Original Article

Evaluation Of Hypotensive Therapy In Patients With Cardiorenal Syndrome

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Abstract

Purpose. To study the effect of sacubitril/valsartan on the circadian rhythm of circadian blood pressure in patients with stage III CKD diabetic nephropathy and chronic heart failure.
Material and methods. The study included 129 patients with type 2 diabetes mellitus with chronic kidney disease and chronic heart failure with an EF less than 40%. They were divided into two groups. The first group of patients took sacubitril/valsartan 200 mg/day, the second group took valsartan at a dose of 160 mg /day during 3 months. Daily monitoring of blood pressure was carried out by a portable automatic monitor for measuring blood pressure "Cardiotic 4000-AD" of the Incart company. The radio-technical device is an automatic blood pressure monitor and ECG, in which blood pressure measurement is carried out in parallel with the Korotkov method and the oscillometric method.
The results. Systolic and diastolic arterial blood pressure in patients of group 1 and group 2 in our study decreased reliably ($\rho<0,001$) after 3 months in groups taking sacubitril/valsartan and valsartan. We observed that patients taking sacubitril/valsartan had a higher level of reliability with lower arterial blood pressure values ($\rho<0,01$). And the number of non-dippers and nite-pickers decreased to a large extent in the first group taking sacubitril/valsartan compared to the second group taking valsartan
Conclusion. Thus, according to the results, we observed a more pronounced positive effect with long-term treatment with sacubitril/valsartan. It can be assumed that such positive changes contribute to a decrease in the manifestations of cardiorenal syndrome in patients with diabetic nephropathy.

Keywords: arterial hypertension, cardiorenal syndrome, chronic kidney disease, diabetic nephropathy.

Introduction

Chronic kidney disease (CKD) is a worldwide epidemic of our time. The end result of CKD is end-stage renal failure (ESRD), which is costly to health care. As kidney function deteriorates, there is also an increase in arterial hypertension (AH), which also accompanies CKD [5,7]. AH is a global medical problem and is one of the major risk factors for cardiovascular disease (CVD) and stroke. CVD is a common cause of AH and a complication of uncontrolled AH. The interaction between AH and CVD is complex, increasing the risk of adverse cardiovascular outcomes (7). The incidence of cardiac and renal complications defines AH and CVD as a significant medical problem [3,8,21]. The prevalence of AH is 25-30% and of CVD 15% in the adult population [8,12].

As reported in the literature, the incidence of AH in patients with CKD is much higher than in the population. According to epidemiological studies, 67-71% of patients with this pathology have AH, and in older people it is found in 82% of cases [12,15]. Already in the advanced stages of CVD, AH is found in 90% of patients [17]. AH is common in patients receiving renal replacement therapy (RRT) [8,15].

AH and CVD are bidirectional in nature; they are closely related pathophysiological conditions [2,11,13]. High-risk AH phenotypes, such as latent, resistant and nocturnal hypertension, are more common in patients with

CVD. Target organ damage and other adverse conditions are more common in latent AH. Recent studies suggest that hidden AH in CKD is associated with an increased risk of left ventricular hypertrophy (LVH), proteinuria and decreased estimated glomerular filtration rate (GFR). Latent AH is also associated with high CVD, end-stage CKD and all-cause mortality. Further studies on latent AH and the search for rational methods of diagnosis and treatment are needed [2,13,20]. Resistant AH is defined when using three antihypertensive drugs of different classes at optimal doses (one of which is a diuretic), BP remains above the target level with "office" and "out-of-office" control [4,6, 19,20].

The literature and numerous studies have shown that renin-angiotensin-aldosterone system blockers are more effective in reducing both arterial hypertension and albuminuria compared to placebo or other antihypertensive drugs in patients with diabetic and nondiabetic nephropathy and CVD, and are also effective in preventing microalbuminuria. In recent years, natriuretic peptides have also been used in experimental studies to achieve the same results. They play an important role in the activation response of the renin-angiotensin-aldosterone system [9,10,16]

Natriuretic peptides are physiological angiotensin II antagonists with respect to stimulation of aldosterone secretion, increased sodium reabsorption and increased vascular tone. In addition, atrial natriuretic peptide (ANP) increases venous permeability, causing movement of the liquid portion of plasma into the extravascular space (reduction of preload) and reduces sympathetic nervous system tone (effect on postload). The main stimulus for increased ANP secretion is atrial volume overload and increased myocardial tension [16]

Among the new drugs being actively developed by pharmaceutical companies that affect the kidneys by normalising cardiac activity is the combined drug sacubitril/valsartan (superio). The use of this drug is posited to increase natriuresis with a consequent moderate reduction in blood pressure through its effect on the natriuretic peptide and the renin-angiotensin aldosterone system. Normally, atrial natriuretic peptide binds to a specific set of receptors: A, B and C (PPP receptors). The A- and B-receptors are responsible for the main action of the hormone, while the C-receptors are located inside the cells, where by binding to the PNP they reduce its effect. Agonist binding to these receptors causes a decrease in circulating blood volume and systemic blood pressure. At the same time there is an activation of lipolysis and a decrease in sodium reabsorption in the renal tubules. The effect of atrial natriuretic peptide is opposite to that of the renin-angiotensin system. According to the literature, this drug also has a nephroprotective effect [14,16].

