PHARMACOKINETICS OF ACETAMINOPHEN ADMINISTERED IN TABLETS AND CAPSULES UNDER LONG-TERM SPACE FLIGHT CONDITIONS

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The pharmacokinetics of acetaminophen in two medicinal forms, tablets and capsules, have been studied in healthy volunteers after single peroral administration at a dose of 500 mg under usual living conditions and during long-term space flight. The rate of drug absorption from tablets decreases significantly whereas the relative bioavailability increases substantially under microgravity conditions (compared with usual conditions). For the encapsulated medicinal form, the time of absorption decreases statistically reliably and the half-elimination time, the average retention time, and the distribution volume increase considerably whereas the bioavailability changes insignificantly.

Key words: acetaminophen, tablets, capsules, pharmacokinetics, space flight.

The onset of a clinical effect and its strength and duration through any administration pathway depend on the bioavailability of the drug. The effects on the pharmacokinetics and bioavailability of acetaminophen of such factors as the age [1, 2] and sex [1, 3] of patients, the excess of body mass [3], the condition of gastro-intestinal tract peristalsis, simultaneous administration with various foods [4, 5], and type of motor activity (including prolonged anti-orthostatic hypokinesia) and sleep [6, 7] are currently widely studied.

Factors such as weightlessness, changes of water-salt balance, mineral saturation of bone, hematological changes, reduction of immunological reactivity, functional changes of neuropsychic status and gastro-intestinal system, etc. are known to have a negative effect on the human organism during long-term space flight. However, the actual trends in the pharmacokinetics of various drugs (including acetaminophen) during long-term space flight are practically unstudied and are very critical because the probability of developing acute diseases and damage increases during planned long-term orbital and interplanetary flights. This requires the use of drugs to correct these maladies.

EXPERIMENTAL PART

The pharmacokinetic investigation involved 10 healthy men (members of the ISS space expeditions) who were divided into two groups of 5 men.

The average age in the first group, i.e., those administered the tablet form of acetaminophen, was 44.6 yr (from 39 to 50 yr); in the second group, i.e., those administered encapsulated acetaminophen, 44.4 yr (from 40 to 47 yr).

The study procedure and method were approved beforehand by the Commission on Biomedical Ethics of the IMBP RAS. Informed consent was obtained from the volunteers for the space experiment.

The pharmacokinetics and bioavailability of the acetaminophen drug forms were studied using its concentration dynamics in saliva because obtaining blood samples under microgravity conditions is difficult and the ability to study acetaminophen pharmacokinetics from its distribution dynamics in saliva had been demonstrated previously [8, 9], including during space flights [10].

The pharmacokinetics of acetaminophen were studied first approximately two months before the start of the space flight (SF) using the standard protocol.

Volunteers were prohibited from taking any drugs, including vitamins, for two days before the start of the study. Tablets (first group) or encapsulated (second group) acetaminophen at a dose of 500 mg were administered on an

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empty stomach on the day of the study, after which the mouth was thoroughly rinsed. Food was allowed one hour after administration at times other than when saliva samples were taken.

Saliva samples for analysis were taken at 0.17, 0.33, 0.5, 0.75, 1, 2, 4, and 6 h after administration. Saliva samples were taken using special swabs that were placed in plastic tubes. Then, saliva was separated by centrifugation. Samples were frozen and stored at –35°C until analysis.

The study was repeated using an analogous procedure during long-term SF.

The acetaminophen concentration in saliva was determined by HPLC with UV spectrophotometric detection at 254 nm [11]. We used a μBondapak^{TM} C18 chromatography column (10 μm, 3.9 × 150 mm, Waters, Ireland). Acetaminophen was isolated from biological fluids by precipitation. Quantitative determination was performed using an internal standard of 2-acetamidophenol. The detection limit of the drug was 0.2 μg/mL of saliva; the regression coefficient $r^2 = 0.9957$.

Data were analyzed using the M-IND program [12] for PC by calculating model-independent parameters such as the maximum concentration C, the time to reach it T, the areas under the concentration-time curve $AUC_{0–t}$ and $AUC_{0–\infty}$, the total clearance *Clt*, the mean retention time of drug in the organism *MRT*, the half-eliminiation time $T_{1/2}$, the distribution volume V_z, and the ratio of maximum concentration and area under the pharmacokinetic curve $C_{max}/AUC_{0–\infty}$ (as a characteristic of the absorption rate [13]).

The relative bioavailability *f*, relative degree of absorption f^{I}, and ratio of maximum concentrations f_{II} of acetaminophen under SF conditions were calculated for the two drug forms and compared with those under usual conditions (from the individual values $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, respectively) [13]. The mean relative bioavailability f_c, relative degree of absorption f_{cI}, and ratio of maximum concentrations f_{cII} of the encapsulated drug were also calculated and compared with those for the tablet form under usual conditions and during SF (using mean values $AUC_{0-\infty}$, $AUC_{0–t}$, and C_{max}, respectively).

Results were treated statistically using the InStat program for PC. Differences were considered reliable for $p < 0.05$.

