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ANTIHYPERTENSIVE EFFICACY OF CANDESARTAN IN PATIENTS WITH ARTERIAL HYPERTENSION

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Abstract:

The benefits of lowering blood pressure (BP) to achieve and maintain target levels to reduce the risk of cardiovascular morbidity and mortality are well established. The renin-angiotensin system plays an important role in the regulation of blood pressure and is a target for some groups of antihypertensive drugs, including AT1 receptor blockers for angiotensin P., which include candesartan. Candesartan 8-32 mg 1 time / day is recommended for the treatment of adult patients with arterial hypertension (AH). Candesartan has been shown in many randomized clinical trials to be effective in reducing the risk of cardiovascular mortality, stroke, heart failure, arterial stiffness, renal failure, retinopathy and migraine in various adult patient populations, including patients with concomitant type 2 diabetes mellitus, metabolic syndrome or impaired renal function. Available data indicate that candesartan is a highly effective drug for the treatment of hypertension.

Keywords: angiotensin receptor blockers P. candesartan, arterial hypertension, Dinesart IAngiotensin II receptor antagonists in the treatment of arterial hypertension

SARTANS IN THE TREATMENT OF CARDIOVASCULAR DISEASES

Arterial hypertension (AH) is one of the main risk factors for morbidity and mortality in the adult population of the Russian Federation. Morbidity and mortality due to hypertension can be significantly reduced with appropriate treatment and control of blood pressure (BP) [1]. The renin-angiotensin-aldosterone system (RAAS) plays an important role in the regulation of blood pressure. The main peptide of the RAAS is angiotensin (AT) II, which, acting on AT1 receptors (one of its two main receptors), causes a large number of biologically adverse effects. Candesartan, a member of the class of AT II receptor blockers (ARB), is a prodrug that interferes with the binding of AT II due to selective and competitive binding to the AT1 receptor [2]. The drug was first used experimentally in 1992, and 2 years later its clinical research program began [3, 4]. Clinical data indicate the high effectiveness of candesartan in lowering blood pressure, treating heart failure, diabetic nephropathy, as well as reducing the risk of developing and reducing the rate of progression of diabetic retinopathy [5, 6]

FEATURES OF THE CLINICAL PHARMACOLOGY OF CANDESARTAN

ARB do not affect circulating AT II and reduce its binding to the receptor. AT1 receptors are located in the smooth muscle layer of the vascular wall and in the adrenal glands. ARB inhibit many of the biological effects of AT II: contraction of vascular smooth muscle, pressor responses, thirst, aldosterone secretion, vasopressin release, adrenal catecholamine release, increased noradrenergic neurotransmission, increased sympathetic tone, changes in renal function, cellular hyperplasia and hypertrophy. ARB do not have a direct effect on angiotensin-converting enzyme (ACE) and, accordingly, bradykinin; but they can increase levels of nitric oxide (NO) release and reduce its breakdown.

ARB differ in their binding characteristics to AT1 receptors. Binding is classified as competitive or noncompetitive depending on the shift of the AT II concentration response curves to the right. In the case of competitive antagonism, the maximum response to AT II does not change; in the case of non-competitive antagonism, the response decreases. Thus, noncompetitive binding cannot be overcome by increasing the concentration of angiotensin I [7]. The non-competitive effect of candesartan is due to the presence of a carboxyl group in its imidazole part. The ARB telmisartan and valsartan are noncompetitive AT1 receptor blockers despite the absence of a carboxyl group [8]. The key clinical significance of the non-competitive mechanism of candesartan binding to the receptor is its long duration of action and the persistence of the effect after skipping the next dose of the drug.

Mechanical stress can activate AT1 receptors via an AT II-independent pathway, and without the participation of AT II, it not only promotes the activation of extracellular signal-regulated kinases and increases the production of phosphoinositides in vitro, but also

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induces myocardial hypertrophy in vivo. Candesartan inhibits mechanical stretch, which induces the association of the AT1 receptor with Janus kinase 2 and the translocation of G proteins into the cytosol. Candesartan, olmesartan and valsartan are able to stabilize AT1 receptors in an inactive state (so-called inverse agonism), in the absence of AT II, thus reducing the development of myocardial hypertrophy regardless of the decrease in blood pressure [8].

