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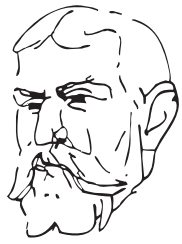

Memory of
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ORIGINAL ARTICLE

S-AMLODIPINE AS A MODERN EFFECTIVE ANTIHYPERTENSIVE AND AN ANTIANGINAL AGENT

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ABSTRACT

The aim: Study of the clinical and hemodynamic effects of S-amlodipine in patients with arterial hypertension associated with coronary artery disease, in individuals with preserved LV systolic function.

Materials and methods: The study includes 51 patients with arterial hypertension associated with coronary artery disease, who were treated with S-amlodipine.

Results: This study shows the high clinical effectiveness of the use of S-amlodipine in patients with arterial hypertension associated with coronary artery disease. We reveal that treatment of hypertensive patients with coronary artery disease with S-amlodipine leads to improvement of LV diastolic dysfunction, bringing it closer to normal values.

Conclusions: Clinical effectiveness was associated with positive changes in hemodynamics, and was expressed in the normalization of the left ventricle diastolic function parameters, about which indirectly indicates decreasing of end-diastolic pressure.

KEY WORDS: S-amlodipine, arterial hypertension, hypertrophy, angina pectoris, threshold physical load, central hemodynamics, diastolic dysfunction

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INTRODUCTION

Progress in basic sciences have made possible to study the mechanisms of coronary blood circulation at the molecular and cellular level. The study of ion channels, in particular those that ensure the penetration of calcium ions into the cell, made it possible to create a fundamentally new drugs group – calcium channel blockers (CCB) [1]. The first clinically used drug was verapamil (1962). Later, in 1967, Fleckenstein announced the discovery of a fundamentally new drug group – CCB (he separated them from b-adrenoblockers). Since then, in different periods, the attitude towards CCB has changed [1].

In recent years, CCB has again found its wide use, especially after cardiosurgical interventions (coronary artery bypass grafting, stenting, balloon angioplasty) [2-4]. One of the reasons for the growing popularity of CCB is metabolic neutrality and improvement of diastolic function of the left ventricle (LV) in hypertensive patients and patients with coronary disease.

Data from multicenter studies indicate the special effectiveness of dihydropyridine CCB group for reducing the risk of strokes [1,5].

Such a representative of the dihydropyridine series of the III generation as amlodipine (known as «norvask», «normodipine», «Amlo») is particularly popular among CCBs [2,3,5,6]. It is characterized by high expected efficiency (60-80% bioavailability) and stability of plasma concentration (24-36 hours), which means that is unnecessary to create retarded forms [1-3,5].

The antihypertensive effectiveness of amlodipine therapy in mild and moderate hypertension is similar to that of other basic antihypertensive drugs, sometimes even better and can reach 60-70%. On the background of therapy, there is an improvement in the daily profile of blood pressure (BP); with long-term use (>4-6 months) develops regression of LV hypertrophy. The reduction of cerebral strokes risk in people with hypertension is one of the important effects of the drug, confirmed in a number of large-scale studies,. Amlodipine combines well with all groups of drugs. In coronary artery disease (CAD), amlodipine is used in patients with stable and vasospastic angina. In patients with CAD, the drug has a coronary dilating effect, which increases the blood supply to the myocardium and reduces the total peripheral vascular resistance. In addition, amlodipine has an antiatherosclerotic effect, which was convincingly confirmed in the PREVENT study (2000) [1,2]. The clinical effects of this drug in CAD include a reduction in the number and duration of

anginal episodes and episodes of painless myocardial ischemia; at the same time, the antianginal effect is more pronounced compared to a number of other CCBs (CAPE-II study, 2002) [1].

The most common side effect of amlodipine in clinical practice is peripheral edema. There are present data that this complication may occur in more than 8% of patients receiving amlodipine [5,7]. The solution to this issue was the use of the levorotatory isomer of S-amlodipine. It is known that optical isomerism is characteristic of almost all molecules in the body. Most proteins consist of levorotatory amino acids. It is believed that drugs based on levorotatory molecules are safer and more effective when used. Most of the drugs used are a mixture of dextrorotatory and levorotatory isomers (R+S). At the same time, the active substance is the levorotatory S-isomer [7-10].

