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CHRONORHYTHMOLOGICAL FEATURES OF THE NEPHROPROTECTIVE PROPERTIES OF CORVITIN IN ACUTE KIDNEY INJURY

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Abstract. *The aim of this study was to investigate the chronorhythmic changes in the functional state of the kidneys in rats under conditions of experimentally induced acute kidney injury (AKI) and to evaluate the efficacy of the water-soluble form of quercetin ("Corvitin", Ukraine). Experiments were conducted on white laboratory rats, in which myoglobinuric AKI was induced by intramuscular administration of glycerol. Corvitin was administered intraperitoneally once, 40 minutes after pathology induction. Renal function parameters (diuresis, glomerular filtration rate, proteinuria) and oxidative stress markers (malondialdehyde, protein oxidative modification products, glutathione peroxidase activity) were evaluated over a 24-hour period at 6-hour intervals.*

The results demonstrated that AKI disrupted the circadian rhythm of renal excretory function, significantly reduced glomerular filtration, and increased urinary protein levels. Administration of Corvitin led to partial normalization of renal parameters and restored circadian rhythmicity. Additionally, Corvitin reduced oxidative stress, as evidenced by decreased levels of malondialdehyde and protein oxidative modification products, and increased glutathione peroxidase activity. The nephroprotective and antioxidant effects of the drug were most pronounced during the evening hours (after 20:00).

In conclusion, the findings suggest that AKI is accompanied by disruptions in circadian regulation of renal function and oxidative processes. The therapeutic effects of quercetin exhibit time-of-day dependence, highlighting the importance of circadian timing in pharmacotherapy. These

results support the potential of quercetin as a chronotherapeutic agent in the treatment of acute kidney injury.

Keywords. *rhabdomyolytic acute kidney injury, corvitin, antioxidant effect, chronorhythms.*

Introduction.

The rhythmicity of biological processes in each cell is an inherent feature of living beings [1, 2]. The spectrum of biological rhythms includes oscillations with periods ranging from fractions of a second to many years. The main role in this spectrum is played by circadian rhythms, to which all functions of a living organism are subordinated — from biochemical processes occurring in the cell to behavior [3]. The period of these rhythms is determined by the Earth's daily rotation. Thus, the circadian rhythms of biochemical indicators in organs and tissues serve as indicators of the body's state under both physiological normality and pathological conditions.

Similar periodic properties are characteristic of the kidneys, as kidney function has a pronounced circadian periodicity [4]. The analysis of changes in biological rhythms enables not only the improvement of disease diagnosis but also the enhancement of pharmacotherapy effectiveness through the optimization of therapeutic and preventive methods that consider the cyclic organization of physiological, metabolic, and immune processes. Therefore, it is relevant to study the influence of exogenous factors, including medicinal substances, on the structure of the biorhythms of living organisms.

The purpose of our study was to establish chronorhythmic changes in the indicators of the functional state of the kidneys under the conditions of pathology modeling (acute renal failure) and with a single injection of the water-soluble drug quercetin («Corvitin», Borshchagivskyi CPP, Ukraine) [5].

Materials and methods. Experiments were conducted on sexually mature purebred white rats weighing 120–160 g. Animals were kept in vivarium conditions at a constant temperature and air humidity with free access to water, which were kept under conditions of normal light regime (12.00C:12.00T). All animals were divided into 4 groups for the purpose of administering the drug at a 6-hour interval during the day. Acute renal failure was induced by intramuscular administration of 50% glycerol

solution at a dose of 10 mg/kg. Corvitin was administered at a dose of 10 mg/kg (corresponding to 370 mg/kg in terms of quercetin) once intraperitoneally, 40 min after glycerol administration. To evaluate the antioxidant effects of quercetin, kidney tissues were collected after rat decapitation 24 h after modeling acute renal failure at 6-hour intervals: 4 times a day — at 8.00, 14.00, 20.00, and 2.00 h. [10]

Experimental results. Rats are typical nocturnal animals; therefore, the level of metabolism and changes in biochemical and biological processes in the body during the night period significantly exceeds the day, which explains the differences in the functional activity of rat kidneys at different times of the day [11].

Experiments were conducted to study changes in the parameters of kidney function in rats under the conditions of aqueous diuresis with myoglobinuric AKI when using corvitin during the day, which is shown in Figures 1-3.