As a result of mechanical stress, the secretion of AT II from secretory granules is stimulated through a natural message in cardiomyocytes [8]. Candesartan is a partial agonist of peroxisome proliferator-activated receptor gamma and accelerates the metabolism of lipids and carbohydrates [8].

AT2 receptors still remain poorly understood. They are thought to mediate mechanisms of inflammation, cell proliferation, modulation of the extracellular matrix, neuronal regeneration, apoptosis, cellular differentiation, and possibly vasodilation and left ventricular (LV) hypertrophy. The use of ARB has shown that they are more than 10,000 times more selective for AT1 than AT2 receptors. One of the drugs with the highest selectivity is candesartan [8]. Its effectiveness has been demonstrated in a number of clinical studies involving patients with hypertension, LV dysfunction, acute coronary syndrome, heart failure (HF), high arterial stiffness, retinopathy, nephropathy, stroke, atrial fibrillation and migraine. The cost-effectiveness of using this drug has also been shown. This review focuses on the role of candesartan in the treatment of hypertension.

DRUG PREVENTION OF HYPERTENSION

The TROPHY (Trial of preventing hypertension) study was conducted to study the possibility of preventing the development of hypertension by blocking the RAAS, determining the degree of effectiveness of candesartan in combination with the prevention of hypertension (in particular, lifestyle changes) [6, 9]. The study involved 809 patients with systolic blood pressure (SBP) of 130–139 mmHg. Art. and diastolic blood pressure (DBP) 89 mm Hg. Art. or lower, or SBP 139 mm Hg. Art. or lower and DBP 85–89 mm Hg. Art. Study participants were randomized to receive candesartan (n=409) or placebo (n=400) for 2 years, and then both groups received placebo for 2 years. Data from 772 participants (391 in the candesartan group and 381 in the placebo group; mean age 48.5 years; 59.6% men) were analyzed. During the first 2 years, the development of hypertension was detected in almost 2/3 of patients (n=154) in the placebo group and in 53 in the candesartan group (relative risk reduction 66.3%, p=0.001). After 4 years, the development of hypertension was observed in 240 patients in the placebo group and in 208 in the candesartan group (relative risk reduction 15.6%, p = 0.007). The uniqueness of the TROPHY study lies in the fact that the possibility of delaying the development of hypertension by blocking the RAAS was clinically confirmed.

ANTIHYPERTENSIVE EFFICACY OF CANDESARTAN IN PATIENTS WITH ARTERIAL HYPERTENSION WITH/WITHOUT DIABETES MELLITUS

Five randomized, double-blind clinical trials of candesartan included patients with hypertension and diabetes mellitus (DM) or without DM [6, 10]. The research design was as follows:

within 4 weeks. - taking a placebo;

4–6 weeks — taking candesartan 8 mg once a day, then, if blood pressure did not normalize, the dosage was doubled (BP <140/90 mm Hg or blood pressure <130/80 mm Hg with diabetes);

further 4–6 weeks. — taking candesartan 8 or 16 mg 1 time/day.

A total of 702 patients participated in the studies (of which 397 were men (56.6%), mean age 60±11 years), including 153 patients with diabetes (21.8%) and 549 without diabetes (78 .2%). The average blood pressure at the initial stage was 160/94/65 mmHg. Art. for SBP, DBP and pulse pressure (PP), respectively. All patients showed a significant decrease in the levels of SBP, DBP and PP after the 2nd and 3rd study periods compared to the initial level, while a more pronounced effect was observed in patients with diabetes.

