The Use of Ultralow Doses of Antibodies to C-Terminal Fragment of Angiotensin II AT1 Receptor (Kardos) in the Therapy of Arterial Hypertension

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 148, Suppl. 1, pp. 80-82, August, 2009
Original article submitted August 1, 2008

Kardos monotherapy allows attaining the target levels of systolic and diastolic blood pressure in patients with high-risk and very-high-risk hypertension. We demonstrated excellent tolerability of the preparation in combination with reliable blood pressure decrease over 24 h, during day and night hours.

Key Words: *kardos; arterial hypertension; 24-h monitoring; ultralow doses of antibodies*

In recent year, the problem of borderline arterial hypertension (AH) and individuals with normally high blood pressure (BP) again attracted much attention. The possibility of preventing transformation of normally high BP into stable AH was clearly demonstrated [4]. In the previous study [4], antagonist of angiotensin II receptors candesartan was used. This preparation is characterized by excellent tolerability profile. Drugs belonging to other groups of antihypertensive preparations are little suitable for the therapy of individuals with normally high BP, because of their side effects. It should be noted that not only BP reduction, but also guaranteed absence of side effects of therapy over many years are of crucial importance for these individuals.

Hyperactivation of the rennin—angiotensin—aldosterone system (RAAS) in AH was demonstrated [5]. It is now accepted that angiotensin II receptors play a key role in the realization of negative changes in the target organs during progression of the cardiovalcular continuum. Therefore, widening of the potencies of drug therapy for RAAS hyperactivation at various levels is an actual problem of modern cardiology and clinical pharmacology.

Until recently, the decrease in RAAS activity was attained via blockade of angiotensin-converting enzyme, angiotensin II receptors (antagonists of angiotensin II receptors), and aldosterone receptors (eplerenone). During the last four years, the possibility of preventing RAAS activation with kardos, a preparation containing ultralow doses of antibodies to C-terminal fragment of AT1-receptor of angiotensin II, was intensively studied in Russia.

Recently developed preparations on the basis of ultralow doses of antibodies are a unique group of drugs producing a modifying effect on the corresponding endogenous regulator, restoring its activity, and modulating processes functionally coupled with this regulator. In particular, the molecular target of kardos is a receptor mediating the key effects of angiotensin II, an important neurohormone involved in the pathogenesis of AH and chronic heart failure [3]. It is known that intracellular C-terminal fragment of angiotensin II receptor is responsible for long-lasting effects of angiotensin II (long-term regulation of the

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0007-4888/09/1482-0332

vascular tone and processes of vascular remodeling). Therefore, modification of its activity under the effect of long-term treatment with kardos and resultant reduction of RAAS hyperactivation can considerably affect progression of the cardiovascular continuum. In experimental studies and pilot clinical trials, the positive effects of this preparation in AH were demonstrated, its therapeutic doses were determined, toxicity was studied, and primary data proving the safety of this preparation were obtained [2]. However, of particular importance are the results of clinical studies evaluating the efficiency of the preparation.

The aim of the present study was an open non-comparative study of the efficiency of kardos in patients with AH.

MATERIALS AND METHODS

The study included 50 patients aging 18-70 years (mean age 53.78±1.93 years), 21 men and 29 women.

TABLE 1. Results of 24-h BP Monitoring during Kardos Therapy (*M±m*)

Parameter	Initial	After 12-week therapy	% of initial
Parameters over 24 h			
Mean SBP	137.39±1.25	132.76±1.19*	-3.48
SBP variability	14.64±0.57	13.59±0.47*	-7.75
Mean DBP	84.43±1.09	81.12±1.45*	-4.1
DBP variability	11.37±0.39	11.77±0.38	3.35
Mean BP	102.47±1.02	98.94±1.24	-3.56
Mean BP variability	12.24±0.43	11.85±0.3	-3.3
SBP>140/120 mm Hg, %	53.33±3.01	44.27±3.47	-20.47
DBP>90/80 mm Hg, %	43.42±3.22	34.73±4.02*	-25.0
Parameters over day hours (active period)			
Mean SBP	138.58±1.33	135.41±1.24	-2.34
SBP variability	13.7±0.64	12.46±0.58*	-10.0
Mean DBP	86.02±1.21	83.76±1.36	-2.69
DBP variability	10.6±0.45	10.86±0.48	2.38
Mean BP	104.02±1.1	101.44±1.25	-2.54
Mean BP variability	11.29±0.47	10.9±0.39	-3.58
SBP>140 mm Hg, %	45.94±3.44	38.11±3.27	-20.55
DBP>90 mm Hg, %	39.57±3.37	32.46±4.06	-21.9
Parameters over night hours (passive period)			
Mean SBP	133.14±1.84	125.58±1.89*	-6.02
SBP variability	12.02±0.53	10.77±0.58*	-11.58
Mean DBP	79.48±1.32	73.94±1.31**	-7.49
DBP variability	9.64±0.4	9.26±0.37	-4.16
Mean BP	98.43±1.4	92.06±1.67**	-6.91
Mean BP variability	10.47±0.47	9.44±0.39	-10.91
SBP>120 mm Hg, %	72.78±3.75	57.08±4.95	-27.5
DBP>80 mm Hg, %	53.01±4.53	40.0±5.24*	-32.51
Night SBP drop	6.14±1.3	9.51±1.15	35.47
Night DBP drop	9.26±1.6	13.05±1.4	29.02

