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CHRONOPHARMACOLOGICAL STUDY OF HEPATOPROTECTIVE ACTIVITY OF THE DRUG «ANTRAL®»

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Abstract

In recent years, in chronopharmacology, daily monitoring of biorhythms has become increasingly important as much more informative and clinically relevant. Antral - as a hepatoprotective agent has been successfully used in the clinical practice of Ukrainian doctors for more than 10 years, and as a drug registered in Ukraine since 1994. Evaluation of the circadianian dependence of the severity of hepatoprotective activity of antral on the background of acute toxic hepatitis simulated in four different periods of the day was performed in the third stage of experimental studies. 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. In general, according to the above analysis of preclinical chronopharmacological study of circadianian features of realization of hepatoprotective properties of antral on the model of acute toxic hepatitis, which was reproduced in four different periods of the day, the most pronounced effect of the drug when taken in the morning and evening.

Keywords: *chronopharmacological study, hepatoprotective activity, antral.*

Introduction

Chronopharmacological studies are an integral part of modern preclinical and clinical studies of drugs, and the relevance of their conduct is undeniable [21, 13, 5, 21]. The complexity of modeling chronopharmacological studies in humans needs to be carried out these studies in laboratory animals. In recent years, in chronopharmacology, daily monitoring of biorhythms has become increasingly important as much more informative and clinically relevant [4, 24, 11,]. In order to obtain reliable results regarding the chronopharmacological dependence of the hepatoprotective effect of drugs and their adequate interpretation, it is necessary to take into account the chronobiological norm - physiological state of the liver (characteristics of healthy body biorhythms), desynchronoziz of liver biorhythms and direct effect of drugs on prevention and treatment of this desynchronoziz [7, 6, 14].

Antral - aluminum anthranilate (TrisN[2,3-dimethylphenyl)anthranilate] aluminum monohydrate) - a complex compound of aluminum with mefenamic acid, the hepatoprotective effect of which is a total manifestation of a pronounced antioxidant, membrane-stabilizing, anti-inflammatory, analgesic, antipyretic, antiviral and immunomodulatory activities [1]. Antral - as a hepatoprotective agent has been successfully used in the clinical practice of Ukrainian doctors for more than 10 years, and as a drug registered in Ukraine since 1994 [17]. Extensive preclinical and clinical study of antral fully confirmed the author's concept that the complex of metals with biologically active organic ligands is characterized by a high level of prolonged hepatoprotective effect and the absence of severe side effects [20, 12, 23]. Today it is produced by the pharmaceutical company PJSC "Farmak" in Ukraine in the form of tablets with a dosage of 100 mg № 30 [9].

Antral is considered a fairly safe drug. With long-term use, it does not disrupt the functions of organs and systems of the body, it does not have cumulative, immunotoxic, local irritant, allergenic, ulcerogenic, embryotoxic and teratogenic properties [3]. The peculiarity of antral in comparison with other hepatoprotectors is the lack of pronounced choleretic action, which allows to prescribe it to patients with intrahepatic cholestasis, biliary obstruction and with removed gallbladder [28, 16]. Anti-inflammatory, antipyretic and antiviral effects of antral open the prospect of its use in infectious and viral diseases with a pronounced inflammatory component - sore throat, erysipelas, typhoid fever, chronic tonsillitis, frequent recurrent SARS [29]. It is noted the positive effect of the drug on the functional state of the liver, especially given its antitoxic function. The study of the effectiveness of antral in the complex therapy of patients with chronic hepatitis determines the competitiveness of this drug in comparison with known hepatoprotectors. The generalization of the results of pharmacological use of antral indicates the feasibility and prospects for its widespread use in clinical practice for the treatment of liver diseases of various origins, which led to the choice of this drug as the object of our chronopharmacological studies.

Methods

Experimental chronopharmacological study of antral 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 antral 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 [22]. 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 "Antral" was used intragastrically at a dose of 8 mg/kg and administered in a therapeutic-prophylactic regimen 1 hour before the use of paracetamol and 2 hours after its administration [23]. In animals of the control pathology groups, blood sampling and liver isolation for further studies were performed 24 hours after administration of paracetamol [22].