Taking into account the available literature data, we conducted our own research.

THE AIM

Study of the clinical and hemodynamic effects of S-amlodipine in patients with arterial hypertension associated with coronary artery disease, in individuals with preserved LV systolic function.

MATERIALS AND METHODS

The study includes 51 patients with arterial hypertension associated with coronary artery disease, who were treated with S-amlodipine. Among them: 27 patients - with first stage hypertension, 24 - with second stage hypertension. It was noted angina pectoris II functional class (FC) in 25 patients, and angina pectoris III FC in 26 patients; there were 25 (49%) women and 26 (51%) men aged from 34 to 73 years (on average 64.1±4.2 years). Exclusion criteria were: acute coronary syndromes, symptomatic hypertension, history of myocardial infarction, stenting or coronary bypass surgery, diabetes mellitus. As a baseline, all patients received standard therapy with enalapril 20 mg per day, bisoprolol 2,5 or 5 mg per day, rosuvastatin 10 mg per day, and acetylsalicylic acid 100 mg per day. Doses of drugs did not change during two months before inclusion in the study.

Clinical effectiveness was assessed by lowering BP to target levels and reducing the number of angina attacks by 30% or more (positive antianginal effect). A positive ergometric effect was considered as an increase in power (W) of the threshold load by one step (25 W). Hemodynamic indicators were studied by echocardiography. LV hypertrophy was ascertained according to the recommendations of A. Canau et al. [10]. To analyze the structural and functional state of the heart, the following indicators were studied: the anterior-posterior size of the left ventricle, left ventricle parameters like end-systolic dimension (ESD), end-diastolic dimension (EDD), interventricular septum (IVS) and posterior wall thickness, were calculated end-systolic volume (ESV), end-diastolic volume (EDV), ejection fraction (EF), myocardial mass index of left ventricle (MMILV). Myocardial mass was calculated according to the formula of R.B. Devereux 1995. MMILV was calculated as the ratio of MMLV to body area (S), which was determined according to the Dubois table. There were distinguished three types of LV geometry: normal geometry – MMILV<125 g/m^2, relative wall thickness (RVS) <0.45; eccentric LV hypertrophy: MMILV >125 g/m^2, RVS <0.45; concentric LV hypertrophy: MMI LV >125 g/m^2, RVS >0.45. The control group consisted of 20 healthy people.

Diastolic heart function was studied by Doppler echocardiography. The following parameters were determined: isovolumic relaxation time (IVRT), maximum speed of early diastolic filling (E), deceleration time of early diastolic filling (DT), maximum speed of late diastolic filling (A) and ratio E/A.

After stabilization of hemodynamic indicators (with enalapril and bisoprolol), treatment with S-amlodipine was prescribed for ten weeks. In the absence of a decrease in blood pressure to the target levels of systolic and diastolic blood pressure, the dose of the drug was increased from 2.5 mg to 5 mg. The studied indicators were determined before the appointment of S-amlodipine and after 10 weeks of taking the drug.

RESULTS

The average systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients from general population before the start of treatment was 162/100 mm Hg. In group patients for which S-amlodipine in dose 2.5 mg was prescribed (n=30) after 10 weeks of treatment BP decreased to 128/83 mm Hg. The decreasing of SBP and DBP was considered statistically significant (p <0.005). The mean SBP and DBP in the group treated with S-amlodipine in dose 5 mg (n=21) decreased to 126/ 81 mm Hg (p <0.005).

In general group, treatment of patients for 10 weeks led to decrease in the number of angina attacks (the need for nitroglycerin (NG) decreased more than twice per week), to increase the power of the threshold load (W), to decrease the threshold demand of oxygen to myocardium (TDO) without significantly affecting on the contractility of the myocardium (see Table I).

