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The Methods of Correction of Endothelial Dysfunction and Systemic Inflammation in Patients with Chronic Pyelonephritis and Hypertension

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The aim of research was to improve treatment of endothelial dysfunction and systemic inflammation in patients with chronic pyelonephritis (CPN) and hypertension (HPT) by using Meldonium and Canephron N. To do this, we examined 105 patients with CPN and HPT, among whom were 64 (60.95%) men and 41 (39.05%) female, aged from 35 to 74 years (average 56.04□4.15 years). In these same patients revealed signs of endothelial dysfunction and systemic inflammation. Application to the basic therapy of CPN and HPT Meldonium and Canephron N improve the elastic properties of elastic arteries, particularly reduce endothelin-1, cardio-ankle vascular index, pulse wave velocity, aortic stiffness index, thickness intima - media complex and increase endothelium dependent vasodilatation and endothelium independent vasodilatation. Meldonium and Canephron N potentiates the decrease in the intensity of systemic inflammation by positive dynamics of C-reactive protein, soluble intercellular adhesion molecule-1, interleukin-1β, interleukin-6 and tumor necrosis factor-α. Thus, the combined use of Meldonium and Canephron N is feasible, effective and safe for prolonged use.

Keyword: Endothelial Dysfunction, Markers of Systemic Inflammation, Chronic Pyelonephritis, Hypertension, Meldonium, Canephron N.

1. INTRODUCTION:

PROBLEM STATING AND ANALYSIS OF RECENT RESEARCHES: in the current recommendations of the European Society of Hypertension (European Society of Hypertension - ESH; 2007, 2009) and the updated European guidelines on prevention of cardiovascular diseases (2012) study of the vascular wall is given attention [4].

Numerous publications suggest that an important role in the development of arterial wall damage in chronic pyelonephritis (CPN) and arterial hypertension (HPT) is endothelial dysfunction (ED), which is an important informative predictor

of future cardiovascular and nephrologic events [4, 8]. Found that the functional state of the endothelium and vascular wall as a whole can be used indices elastic-elastic properties of the arteries, in particular such as aortic stiffness index (ASI), the thickness of intima-media complex (TIMC), *pulse-wave velocity* (PWV) [8]. There is another marker of arterial stiffness - it CAVI (cardio-ankle vascular index), which is independent of blood pressure and also an objective marker of ED [5, 7].

Among proinflammatory factors involved in the occurrence of ED in the development of comorbid diseases, such as CPN and HPT, noteworthy tumor necrosis factor - alpha (TNF-α). TNF-α - a protein belongs to the group of cytokines and is the main endogenous mediator of the inflammatory response. The appearance of this cytokine in the blood observed already in the early stages of the pathological process, as it has a wide range of regulatory activity [2]. To the basic biological properties of TNF - α stimulation include adhesion processes, stimulation of production of interleukin-1β (IL-1), interleukin-6 (IL-6), and indirectly increase income levels of acute phase proteins (C-reactive protein - CRP) [1, 2].

So important in modern medicine is to study possibilities of correction of ED and systemic inflammation in patients with CPN and HPT.

2. THE AIM OF RESEARCH: to improve treatment of ED and systemic inflammation in patients with CPN and HPT by using Meldonium and Canephron N.

3. MATERIAL AND METHODS. To achieve this purpose we examined 105 patients with CPN and HPT, among whom were 64 (60.95%) men and 41 (39.05%) female, aged from 35 to 74 years (average 56.04±4.15 years). The criteria of inclusion of patients in the study were the presence of Chronic Kidney Disease (CKD) stage I-II and Hypertension stage II, degree II, without adequate systematic antihypertensive therapy, the patient's written consent. Exclusion criteria from the study were abnormalities of the kidneys, chronic renal failure, refusal of study, intolerance proposed drugs.

In the application of clinical diagnostic and therapeutic measures were based on protocols of diagnosis and treatment, approved by the Ministry of Health of Ukraine dated 12.12.2004, №593, Order of the Ministry of Health of Ukraine dated 03.07.2006, №436, the recommendations of the European Society of Hypertension and Nephrology diagnostic and treatment of HPT and CKD.

All patients were divided into four groups. The criterion, by which the distribution took place, was the inclusion of study drugs to complex antihypertensive treatment. Basic therapy (BT) CPN in all groups was the appointment of fluoroquinolones and anti-inflammatory drugs, and BT HPT - fixed low-dose combination of angiotensin-converting enzyme inhibitor Perindopril arginine 2 mg and thiazide diuretic Indapamide 0.625 mg ("NOLIPREL", Servier, France), Amlodipine 5-10 mg per day ("AMLODIPINE", Kievmedpreparat, Ukraine) and statin. The first group consisted of 30 patients who received BT CPN and HTN, the second - 30 patients who received the background of BT CPN and HTN Meldonium ("METAMAX", Darnitsa, Ukraine) at a dose of 5 ml of 10.0% solution intravenously within 10 days and continue to 1 tablet (0.25 g), 2 times a day orally, the third - 30 patients who received the background of BT CPN and HTN Canephron H ("CANEPHRON N", Bionorica, Germany) 50 drops or 2 pills 3 times a day, the fourth group - 30 patients who received the background of BT CPN and HTN Meldonium and Canephron N. Combined treatment course was conducted within 1 month of a break for 6 months, during which patients received a comprehensive antihypertensive treatment.