RESULTS AND DISCUSSION

Figure 1 shows the dynamics of average acetaminophen concentration in saliva of crew members after administration of tablets and capsules at a dose of 500 mg under usual conditions (baseline) and during SF. Obviously the paths of the acetaminophen pharmacokinetic curves differ substantially.

Absorption of acetaminophen was delayed after administration of tablets during SF. The drug concentration in saliva of volunteers was less than the baseline level at 0.17 – 0.33 h. Two peaks in the acetaminophen concentration in saliva were observed on the pharmacokinetic curve during SF. These occurred 0.5 and 2 h after administration of the drug (3.06 ± 1.49 and 3.84 ± 0.69 μg/mL, respectively). Then the acetaminophen concentration in saliva of the volunteers gradually decreased. However, its values during SF were

TABLE 1. Pharmacokinetic Parameters of Acetaminophen After Single Peroral Administration at a Dose of 500 mg

Parameter	Usual living conditions		Space flight	
	tablets (n = 5)	capsules (n = 5)	tablets (n = 5)	capsules (n = 5)
C_{max}, μm/mL	5.13 ± 0.74	5.00 ± 0.75	4.80 ± 1.06	4.17 ± 0.62
T_{max}, ÷	1.12 ± 0.37	0.90 ± 0.06	1.80 ± 0.64	0.60 ± 0.06 *
AUC_{0-1}, μg · h/mL	12.76 ± 1.54	12.35 ± 2.43	15.03 ± 2.57	11.12 ± 2.39
$AUC_{0–\infty}$, μg · h/mL	16.21 ± 1.60	14.81 ± 3.13	19.79 ± 3.15	17.23 ± 3.82
Clt, Cl_t, L/h	31.99 ± 2.93	41.13 ± 9.18	27.73 ± 4.01	36.17 ± 8.50
$T_{1/2}$, L	3.01 ± 0.83	1.82 ± 0.32	3.24 ± 1.04	3.72 ± 0.58*
MRT, h	4.24 ± 0.70	3.01 ± 0.38	4.79 ± 0.67	5.52 ± 0.92*
V_z, L	146.7 ± 53.9	92.9 ± 16.5	124.6 ± 38.5	176.9 ± 27.0*
$C_{max}/AUC_{0–\infty}$, 1/h	0.336 ± 0.073	0.233 ± 0.022	0.365 ± 0.057	0.294 ± 0.073
f, %	–	–	126.72 ± 24.04	119.26 ± 16.35
f^{I}, %	–	–	124.45 ± 24.27	93.22 ± 10.27
f^{II}, %	–	–	107.65 ± 36.43	92.52 ± 19.64
f^{c}, %	–	91.36	–	87.06
f_c^I, %	–	96.79	–	73.99
f_c^{II}, %	–	97.47	–	86.88

* Statistically reliable differences compared with administration of this same drug form under usual conditions.

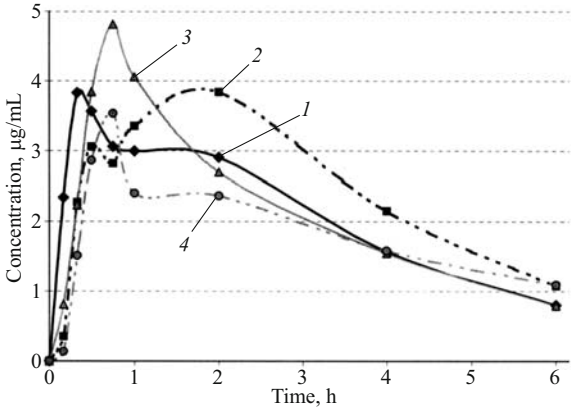

Fig. 1. Average pharmacokinetic curves of acetaminophen: tablets, baseline (*1*); tablets, SF (*2*); capsules, baseline (*3*); capsules, SF (*4*).

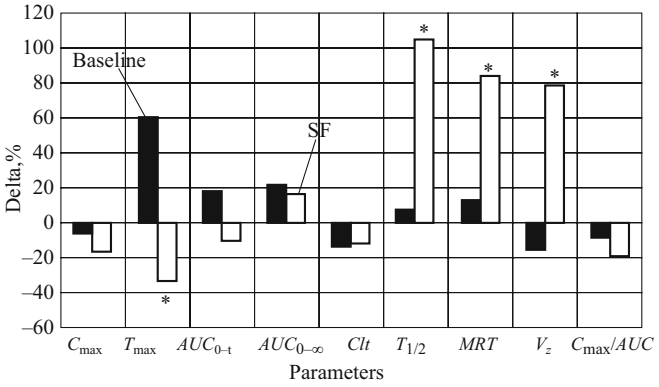

Fig. 2. Dynamics of change of acetaminophen pharmacokinetic parameters during long-term space flight (*statistically reliable differences compared with usual conditions).

greater than the baseline values. The acetaminophen level in saliva 6 h after administration was 0.8 ± 0.16 and 1.08 ± 0.21 μg/mL for the baseline and SF, respectively. The observed differences were statistically reliable at the 0.17 h point.