The kidneys control and maintain the stability of bulk, osmotic, acid-base, and ionic homeostasis and belong to organs with distinct circadian periodicity [4]. In all living organisms, it is possible to study rhythmic changes in biochemical and biological processes in the body, however, the study of the nephroprotective properties of drugs, taking into account their daily effect on the kidneys, remains relevant due to high mortality due to acute kidney damage, as well as the analysis of changes in biological rhythms will improve the diagnosis of a number of diseases and increase the effectiveness of pharmacotherapy due to the optimization of therapeutic ones.

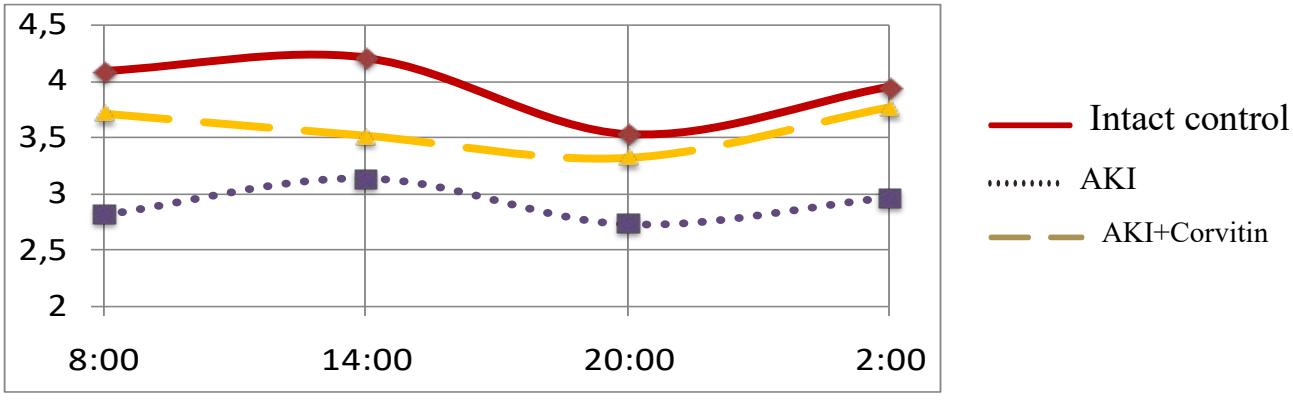

Figure 1 – Diuresis chronorhythms (ml/2 h) in the urine of animals with myoglobinuric AKI when using corvitin compared to model pathology and intact animals (M±m, n=6)

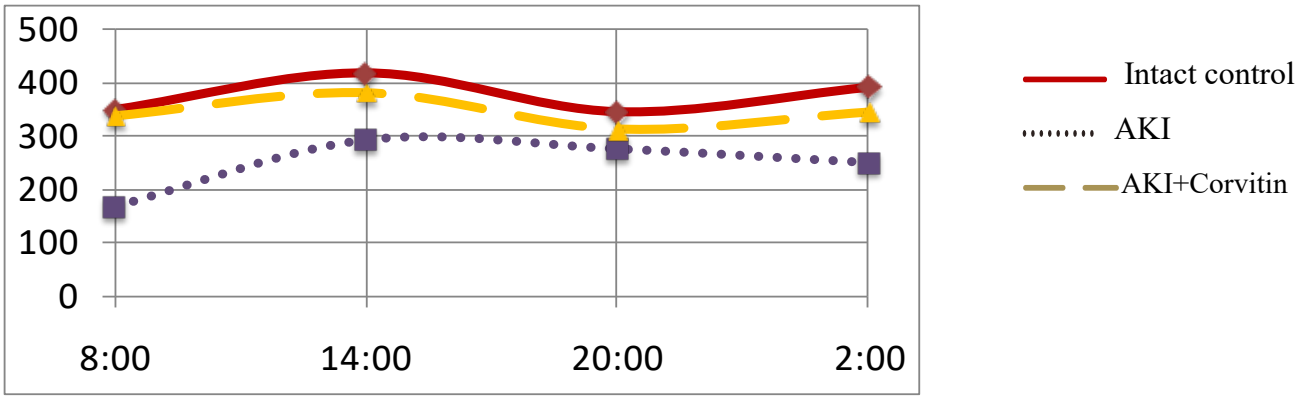

Figure 2 – Chronorhythms of the rate of point filtration club (µl/min) in the urine of animals with myoglobinuric AKI when using corvitin in comparison with model pathology and intact animals (M±m, n=6)

