NUPh CSRL with a controlled temperature regime and relative humidity, on a day/night cycle that corresponded to the natural one in the studied season of the year.

To neutralize the influence of light factor on the synthesis of melatonin in the evening and night, the study was performed under an infrared lamp, the radiation of which does not fall in the wavelength range 450-485 nm, ie does not excite retinal ganglia containing melanopsin pigment sensitive to the light of this region of the spectrum, and accordingly, the process of melatonin synthesis is not disturbed.

Results and Discussion

The use of arginine glutamate on the background of modeling the pathology at night (3 a.m.), morning (9 a.m.) and daytime (3 p.m.) periods contributed to the growth of reduced glutathione by 32%, 11%, 18%, respectively, in the absence of almost significant changes in this indicator in the evening (9 p.m.) (Table 1). Therefore, an increase in the mesor rhythm of reduced glutathione was registered with the introduction of arginine glutamate in 1.2 times, while the amplitude was at the level of control animals (Table 2). Acrophase (3 p.m.) and bathyphase (9 p.m.) the content of reduced glutathione in the groups of arginine glutamate is synchronous with intact animals and rats with hepatitis (Table 1).

There were no changes in superoxide dismutase activity when taking arginine glutamate relative to rats with hepatitis (Table 1), which was confirmed by the mesor rhythm of this indicator in the group of arginine glutamate, which did not differ significantly from control animals, while the amplitude decreased by 1.5 under similar conditions (Table 2). The acrophase and bathyphase activity of superoxide dismutase in the arginine glutamate group were synchronous in intact rats and animals with hepatitis and were recorded at 9 a.m. and 9 p.m., respectively (Table 7.1).

Catalase activity when taking arginine glutamate also did not change significantly in all study periods, as indicated by the mesor rhythm of activity of this enzyme, which was almost on a par with the mesor activity of control rats, while the amplitude increased 5.0 times, similar conditions (Table 2).

Synchrony of acrophase catalase activity in the group of arginine glutamate, which was recorded at 9 p.m., with intact or control animals was not observed, while the bathyphase was synchronous with intact rats and was registered at 3 a.m. (Table 1).

When taking arginine glutamate there was a moderate tendency (10%) to reduce the content of thiobarbituric acid -active products in the group of arginine glutamate at night (3 a.m.) and in the evening (9 a.m.) (Table 1). The rhythm rhythm of thiobarbituric acid content-active products in the group of arginine glutamate changed insignificantly - 1.1 times, while the amplitude decreased 1.4 times relative to animals of control pathology (Table 2). Acrophase and bathyphase of content of thiobarbituric acid-active products in the use of arginine glutamate synchronous with intact and control animals and were observed at 9 p.m. and 9 a.m., respectively (Table 1).

Thus, according to the analysis of the effect of arginine glutamate on prooxidant-antioxidant imbalance on the background of acute toxic hepatitis simulated at different times of the day, there were different circadian manifestations of antioxidant properties of this drug. The most significant increase in the content of reduced glutathione (by 32%) when taking arginine glutamate was on the background of modeling hepatitis at night, the trend (11-18%) in the morning and the absence of virtually significant changes in reduced glutathione in the evening. Also, it should be noted the absence of changes in the activity of superoxide dismutase and catalase when taking arginine glutamate in all study periods. Regarding the content of thiobarbituric acid-active products, there was a vague tendency to reduce it in the evening and night.

The effect of the drug on the activity of markers of cytolysis under conditions of pathology directly depends on the ability of the drug to correct prooxidant-antioxidant imbalance [161]. In particular, it was found that the use of arginine glutamate on the background of hepatitis simulated at night (3 p.m.) characterized by a decrease in alanine aminotransferase and aspartate aminotransferase activity by 40% and 42%, respectively by 15% (alanine aminotransferase) and 25% (aspartate aminotransferase) during the day (3 p.m.). Taking the drug in the evening simulation of the pathology (9 a.m.) was characterized by a tendency to decrease the activity of alanine aminotransferase (by 22%) with constant values of aspartate aminotransferase activity against rats with hepatitis. The use of arginine glutamate on the background of hepatitis simulated in the morning (9 a.m.) there were no significant changes in the activity of markers of cytolysis (Table 3).