Although awareness of AH treatment in patients with CKD is improving, BP control at all stages of CKD remains suboptimal. Accordingly, patients with CKD should receive full treatment according to national and international guidelines, unless there are contraindications.

The aim of this study was to evaluate the effect of sacubitril/valvsartan on the circadian rhythm of daily blood pressure in diabetic nephropathy patients with stage III CKD and chronic heart failure.

Study materials and methods. The study enrolled 129 patients with type 2 diabetes mellitus with chronic kidney disease and chronic heart failure with EF less than 40%. All patients underwent instrumental, laboratory and clinical and biochemical investigations, which were then selected and divided into groups. The first group included 66 patients, of whom 30 women (45.5%) and 36 men (54.5%). In these patients sacubitril/valsartan 200 mg/day, which belongs to the ARNI group, was recommended as hypotensive therapy in combination with conventional therapy. The mean age of the patients in the first group was 60.9 ± 0.97 years old. The second group consisted of 63 patients who received valsartan at a dose of 160 mg/day as a hypotensive treatment regimen in combination with conventional therapy. The mean age of patients in this group was 62.6 ± 0.88 years old.

Daily blood pressure monitoring was performed by a portable automatic blood pressure monitor "Cardiotik 4000-AD" by Inkart (St. Petersburg Institute of Cardiology Technologies). The cardiotic device is an automatic blood pressure and ECG monitor in which blood pressure measurement is carried out in parallel with the Korotkoff and oscillometric methods.

Results and discussions.

In patients in groups 1 and 2 of our study daily mean systolic blood pressure (SBP) decreased in levels of significance by 23.1% and 19.3% after 3 months in the groups receiving sacubitril/valsartan and valsartan. At the same time, daytime variability of

MAP decreased by 65.4% in group 1 and by 43.4% in group 2 compared with pre-treatment levels. In patients treated with sacubitril/valsartan, we observed a significant reduction in daytime BP variability (Table 1).

Table 1 Dynamics of mean daily blood pressure, blood pressure variability and temporal blood pressure index as a result of antihypertensive therapy in the groups

Indicators	Sacubitril/valsartan, n=66 Valsartan, n=63		
	Before treatment	After treatment (1 month)	After treatment (3 month)
Daily SBP, mmHg	164,4±2,20 167,0±1,97	133,4±0,87**^ 139,0±0,49**	126,5±0,76***^^ 134,8±0,33***
Variability in daily SBP	18,2±2,27 18,7±2,366	11,6±2,14*^ 14,9±2,44*	6,3±1,68***^^ 10,6±2,21**
Daily DBP, mmHg	95,1±1,46 97,2±0,91	80,3±1,03**^ 87,8±0,31**	75,3±0,89***^^ 83,5±0,40**
Variability in daily DBP	15,6±2,28 16,1±2,34	9,2±2,15*^ 10,8±2,47*	6,2±2,26***^^ 8,5±2,25**
Daily mean BP, mm.syst.	118,2±4,51 120,4±4,27	98,1±3,37***^^ 104,8±3,2**	92,3±2,21***^^^ 100,6±2,37***
Variability in mean daily BP	16,4±2,45 16,9±2,53	10,0±2,18*^ 12,1±2,1*	6,2±1,47***^^ 9,2±2,08**
Night SBP, mmHg	158,9±6,65 162,8±5,43	126,7±5,15**^^ 133,9±3,42**	117,7±5,26***^^ 127,2±5,15***
Nocturnal SBP variability	16,6±2,20 17,1±2,75	10,2±2,14**^ 13,5±3,24*	5,2±1,63***^^ 9,5±2,12**
Night DBP, mmHg	91,7±5,32 94,2±5,11	76,3±4,21**^ 84,3±4,52*	69,9±3,87***^^ 77,4±4,21**
Night-time DBP variability	13,3±1,85 14,2±1,68	7,9±1,47**^ 9,2±1,52*	5,3±1,36***^^ 7,3±1,47**
Average night-time BP, mmHg	112,7±6,87 117,1±6,42	93,1±4,23**^^ 100,8±4,61**	85,8±3,79***^^ 94,0±4,21***
Variability in mean night-time BP	14,4±3,13 15,1±2,64	8,6±2,17*^ 10,6±2,24*	5,2±1,32**^ 8,1±2,15**
Level of reduction in night-time BP %	3,4±0,58 2,7±0,65	5,1±1,48 3,8±1,42	7,04±1,62*^ 6,5±1,66*
Level of reduction in night-time SBP %	3,3±0,86 3,1±0,79	5,02±1,12 3,6±1,08	6,9±1,54**^ 5,6±1,58*
Level of reduction in night-time DBP %	3,5±0,47 3,1±0,23	4,9±1,53 4,1±1,67	7,2±1,78**^ 5,9±1,83*