Note. *$p<0.05$, **$p<0.01$ compared to initial values.

Of them, 12 patients had a night-peaker profile by SBP (of them 9 patients by DBP) and 32 patients had a non-dipper profile by SBP (of them 28 patients by DBP).

All patients signed informed consent before the start of the trial.

Inclusion criteria were the presence of I-II degree high-risk and very-high-risk AH. Exclusion criteria were: BP above 180/110 mm Hg, severe hepatic or renal failure, stages I-IV chronic heart insufficiency, malignant neoplasms and other grave diseases, alcohol or drug abuse, impossibility of long-term observation, and pregnancy.

After 14-day washout period (patients received no antihypertensive drugs), all patients received kardos in a dose of 2 tablets 3 times a day for 3 months.

The efficiency of antihypertensive therapy was evaluated by the percent of patients attaining the target level of BP (below 140/90 mm Hg). After signing informed consent and washout period and 3 months after treatment with kardos, 24-h BP monitoring was carried out (DIASYS Integra, Novacor). In all patients, fundus of eye was examined, fasting blood glucose level, lipid spectrum, and blood concentrations of electrolytes (K, Na, Mg) and creatinine were measured.

The data were processed statistically using Student's *t* test, parametric Wilcoxon *W* test, two-way Student's *t* test, nonparametric Mann—Whitney *U* test, and χ^2 test; 95% confidence interval was determined; methods of descriptive statistics were used for evaluation of safety parameters.

RESULTS

Kardos was well tolerated by patients, no side effects were noted, and no cases with negative dynamics of laboratory parameters were revealed.

According to the results of 24-h BP monitoring, the target levels of SBP and DBP were attained in 71 and 79% patients, respectively.

A positive dynamics of 24-h BP profiles was observed; it was more pronounced in patients with circadian rhythm of BP, non-dippers. Against the background of kardos therapy, 38.8% non-dippers by SBP and 77.9% non-dippers by DBP became dippers.

The diurnal rhythm of BP normalized in 22% night-peakers by SBP and positive dynamics of diurnal rhythms was noted in 67% patients. Similar dynamics of 24-h BP profile was observed in night-peakers by DBP (67 and 33% patients, respectively).

Kardos considerably decreased SBP and DBP over 24 h, during day and night hours (Table 1). The decrease in SBP and DBP during night hours was more pronounced than during daytime (by 6 and 7% vs. 2 and 3%, respectively).

Kardos considerably decreased SBP variability during all studied periods (by 8, 10, and 11% over 24 h and during day and night hours).

Thus, our study confirmed pronounced hypotensive activity and excellent tolerability of kardos.

Twenty-four hour BP monitoring in AH patients with high and very high risk of cardiovascular complications showed that SBP and DBP values over 24 h and during day and night hours considerably decreased under the effect of long-term kardos therapy. This provides a principally new possibility of corrective RAAS hyperactivation in AH. Previous clinical studies showed that kardos is comparable with angiotensin II receptor losartan [1] by its hypotensive effect. Simultaneous administration of ACE inhibitors and diuretics potentiated hypotensive activity of kardos [1,2]. Further studies of the effect of kardos on the level of SBP and DBP in AH are required. However, we can now hypothesize that kardos, a preparation suppressing RAAS activity and characterized by excellent tolerability, can be successfully used for prevention of transformation of normally high BP into true AH.

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