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Peculiarities of Pharmacokinetics and Bioavailability of Some Cardiovascular Drugs under Conditions of Antiorthostatic Hypokinesia

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We studied pharmacokinetics and bioavailability of verapamil, propranolol, and ethacizine in healthy volunteers after single oral administration under normal conditions and on the second day of simulated antiorthostatic hypokinesia modeling some effects of microgravity. Under conditions of antiorthostatic hypokinesia, a tendency to a decrease in half-elimination period, mean retention time, and volume of distribution and an increase in the rate of absorption, ratio of maximum concentrations, and relative rate of absorption of verapamil and propranolol were revealed. For ethacizine, a statistically significant increase in the time of attaining maximum concentration and volume of distribution and a decrease in the maximum concentration, rate of absorption, ratio of maximum concentrations, and relative rate of absorption under conditions of antiorthostatic hypokinesia were found.

Key Words: *verapamil; propranolol; ethacizine; pharmacokinetics; antiorthostatic hypokinesia*

Prolonged exposure to microgravity is associated with changes in the function of many body systems, including the cardiovascular system. Among possible cardiac disorders, a special place is occupied by various cardiac rhythm disorders, hypertensive reactions, and changes in the terminal part of the ventricular complex recorded by ECG. These changes can increase medical risks and threaten the health and life of the astronauts during space flights [4]. In this context, the search for optimal pharmacological means (from the point of view of space medicine) for the treatment of acute cardiological diseases during space flight is extremely important.

The choice of cardiovascular drugs most appropriate for use during real space flight is difficult because their pharmacodynamics and pharmacokinetics can undergo significant changes under conditions of microgravity, which can require correction of the therapeutic schemes. The results of few pharmacokinetic studies performed under conditions of short-term space flights [6,14] and during model experiments [12,13] confirm this assumption.

As various cardiovascular disorders can develop during space flight, analysis of pharmacokinetics and relative bioavailability of cardiovascular drugs under conditions simulating the effects of some space flight factors are extremely relevant.

In the present study we compared the pharmacokinetics and relative bioavailability of verapamil, propranolol, and ethacizine under normal conditions and during antiorthostatic hypokinesia simulating some effects of microgravity.

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MATERIALS AND METHODS

The pharmacokinetic study included 25 healthy volunteers (men aged 23-48 years with similar anthropometric parameters). Group 1 (8 subjects) received 80 mg verapamil (finoptin, Orion Pharma), group 2 (8 subjects) received 80 mg propranolol (anaprilin, Tatkhimfarmpreparaty), group (9 people) received 100 mg ethacizine (Atts-Farm).

Seven-day anti-orthostatic hypokinesia (ANOH) with an angle of 8° was used as the model reproducing some effects of microgravity. All volunteers were familiarized with the research methodology; informed consent was obtained from each participant.

Two successive series were performed: series 1 (background; normal values) unrestricted motion prior to the start of ANOH; series 2 — on day 2 of ANOH; a 7-day break was made between the end of the first and the beginning of second series.

The volunteers received no medication, vitamins, and dietary supplements (except the test drug) 5 days before the start and throughout the study.

In all series, the study was carried out according to the standard protocol: in the morning, after installing B. Braun Teflon cannula into the cubital vein, the initial blood sample was taken. Then, the volunteers received the drug (verapamil, propranolol, or ethacizine) on an empty stomach at the same time with 100 ml boiled water at room temperature. Standard breakfast was given 1 h after drug intake.

The blood for analysis was taken from the cubital vein into heparinized tubes before taking the drugs and then at discrete time intervals: 1, 2, 3, 4, 5, 6, and 8 h after taking verapamil; 0.33, 0.75, 1, 2, 3, 5, 8 h after taking propranolol and 1, 2, 3, 4, 6 h after taking ethacizine. Blood plasma was separated by centrifugation and stored at 20°C until analysis.

Plasma concentration of verapamil and propranolol was measured by HPLC with fluorometric detection [7,10] at λ_{ex} of 203 and 276 nm and λ_{em} of 320 and 340 nm, respectively. Isolation of drugs from blood plasma was carried out by the method of liquid-phase extraction using heptane for verapamil and a mixture of diethyl ether and dichloromethane (4:1 v/v) for propranolol as the extractant; diluted sulfuric acid solution was used as the re-extractant. Quantitative analysis of verapamil and propranolol was performed by the method of absolute calibration and by the method of internal standard using prazosin hydrochloride, respectively. The detection limit was 2 and 5 ng/ml plasma, and regression coefficient r^2 was 0.9954 and 0.9978 for verapamil and propranolol, respectively.