Serum was obtained from whole blood according to conventional methods [22, 15]. 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 [15] Determination of the studied indicators was performed using standard kits by SPE "Philisit-Diagnostics" (Ukraine), LLC "SpineLab" (Ukraine).

Indicators that reflect the prooxidant-antioxidant 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 [26], to determine GSH used a modification of G. L. Ellman's method [19], catalase activity was determined by the amount of hydrogen peroxide decomposed per unit time [18], and the activity of SOD was determined kinetically by determining the degree of inhibition of adrenaline autooxidation [25].

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 [8].

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 [7]. Mesor and amplitude were determined using Cosinor-Analisis 2.4 for Excel 2000/XP software [2].

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 [27].

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 [7].

Results

The introduction of antral in the treatment-and-prophylactic mode contributed to an increase in the content of HCV by 29% and 42% against the background of modeling hepatitis in the morning (09.00) and evening (21.00), respectively, while under similar conditions at night (03.00) and day (15.00) periods VG practically did not differ from the content of VG in control pathology (tab. 1). Therefore, the mesor rhythm of this indicator increased insignificantly: 1.1 times relative to animals with hepatitis, and the amplitude decreased 1.4 times under similar conditions (Table 2). Acrophase of VG rhythm in the antral (HA) group was synchronous with control and intact animals and was observed during the day (15.00), while the bathyphase was shifted from 21.00 (in control and intact rats) at night (03.00) under the influence of the drug (Table 1).

Similar circadianian changes were observed with the activity of SOD under this regimen mode of application of antral, namely in the morning (09.00) and evening (21.00) periods. In particular, there was an increase in enzyme activity by 19% in the morning (09.00) and by 23% in the evening (21.00). The mesor of the rhythm of SOD activity did not change significantly (increased by 1.1 times), and the amplitude was at the level of animals with hepatitis (Table 2). The acrophase of the rhythm of SOD activity in HA was observed at 09.00 and was synchronous in intact and control animals, and the bathyphase at 03.00, ie synchrony with rats with hepatitis and intact was not registered (Table 1). Catalase activity did not change during all circadianian periods studied, except for the use of antral on the background of modeling hepatitis in the evening (21.00), which showed a tendency to increase enzyme activity by 10% relative to control pathology rats (Table 1).

Therefore, the mesor of the rhythm of catalase activity in HA did not differ significantly from the mesor of enzyme activity in the control group, with a clear change in amplitude (8 times) (Table 2). The acrophase and bathyphase of the rhythm of catalase activity in HA were synchronous with intact animals and were observed at 15.00 and 03.00, respectively (Table 1). The use of antral contributed to a decrease in the content of TBK-AP on the background of hepatitis simulated at night (03.00) and in the evening (21.00) by 22% and 19%, respectively, in the absence of changes in the morning (09.00) and daytime (Table 1). Also, in GA at 03.00 and 21.00 the content of TBK-AP was slightly lower (by 12%) than in intact rats (Table 1). The mesor rhythm of TBK-AP in HA decreased by 1.1 times relative to animals with hepatitis, while the amplitude decreased by 1.7 times under similar conditions (Table 2). Acrophase and bathyphase of the rhythm of the content of TBA-AP in GA synchronous intact and control animals and were observed at 21.00 and 09.00, respectively (Table 1).

Therefore, the introduction of antral in the treatment-and-prophylactic regimen under conditions of HCDP was characterized by a differentiated effect of the drug on 100 indicators of the system POL-AOZ. The most pronounced manifestation of antioxidant properties of the drug was observed when it was administered against the background of modeling pathology in the morning (09.00) and evening (21.00) periods. Under the conditions of GCDPG, the circadianian dependence of antral not only antioxidant but also membrane-stabilizing action was established. The latter was assessed by changes in the activity of markers of cytolysis in the blood. It was found that the introduction of the drug on the background of modeling pathology at 09.00 was characterized by a significant decrease in the activity of ALT and AST by 46% and 32%, and at 21.00 - by 37% and 39%, respectively. The use of antral in modeling the pathology at night (03.00) and day (15.00) was not characterized

by normalization of transminase activity (Table 3).

The mesor rhythm of transminase activity decreased: 1.4 times for ALT activity and 1.2 times for AST activity, while changes in rhythm amplitude with when applied antral were not significantly significant for both enzymes (Table 4).

