the injection of Zn-MT at a dose of 2 mg/kg corresponds to that of the metal at a dose of 0.11 mg/kg. The Zn basal level in mouse plasma was found to be 1-1.1 μg/ml [11]. If the plasma content per mouse does not exceed 2 ml, the Zn basal level in mouse plasma has been estimated to be 0.08-0.088 mg/kg for a 25 g mouse. This is comparable to the amount of Zn injected with MT. However, the free Zn injection in the control mixture caused no changes in ED_{50} of ethanol. Probably, the Zn from the MT is more biologically active than in the free state (for instance, owing to differences in clearance).

3) It was shown that in alcohols intoxication changes in the antioxidant protection enzyme activity and a drop in the reduced glutathione content result in an increase in the level of lipid peroxidation [2, 4]. Since MT are able to reduce the latter process [12] and contain up to 30% cysteine [8], the protective effect of these proteins can be associated both with the stabilization of lipid peroxidation in the liver and with the replenishment of the pool of thiol groups. The thiol groups in the MT molecule appear to be far more biologically active than in free cysteine.

The investigation of changes in the toxicity of chemical substances brought about by the Zn-MT preparation may be of certain practical interest. Indeed, the Zn-MT active dose (2 mg/kg) is many times lower than its toxic dose (in the experiments in rats Zn-MT was nontoxic up to the extreme dose tested of 43 mg/kg) [14].

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0007-4888/93/0001-0042$12.50

PHARMACOLOGY

Chronobiological Effects of Verapamil on Arterial Blood Pressure and Some Indices of Cardiac Contractility in Rabbits with Vasorenal Hypertension

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UDK 616.12=008.39:1=02:616.61]=07:616.127=008.3=092.9

Translated from *Byulleten' Experimental'noi Biologii i Meditsiny*, Vol. 115, No. 1, pp. 41-43, January, 1993
Original article submitted January 18, 1991

Key Words: *Hypertension, verapamil, myocardium, chronobiology*

The accumulated experimental data and clinical observations clearly demonstrate [1,4,5,9] that the dynamics of various functional indices of the cardiovascular system, including arterial blood pressure, is dependent on diurnal as well as on seasonal chronobiological factors. At the same time, it is

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Table 1. Season Dynamics of Arterial Pressure in Rabbits with Vasorenal Arterial Hypertension without Treatment and after Administration of Verapamil at 12:00 and 18:00 h.

Index, mm Hg	Season			
	spring	summer	fall	winter
APmax, without treatment	164±6,00	174±6,70	151±2,70	184±3,80
APmax, verapamil 12:00 h	148±3,60*	143±4,20*	142±2,70*	**192±3,50**
APmax, verapamil 18:00 h	**167±4,40**	189±6,50	**151±3,90**	201±5,20*
APmin, without treatment	121±3,20	130±5,90	120±2,50	141±3,80
APmin, verapamil 12:00 h	115±7,70	111±1,40*	115±3,70	**144±2,00**
APmin, verapamil 18:00 h	125±3,40	136±4,70	119±1,60	138±5,90

Note: Here and in Tables 2,3 in every group of indices the data reliably deviating from all the others are underlined. Asterisks denote the data in every season for animals after treatment with verapamil which reliably differ from the analogous indices for hypertensive animals which did not receive treatment.

known that the pharmacological effect of medicinal agents is determined to a significant extent by the time of their administration to the organism [2,3,8]. In view of this, we found it of interest to study the correlation between chronobiological factors and the pharmacological effect of remedies widely used in clinical practice, such as calcium blockers [10].

MATERIAL AND METHODS

Experiments were performed on 84 mature male rabbits (chinchilla) with a body weight of 2.5-3.5kg in March, June, September, and December, 1988. Each season, the animals were divided into three experimental groups, 7 rabbits to a group. In animals of the first group, vasorenal hypertension was modeled in operative intervention under hexenal anesthesia by constriction of the abdominal aorta by one third of its initial diameter above the place of renal artery branching. One month after the operation, a stable arterial hypertension developed in these animals [6]. The experiment was carried out two months after consekiction. Rabbits of the second group underwent the same operation but two months later, and during two weeks before the experiment they received daily intravenous injections of verapamil in a dose of 0.5 μg/kg at 12:00 h. In the third group of hypertensive animals, the same dosage of verapamil was administered during two weeks before the experiment at 18:00 h. Animals of the first group received intravenous injections of the corresponding amount of physiological saline.

