Phenotypical Peculiarities of Captopril Pharmacokinetics

V. V. Udut, V. A. Khazanov, R. V. Gurto, E. V. Borodulina, Yu. E. Postnikova, S. A. Gribov, A. V. Ivanov, I. V. Tarasova, and E. Yu. Demchenko

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Supplement 1, pp. 45-48, January, 2007
Original article submitted November 11, 2006

Individual pharmacokinetic profiles of captopril and capoten depend on adaptation reactions of the organism and variants of autonomic regulations of functions. Maximum bioavailability and peak concentrations of captopril in blood plasma were observed during phenotypically determined physiological adaptation reactions of the general adaptation syndrome ("training" and "zone of mild activation") and decreased during reactions of "enhanced activation" and "hyperactivation" The observed relationships can be explained by the existing gradient of sympathetic influences in the regulation of variants of adaptation reactions.

Key Words: *pharmacokinetic profile; capoten; captopril; phases of adaptation reactions; autonomic regulation of functions*

Nonspecific response of the organism to various stimuli, apart from specific changes in homeostatic systems, is a real empirically determined and regular complex of signs of phenotypic polymorphism affecting drug pharmacokinetics and pharmacodynamics. Qualitative and quantitative characteristics of the general adaptation syndrome reactions can be used for operative evaluation of adaptation phenotype of an individual at the organism level, which theoretically allows us to predict the effects of drugs. The proposed study is based on previously demonstrated dependencies of pharmacokinetics of some drugs on phases of the formation of the adaptive reaction of the energy-producing system to a load, *e.g.* to pharmacological aggression, and its parallels with general adaptation reactions of the organism [6,9-11,15]. In light of this, the aim of the present study was to analyze pharmacokinetic profiles (PP) of captopril depending on the functional state of the organism evaluated by phases of the general adaptation syndrome and parameters of autonomic regulation of functions.

MATERIALS AND METHODS

The study was carried out in the framework of randomized comparative double-blind crossover trial of PP of captopril (Asfarma) and capoten (Bristol-Myers Squibb Company, Akrikhin) including 18 healthy volunteers (9 men and 9 women) aging 21-54 years (mean age 38.5±4.9 years) divided into 2 sex- and body weight-matched groups.

The study was carried out in accordance with requirements to bioequivalency studies in the Russian Federation (2002).

The study required two hospitalizations of the volunteers with a 7-day interval. At the day of the study, blood test were performed, blood pressure was measured, and electrocardiogram was recorded in all volunteers, after that a cannula was inserted

Institute of Pharmacology, Tomsk Research Center, Siberian Division of Russian Academy of Medical Sciences. ***Address for correspondence:*** evbor@hotbox.ru. V. V. Udut.

0007-4888/07/Supp-038

into the cubital vein, and 10 ml blood was taken for measuring the initial biochemical parameters. All examinees received *per os* 25 mg captopril (group 1) or capoten (group 2). In both groups, blood samples (5 ml) were then taken 30 and 45 min, and 1, 2, 3, 4, 6, and 8 h after administration of the drugs.

After 7 days (washout period) the study was performed according to the same protocol, but group 1 volunteers received capoten and group 2 volunteers received captopril. The serum was collected into sterile sealed disposable plastic tubes and stored at -18°C. The content of the test drugs in the sera was measured not later than on the 2nd day.

During the study, monitoring (general state, blood pressure, allergic reactions) was performed in all volunteers.

Maximum concentration (C_{max}), time of attaining maximum concentration (T_{max}), elimination half-time ($T_{1/2}$), and area under pharmacokinetic curve (AUC_t) were determined, as well as C_{max}/AUC_t ratio was calculated for evaluation of bioequivalency using M-IND software. The relative degree of absorption was evaluated by the ratio (f') of AUC_t for the test captopril to AUG∞ for the reference drug capoten, the ratio (f'') of their C_{max} was also calculated. The arithmetic mean, standard deviation, and variation coefficient were calculated. Dispersion analysis of AUC_{0-t}, C_{max}, and C_{max}/AUC_{0-t} was performed after their logarithmic transformation. Equivalency of pharmacokinetic characteristics C_{max}/AUC_{0-t} of the studied parameters was evaluated by nonparametric methods using Wilcoxon—Mann—Whitney test, in particular paired comparison method, at P=0.95 [1,5,7]. The null hypothesis was the assumption that general parameters of the studied samples do not differ.