The ability of arginine glutamate to correct the activity of cytolysis markers in certain circadian periods of control pathology was confirmed by a decrease in the mesor rhythm of these enzymes: alanine aminotransferase - 1.3 times and aspartate aminotransferase 1.2 times. The amplitude of the rhythm of alanine aminotransferase activity decreased by 1.8 times and aspartate aminotransferase significantly with the use of arginine glutamate (Table 4). Acrophase and bathyphase of alanine aminotransferase activity when taking arginine glutamate synchronous with control rats and recorded at 9 p.m. i 3 p.m., respectively, while the acrophase activity of aspartate aminotransferase was at 9 a.m. and bathyphase similar to alanine aminotransferase activity at 3 p.m. (Table 3).

Thus, according to the above, the most pronounced decrease in the activity of cytolysis markers was observed with the use of arginine glutamate on the background of modeling hepatitis at night and during the day, which is probably due to circadian features of antioxidant and membrane stabilizing properties of this drug.

The use of arginine glutamate was not characterized by changes in glucose content in all study periods of the day (Table 5), which is confirmed by the mesor rhythm of this indicator, which was almost on a par with control animals and intact control rats, while the amplitude of the rhythm decreased by 2 times rats with hepatitis (Table 6). Acrophase of glucose content in the group of arginine glutamate synchronous with control animals and was recorded at 9 p.m., and the bathyphase was synchronous with intact and control rats at 9 a.m. (Table 5).

The introduction of arginine glutamate contributed to the trend increase in glycogen content by 18%, 15% and 10% in the group of arginine glutamate at 3 a.m., 9 a.m. and 9 p.m., accordingly, in the absence of significant changes during the day (3 p.m.) (Table 5). Therefore, the mesor rhythm of this indicator with the use of arginine glutamate increased 1.1 times relative to animals of control pathology, with a significant decrease in amplitude

(1.4 times) (Table 6). The acrophase and bathyphase of glycogen content in the arginine glutamate group were synchronous with rats with hepatitis and were observed at 3 p.m. and 9 a.m., respectively (Table 5).

The content of corticosterone when taking arginine glutamate in all daily groups of the drug did not differ significantly from the corresponding circadian groups of rats with hepatitis and intact control animals (Table 5). Therefore, the rhythm mesor of this indicator was almost at the same level in three different groups of rats studied (Table 6). The rhythm amplitude of corticosterone in the arginine glutamate group was at the level of control animals (Table 6). Acrophase (3 a.m.) and bathyphase (3 p.m.) corticosterone content in animals treated with arginine glutamate, synchronous acrophase and bathyphase content of this indicator in intact and control rats (Table 5).

Thus, the introduction of arginine glutamate in the treatment-and-prophylactic regime against the background of acute toxic hepatitis modeled at different times of the day was characterized by unequal effect of the drug on hepatocyte energy supply, which was confirmed by circadian-differentiated increase in glycogen The use of arginine glutamate did not change the content of glucose and corticosterone in all daily groups of the drug.

The use of arginine glutamate in acute paracetamol hepatitis simulated at different times of the day was not characterized by significant changes in total protein, as evidenced by the magnitude of the mesor rhythm in this group of arginine glutamate, which was almost at the same level in control animals and intact rats.(Table 7, Table 8). The rhythm amplitude of total protein in the groups of arginine glutamate is 1.4 times lower than in animals with hepatitis, and 1.7 times compared with intact rats (Table 8). The acrophase of the total protein content when using arginine glutamate was synchronous with the acrophase of the content of this indicator in animals with hepatitis and was registered at 3 p.m., and the bathyphase – at 9 a.m. (there were no synchronies with other research groups) (Table 7).

When using arginine glutamate, the albumin content did not change in comparison with rats with hepatitis (Table 7), as indicated by the mesor of this indicator, which was at the same level in animals with hepatitis and treated with the drug (Table 8). There was an increase in the amplitude of the rhythm of albumin content in animals treated with arginine glutamate in 2.4 times relative to rats of control pathology (Table 8).