ANTIHYPERTENSIVE EFFICACY OF CANDESARTAN AND OTHER ARB

A special meta-analysis was devoted to the comparative effectiveness of candesartan and losartan, which included 14 studies (8 on hypertension and 6 on HF) [11]. Its secondary objective was to examine the comparative cost-effectiveness of both drugs. All studies involving hypertensive patients directly compared candesartan and losartan. The difference between the blood pressure values was -1.96 mm Hg. Art. (95% CI -2.40 to -1.51) for DBP and -3.00 mmHg. Art. (95% CI -3.79 to -2.22) for SBP in favor of candesartan. These differences were determined using a Markov model that estimates the cost of 1 year of quality life; the analysis demonstrated the economic feasibility of using candesartan.

EFFECT OF CANDESARTAN ON ARTERIAL STIFFNESS

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In a study [6, 12] that assessed the effect of candesartan on arterial elasticity, as well as inflammatory and metabolic parameters, hypertensive patients with multiple cardiovascular risk factors were divided into 3 groups: group 1 received 32 mg of candesartan, group 2 received 32 mg of candesartan. 16 mg candesartan, group 3 - antihypertensive therapy without ARBs or ACE inhibitors. Arterial elasticity was assessed using pulse wave contour analysis (HDI CR 2000, USA). In patients taking 32 mg of candesartan, the elasticity index of large arteries (LEICA) increased from 8.6 ± 2.8 to 16.6 ± 5.1 ml/mm Hg. Art. ×100 after 6 months. treatment (p=0.0001); elasticity index of small arteries (IEMA) - from 2.7±1.3 to 5.9±2.8 ml/mm Hg. Art. ×100 (p=0.0001); systemic vascular resistance (SVR) decreased from 1881.5±527.5 to 1520.9±271.8 (p=0.0006). In patients receiving 16 mg of candesartan, the ECA increased from 11.0 ± 3.5 to 14.4 ± 3.2 ml/mmHg. Art. ×100 (p=0.0001), IEMA - from 3.7±1.4 to 5.4±2.1 ml/mmHg. Art. ×100 (p=0.0001), CVS decreased from 1699.8±327.6 to 1400.7±241 (p=0.0001). In the control group, despite a comparable decrease in blood pressure, neither IECA nor IEMA improved during the treatment period. Thus, an improvement in the elasticity of arteries of different calibers was observed only when taking ARBs.

THE EFFECT OF CANDESARTAN ON RENAL FUNCTION AT VARYING DEGREES OF IMPAIRMENT AND IN PATIENTS AFTER KIDNEY TRANSPLANTATION

SECRET STUDY

The SECRET study (Study on Evaluation of Candesartan Cilexetil after Renal Transplantation) is an international multicenter, double-blind, randomized study of candesartan compared with placebo in patients after kidney transplantation. Initially, 700 patients were planned to participate in the study for 3 years [6, 13]. In order to achieve DBP less than 85 mm Hg. Art. the dose of candesartan was increased from 4 to 16 mg/day, and additional drugs were added if necessary. The primary endpoints of the study were composite of all-cause mortality, cardiovascular disease (CVD) incidence, and graft failure. The study was terminated early because the rate of achievement of the primary endpoints was much lower than expected (13 in each group). At the time the study was stopped, there were 502 patients: 255 receiving candesartan and 247 receiving placebo. Control of both SBP and DBP was more effective in the group receiving candesartan. Urinary protein excretion and protein/creatinine ratio decreased in the candesartan group but increased in the placebo group. Serum creatinine and potassium levels increased slightly in candesartan users. In a small study of patients with stage 4–5 chronic kidney disease (CKD) [6, 14], 7 patients were prescribed candesartan; the control group consisted of 6 people using drugs other than ARBs, with a serum creatinine level of 2.52–5.95 mg/dL and blood pressure below 140/90 mm Hg. Art. Within 48 weeks. 26 routine measurements were performed and a 3-year renal survival analysis was performed with endpoints including creatinine doubling, hemodialysis requirement, and death. No significant changes in blood pressure were observed in the 2 groups of patients. The level of proteinuria significantly decreased from 0.95±0.51 to 0.39±0.12 g/day (paired T-test, p=0.033) in the candesartan group, but did not change in the control group. Creatinine clearance in the control group decreased significantly from 16.2±5.7 to 10.4±4.8 ml/min per 1.73 m2 (paired T-test, p=0.011), and remained the same in the comparison group. The reduction in the rate of decline in renal function with candesartan compared with the control group was illustrated using a curve of reciprocal changes in creatinine levels (-0.002 ± 0.015 vs. -0.025 ± 0.015 dl/mg per month; unpaired T-test, p = 0.019). ARBs were superior to placebo for renal survival at 3 years in Kaplan-Meier analysis (log-rank, p=0.025). No serious side effects were observed in patients participating in the study. Thus, the ability of candesartan to reduce the level of proteinuria and maintain renal function even in cases of progressive renal failure was demonstrated.