On the day of the experiment, performed during the period from 12:00 h to 15:00 h, the drug was not injected at all to avoid the undesirable effect of acute administration. In the acute experiment under novocain anesthesia, systolic (AP_{max}) and diastolic (AP_{min}) blood pressure was recorded electromanometrically in the central terminus of the left carotid artery. Subsequently, under light hexenal anesthesia the thorax was dissected in the third intercostal space, the left and right heart ventricles were catheterized, and the peak systolic pressure in the ventricle chambers (IVR_{real} l.v. - real intraventrical pressure in the left ventricle; IVR_{real} r.v. - real intraventrical pressure in the right ventricle) was recorded on a Mingograf-82 polygraph. Then a 5-sec occlusion of the aorta (for the left ventricle) and pulmonary artery (for the right ventricle) was performed and maximal systolic intraventrical pressure was registered under conditions of practically isometric contraction of the heart chambers (IVR_{max} l.v. and IVR_{max} r.v.). The numerical data obtained were subjected to statistical processing and correlation analysis in an IBM PC/AT computer, using software elaborated by our group. The difference between the

Table 2. Seasonal Dynamics of IVR_{real} of Left ant Right Ventricles in Rabbits with Vasorenal Arterial Hypertension without Treatment and after Administration of Verapamil at 12:00 and 18:00 h.

Index, mm Hg	Season			
	spring	summer	fall	winter
IVPreal l.v., without treatment	116±6,00	118±8,10	91±2.10	102±7,90
IVPreal l.v., verapamil 12:00 h	99±7,80	81±3,70*	**57±2,50***	**140±8,10***
IVPreal l.v., verapamil 18:00 h	110±8,00	122±5,70	**63±2,80***	137±7,50*
IVPreal r.v., without treatment	24±1,40	21,4±1,20	19±0,70	24,6±1,00
IVPreal r.v., verapamil 12:00 h	24±1,40	15,3±1,40*	17,6±1,40	32,6±2,40*
IVPreal r.v., verapamil 18:00 h	23±1,80	16,3±1,30*	19,1±0,90	28,0±1,20*

Table 3. Seasonal Dynamics of IVR_{max} of Left and Right Ventricles in Rabbits with Vasorenal Arterial Hypertension without Treatment and after Administration of Verapamil at 12:00 h and 18:00 h.

Index, mm Hg	Season			
	spring	summer	fall	winter
IVPmax l.v., without treatment	180±6,30	**215±4,70**	185±8,00	189±4,50
IVPmax l.v., verapamil 12:00 h	165±7,90	**202±3,90***	178±8,80	**251±8,70***
IVPmax l.v., verapamil 18:00 h	166±13,0	223±4,30	167±1,40*	206±11,0
IVPmax r.v., without treatment	41±1,80	36,9±2,70	39,0±2,00	36,7±1,80
IVPmax r.v., verapamil 12:00 h	44,0±2,80	37,0±2,70	33,6±1,20*	**57,3±1,80***
IVPmax r.v., verapamil 18:00 h	37,0±1,50	32,5±3,10	27,0±1,60*	42,0±2,30

mean values was taken as significant if $p \leq 0.05$. In the correlation analysis, correlation was evaluated as strong at the absolute correlation coefficient value $p \geq 0.07$, as moderate at p=0.69-0.3, and as weak at $p \leq 0.29$. The statistical program assessed the degree of correlations reliability in accordance with the number of observation, the value of the correlation coefficient, and the nature of the correlation curve. In the correlation analysis, we pursued the following objective. As established in our previous study [7], there is a strong, reliable positive correlation between two indices of cardiac contractility - IVR_{real} and IVR_{max} in the left and right ventricles of the intact heart taken in all possible combination. This finding points to a high synchronization in the activity of the myocardiac contractile elements. These interrelations become disturbed only under conditions of heart muscle injury that is manifested in latent cardiac insufficiency. Since this test is a rather objective characteristic of the functional state of the myocardium, we used it in the present study in combination with the correlation analysis of the following pairs: AP_{min}-AP_{max} (as a characteristic of vascular tonus stability) and IVR_{real} l.v. - AP_{min} (consistency between the intensity of left ventricle contraction and the value of peripheral vascular resistance).

RESULTS

The results obtained on arterial pressure and functional indices of heart contractility are summarized in Tables 1-3. As follows from Table 1, administration of verapamil in noon spring, summer, and fall induced a reliable drop in AP_{max} and, in summer, in AP_{min} additionally. The hypotensive effect of the drug was not registered in the winter period. On the contrary, verapamil administration at 18:00 h did not produce any effect in spring, summer, and fall, while in winter time we observed a reliable elevation of AP_{max}, i.e., a hypertensive effect of the drug. The effect of verapamil on the myocardium proved dependent on the administration time as well.