The acrophase of albumin content in the group of arginine glutamate is synchronous with the acrophase of the content of this indicator in intact rats and was observed at 9 p.m., whereas the bathyphase – at 3 a.m. (synchronies with other research groups were not registered) (Table 7).

Arginine glutamate contributed to an increase in urea content by 10-33% depending on the study period of the day (Table 7). The rhythm of urea content in the group of arginine glutamate increased 1.2 times, while the amplitude decreased 2.5 times relative to animals with hepatitis (Table 8). Acrophase of urea content in the group of arginine glutamate synchronous with rats with pathology and was observed at 9 a.m., whereas the bathyphase – at 3 a.m. (synchronies with other research groups were not registered) (Table 7).

When using arginine glutamate there was a significant 24% reduction in uric acid in the group of arginine glutamate in the morning (9 a.m.) in relation to animals of control pathology, in the absence of practically significant changes in the value of this indicator in other study periods (Table 7). Therefore, the decrease in the uric acid rhythm mesor was indistinct, while the amplitude decreased significantly (3.2 times) and almost reached the size of intact control rats (Table 8). Acrophase and bathyphase of uric acid in the group of arginine glutamate are synchronous with intact and control animals and were registered at 9 a.m. and 3 p.m., respectively (Table 7).

Thus, the introduction of arginine glutamate on the background of acute toxic hepatitis simulated at different times of the day was characterized by a tendency to increase urea (10-33%) in all study periods and a decrease in uric acid in the morning (9 a.m.). The use of arginine glutamate did not alter the total protein and albumin content of intact animals and rats with hepatitis.

The introduction of arginine glutamate did not contribute to changes in cholesterol in all study periods of the day (Table 9). The mesor rhythm of cholesterol in the group of arginine glutamate was

almost on the same level with animals of control pathology (Table 9; Table 10). The rhythm amplitude was constant in comparison with animals with hepatitis (Table 10). Acrophase and bathyphase of cholesterol in the group of arginine glutamate synchronous with rats with hepatitis and were observed at 9 a.m. and at 9 p.m., respectively (Table 9).

The use of arginine glutamate did not reduce the content of total bilirubin in all study periods (Table 9). This was reflected in a slight change in the mesor and rhythm amplitude of this indicator in the group of arginine glutamate (Table 10).

Acrophase and bathyphase of total bilirubin in arginine glutamate group synchronous with intact animals and rats with hepatitis and recorded during the day (3 p.m.) and at night (3 a.m.), respectively (Table 9).

Under the action of arginine glutamate there was a weak tendency to reduce the activity of the dosage form by 1.1-1.2 times in all study periods, except for the daily (3 p.m.) (Table 9). The mesor rhythm of the activity of the dosage form in the group of arginine glutamate decreased by 1.2 times relative to animals of control pathology. Also, similarly to the mesor, there was a decrease in the amplitude of the activity of this enzyme by 2.0 times (Table 10). Acrophase and bathyphase activity of the dosage form in the group of arginine glutamate were observed at 3 p.m. and at 3 a.m. and were synchronous with intact rats (Table 9).

Thus, the use of arginine glutamate in acute toxic hepatitis simulated at different times of the day was not characterized by significant changes in cholesterol and total bilirubin, while for the dosage form there was a decrease in enzyme activity in all study periods except day.

Conclusions

Summarizing the results of the analysis of the daily dependence of hepatoprotective activity of arginine glutamate on prooxidant-antioxidant imbalance, the course of metabolic, excretory and detoxification processes in acute paracetamol hepatitis established periods of the day when the drug is most pronounced hepatitis.