In another study, a double-blind, randomized, crossover study consisting of 4 treatment periods of 2 months. each, 23 patients with hypertension, type 2 diabetes and nephropathy took part [6, 15]. They were randomized to receive candesartan 8, 16, or 32 mg/day and placebo. Antihypertensive medications were discontinued and patients received only long-acting furosemide throughout the study period at a mean dose of 40 (30–160) mg/day. The end points of the study were albuminuria, 24-hour blood pressure and eGFR. While taking placebo, the results were as follows: albuminuria 700, 95% CI 486–1007 mg/day; Blood pressure - 24 hours 147±4/78±2 mm Hg. Art. and GFR 84±6 ml/min/1.73 m2. When taking all 3 doses of candesartan, the level of albuminuria

CANDESARTAN AND CEREBROVASCULAR ACCIDENTS

SCOPE Study

The SCOPE (Study on Cognition and Prognosis in the Elderly) study examined whether the use of candesartan in elderly patients with moderately elevated blood pressure reduces the incidence of fatal and non-fatal stroke, cardiovascular events, cognitive decline and dementia [6, 16] . This study, conducted at

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527 centers in 15 countries, included 4964 patients aged 70–89 years with SBP 160–179 mmHg. Art. and/or DBP 90–99 mm Hg. Art. Study participants were randomized to receive candesartan or placebo, and, if necessary, active antihypertensive therapy. This therapy was widely used in the control group (84% of patients). The average follow-up period was 3.7 years. In the candesartan group, blood pressure decreased by 21.7/10.8 mmHg. Art., in the control group - by 18.5/9.2 mm Hg. Art. Achievement of primary endpoints was recorded in 242 patients treated with candesartan and in 268 patients in the control group; the risk reduction with candesartan was 10.9% (95% CI -6.0 to 25.1, p=0.19). Therapy with candesartan reduced the likelihood of non-fatal stroke by 27.8% (95% CI 1.3–47.2, p = 0.04), all types of stroke by 23.6% (95% CI -0.7 up to 42.1, p = 0.056). No significant differences were found in the incidence of myocardial infarction and mortality from CVD. The mean MMSE score decreased from 28.5 to 28.0 in patients taking candesartan and from 28.5 to 27.9 in the control group (p=0.20). The proportion of patients with significant cognitive decline or development of dementia did not differ between treatment groups.

ACCESS Study

The ACCESS (Acute Candesartan Cilexetil therapy in Stroke Survivors) study assessed the safety of a moderate reduction in blood pressure while taking candesartan in the early period in patients with stroke [6, 17]. 500 patients were expected to participate. The study was stopped early after randomization of 342 patients due to unbalanced endpoints. Demographics, cardiovascular risk factors, and blood pressure levels at baseline and throughout the study period were essentially the same between the two groups. But overall mortality rates and the number of vascular events were significantly different in favor of the candesartan group compared with placebo (hazard ratio (HR): 0.475, 95% CI 0.252–0.895).