As follows from Table 2, in spring, summer, and fall verapamil administered at midday significantly reduced the real functional activity of the left ventricle and slightly reduced the real function of the right ventricle. In the winter period we registered a reliable increase in both indices.

Administration of verapamil at 18:00 h in the fall experiment resulted in a reliable reduction of the real heart function, while in the winter experiment the outcome was a reliable activation. As for the right ventricle, its real functional activity fell off reliably in summer and increased in winter. Thus, it may be concluded that for verapamil administration at 12:00 h in all seasons except for winter, a certain unloading of the myocardium occurs. Such an unloading is much less pronounced when the drug is administered at 18:00 h. In the winter, administration of verapamil either at midday or at 18:00 h leads to a pronounced hyperfunction of the myocardium in both ventricles.

The data on heart reserve capacities assessed from the activity of the ventricles under conditions of isometry are presented in Table 3. In spring, summer, and fall, in both cases verapamil either did not alter this index or slightly reduced the contractility reserves of both ventricles (for the left ventricles when the agent was administered

Table 4. Seasonal Variation in Correlation Strength (According to Average Absoluted Values of Correlation Coefficients) in Rabbits with Vasorenal Arterial Hypertension without Treatment and after Administration of Verapamil at 12:00 h and 18:00 h.

Experimental group	Season			
	spring	summer	fall	winter
Hypertension without treatment	0,76±0,05	0,94±0,01	0,81±0,05	0,65±0,05
Verapamil, 12:00 h	0,55±0,12*	0,67±0,10*	0,89±0,06	0,83±0,04*
Verapamil, 18:00 h	0,94±0,03*	0,93±0,02	0,92±0,03	0,78±0,05*

Note: In every season asterisks denote the average values reliably differing from the corresponding indices for hypertensive animals without treatment.

at midday in summer and at 18:00 h in the fall; for the right ventricle in the fall at either time).

In the winter period, verapamil reliably increased the contractility reserves of both ventricles when administered at 12:00 h, whereas only a tendency to an increase was observed when the drug was administered at 18:00 h.

Analysis of the correlation between different functional indices of the cardiovascular system has revealed that in hypertensive rabbits in spring, summer, and winter the interrelation between IVR_{real} l.v. and AP_{min} becomes less marked; in other words, cardiac output is not adequate to the peripheral vascular resistance. In both cases, administration of verapamil has a negative effect on the above correlation as well as on the interrelation between AP_{max} and AP_{min}. The average absolute values of the correlation coefficients upon verapamil administration or without treatment are compared in Table 4.

As follows from Table 4, administration of the drug at 18:00 h proved to have a higher normalizing effect on hypertension-induced disturbances in the correlations compared to administration at 12:00 h.

Thus, the hypotensive effect of verapamil is much more pronounced when the drug is administered at midday than at 18:00 h. However, in winter a hypertensive effect of the drug was registered at any time of its administration. The action of verapamil on the myocardium was also time-dependent: the heard muscle functioned in a more "sparing" regime when the drug was administered at 12:00 h compared to 18:00 h. But in winter myocardial hyperfunction was recorded in both cases.

The results obtained allow us to conclude that in terms of the intensity of the hypotensive effect and extent of myocardium involvement, administration of verapamil to animals with vasorenal arterial hypertension at 12:00 h yields better results than administration at 18:00 h. This conclusion is valid for spring, summer, and fall. As for the winter period, verapamil does not exert a hypotensive effect but even provokes a drastic overloading of the myocardium.

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Disturbed Behavior of Rats Suffering Intrauterine Hypoxia is Corrected by Postnatal Treatment with Piracetam

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UDC 616.8-008.47-092.9]-092:618.33-008.64]-085

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 115, No. 1, pp. 43-45, January, 1993
Original article submitted July 7, 1992

Key Words: *prenatal hypoxia; cognitive functions; piracetam*

Fetal hypoxia is one of the most widespread causes of disturbances in brain development exhibited at later dates in neuropsychic disorders [8,9]. In the treatment of such disorders nootropic drugs can be assumed to be effective. In pediatrics nootropics are used in the therapy of mental disturbances of diverse origin in the presence of obvious symptoms of illness [10, 15]). At the same time, the consequences of oxygen deficiency

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