Note: The numerator is Group 1 and the denominator is Group 2

* ρ<0,05, **- ρ<0,01, ***- ρ<0,001 - the differences are significant compared to the pre-treatment figures

^ρ<0,05, ^^- ρ<0,01, ^^^- ρ<0,001 - differences are significant when compared to values at day 30 and day 90 of treatment between the groups.

We observed a similar trend in mean daily diastolic blood pressure (DBP) values, i.e., their values, compared with baseline values, decreased at a confidence level by 15.6% and 20.9% in Group 1 and by 9.7% and 14.1% in Group 2, respectively. It was also noted that daily BP variability decreased at the confidence level at 1 month and 3 months in group 1 by 41.1% and 60.3%, and in group 2 by 32.9% and 47.3%, respectively, compared with pre-treatment values. This resulted in a 17.1% and 21.9% reduction in mean daily BP and a 12.9% and 16.5% reduction at 1 and 3 months of treatment in both groups, respectively.

In patients with diabetic nephropathy, treatment with sacubitril/valsartan and valsartan reduced night-time BP by 20.3% and 17.8% after 1 month and by 25.9% and 21.9% after 3 months, respectively. Slight stabilisation of night-

time BP in both groups resulted in significant reductions of 1.6 and 1.2 times the pre-treatment variability at month 1 and 3.1 and 1.8 times the pre-treatment variability at month 3, respectively.

Mean nocturnal DAP also decreased by a factor of 1.20 and 1.11 and by a factor of 1.31 and 1.21 in level of confidence across groups, respectively. At the same time, nocturnal DBP also decreased by a factor of 1.68 and 1.54, and then by a factor of 2.50 and 1.94. Mean nocturnal BP, compared with pre-treatment values in both groups, during treatment decreased at a confidence level by 1.21 and 1.16 times, by 1.31 and 1.24 times, and by 1.67 and 1.42 times, while variability decreased by 2.76 and 1.86 times.

As can be seen from the above data, during long-term treatment with sacubitril/valsartan and valsartan, daytime and night-time blood pressure decreased in confidence and approached normal values, its range of changes decreased, leading to stabilisation of both daytime and night-time blood pressure. Clear changes were seen in patients treated with sacubitril/valvsartan.

The long term use of antihypertensive drugs was studied to determine their effect on the reduction of night-time blood pressure in diabetic patients with CKD by comparing the groups. This study showed an increase in the level of significance of the mean reduction in nocturnal BP, reduction in nocturnal SBP and DBP in the groups. Thus, these indices increased by a factor of 1.5 and 7.04 in patients treated with sacubitril/valsartan compared with those before treatment; by a factor of 1.5 and 2.1; 1.4 and 2.05; and with treatment with valsartan by a factor of 0.7 and 2.4; 1.16 and 1.80; 1.32 and 1.90, respectively.

Thus, CKD patients with chronic heart failure showed a significant increase in the reduction of nocturnal BP during antihypertensive therapy. The greatest changes were observed in the group of patients receiving sacubitril/valvsartan. The results suggest that sacubitril/valvalsartan should be introduced into the treatment of patients with CKD of diabetic etiology.

In view of the above, after long-term antihypertensive therapy we analysed the incidence of non-dipper and night-peaker patients in the groups with insufficient reduction in nocturnal BP. The study showed that, as a result of antihypertensive pharmacotherapy with drugs, the distribution of patients in the study groups changed significantly due to a reduction in nocturnal BP (Table 2). During long-term (results for 1 month, 3 months) treatment with Sacubitril/Valsartan, 27 (41%) patients were included in "dipper" group, 28 (42%) patients - in "non-dipper" group, 11 (17%) patients - in "night-peaker" group. As can be seen from the above data, in the course of treatment the number of patients with "non-dipper" and "night-peaker" groups decreased by 1.25 and 2.8 times compared to the pre-treatment figures, respectively. In the group of patients who received valsartan for a long time 18 (29%) patients were included in the "dipper" group, 28 (44%) patients in the "non-dipper" group and 17 (27%) patients in the "night-peaker" group. During treatment, the number of patients in this group with "non-dipper" and "night-peaker" decreased by a factor of 1.17 and 1.76, respectively, compared to the pre-treatment figures. Comparing the antihypertensive efficacy of the two drugs, sacubitril/valsartan was more effective, as compared to the group receiving valsartan, the percentage of patients with "dipper" was higher and the percentage of patients with "non-dipper" and "night-peaker" was lower.