When using antral, the acrophase of ALT activity is synchronous with control animals and was observed at 21.00, while the bathyphase at 09.00, its synchrony with other study groups was not observed. The acrophase of AST activity was registered at 03.00, and the bathyphase at 21.00 (Table 3). Therefore, according to the above analysis, the most pronounced decrease in transminase activity with antral was observed in the morning (09.00) and evening (21.00), which is associated with an increase in HCV and activity SOD and catalase under the action of the drug at this time and probably due to maximum its antioxidant, membrane stabilizing and anti-inflammatory action during these periods.

When using antral, the cholesterol content did not change in comparison with animals of control pathology and intact rats in all study periods of the day, which is confirmed by the magnitude of the mesor rhythm of this indicator, which was almost at the same level in all three different experimental groups of rats. However, the amplitude of the rhythm when taking the drug decreased to 0.09 ± 0.04 mmol / l compared with intact rats (0.14 ± 0.06 mmol / l) and animals with hepatitis - (0.11 ± 0.04 mmol / l) (Table 5; Table 6). The acrophase of cholesterol content in HA is synchronous with intact animals (15.00), while the bathyphase of rats with hepatitis (21.00) (Table 5). When using antral, the content of total bilirubin, as well as cholesterol, did not change in comparison with animals of control pathology, which is confirmed by the size of the mesor rhythm of this indicator, which was on a par with control animals, and the amplitude was slightly higher (1.2 times) than in rats with hepatitis (Table 6).

Acrophase and bathyphase of total bilirubin in HA are synchronous with intact rats and animals with hepatitis and were observed at 15.00 and 03.00, respectively (Table 5). The introduction of antral contributed to a tendency to decrease the activity of LF in 1.2 times in HA at 03.00 and 09.00 and 1.1 times in HA at 21.00, while during the day (15.00) changes in LF activity against rats of control pathology were not observed (Table 5). The mesor of the LF rhythm in the antral groups decreased by 11% relative to animals with hepatitis, at the same time the amplitude increased 2.0 times under similar conditions (Table 6).

The acrophase of LF activity in HA was observed at 09.00 (synchronous with intact animals), and the bathyphase at 03.00, which was synchronous with intact and control rats (Table 5.9). Thus, the intake of antral on the background of HCDPG was characterized by a tendency to decrease the content of total bilirubin by 13% only in the morning, while changes in the activity of LF there was a decrease in enzyme activity, which was tendentious: 1.1-1.2 times in all periods except day (15.00). As for the changes in cholesterol content under the action of antral, such were not observed.

Discussion

The authors-developers of the original drug antral claim that the dominant pharmacological effect that provides hepatoprotective activity of the drug is the manifestation of antioxidant properties of the coordination compound underlying the drug [20, 12, 23]. It is believed that the antiradical effect of antral is realized due to the intervention of the drug in the processes of microsomal oxidation by competitive interactions with the iron ion, which is part of the succinate dehydrogenase system [20]. Inhibition of enzymatic systems of

oxidative phosphorylation leads to inhibition of LPO processes. On the other hand, LPS processes are inhibited by mefenamic acid [17, 12], as antral in chemical structure is aluminum anthranilate. Inhibition of COX also promotes the accumulation of arachidonic acid, which has a positive effect on the stabilization of cell membranes [20]. Probably the daily dependence of the implementation of the above mechanisms of manifestation antioxidant action underlies the circadianian dependence severity of the of hepatoprotective activity of this drug. Summarizing the results of the analysis of the circadian dependence of hepatoprotective activity of antral should be distinguished morning (09.00) and evening (21.00) periods in which the drug showed the most pronounced pharmacological effect, as evidenced by the positive dynamics of changes in ALT, AST, content of HCV, glycogen, uric acid, total bilirubin and LF activity. It should also be noted that the severity of the pharmacological effect of antral depends on the severity of GHDPG: with minimal severity of the pathological process, the study drug showed minimal protective effect (at 15.00 - minimal pathology, and at 03.00 less pronounced than in the morning and evening), and pronounced hepatoprotective effect on the background of the registered most pronounced form of pathology during the day (21.00 and 09.00 - maximum pathological changes).