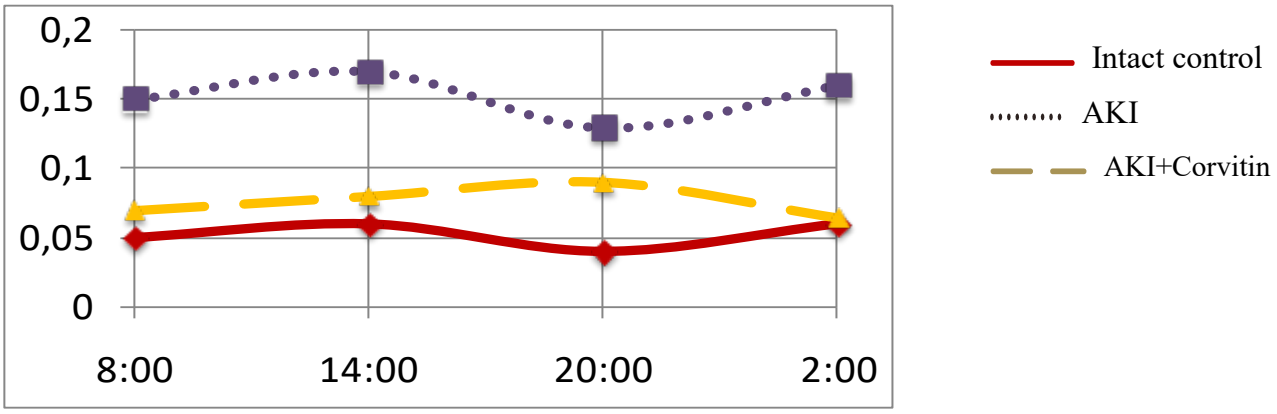

Figure 3 – Chronorhythms of protein content (g/l) in urine of animals with myoglobinuric AKI when using corvitin in comparison with model pathology and intact animals (M±m, n=6), * – probability of difference in comparison between indicators ($p<0.05$)

Chronorhythms of excretory function of the kidneys, which were determined by the indicator of diuresis, in control animals had a sinusoidal character and circadian periodicity, with the maximum indicator of diuresis at 14.00, and the bathyphase was observed at 20.00. The AKI was also subject to changes during the day, with an acrophase at 2:00 p.m. and a bathyphasis at 8:00 p.m. The daily rhythm of proteinuria was single-phase with a low amplitude of oscillations - 12.3%.

The glycerol model of AKI was characterized by a decrease in mesor diuresis by 38% compared to the control group, with acrophase and bathyphase, similar to groups of intact animals. The amplitude of the rhythm decreased by a factor of 1.45. Changes in diuresis were caused by a violation of the filtration process in the kidneys. GFR decreased in all periods of the day, but it was a significant drop was noted at 08.00 by 2.4 times, which affected the amplitude increase by 3.4 times. The AKI mesor was lower than the control group animals by 63.2%. At AKI, significant proteinuria was detected: the mesor of protein concentration in urine increased by 2.6 times, while the amplitude increased by only 1.8%. The obtained results indicate severe damage by myoglobin cylinders as a result of rhabdomyolysis.

Administration of the water-soluble drug quercetin («Corvitin», Borshchagivskyi CCP, Ukraine) to animals with model pathology led to an improvement in the functional state of the kidneys [6-8]. Mesor diuresis increased by 28% compared to a group of animals with pathology. The maximum diuresis under the influence of corvitin was noted at 08.00, the bathiphase fell on 20.00. GFR was also restored, as there was a 43% increase in mesores and a normalization of the GFR amplitude, which decreased by 2.8 times compared to the group of untreated animals. The decrease in proteinuria with corvitin administration was significant, manifested in a 2.2-fold decrease in mesores with acrophase at 14.00 and bathyphasis at 08.00.