The types of adaptation reaction of the organism were determined by the calculated index of lymphocyte/segmented neutrophil ratio in peripheral blood characterizing the phases of the general adaptation syndrome. Index ≤0.3 corresponded to stress reaction, 0.30-0.49 to training, 0.50-0.68 to zone of mild activation (ZMA), 0.69-0.90 to zone of enhanced activation (ZEA), and >0.9 to hyperactivation [2,4].

Functional activity of the autonomic nervous system was evaluated by heart rhythm variability determined by the wave structure of the heart rhythm recorded over 5 min. The following parameters were used: total spectrum power (TP); low-frequency oscillations (LF) reflecting the influence of the sympathoadrenal system; high-frequency oscillations (HF) reflecting parasympathetic influences, and their ratio LF/HF characterizing the balance of activity of subdivisions of the autonomic nervous system. Reactivity of the autonomic nervous system was determined using active orthostatic challenge [2,10].

RESULTS

The integral PP of the test drugs during 8-h observation period suggests their pharmacokinetic identity (Fig. 1). The presence of two peaks of serum concentration of the test drugs is determined by metabolic conversions.

The results of dispersion analysis of pharmacokinetic parameters demonstrated the absence of significant differences in the absorption of the active matter of capoten and captopril (Table 1). Parameter f' determined as AUC_tT/AUC_tR ratio and parameter f'' determined as C_{max} captopril/C_{max} capoten ratio also confirmed bioequivalence of these drugs. The mean confidence interval for f' was 93.76% and lay within the permissible interval 90-100%, the mean confidence interval for f'' was 90.14% and lay within the permissible interval 85-115%.

The observed bioequivalency of the compared drugs (judging from the results of preclinical studies, equal AUG, C_{max}, T_{max}, and the main parameters of bioavailability, rate and degree of absorption) allowed us to analyze the dependency of their pharmacokinetics on individual adaptation phenotypes evaluated by the characteristics of adaptation reactions and the state of autonomic regulation of functions.

Of 36 healthy volunteers, stress reaction was revealed in 2 individuals, training in 12, ZMA in 10, ZEA in 6, and hyperactivation in 6 individuals. This allowed us to divide them into subgroups ac-

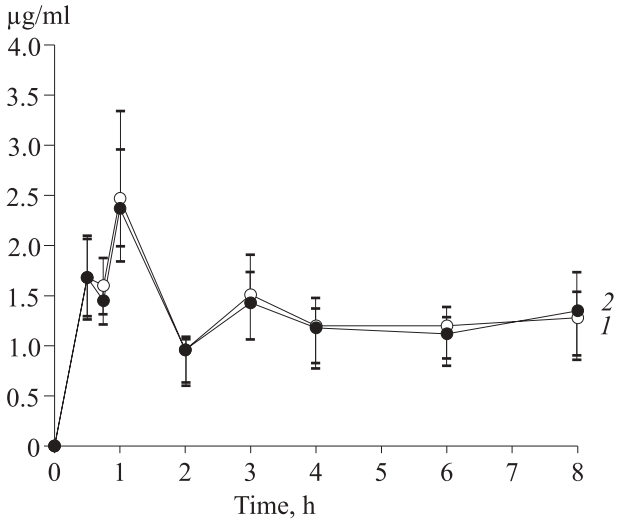

Fig. 1. Integral PP of captopril (*1*) and capoten (*2*).