The criteria for terminating the test with dosed physical activity were also not significantly different. We also did not notice any side effects from S-amlodipine in

Table I. Clinical and instrumental indicators of the effectiveness of treatment patients with AH and CAD by S-amlodipine (M±m)

Stages of research	Indicators of treatment effectiveness				
	Number NG tablets in a week	Power (W)	Threshold demand of oxygen (TDO) at rest, conditional units	TL (threshold load), conditional units	EF, %
Hypertensive patients with coronary artery disease before treatment	28,7±2,3	81,9±3,0	87,1±6,2	177±5,8	59,2±2,4
Hypertensive patients with coronary artery disease after treatment	12,9±25	123,7±2,8	88,0±2,9	149±4,5	58,6±3,7
P	<0,01	<0,01	>0,05	>0,05	>0,05

Table II. Indicators of the effectiveness of treatment of patients with arterial hypertension and concomitant coronary artery disease depending on the severity of coronary artery disease

Hypertensive patients with coronary artery disease	Number patients (n=51)	Threshold load power, W (Вт)		P
		Before treatment	After treatment	
Angina pectoris II FC	25	100,2±4,1	149,0±3,8	<0,01
Angina pectoris III FC	26	49,4±2,3	74,5±2,8	<0,05

Table III. Clinical and instrumental parameters of the effectiveness of patients treatment with S-amlodipine depending on the type of LV hypertrophy (M±m)

Indicators of treatment effectiveness	Patients with concentric type of LV hypertrophy, n=25			Patients with eccentric type of LV hypertrophy, n=22		
	Before treatment	After treatment	P	Before treatment	After treatment	P
Number of nitroglycerine tablets in a week	26,7±1,5	11,9±2,0	<0,01	29,4±3,1	15,7±1,8	<0,01
Power (W)	79,7±2,0	134±4,1	<0,01	82,1±3,6	119±3,1	<0,01
Threshold demand of oxygen (TDO) at rest, conditional units	87,0±2,1	86,8±1,5	>0,05	87,3±2,2	88,9±1,5	>0,05
Ejection fraction (EF), %	59,0±1,4	58,8±1,8	>0,05	58,9±1,5	58,7±1,9	>0,05

Table IV. Indicators of central and intracardiac hemodynamics in patients with hypertension associated with CAD under the influenceof S-amlodipine treatment (M±m)

Hemodynamic indicators	Patients with hypertension associated with coronary artery disease		
	Before treatment	After treatment	P
Heart rate, bpm	71,9±2,5	72,1±3,1	>0,05
BP, mmHg	161,2±5,0	127,4±3,8	<0,02
Threshold demand of oxygen (TDO) at rest, conditional units	90,1±3,7	88,1±2,9	>0,05
EDV, cm^3	145,7±3,4	141,8±3,7	>0,05
ESV, cm^3	74,8±3,1	71,2±2,8	>0,05
EF, %	59,2±2,4	59,1±3,0	>0,05

patients with arterial hypertension in combination with CAD. Blood pressure decreased to target levels in 87% of patients.

The initial functional condition of myocardium, that is, the functional class of angina pectoris, is important for the effectiveness of treatment. Table II shows data on the effectiveness of course treatment of patients with S-amlodipine depending on the severity of the disease (presence of concomitant CAD).

Treatment with S-amlodipine significantly increases the level of threshold load power (W) both in patients with hypertension and II FC of angina as in patients with III FC.

LV hypertrophy was noted in the majority of patients with hypertension and coronary heart disease (in 47 of 51 patients). Only four patients with hypertension combined with coronary artery disease did not have LV hypertrophy. This phenomenon can be explained by the increased inotropic properties of the myocardium and the relatively short-term history of hypertension in these patients.

Table III presents the results of the study of the clinical effectiveness of S-amlodipine in patients with AH and CAD, depending on the type of LV hypertrophy.