The concentration of ethacizine in the blood plasma was measured by HPLC with UV spectrophotometric detection at 254 nm. Ethacizine from the plasma was extracted with chloroform. The obtained chloroform extract was evaporated to dryness on a rotary evaporator under vacuum. The dry residue was dissolved in 200 μl mobile phase (acetonitrile and 0.1 M acetate buffer, 75:25 v/v, pH 8.0), an aliquot (100 μl) was injected into a chromatograph with a Spherisorb ODS column (5 μ, 250×4.6 mm); the elution rate was maintained at 1.5 ml/min. Quantitative determination was performed by the method of absolute calibration. The detection limit for ethacizine was 5 ng/ml plasma; regression coefficient r^2=0.9981.

The used methods met the basic requirements for analytical methods used for analysis of drug pharmacokinetics and relative bioavailability [8,9].

A total of 364 plasma samples were analyzed: verapamil content was measured in 128 samples, propranolol in 128 samples, and ethacizine in 108 samples.

The data were analyzed using M-IND software [2,3] for a personal computer, calculating model-independent parameters: maximum concentration (C_{max}), time of attaining maximum concentration (T_{max}), area under pharmacokinetic curve (AUC_{0-t} and $AUC_{0-\infty}$), total clearance (Cl_t), mean time of drug retention in the body (MRT), half-elimination period ($T_{1/2}$), and volume of distribution (V_z).

The ratio $C_{max}/AUC_{0-\infty}$ (rate of absorption), relative bioavailability (f), ratio of maximum concentrations (f^{II}), and the relative rate of drug absorption under conditions of ANOH in comparison with normal conditions (for individual values of $AUC_{0-\infty}$, C_{max} and $C_{max}/AUC_{0-\infty}$ respectively) [9,11].

The maximum bioavailability of drugs was calculated using the formula $\overline{F}=Q/(Q+C_{lt})\times100\%$, where Q is blood flow rate through the liver (in humans, Q=1.5 liter/min) [15].

The obtained results were processed using the InStat program. The differences were significant at $p<0.05$.

RESULTS

The profiles of averaged pharmacokinetic curves for verapamil under normal conditions and during ANOH (Fig. 1, *a*) were identical, but after taking the drug under conditions of ANOH, the concentration of verapamil in 2 h and during the time interval of 5-8 h slightly surpassed the background values. Individual maximum plasma levels of verapamil under normal conditions and during ANOH were observed within time intervals of 1-4 and 1-5 h after drug intake, respectively, and varied between 10-130 and 26-121 ng/ml, respectively.

The profiles of the averaged pharmacokinetic curves of propranolol under normal conditions and