Many pathological processes are accompanied in the body by a violation of the temporal organization of physiological functions [9-10]. In the pathogenesis of the development of ARF, there is a violation of redox processes, namely, the activation of free radical oxidation processes is observed against the background of an imbalance of antioxidant protection.

According to the results of the study, it was found that during the day, the content of maalon dialdehyde in the kidney tissues of animals with model pathology without the use of quercetin reached the minimum value at 20.00 hours and increased as much as possible to 2.00 hours, and was 1.8 times higher than the control indicators. After the administration of quercetin, the content of malondialdehyde in group of animals with AKI decreased by 1.2 times per 2.00 hours, although at 8.00 hours, the antioxidant

effect of the drug on the intensity of lipid peroxidation was practically not manifested. The content of products of oxidative modification of proteins increased the most in animals with acute renal failure by 20.00 hours (1.3 times compared to the control). At the same time, the introduction of quercetin most reduced the intensity of the formation of products of oxidative modification of proteins by 14.00 hours. The activity of glutathione peroxidase in kidney tissues was the lowest in the group of animals untreated with quercetin compared to the control group at 20.00 hours. Also, the normalizing effect of the drug on the activity of this antioxidant enzyme was more evident at the same hour of the day.

According to the results of the study, it was found that during the day, the content of maalon dialdehyde in the kidney tissues of animals with model pathology without the use of quercetin reached the minimum value at 20.00 hours and increased as much as possible to 2.00 hours, and was 1.8 times higher than the control indicators. After the administration of quercetin, the content of malondialdehyde in acute renal failure decreased by 1.2 times per 2.00 hours, although at 8.00 hours, the antioxidant effect of the drug on the intensity of lipid peroxidation was practically not manifested. The content of products of oxidative modification of proteins increased the most in animals with acute renal failure by 20.00 hours (1.3 times compared to the control). At the same time, the introduction of quercetin most reduced the intensity of the formation of products of oxidative modification of proteins by 14.00 hours. The activity of glutathione peroxidase in kidney tissues was the lowest in the group of animals untreated with quercetin compared to the control group at 20.00 hours. Also, the normalizing effect of the drug on the activity of this antioxidant enzyme was more evident at the same hour of the day.

Therefore, in animals with model pathology, there are changes in the structure and nature of daily rhythms of nephroprotective processes in kidney tissue. Based on the results of the obtained data, it can be concluded that the correction of acute renal failure in rats with the water-soluble drug quercetin increases in the evening hours of the day, from 8:00 p.m.

Conclusions.

1. In animals with model pathology, there are changes in the daily rhythms of the excretory function of the kidneys.

2. Based on the results of the obtained data, it can be concluded that the correction of acute renal failure in rats with the water-soluble drug quercetin increases in the evening hours of the day, from 8:00 p.m.

Prospects for further research.

It is promising to study the pharmacotherapy of acute renal failure should be selected taking into account the circadian rhythm of antioxidant protection processes in kidney tissue.

Table 1 – Chronorhythms of LP parameters in rats under conditions of aqueous diuresis with myoglobinuric AKI when using corvitin during the day (M±m, n=6)

Показники	Година доби											
	8 .00			14.00			20.00			02.00		
	Control	AKI	AKI+Corvitin	Control	AKI	AKI+Corvitin	Control	AKI	AKI+Corvitin	Control	AKI	AKI+Corvitin
Malondialdehyde, μmol/g	51,72± 1,99	79,01± 3,17	5,16± 2,66	62,96± 3,03	85,89± 2,13	77,87± 2,83	69,70± 0,59	81,39± 1,58	71,94± 2,66	52,38± 2,41	95,09± 6,57	77,32± 2,99
Oxidative protein modification products, units/g	14,21± 0,64	16,39± 0,11	5,73± 0,33	14,83± 0,63	16,00± 0,39	13,23± 0,14	14,40± 0,70	18,56± 1,61	17,21± 0,43	14,34± 2,02	16,24± 0,32	13,17± 0,55
Glutathione peroxidase, nmol/min×mg	238,3 ± 7,23	190,7 ± 6,82	217,8 ± 7,52	236,4± 3,47	170,3± 3,81	216,6± 5,24	244,9± 2,69	170,6± 2,61	226,9± 8,35	183,9± 9,05	164,2± 10,69	199,2± 16,34

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