The frequency of concentric and eccentric types of LV hypertrophy was approximately the same (25 versus 22

patients). According to literature data, in patients with hypertension, this ratio is 4:1 [11,12]. The addition of ischemic heart disease to hypertension leads to increase in the frequency of eccentric LV hypertrophy, as well as to increase the risk of developing LV dilatation - an increase in EDV (LV dilatation index) [11,12].

The analysis of Table III shows the positive dynamics of indicators. Irrespective of the type of LV hypertrophy, in both groups, the clinical efficacy of S-amlodipine was high, which was expressed in a decrease of using of nitroglycerine per week and an increase in the level of threshold exercise power (W). The criteria for terminating the test with dosed physical activity were not significantly different.

Performance of higher threshold loads by patients with AH associated with CAD, after treatment with amlodipine, occured on the background of minor changes in the parameters of central hemodynamics (see Table IV**)**

We note a positive trend of LV volumetric indicators (EDV, ESV) on the background of practically unchanged EF and threshold demand of oxygen. The pronounced antihypertensive effect was observed on the background of unchanged heart rate (without activation of the sympatho-adrenal system).

It is impossible to explain the high clinical effectiveness of amlodipine in patients with AH and CAD, based on the data of changes in the specified hemodynamic parameters.

The study of the hemodynamic structure of diastole made it possible to establish in the examined patients hypertrophic type of diastolic dysfunction (in 27 persons) and «pseudonormal» type (in 24 persons).

In patients with a hypertrophic type of diastolic dysfunction was found a lengthening of IVRT (82.3±1.7 relative to 68.3±1.3 ms, P<0.05) and decreasing of late diastolic filling speed (A; 64.2±1.5 relative to 43,0±1.6 cm/sec, P<0.05). At the same time, the speed of early diastolic filling (E; 60.2±0.9 relative to 70.5±0.9 cm/sec, P<0.05) and the E/A ratio (0.96±0.6 relative to 1,65±0.04 conditional units, P<0.05) increased. Unreliable increasing in DT was noted (190.0±8.2 relative to 181±9.7 ms, P>0.05).

With the «pseudo-normal» type of filling of the left ventricle, the following changes were noted: IVRT increased (62.4±2.5 relative to 66.7±1.8 ms, P<0.05) and DT increased (171.4±8.2 relative to 182,4±10.7 ms, P>0.05) and the E indicator decreased (78.7±1.9 relative to 71.2±1.8 cm/sec, P<0.05). The E/A ratio approached normal values (1.59±0.05 relative to 1.65±0.04 conventional units, P>0.05). This orients us to increase in end-diastolic pressure in the left parts of the heart (left atrial and LV).

During treatment with S-amlodipine for 10 weeks, a decrease in systolic and diastolic blood pressure was noted. Average daily SBP decreased by 36.5±2.20 mm Hg, or by 20.1±0.8% from the initial level (P<0.05), DBP – by 26.2±0.86 mm Hg , or by 18.1±0.8% (P<0.05). At the same time, heart rate did not increase.

S-amlodipine therapy in patients with hypertrophic type of diastolic dysfunction significantly reduced IVRT (82.3±1.7 to 69.0±1.9 ms, P<0.05), not significantly – DT (from 190.0±8.2 to 175.4±8.9 ms, P>0.05) and late diastolic filling speed (A; from 64.2±1.5 to 59.3±1.6 cm/sec, P>0.05). Under the influence of amlodipine treatment, the speed of early diastolic filling significantly increased (E; from 60.2±0.9 to 71.4±1.2 cm/sec, P<0.05), and as a result E/A value also increased (from 0.96±0.06 to 1.28±0.04 conventional units, P<0.05). All this indicates hemodynamic unloading of the LV due to a reduction of preload, first of all, – decreasing in pressure in the left heart.

The following hemodynamic effects of S-amlodipine were noted in patients with the «pseudonormal» type of diastolic dysfunction: rasing of IVRT (from 62.4±2.5 to 84.5±1.7 ms, P<0.05), lowering of E (from 78.7±1.9 to 67.2±1.6 cm/sec, P<0.05) and E/A ratio (from 1.59±0.05 to 1.24±0.06 conventional units, P<0.05). There was revealed a tendency to increase the speed of late diastolic filling (A; from 50.1±1.5 to 56.4±2.7 cm/sec.; P>0.05) and DT (from 171.4±8.2 to 182,0±8.1 ms, P>0.05). These changes were considered as positive, i.e. hemodynamic indicators approached the hypertrophic type of diastolic dysfunction.