1. It was found that the most significant positive changes in prooxidant-antioxidant imbalance with glutargine were observed under conditions of its use against the background of night and day simulations of hepatitis, which is confirmed by the most pronounced increase in reduced glutathione (18-32%) and decrease in thiobarbituric acid %).
2. It was investigated that in the night and day periods under the action of arginine glutamate the most pronounced daily decrease in the activity of cytolysis markers was observed, while in the morning and evening only the tendency to decrease was registered.
3. It was found that the most pronounced tendency to normalize the glycogen content of arginine glutamate was observed against the background of modeling hepatitis at night.
4. It was investigated that under the influence of arginine glutamate an increase in urea content by 10-34% was observed in all study periods of the day.

Thus, based on the chronopharmacological preclinical study of the daily dependence of hepatoprotective properties of arginine glutamate, the most pronounced effect of the drug on the integrated effect on the study of the system and the exchange for its use at night and day

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Table 1. The effect of arginine glutamate on the circadian rhythms of proxidant-antioxidant imbalance in conditions of acute toxic hepatitis simulated at different times of the day (n=6-8, M±SEM)

Conditions experiment	Hour of the day			
	03.00	09.00	15.00	21.00
	Reduced glutathione, conventional units			
Intact control	87,52±8,25	105,21±11,65	154,25±13,52	78,33±14,54
Control pathology	70,02±19,78	75,49±12,45	123,84±8,57*	68,45±16,93
Control pathology + Arginine glutamate	92,44±9,05	84,07±5,81	146,79±9,34	72,28±11,26
	Superoxide dismutase, conventional units			
Intact control	42,59±3,18	48,83±2,59	46,04±3,63	39,36±3,73
Control pathology	39,16±3,94	43,48±2,56	43,00±2,84	35,34±2,88
control pathology + Arginine glutamate	44,31±3,95	44,48±4,58	41,99±3,26	39,13±3,59
	Katalaza, mkkat/l			
Intact control	43,60±2,89	50,46±4,24	78,22±3,74	50,08±3,07
Control pathology	48,15±6,76	46,27±5,56	48,98±8,19*	46,58±5,25
control pathology + Arginine glutamate	46,06±6,14	49,05±4,99	49,39±8,22	52,86±4,89
	Thiobarbituric acid active products, µmol/g			
Intact control	25,85±2,85	16,24±2,36	17,21±3,37	30,51±0,81
Control pathology	29,06±3,88	16,23±3,60	19,02±2,03	33,12±3,61
Control pathology + Arginine glutamate	26,49±2,72	17,31±2,11	18,80±2,21	29,49±2,96

Notes: n - number of animals in the group; * - the deviation of the indicator is significant relative to the rate of intact animals (p <0,05).

Table 2. Influence of arginine glutamate on daily rhythms of prooxidant-antioxidant imbalance in conditions of acute toxic hepatitis modeled at different times of the day according to the program Cosinor-Analisis 2.4 for Excel 2000/XP

Conditions experiment (n=6-8)		Reduced glutathione, conventional units	Superoxide dismutase, conventional units	Katalaza, mkkat / l	Thiobarbituric acid active products, µmol / g
Mezor	Intact control	106,33	44,20	55,59	22,45
	Control pathology	84,45	40,24	47,49	24,36
	Control pathology + Arginine glutamate	98,89	42,48	49,34	23,02
Amplitude	Intact control	35,97	5,04	17,31	8,34
	Control pathology	27,14	4,50	0,44	9,82
	Control pathology + Arginine glutamate	27,81	2,92	2,53	7,20

Table 3. Influence of arginine glutamate on circadian rhythms of cytolysis markers under conditions of acute toxic hepatitis simulated at different times of the day (n=6-8, M±SEM)

Conditions experiment	Hour of the day			
	03.00	09.00	15.00	21.00
	Alanine aminotransferase, µmol / hour*ml			
Intact control	0,97±0,12	0,94±0,05	1,19±0,09	0,87±0,05
Control pathology	1,68±0,33	2,36±0,44*	1,26±0,10	2,92±0,22*
Control pathology + Arginine glutamate	1,17±0,04	2,00±0,12	0,90±0,09**	2,27±0,10
	Aspartate aminotransferase, µmol / hour*ml			
Intact control	0,74±0,16	0,75±0,09	0,95±0,05	0,51±0,09
Control pathology	1,86±0,22*	2,25±0,23*	1,44±0,17*	1,75±0,23*
Control pathology + Arginine glutamate	1,08±0,07**	2,02±0,08	1,07±0,05	2,01±0,16

Note: n - the number of animals in the group; * - the deviation of the indicator is significant relative to the rate of intact animals (p <0,05). ** - deviation of the indicator is significant relative to the indicator in the group of animals with hepatitis (p <0,05).