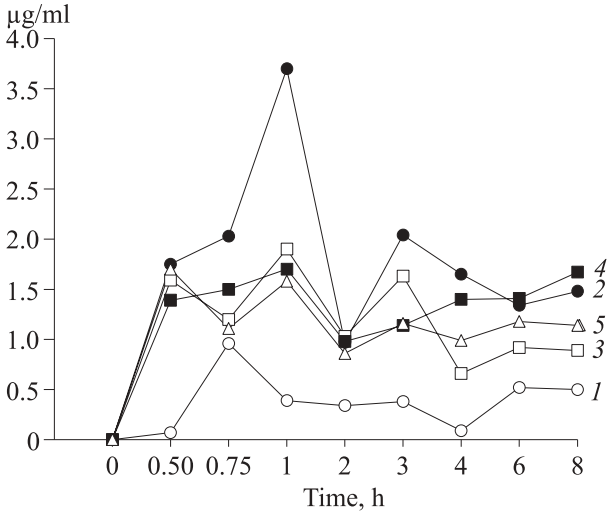

Fig. 2. PP of captopril depending on the phase of the general adaptation syndrome. *1*) stress, *2*) training, *3*) ZMA, *4*) ZEA, *5*) hyperactivation.

cording to the phases of the general adaptation syndrome. PP of captopril in these subgroups showed that adaptation reactions considerably affected the processes of absorption, metabolism, and elimination of the drugs from the blood (Fig. 2). The results of evaluation of PP in the subgroups with training reaction, ZMA, and ZEA suggest that despite C_{max} of the preparation was attained by the 1st hour of the study, it had a pronounced decreasing gradient in view of energy expenditures of the phases of the general adaptation syndrome. The increase in serum concentration of captopril during the 3rd hour of observation in training reaction, ZMA, and strain reaction can be explained by its metabolic transformations. In case of ZEA reaction, the concentration peak determined by preparation metabolites is shifted to the 4th hour. In case of hyperactivation reaction, C_{max} was seem between the 30th and 45th minutes after drug administration and was similar by its amplitude to the peak of metabolite concentration recorded by the 3rd hour.

Despite the fact that we observed only two cases of stress reaction, we believe that the characteristics of PP of captopril in volunteers with stress reaction reflect most demonstrative differences from the adaptive norm. During stress reaction, C_{max} of the drug in the serum was attained on minute 45 of the experiment lagging behind to that in the hyperactivation group and anticipating that in physiologically optimal reactions (training, ZMA, and ZEA). Serum concentration of the test preparation was also minimum compared to cases with other variants of adaptation reactions. Moreover, the orthostatic challenge in this individual revealed decreased reactivity of the parasympathetic nervous system ($K_{30:15}$ was 1.1) Analysis of heart rhythm spectrogram showed predominance of humoral and metabolic regulatory influences (the percent of VLF was 75.9%). The balance of subdivisions of the autonomic nervous system was characterized by pronounced sympathicotony (LF/HF=4.23), the total spectral power was high (TP=3972 msec^2/Hz). All these data attest to the strain of adaptation processes and centralization of the autonomic regulation of functions with elements of hypersympathicotony.

The formation of subgroups based on the presence of certain phases of the general adaptation syndrome in volunteers allowed us to study the dependency of PP on the type of adaptation reactions, which had clear-cut parallels with the state of autonomic regulation of functions (Table 2).

Taking into account the fact that the presentation of adaptation reactions is an integral characteristics of the state of neuroimmunoendocrine homeostasis, our findings demonstrate gradient changes in the state of autonomic regulation of functions: from eutony (with minor predominance of parasympathetic influences in case of training) through balances sympathetic-parasympathetic tone in case of ZMA to moderate sympathicotony in cases of strain and stress reactions [1-3]. In this case, the decreasing gradient of bioavailability and peak concentrations of the drug in the plasma from training reaction through ZMA and ZEA to hyperactivation reaction and stress can be explained by enhanced sympathetic influences, inhibition of gastrointestinal motility and tissue hypoperfusion [3,9,11,12, 14,15].