Summarizing the above, we reveal that treatment of hypertensive patients with coronary heart disease with S-amlodipine leads to improvement of LV diastolic dysfunction, bringing it closer to normal values.

DISCUSSION

The literature describes, mainly, data relating to the improvement of LV systolic function in patients with AH and CAD under the influence of amlodipine therapy. In our study we found the superiority in the mechanism of therapeutic action of S-amlodipine in hypertensive patients, evaluating systolic function by volumetric indicators, and diastolic function by transmitral blood flow [1-3,8,11,12].

We note the safety of treatment with S-amlodipine, which indicates the rare frequency of side effects. Similar conclusions are given in the literature.

Thus, the SESA study [13] was conducted to estimate the effectiveness and tolerability of S-amlodipine (2.5/5 mg) - pure levorotatory amlodipine in the treatment of patients with AH. The study showed that S-amlodipine in doses of 2.5/5 mg is an effective drug for the treatment of hypertension, well tolerated, and can also be an ideal replacement therapy for patients with peripheral edema when using racemic amlodipine.

Despite the fact that the study was published back in 2002, and the recommendations for the treatment of

hypertension have been revised four times since then, these data were not reflected in relation to S-amlodipine.

There is an opinion that the presence of two isomers provides the therapeutic properties of amlodipine, which have brought the drug to the forefront in the treatment and prevention of major cardiovascular events.

Analyzing the data of the latest epoch-making large-scale multicenter studies and taking into account the results of our study, it is possible to assert with high probability the positive effects of the use of the levorotatory isomer of amlodipine (S-amlodipine) [7-10,14].

But the use of monotherapy, as a rule, cannot control all pathogenetic mechanisms of BP increasing: activity of the sympathetic nervous system, renin-angiotensin-aldosteron system, volume-dependent and other secondary mechanisms. Today, necessity of use combined antihypertensive drugs is obvious, especially in the treatment of high-risk patients.

The most effective combination of hypotensive drugs, based on the modern research base (ACCOMPLISH, ADVANSE, HYYET, ASCOT, ONTARGET), is ACE inhibitors + CCB, angiotensin II receptor antagonists + CCB, ACE inhibitor + thiazide diuretic or angiotensin II receptor antagonists (ARA) + thiazide diuretic.

Among modern combinations of antihypertensive drugs, the combination of CCB and ACE inhibitors receives special attention. This combination, according to the data of two large-scale international studies ASCOT and ACCOMPLISH, allows to further reduce the risk of major cardiovascular events.

Given that CCBs (including levorotatory isomers) are almost ideal drugs for combined therapy, which can be used in combination with ACE inhibitors, ARA, diuretics, ready-made combined drugs, which include amlodipine, appeared on the pharmacological market [14-16]. These combined drugs have proven themselves well in the treatment of arterial hypertension with diabetes, chronic kidney diseases, coronary heart disease (angina pectoris, vasospastic angina). Therapy with these combined medicines is highly effective, convenient for patients (one tablet with two active substances), safe and relatively unexpensive.

CONCLUSIONS

1. S-amlodipine is characterized by high clinical efficacy and safety, which makes it the drug of choice in the treatment of low-renin arterial hypertension in combination with coronary heart disease.
2. The high clinical effectiveness of S-amlodipine is due to positive changes in hemodynamics, which are expressed in the normalization of indicators of LV diastolic function. These changes are represented in a decrease of preload, and also indirectly indicate about the reduce of LV end-diastolic pressure.
3. The use of combined drugs therapy of amlodipine and ACE inhibitors or amlodipine and ARA in patients with hypertension and CAD significantly reduces the risk of cardiovascular complications.

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