Retinopathy in diabetes mellitus types 1 and 2

DIRECT-prevent 1 and DIRECT-protect 1 studies

The DIRECT (DIabetic Retinopathy Candesartan Trials) study was conducted to study the effectiveness of candesartan for the prevention (DIRECT-prevent 1) and slowdown of progression (DIRECT-protect 1) of diabetic retinopathy (DR) in type 1 diabetes [6, 18]. Patients aged 18–55 years with type 1 diabetes, normotension and normoalbuminuria, without DR were included in DIRECT-prevent 1 (710 - in the candesartan group, 710 - in the placebo group), patients with DR - in DIRECT-protect 1 (1905 - to the candesartan group, 954 to the placebo group) and were prospectively randomized to treatment with candesartan 16 mg once a day or placebo. After 1 month the dose of candesartan was increased to 32 mg. Primary endpoints are incidence and progression of DR: at least a 2-point increase or a 3-point increase, respectively, on the DR scale. The occurrence of DR was observed in 178 (25%) participants in the candesartan group versus 217 (31%) in the placebo group, RR 0.82 (95% CI 0.67–1.00, p=0.0508). Progression of DR occurred in 127 (13%) participants in the candesartan group versus 124 (13%) in the placebo group, RR 1.02 (95% CI 0.80–1.31, p=0.85) for the DIRECT-protect group 1. In a post-hoc analysis, for an increase in DR score of at least 3 points, the RR was 0.65 (95% CI 0.48–0.87, p=0.0034), this risk reduction remained significant after adjustment by baseline characteristics - RR 0.71, 95% CI 0.53–0.95, p=0.046. At the end of the study, the odds of having a lower DR score were higher among those taking candesartan in both DIRECT-prevent 1 (RR 1.16, 95% CI 1.05–1.30, p=0.0048) and DIRECT-protect 1 (RR 1.12 , 95% CI 1.01–1.25, p=0.0264).

DIRECT-protect 2 study

The DIRECT-protect 2 study examined the effect of candesartan on the progression and regression of DR in type 2 diabetes [6, 19]. 1905 patients aged 37–75 years with normoalbuminuria, normotension or hypertension with type 2 diabetes, with mild and moderately severe DR were randomized into 2 groups - to receive candesartan at a dose of 16 mg 1 time / day (n = 951) or placebo (n=954). After 1 month the dose was increased to 32 mg 1 time/day. Progression of DR was the primary endpoint, regression of DR was the secondary endpoint. 161 patients (17%) treated with candesartan and 182 patients (19%) treated with placebo showed progression of DR by 3 points on the DR rating scale. The risk of DR progression was nonsignificantly lower (13%) in those receiving candesartan compared with those receiving placebo (RR 0.87, 95% CI 0.70–1.08, p=0.20). Regression during active treatment was observed significantly more often - by 34% (RR 1.34, 95% CI 1.08–1.68, p = 0.009). The risk reduction remained the same after adjusting for the magnitude of the BP decline during the study. A decrease in the severity of DR at the end of the study was observed in the candesartan group (RR 1.17, 95% CI 1.05–1.30, p=0.003). The incidence of side effects did not differ between treatment groups.

PREVENTION OF DIABETES

CASE-J Study

The prospective, randomized, open-label CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan) trial compared the long-term effects of candesartan and amlodipine on the incidence of cardiovascular events (sudden death and

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cerebrovascular, cardiac, renal and vascular events) among Japanese patients with hypertension and high risk of cardiovascular disease. -vascular complications [6, 20, 21] for 3.2 years. It included 4728 patients, the average age was 63.8 years, the average body mass index (BMI) was 24.6 kg/m2. With both treatment regimens, after 3 years of follow-up, good blood pressure control was achieved: 136.1/77.3 mm Hg. Art. when taking candesartan, 134.4/76.7 mmHg. Art. - when taking amlodipine. Treatment regimens did not differ in risk of outcome (RR 1.01, 95% CI 0.79–1.28, p=0.969), but all-cause mortality was significantly higher with amlodipine than with candesartan among patients with BMI >27.5 kg/m2 (adjusted RR 0.32, 95% CI 0.13–0.75, p=0.009). New-onset diabetes was less common with candesartan (8.7/1000 person-years) than with amlodipine (13.6/1000 person-years), corresponding to a relative risk reduction of 36% (RR 0.64, 95% CI 0.43–0.97, p=0.033). In addition, in patients taking amlodipine, the increase in the number of new cases of diabetes depended on BMI, while no such dependence was found for candesartan. Thus, treatment with candesartan may reduce all-cause mortality and the incidence of diabetes in obese and high-risk hypertensive patients.