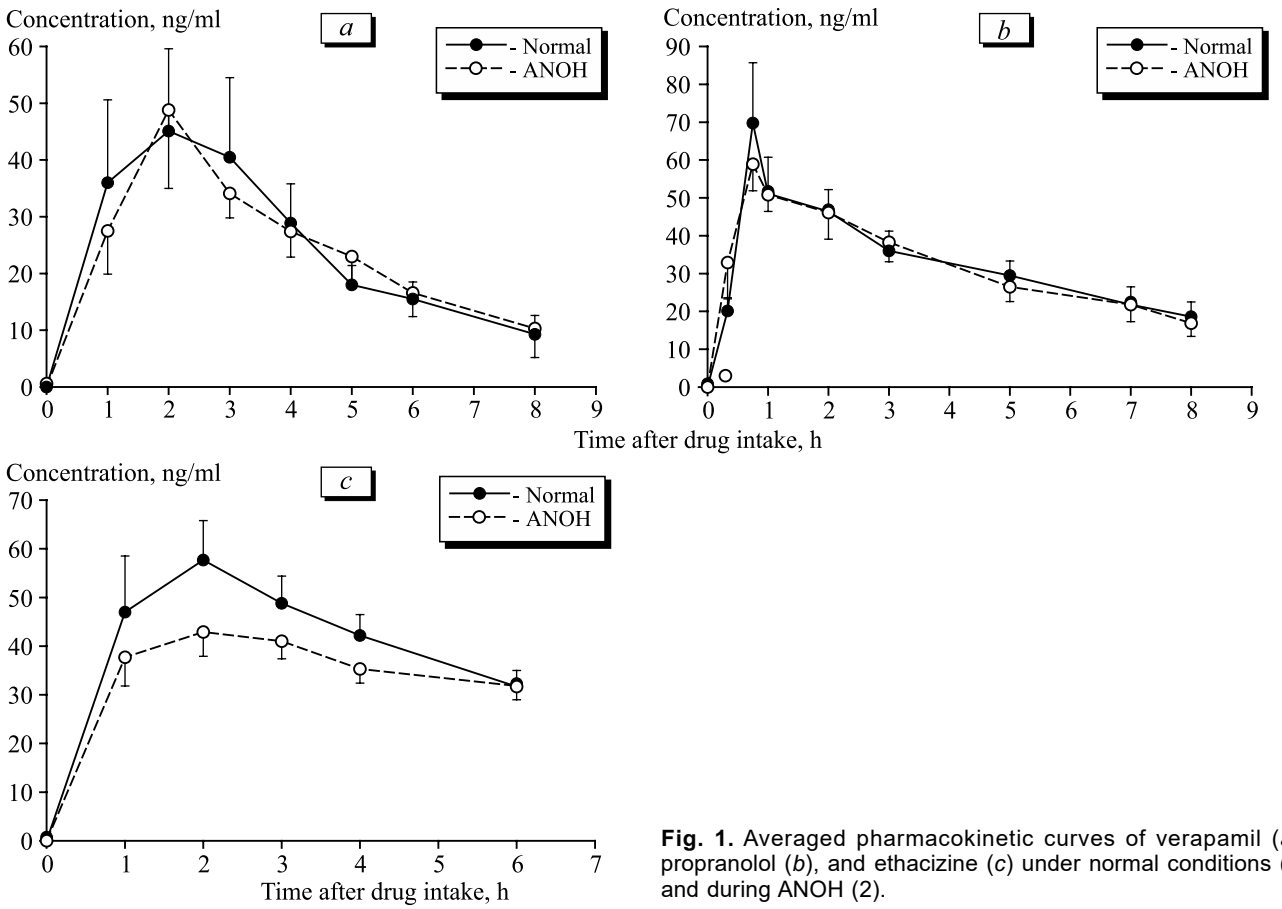

Fig. 1. Averaged pharmacokinetic curves of verapamil (*a*), propranolol (*b*), and ethacizine (*c*) under normal conditions (*1*) and during ANOH (2).

during ANOH (Fig. 1, *b*) were identical, but higher maximum concentration of propranolol in the plasma was achieved under normal conditions. Individual maximum plasma concentrations of propranolol were recorded within the time interval 0.75-2 h (background) and 0.33-2 h (ANOH) after drug administration and varied within 31-164 and 38-89 ng/ml, respectively.

The profiles of averaged pharmacokinetic curves of ethacizine under normal conditions and during ANOH (Fig. 1, *c*) differed significantly: under conditions of ANOH, ethacizine concentration in the plasma was significantly lower than under normal conditions within the time interval of 2-4 h. Under normal conditions, individual maximum levels of ethacizine (39-110 ng/ml) were achieved in 1-2 h after drug intake; during ANOH, individual maximum levels (34-74 ng/ml) were achieved in 1-3 h.

Under conditions of ANOH, a tendency to a decrease in $T_{1/2}$, MRT, and V_z and an increase in $C_{max}/AUC_{0-\infty}$ was revealed. The differences in the pharmacokinetic parameters of verapamil and propranolol under normal conditions and during ANOH were statistically insignificant. For ethacizine, statistically significant decrease in C_{max}, AUC_{0-t}, and $C_{max}/AUC_{0-\infty}$ and an increase in T_{max} and V_z were observed during ANOH in comparison with normal conditions. For ethacizine, the changes in $T_{1/2}$, MRT, V_z, and $C_{max}/AUC_{0-\infty}$ during ANOH were opposite to those observed for verapamil and propranolol.

Under conditions of ANOH, the relative bioavailability of verapamil (122.9±17.5%) and ethacizine (139.9±26.6%) was significantly higher than under normal conditions, while that of propranolol practically did not change during ANOH (95.2±13.1%). The obtained data agree with the dynamics of changes in the maximum possible bioavailability of verapamil, propranolol, and ethacizine under conditions of ANOH expresses in Δ% (+24.7Δ%, -8.4Δ% and, +18.6Δ%, respectively). The ratio of the maximum concentrations of verapamil (170.21±40.11%) and propranolol (124.9±22.9%) during ANOH significantly surpassed the values observed under normal conditions, while for ethacizine, a trend towards a decrease in this parameter was revealed (83.3±7.7%). The relative rate of absorption of verapamil and propranolol during ANOH increased significantly in comparison with normal (141.6±28.6 and 157.9±47.5%, respectively), while relative absorption rate of ethacizine decreased (80.7±19.7%).