The paths of pharmacokinetic curves for encapsulated drug were identical. However, the acetaminophen concentrations in saliva of volunteers during SF were less than the baseline at 0.17 – 2 h. The observed differences were statistically reliable at the 0.17 and 1 h points.

It was found that the paths of the average curves of the two drug forms were identical under usual conditions. However, acetaminophen was absorbed slightly slower after administration of capsules than after administration of tablets. A peak in the saliva concentration was observed an average of 0.42 h later. The maximum acetaminophen level in saliva after administration of capsules was greater than after administration of tablets (4.81 ± 0.8 and 3.83 ± 1.2 μg/mL, respectively). The pharmacokinetic curves were practically identical during the elimination stage.

The paths of the pharmacokinetic curves of the studied drugs differed substantially during SF. Two peaks in acetaminophen concentration in saliva were recorded after administration of tablets during SF. These occurred 0.5 and 2 h after administration (3.06 ± 1.5 and 3.84 ± 0.7 μg/mL, respectively). However, one peak was seen after administration of capsules (3.53 ± 0.7 μg/mL) at 0.75 h. The differences were statistically reliable at the 0.17 h point.

TABLE 1 shows the pharmacokinetic parameters of acetaminophen (as mean ± standard deviation of the mean). Figure 2 shows the dynamics of the change of pharmacokinetic parameters during SF as compared with usual conditions. The results indicate that the time to reach the maximum concentration, the level of which was slightly decreased, was clearly longer during SF. The values $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were substantially greater; Cl_t and V_z, somewhat less with longer $T_1/_2$ and *MRT*. The relative bioavailability of acetaminophen increased. A comparison of our results with the literature indicated that other researchers [10] also noted a significant slowing of acetaminophen absorption and a reudction of its maximum concentration during SF (for 7 – 10 d). However, a significant effect on other pharmacokinetic parameters was not observed. The identified differences were apparetly due to the different durations of the SF.

Encapsulated acetaminophen during SF had T_{max} that was statistically reliably shortened. The values C_{max}, AUC_{0-t}, and Cl_t were slightly less with an insignificant increase of $AUC_{0-\infty}$. The values $T_1/_2$, *MRT*, and V_z increased (statistically reliably) during SF. The relative bioavailability of acetaminophen from the encapsulated form under microgravity conditions changed insignificantly compared with usual conditions. It should also be noted that the individual scatter of the pharmacokinetic parameters of the encapsulated form of acetaminophen both under baseline conditions and during SF was less (C. V. = 15 – 55%) than for the tablet form (C. V. = 21 – 82%).

Thus, the dynamics of change of C_{max}, $AUC_{0-\infty}$, and Cl_t are identical for the two drug forms during SF; for $T_1/_2$ and *MRT*, in the same direction but more distinct for the capsules; and for AUC_{0-t}, V_z, and T_{max}, in different directions.

Figure 3 compares the pharmacokinetics of encapsulated acetaminophen (in Δ% compared with the tablet form). It can be seen that the dynamics of change of C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $C_{max}/AUC_{0-\infty}$, and Cl_t under baseline conditions and during SF are in the same direction but more distinct during SF. However, the tendency occurring under usual conditions (decrease compared with tablets) that was observed during SF for $T_1/_2$, *MRT*, and V_z not only was neutralized but also increased significantly compared with the tablet form.

The parameters of the relative bioavailability of acetaminophen from the encapsulated form as compared with the tablet form indicated that the bioavailability under usual conditions was practically the same whereas it tended to decrease moderately during SF.

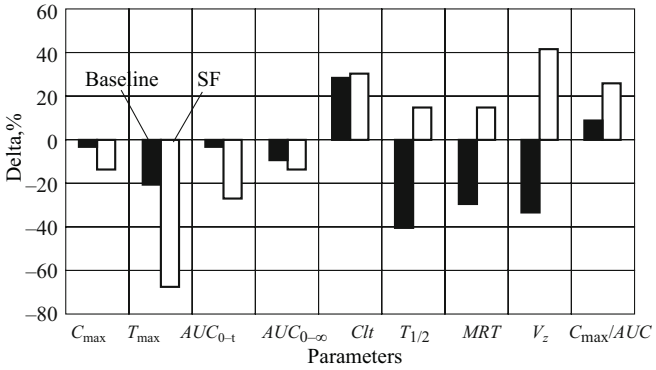

Fig. 3. Comparative pharmacokinetics of encapsulated drug relative to tablet form.

Thus, administration of the encapsulated drug resulted in absorption that was significantly accelerated with a moderate decrease of acetaminophen bioavailability, an increase of half-elimination time, an average retention time in the organism, and a significant increase in the distribution volume as compared with the tablet form. The individual scatter of pharmacokinetic parameters of the encapsulated drug (C. V. = 15 – 55%) was less than that of the tablet form (C. V. = 21 – 82%). The results led to the conclusion that use of encapsulated acetaminophen was more preferred than the tablet form during SF.

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