Thus, the most complete information of phenotypically determined adaptive norm of individual reaction in clinical practice can be obtained from the analysis of phases of the general adaptation syndrome and competence of the autonomic regulation of functions. In healthy individuals, some parameters of PP of captopril depend on adaptation

TABLE 1. Mean Values of Relative Absorption Degree for Captopril and Capoten

Parameter	Mean	Standard deviation	Confidence interval	Normal
f'	193.06	202.97	93.76	90-110
f''	181.58	195.13	90.14	85-115

TABLE 2. State of Autonomic Regulation of Functions in Various Types of Adaptation Reactions (*M*±*m*)

Parameter	Training	ZMA	ZEA	Hyperactivation	Stress
TP, msec^2	2430±496	2463±879	1275±725	3972±614	3972±457
LF, %	24.5±1.8	30.2±2.4	39.8±2.9	35.1±3.8	19.5±1.3
HF, %	32.7±1.3	25.5±3.2	14.9±5.7	11.7±4.2	4.6±1.8
VLF, %	42.8±12.6	44.3±6.8	45.3±11.1	53.2±9.7	75.9±5.2
LF/HF	0.74±0.25	1.18±0.40	2.7±0.8	3.00±0.72	4.23±0.25
$K_{30:15}$	1.42±0.18	1.38±0.21	1.25±0.24	1.21±0.12	1.1±0.1

phenotype evaluated by the state of compensatory and adaptation reactions and peculiar phasic nature of the general adaptation syndrome.

REFERENCES

1. Yu. B. Belousov and K. G. Gurevich, *Clinical Pharmacokinetics. Practical Drug Dosage* [in Russian], Moscow (2005).
2. *Autonomic Disorders. Clinical Picture, Diagnosis, Treatment*., Ed. A. M. Vein [in Russian], Moscow (1998).
3. L. Kh. Garkavi, E. B. Kvakina, and T. S. Kuz'menko, *Antistress Reactions and Activation Therapy* [in Russian], Moscow (1998).
4. L. Kh. Garkavi, E. B. Kvakina, T. S. Kuz'menko, and A. I. Shikhlyarova, *Antistress Reactions and Activation Therapy. Reactions of Activation as a Way to Health through Self-Organization Processes* [in Russian], Ekaterinburg (2003).
5. *Dysregulation Pathology*. Ed. by G. N. Kryzhanovskii [in Russian], Moscow (2002).
6. A. Yu. Dish, K. Yu. Vasil'ev, R. V. Gurto, and V. A. Khazanov, *Regulators of Energy Metabolism. Clinical and Pharmacological Aspects*. Ed. V. A. Khazanov [in Russian], Tomsk (2004), pp 119-126.
7. V. G. Kukes, *Klin. Lab Diagn*., No. 3, 25-32 (1998).
8. V. G. Kukes, *Clinical Pharmacology* [in Russian], Moscow (1999), pp. 3-36.
9. F. Z. Meerson and M. G. Pshennikova, *Adaptation to Stress Situations and Physical Exercises* [in Russian], Moscow (1988),
10. V. M. Mikhailov, *Heart Rhythm Variability: Practical Application of the Method* [in Russian], Ivanovo (2002).
11. G. A. Popova, E. V. Borodulina, and V. V. Udut, *Byull. Sib. Med*., No. 1, 36-37 (2005).
12. K. V. Sudakov, *Individual Resistance to Emotional Stress* [in Russian], Moscow (1998),
13. V. V. Udut, E. V. Borodulina, S. A. Gribov, *et al*., *Byull. Eksp. Biol. Med*., Suppl. 2, 50-55 (2003).
14. V. V. Udut, E. V. Borodulina, G. A. Popova, and V. G. Solov'eva, *Sib. Onkol. Zh*., No. 1, 16-22 (2005).
15. V. A. Khazanov, R. V. Gurto, and Yu. Dish, *Actual Problems of Experimental and Clinical Pharmacology* [in Russian], Tomsk (2002), pp. 159-162.