The pharmacokinetic parameters of verapamil,

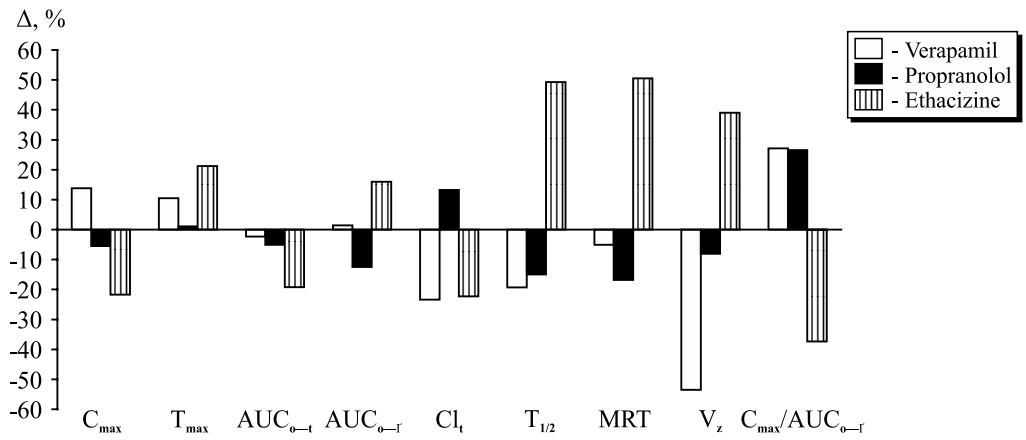

Fig. 2. Dynamics of changes in pharmacokinetic parameters of verapamil, propranolol, and ethacizine under conditions of ANOH.

propranolol, and ethacizine under normal conditions are consistent with published data [1-3,8], and the observed changes in the pharmacokinetics of verapamil and propranolol under the conditions of ANOH agree with previous data for acetaminophen [5].

Thus, we studied pharmacokinetics and relative bioavailability of verapamil, propranolol, and ethacizine under normal conditions and on day 2 of ANOH. A tendency to a decrease the half-elimination period, mean retention time, volume of distribution and to an increase in the rate of absorption, ratio of maximum concentrations, and relative rate of absorption under conditions of ANOH were found for verapamil and propranolol; for ethacizine, a significant increase in the time to reach the maximum concentration and volume of distribution and a decrease in the maximum concentration, rate of absorption, ratio of maximum concentrations, and relative rate of absorption were revealed.

These findings suggest that pharmacokinetics and bioavailability of verapamil and propranolol do not significantly change under conditions of microgravity, which allows us to recommend them for rational pharmacotherapy of cardiovascular diseases in manned space flight.

Some changes in the pharmacokinetic parameters and bioavailability of ethacizine under conditions of ANOH do not exclude the possibility of its use under

TABLE 1. Pharmacokinetic Parameters of Verapamil, Propranolol, and Ethacizine after Single Oral Dose (*M*±*m*)

Parameter	Verapamil, 80 mg (*N*=8)		Propranolol, 80 mg (*N*=8)		Ethacizine, 100 mg (*N*=9)	
	normal	ANOH	normal	ANOH	normal	ANOH
C_{max}, ng/ml	50.9±14.8	57.9±11.5	70.9±15.4	67.0±6.20	63.7±7.6	49.9±4.2*
T_{max}, h	2.38±0.35	2.63±0.42	0.91±0.16	0.92±0.17	1.56±0.20	1.89±0.30*
AUC_{0-t}, ng×h/ml	199.6±53.6	195.0±33.8	268.1±37.7	254.5±28.2	255.3±28.3	206.3±17.0*
$AUC_{0-\infty}$, ng×h/ml	263.4±64.2	267.0±55.3	448,9±64.8	392.9±51.3	571.6±84.6	663.3±81.4
Cl_t, liter/h	504.4±123.3	386.6±64.6	206.4±30.2	233.7±35.6	212.6±36.0	165.1±15.7
$T_{1/2}$, h	4.0±0.5	3.26±1.10	5.9±0.6	5.0±0.6	6.7±1.6	10.0±.1.0
MRT, h	6.3±0.7	6.0±1.4	8.6±0.9	7.2±0.8	10.3±2.3	15.5±1.8
V_z, liter	3018.4±993.4	1409.8±347.2	1630.6±197.6	1498.4±146.8	1627.9±177.4	2263.2±204.7*
$C_{max}/AUC_{0-\infty}$, 1/h	0.1872±0.0144	0.2379±0.0311	0.1600±0.0296	0.2024±0.0459	0.1264±0.0157	0.0791±0.0065*
DT_{max}, h	—	0.25±0.41	—	0.01±0.22	—	0.33±0.17
F, %	15.14	18.88	30.36	27.80	29.76	35.29
f, %	—	122.91±17.50	—	95.21±13.10	—	139.90±26.62
f^{II}, %	—	170.21±40.11	—	124.92±22.85	—	83.34±7.70
RAR, %	—	141.55±28.62	—	157.85±47.52	—	80.70±19.67

Note. RSA: relative absorption rate. *p<0.05 in comparison with normal values.

space flight conditions, but the identified features of this drug should be considered.

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