Table 4. Influence of arginine glutamate on circadian rhythms of cytolysis markers under conditions of acute toxic hepatitis simulated at different times of the day according to the program Cosinor-Analisis 2.4 for Excel 2000/XP

Conditions experiment (n=6-8)		Alanine aminotransferase, µmol/hour*ml	Aspartate aminotransferase, µmol/hour*ml
Mezor	Intact control	0,99	0,74
	Control pathology	2,06	1,83
	Control pathology + Arginine glutamate	1,59	1,55
Amplitude	Intact control	0,11	0,16
	Control pathology	0,35	0,33
	Control pathology + Arginine glutamate	0,19	0,01

Note: n - the number of animals in the group.

Table 5. The effect of arginine glutamate on the circadian rhythms of carbohydrate metabolism in acute toxic hepatitis modeled at different times of the day (*n*=6-8, *M±SEM*)

Conditions experiment	Hour of the day			
	03.00	09.00	15.00	21.00
	Glucose, mmol/l			
Intact control	8,49±0,50	7,04±0,59	7,06±0,49	8,16±0,79
Control pathology	7,04±0,49	6,79±0,19	7,65±0,37	8,27±0,51
Control pathology + Arginine glutamate	7,29±0,49	7,19±0,32	7,57±0,32	8,01±0,27
	Glycogen, mg/g			
Intact control	3,04±0,20	1,85±0,18	2,25±0,21	1,96±0,19
Control pathology	1,85±0,18*	1,03±0,10*	2,12±0,16	1,32±0,19*
Control pathology + Arginine glutamate	2,18±0,11	1,19±0,10	2,19±0,10	1,49±0,12
	Corticosterone, pkg/ml			
Intact control	139,97±6,35	60,52±1,03	52,12±0,81	106,80±4,90
Control pathology	121,48±1,58	67,12±11,23	50,35±1,12	98,17±2,00
Control pathology + Arginine glutamate	121,22±2,40	70,68±6,46	51,02±1,79	100,89±3,02

Notes: n - number of animals in the group; * - deviation of the indicator is significant relative to the rate of intact animals (p <0,05); ** - deviation of the indicator is significant relative to the indicator in the group of animals with hepatitis (p <0,05).

Table 6. The effect of arginine glutamate on the circadian rhythms of carbohydrate metabolism in conditions of acute toxic hepatitis modeled at different times of the day according to the program Cosinor-Analisis 2.4 for Excel 2000/XP

Conditions experiment (n=6-8)		Glucose, mmol/l	Glycogen, mg / g	Corticosterone, pkg / ml
Mezor	Intact control	7,69	2,27	89,85
	Control pathology	7,44	1,58	83,83
	Control pathology + Arginine glutamate	7,51	1,76	85,95
Amplitude	Intact control	0,91	0,40	49,64
	Control pathology	0,80	0,20	39,17
	Control pathology + Arginine glutamate	0,43	0,14	38,21

Note. n - the number of animals in the group.

Table 7. Influence of arginine glutamate on circadian rhythms of protein and purine metabolism in conditions of acute toxic hepatitis modeled at different times of the day (n=6-8, *M±SEM*)