Migraine

A prospective, randomized, double-blind, crossover study evaluated the efficacy of candesartan in 60 patients with migraine [6, 22]. It was found that taking candesartan at a dose of 16 mg/day reduced the average number of days with headache and migraine compared with those when taking placebo (13.6 versus 18.5 days, respectively, with headache, p = 0.001; 9.0 versus 12 .6 days, respectively, with migraine, p=0.001). The use of candesartan significantly reduced the severity of headaches, as well as the number of sick days for this reason. The response rate to candesartan, defined as a reduction in the number of migraine days by 50% or more, reached 40.4%, and to placebo - 3.5% (p = 0.001). The incidence of side effects with candesartan was comparable to that with placebo.

Tolerability and safety of candesartan

Candesartan, like other ARBs, is generally well tolerated, with withdrawal rates comparable to those with placebo. The safety of candesartan is not affected by concomitant administration of α-blockers, β-blockers, diuretics and calcium antagonists. It is known that RAAS blockers can lead to fetal malformations and neonatal complications when taken during pregnancy, which limits their use in women of childbearing age. The teratogenic potential of RAAS blockers in the second and third trimesters of pregnancy has been well studied. An important question is: is it dangerous if pregnancy occurs while taking an ARB, and then this drug is discontinued? The safety of candesartan was assessed in women who became pregnant after randomization into the DIRECT-prevent 1, DIRECT-protect 1 and DIRECT-protect 2 studies: 615 (43.3%), 813 (42.3%) took candesartan 32 mg/day or placebo. 7%) and 957 (50.2%) women, respectively. Among women who took at least 1 dose of candesartan, 178 patients (73 in the Prevent 1 group and 105 in the Protect 1 group) became pregnant (86 in the candesartan group and 92 in the placebo group). Pregnancy outcomes were similar for both groups: full-term birth occurred in 51 women taking candesartan and 50 women taking placebo, preterm birth in 21 and 27, spontaneous miscarriage in 12 and 15, early termination of pregnancy in 15 and 14 Most of the babies were healthy, both full-term and premature. There were 2 stillbirths in the candesartan group and 1 in the placebo group, 2 "sick babies" in the candesartan group and 8 in the placebo group. The only congenital malformation was ventricular septal defect in the placebo group. Thus, it was revealed that the effect of a relatively high dose of 32 mg/day of candesartan for up to 8 weeks. in the first trimester of pregnancy does not lead to a higher incidence of malformations than placebo in normotensive women with normoalbuminuria and type 1 diabetes [6, 18, 19, 23].

Candesartan showed good tolerability in clinical studies involving children and adolescents with hypertension. Its pharmacokinetic profile was independent of age, gender and weight and was similar to that in adults [23, 24]. The effects of candesartan and other ARBs on cancer incidence were assessed in 15 large, long-term, multicenter, double-blind clinical trials involving 138,769 patients. 6.8% of patients had cancer at inclusion in the studies. There were no significant differences in cancer incidence between the ARB and control treatment groups during the study period. This meta-analysis indicates that there is no significant increase in cancer incidence with ARBs compared with controls or with any specific ARB drug. In addition, throughout previous placebo-controlled studies of candesartan, no significant differences in the occurrence of fatal and non-fatal neoplasms were recorded when treated with this drug [9, 15, 25].

Currently, thanks to the advent of generic drugs, the availability of sartans for patients has increased significantly. In Russia, the drug Giposart [26], which is produced by the pharmaceutical plant POLFARMA, is widely used [27]. The bioequivalence of Giposart to the original candesartan was confirmed in a clinical study [28].

CONCLUSION

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Candesartan is an effective antihypertensive drug with a tolerability profile similar to that of placebo. Comparative data show that candesartan has the same (and in some cases even more pronounced) antihypertensive effect as other ARB and has a long duration of action. The drug is effective and safe in broad populations of patients with hypertension, including patients with diabetes and CKD.

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