Table 2 Frequency of AH patients with CKD in groups according to the degree of reduction in nocturnal BP before and after antihypertensive treatment
(3 months)

Groups	Sacubitril/valsartan, n=66		Valsartan, n=63	
	Before treatment	After treatment	Before treatment	After treatment
Dipper	-	27 (41%)	-	18 (29%)
Non-dipper	35 (53%)	28 (42%)	33 (52%)	28 (44%)
Night-peaker	31 (47%)	11 (17%)	30 (48%)	17 (27%)

The results from the study showed a reduction in the risk of nocturnal nuisance hypertensive crises in both study groups, especially in the group of patients treated with sacubitril/valzartan. In our opinion, the positive dynamics of BP reduction is a good haemodynamic factor in slowing the acceleration of chronic renal failure (CRF) and cardiac remodelling in DN patients with CKD.

Previous studies have shown a significant increase in the vascular tension index in patients with diabetic nephropathy. Prolonged hypotensive pharmacotherapy significantly decreased the time index (time index) in diabetic patients with CKD (Table 3). Thus, after long-term treatment with sacubitril/valvsartan, daily SBPTI, daytime SBPTI

and night-time SBPTI statistically decreased in level of confidence by 4.49; 4.95; 4.38 times, respectively; daily DBPTI, daytime DBPTI and night-time DBPTI statistically decreased in level of confidence by 4.85; 4.84; 4.84 times, respectively.

As a result of long-term therapy with valsartan, daily SBPTI, daytime SBPTI and night-time SBPTI were reduced with statistical significance by a factor of 3.19; 3.21; 2.96, respectively; daily, daytime and night-time DBPTI were reduced with statistical significance by a factor of 3.25; 3.34; 3.20, respectively.

The percentage of BP values during the day, as well as in some periods of the day (night, day) exceeded the normal daily values and were lower at the statistical level of confidence by 1.42; 1.54 and 1.47 times compared to the group of patients treated with valsartan, respectively. DBP values both as a percentage and daily and at some periods of the day (night, day) exceeded the normal daily values and were lower at a statistical level of confidence by 1.45; 1.44 and 1.43 times, respectively.

Table 3 Time index before and after hypotensive therapy in patients with cardio-renal syndrome

Indicators	Sacubitril/valsartan, n=66		Valsartan, n=63	
	Before treatment	After treatment (3 month)	Before treatment	After treatment (3 month)
TI of daily SBP, %	92,6±5,49	20,6±4,46***^	93,6±5,31	29,3±4,96***
TI of daytime SBP, %	91,7±5,70	18,5±5,28***^	92,0±5,38	28,6±5,18***
TI of night-time SBP, %	95,5±6,21	21,8±4,17***^	95,2±5,81	32,1±7,15***
TI of daily DBP, %	93,2±4,89	19,6±4,82***^	92,7±5,14	28,5±6,34***
TI of daytime DBP,%	93,1±6,21	19,2±4,27***^	92,6±4,87	27,7±6,25***
TI of night-time DBP, %	94,5±5,48	20,5±4,64***^	94,2±4,92	29,4±5,87***

Note: * - values of difference (*-ρ<0.05, **- ρ<0.01, ***- ρ<0.001) compared to those before treatment.
^ - values of difference (^-ρ<0,05, ^^- ρ<0,01, ^^^- ρ<0,001) compared to inter-group values.

As can be seen from the above data, patients with cardio-renal syndrome prior to treatment experienced constant 'pressure tension', which in turn is considered one of the haemodynamic factors that negatively affect vital organs. The used hypotensive drugs significantly reduced this tension, although significantly different from the normal values. We noted a more pronounced positive effect with long-term treatment with sacubitril/valsartan. It may be assumed that such positive changes contribute to a reduction in the manifestations of the cardiorenal syndrome in diabetic nephropathy patients.

Conclusion. Circadian rhythm disturbances in the cardio-renal syndrome patients studied, namely those with stage III CKD, were observed to a greater extent in non-dippers and night-pikers, indicating the need to slow the rate of renal failure, not only to achieve a target level of blood pressure, but also to normalise its circadian profile.

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