Conclusions. In general, according to the above analysis of preclinical chronopharmacological study of circadianian features of realization of hepatoprotective properties of antral on the model of acute toxic hepatitis, which was reproduced in four different periods of the day, the most pronounced effect of the drug when taken in the morning and evening.

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Table 1. Influence of antral on circadianian rhythms of indicators of prooxidate-antioxidant imbalance against acute chronodermized paracetamol hepatitis (n=6-8, M±SEM)

	Time of day			
	03.00	09.00	15.00	21.00
	GSH, st.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
Antral	75,04±8,00	97,18±9,16	113,63±6,63	97,26±6,58
	SOD, st.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
Antral	41,49±2,61	51,65±1,98**	47,99±2,48	43,68±2,74**
	Catalase, μkat/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
Antral	46,94±1,97	49,20±6,14	53,48±4,04	51,73±4,02
	TBA-AP, 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
Antral	22,65±2,00	16,02±2,29	18,80±2,06	26,92±0,81

Notes: n – number of animals in the group; * – the deviation of the indicator in the group of animals is relative ($p < 0,05$) to the indicator in the group of intact control; **– the deviation of the indicator in the group of animals is relative ($p < 0,05$) to the indicator in the group of control pathology.

Table 2. Influence of antral on circadianian rhythms of prooxidant-antioxidant imbalance under conditions of acute chronoderm paracetamol hepatitis according to the program Cosinor-Analisis 2.4 for Excel 2000/XP

		GSH, st.units	SOD, st.units	Catalase, µkat/l	TBA-AP, µmol/g
Mesor	Intact control	106,33	44,20	55,59	22,45
	Control pathology	84,45	40,24	47,49	24,36
	Antral	95,78	46,20	50,34	21,10
Amplitude	Intact control	35,97	5,04	17,31	8,34
	Control pathology	27,14	4,50	0,44	9,82
	Antral	19,30	5,14	3,51	5,78

Table 3. Influence of antral on circadianian rhythms of activity of cytolysis markers on the background of acute chronoderm paracetamol hepatitis (n=6-8, M±SEM)

	Time of day			
	03.00	09.00	15.00	21.00
	ALT, µmol/h*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*
Antral	1,6±0,19	1,26±0,14**	1,37±0,08	1,82±0,14**
	AST, µmol/h*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*
Antral	1,80±0,11	1,53±0,24**	1,43±0,14	1,10±0,07**

Notes: n – number of animals in the group; * – the deviation of the indicator in the group of animals is relative ($p < 0,05$) to the indicator in the group of intact control; **– the deviation of the indicator in the group of animals is relative ($p < 0,05$) to the indicator in the group of control pathology.

Table 4. Influence of antral on circadianian rhythms of activity of cytolysis markers under the conditions of acute chronoderm paracetamol hepatitis according to the program Cosinor-Analisis 2.4 for Excel 2000/XP

		ALT, µmol/h*ml	AST, µmol/h*ml
Mesor	Intact control	0,99	0,74
	Control pathology	2,06	1,83
	Antral	1,51	1,46
Amplitude	Intact control	0,11	0,16
	Control pathology	0,35	0,33
	Antral	0,30	0,28

Table 5. Influence of antral on circadian rhythms of indicators of excretory and detoxification processes in the conditions of acute chronodermized paracetamol hepatitis (n=6-8, M±SEM)

	Time of 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
Antral	1,78±0,11	1,85±0,09	1,90±0,06	1,70±0,11
	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
Antral	12,82±0,62	15,79±0,77	18,12±0,95	14,42±0,67
	AP, 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
Antral	127,97±8,50	160,60±11,84	170,50±34,81	160,42±3,46

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

Table 6. Influence of antral on circadian rhythms of indicators of excretory and detoxification processes in the conditions of acute chronodermized paracetamol hepatitis according to the program Cosinor-Analisis 2.4 for Excel 2000/XP

		Cholesterol, mmol/l	Total bilirubin, µmol/l	AP, U/l
Mesor	Intact control	1,71	12,85	151,34
	Control pathology	1,87	16,31	174,03
	Antral	1,81	15,29	154,87
Amplitude	Intact control	0,14	4,41	56,65
	Control pathology	0,11	3,22	10,77
	Antral	0,09	2,73	21,27