CIRCADIAN BIORHYTHMS AND THE ACTION OF DRUGS
(A SURVEY OF THE LITERATURE)

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The idea of rhythmic nature of physiological processes is not new. Hippocrates reported 2400 years ago on "rises" and "falls" inherent in the physiological state of humans, calling upon his students to take these fluctuations into consideration in the treatment of patients [1]. However, the intensive study of biorythms has been begun comparatively recently, and as yet searches for the true mechanism of the "biological clocks" characteristic of all life have been fruitless.

The concept of the circadian rhythm, possessing a period of about 24 h, was introduced by Halberg et al. [2]. The modern concepts of circadian rhythms have been treated in detail in the classic studies of Bunning [3], Aschoff [4], and Agadzhanyan [5].

At the present time, more than 100 physiological functions of humans subject to periodic fluctuations over a 24 h period are known [6]. There is evidence of a hereditary, innate, endogenous character of the biorhythms and of their important role in the adaptation of the organism to the environment [7].

In connection with the rhythmic nature of the force of physiological processes, responses of the organism to identical stimuli (chemical, physical) differ at different times of the day.

This literature survey is one of the first attempts to generalize the growing factual material on the extremely important dependence of the pharmacological and toxic action of drugs on the daily biorhythms.

Unfortunately, the relative "youth" of this problem as yet prevents an explanation of the mechanisms of the modification of pharmacological effects as a function of the time of their appearance.

BARBITURATES, ANESTHETICS, ANALGESICS, AND PSYCHOTROPIC PREPARATIONS

Studies are known on the daily variations of the sensitivity of experimental animals to barbiturates [8-11]. The authors have established that large doses of nembutal are necessary for inducing sleep in rodents during the night. The duration of sleep under the action of nembutal is shorter at the active phase than in the inactive phase of the cycle for rodents.

An analogous periodicity in the duration of sleep in white rats has been noted after the administration of hexobarbital. The latter induced a significantly longer sleep at 2:00 p.m. than at 10:00 p.m.

The detected phenomenon may be explained by a circadian rhythm in the activity of the enzymes of the liver, which metabolize xenobiotics. In particular, hexobarbital oxidase has a maximum activity in the case of the shortest sleep and a minimum activity in the case of the longest sleep [12, 13].
The same authors attempted to determine the dependence of the activity of hexobarbital oxidase on the exposure to light and darkness in experiments in vivo. A constant maintenance of the animals in darkness led to a substantial increase in the activity of the enzyme.

Under conditions of adrenalectomy, the rhythm of hexobarbital oxidase activity is reduced [14].

Damage to the hypothalamus in rats is accompanied by an inhibition of the hexobarbital oxidase activity of the liver, while disruptions of the integrity of other brain formations do not give such an effect [15]. This is evidence of a hypothalamo-pituitary-adrenal regulation of the activity of the above-mentioned enzyme.

Together with indirect evidence, there are direct experimental observations of the relationship of the circadian rhythm of liver hexobarbital oxidase activity to the level of corticosteroids in the blood plasma of animals [16].

The circadian variations of the death of animals from barbiturates under the influence of toxic doses are of a different type. The maximum sensitivity was noted during the night and the minimum during the day. This phenomenon is not correlated with barbiturate metabolism in the liver and is attributed by the authors to an independent rhythm of the sensitivity of the brain to their toxic doses [17]. Actually, the direct introduction of low doses of pentobarbital into the lateral ventricles of the animal brain leads to an inversion of the circadian rhythm of sleep.

A certain analogy to barbiturates may be detected in the daily periodism of the narcotic and toxic effects of inhalation anesthetics. Sensitivity to the minimum alveolar concentrations of cyclopropane and fluothane in animals is the greatest during the day (12 noon) and the least in the evening (8:00 p.m.). Cyclic changes in the minimum alveolar concentration are correlated with the circadian variations of the electroencephalographic activity [18], and the content of catecholamines in the rat brain [19]. The daily rhythm of the lethal effect of inhalation anesthetics is inverse with respect to the periodism of their narcotic action [20, 21].

Thus, the therapeutic index is the highest for anesthetics during the inactive period of the day for rodents and decreases during the active period.

The daily periodicity of analgesia induced by morphine in mice is of a different nature. In a dose equal to ED$_{50}$, morphine exhibits the maximum analgesic effect in the dark period (9:00 p.m.) and the minimum in the light period (3:00 p.m.). Moreover, Morris et al. note a correlation of the greatest effect with the "peak" of motor activity and rectal temperature [22].

Fourteenfold differences in the lethal action of lidocaine over a 24-h period have been established. The spasmodic effect under the influence of lidocaine has a maximum at 9:00 p.m. and a minimum at 3:00 p.m. The fact cited are considered by the authors as a function of circadian variations of the lidocaine metabolism in the liver; only 10–20% of it is excreted in unchanged form by animals and even less for man. Moreover, the difference in absorption, membrane permeability, and distribution of the preparation at different times of day are probably substantial [23].

In the opinion of Lutsch et al. [23], we can also assume an increased sensitivity to lidocaine in humans during the active phase of the day.

During the dark period of the day (10:00 p.m.), significant differences in the spasmodic action of indoklon (hexafluorodiethyl ether) are detected in comparison with its effect at 10:00 a.m. The latent period of development of the clonic and tonic components of convulsions and the beginning of the state of inhibition are significantly shorter at 10:00 p.m. [24].

The mortality of animals from chlordiazepoxide (elenium), at maximum during the dark period of the day, reaches a "peak" of action at 8:00 p.m. to 12:00 noon and coincides with the period of high motor activity [23].

In the experiment, a tenfold difference in the mortality of rats from amphetamine at 3:00 a.m. was established in comparison with the light period of the day (8:00 a.m.). The lowest mortality corresponded to the time of normal sleep of the animals [23].

Probably some clarity may be introduced into this question by experiments on volunteers, in which a dependence of the amphetamine excretion on the pH of the urine was established. When the pH of the urine was acid, the percent excretion of the indicated preparation in 16 h reached 54.5 and in the case of an alkaline pH, 2.9 [26-28].