Conditions experiment	Hour of the day			
	03.00	09.00	15.00	21.00
	Total protein, g / l			
Intact control	80,22±4,05	75,06±2,05	71,06±4,16	73,60±2,44
Control pathology	69,97±1,41*	71,06±2,56	74,68±2,82	72,65±3,86
Control pathology + Arginine glutamate	75,51±4,04	74,87±1,55	77,48±1,47	77,10±2,89
	Albumin, g / l			
Intact control	41,85±1,52	37,31±1,18	42,26±0,90	45,17±3,48
Control pathology	41,23±0,90	40,88±1,13	38,88±2,25	40,79±1,55
Control pathology + Arginine glutamate	39,03±0,33	39,63±1,26	42,73±2,22	43,77±3,31
	Urea, mmol / l			
Intact control	13,61±1,53	12,10±1,03	11,51±1,12	12,43±1,11
Control pathology	9,75±0,21*	11,43±0,73	9,69±0,24	9,29±0,29*
Control pathology + Arginine glutamate	11,10±0,71	12,60±1,10	11,92±0,62**	12,36±0,48**
	Uric acid, µmol / l			
Intact control	13,16±1,01	14,24±1,37	12,44±0,83	13,07±0,73
Control pathology	15,14±1,62	24,07±0,90*	11,00±1,90	21,73±2,16*
Control pathology + Arginine glutamate	14,06±0,42	18,30±1,94**	12,80±1,43	19,11±0,99

Notes: n - number of animals in the group; * - deviation of the indicator is significant relative to the rate of intact animals (p <0,05); ** - deviation of the indicator is significant relative to the indicator in the group of animals with hepatitis (p <0,05).

Table 8. Influence of arginine glutamate on circadian rhythms of protein and purine metabolism in conditions of acute toxic hepatitis modeled at different times of the day according to the program Cosinor-Analisis 2.4 for Excel 2000/XP

Conditions experiment (n=6-8)		General protein, g / l	Albumin, g / l	Urea, mmol / l	Uric acid, µmol / l
Mezor	Intact control	74,98	41,65	12,41	13,23
	Control pathology	72,09	40,44	10,04	17,98
	Control pathology + Arginine glutamate	76,24	41,29	11,99	16,07
Amplitude	Intact control	4,64	3,94	1,06	0,69
	Control pathology	2,48	1,18	1,07	2,38
	Control pathology + Arginine glutamate	1,49	2,77	0,43	0,75

Table 9. The effect of arginine glutamate on the circadian rhythms of excretory and detoxification processes under conditions of acute toxic hepatitis modeled at different times of the day (n=6-8, *M±SEM*)

Conditions experiment	Hour of the day			
	03.00	09.00	15.00	21.00
	Cholesterol, mmol / l			
Intact control	1,60±0,11	1,70±0,06	1,89±0,06	1,66±0,13
Control pathology	1,82±0,09	1,95±0,08	1,94±0,06	1,76±0,12
Control pathology + Arginine glutamate	1,80±0,11	1,95±0,06	1,90±0,07	1,74±0,05
	Total bilirubin, µmol / l			
Intact control	9,01±0,39	12,46±0,97	17,82±1,16	12,12±0,98
Control pathology	13,09±0,40*	18,12±0,93*	18,93±1,20	15,09±0,96
Control pathology + Arginine glutamate	13,27±0,37	17,43±0,59	17,90±0,53	14,20±0,87
	Dosage form, U / l			
Intact control	105,97±11,04	140,07±14,74	219,00±38,30	140,07±21,27
Control pathology	152,53±12,55*	193,78±14,47*	169,00±47,90	180,40±16,39
Control pathology + Arginine glutamate	125,77±13,35	168,85±9,17	173,62±15,83	164,27±14,35

Notes: n - number of animals in the group; * - the deviation of the indicator is significant relative to the rate of intact animals (p <0,05).

Table 10. Influence of arginine glutamate on circadian rhythms of excretory and detoxification processes under conditions of acute toxic hepatitis modeled at different times of the day according to the program Cosinor-Analisis 2.4 for Excel 2000/XP

Conditions experiment (n=6-8)		Cholesterol, mmol / l	Total bilirubin, µmol / l	Dosage form, Od / l
Mezor	Intact control	1,71	12,85	151,34
	Control pathology	1,87	16,31	174,03
	Control pathology + Arginine glutamate	1,85	15,70	158,12
Amplitude	Intact control	0,14	4,41	56,65
	Control pathology	0,11	3,22	10,77
	Control pathology + Arginine glutamate	0,12	2,82	24,03

Note. n - the number of animals in the group.