All patients were representative for demographic, gender and performance, the stages of chronic kidney disease and hypertension, glomerular filtration rate, drug therapy.

Period of observation in all groups study was 12 months. Advanced clinical and laboratory monitoring of patients was performed three times: before treatment, after 1, 6 and 12 months of treatment. The term research is needed to assess effectiveness.

Table 1: Indicators of endothelial dysfunction in patients with CPN and HTN during treatment (M±m)

Groups	Period research	ET-1,ng/ml	EDVD, %	EIVD, %	CAVI	PWV, m/s	ASI,mm Hg/ml	TIMC,mm
I group (n=30) BT CPN and HTN	before treatment	18,97±2,61	5,09±0,91	12,54±0,95	10,21±0,44	19,83±0,84	0,89±**0,07**	0,93±0,04
	after 10 days of treatment	10,97±2,47*	7,76±0,84*	15,52±0,72*	9,11±0,31*	17,55±0,81*	0,75±0,06	0,88±0,03
	after 1 month of treatment	10,09±3,44*	8,31±0,71**	16,01±0,84**	8,67±0,34**	17,32±0,76*	0,72±0,04*	0,86±0,03
	after 12 months of treatment	10,38±1,06*	8,42±0,77**	16,21±0,73**	8,02±0,33***	16,64±0,68**	0,70±0,05*	0,83±0,02*
II group (n=30) BT CPN and HTN + Meldo-nium	before treatment	18,07±3,32	4,70±0,73	12,78±0,92	10,93 ±0,47	20,15±0,89	0,90±0,06	0,92±**0,03**
	after 10 days of treatment	9,86±2,18*	7,78±0,79**	16,27±0,81*	9,32±0,34**	17,69±0,72**	0,75±0,04*	0,86±0,04
	after 1 month of treatment	9,67±1,58*	7,96±0,65**	17,24±0,75***	8,92±0,37**	16,97±0,73**	0,71±0,02**	0,85±0,01*
	after 12 months of treatment	9,59±1,35*	8,12±0,82**	17,13±0,73***	8,42±0,36***	15,98±0,70***	0,70±0,04**	0,80±0,02*
III group (n=30) BT CPN and HTN + Cane-phron N	before treatment	18,13±2,59	4,81±0,86	13,16±0,84	9,89±0,45	19,99±0,76	0,92±**0,08**	0,87±**0,02**
	after 10 days of treatment	10,33±2,04*	7,89±0,69**	15,66±0,84*	8,44±0,35*	17,58±0,73*	0,77±0,05	0,82±0,02
	after 1 month of treatment	9,97±2,29*	7,98±0,74**	16,71±0,74**	8,39±0,30**	17,32±0,65**	0,74±0,03*	0,81±0,01*
	after 12 months of treatment	9,81±1,26**	8,01±0,76**	16,84±0,72**	7,98±0,26***	16,41±0,60***	0,72±0,05*	0,78±0,01*
IV group (n=30) BT CPN and HTN + Meldo-nium + Cane-phron N	before treatment	19,88±2,83	5,14±0,72	13,02±0,97	10,86±0,38	21,04±0,81	0,92±0,07	0,95±**0,04**
	after 10 days of treatment	9,96±2,23*	8,88±0,68***	16,86±0,85**	8,98±0,34***	17,68±0,75**	0,73±0,05*	0,85±**0,02***
	after 1 month of treatment	9,71±1,31**	9,13±0,76***	18,15±0,82***	8,72±0,39***	16,69±0,75***	0,70±0,03**	0,83±0,02*
	after 12 months of treatment	9,82±1,24**	9,42±0,81***	18,13±0,81***	8,11±0,42***	16,11±0,88***	0,69±0,04**	0,80±0,03**

Notices. ET-1 – Endothelin-1, EDVD – **Endothelin dependent vasodilation**, EIVD – **Endothelin independent vasodilation**, CAVI – Cardio-ankle vascular index, PWV – *Pulse-wave velocity,* ASI – Arterial stiffness index, TIMC – Thickness of the intima-media complex, * - p<0,05, ** - p<0.01, *** - p<0.001 – value of the difference data in comparison with the values before treatment.

The intensity of systemic inflammation assessed by dynamic levels of TNF - a, IL-1β, IL-6 and CRP, which determined the ELISA ("Vector-Best", Russia). The content of *soluble intercellular adhesion molecule-1* (sICAM) determined by a set of firm «Bender Medsystems» (Austria). For the norm taken survey results 20 healthy people.

Table 2: Indicators of systemic inflammation in patients with CPN and HTN during treatment (M±m)

Groups	Period research	CRP mg/l	sICAM-1, ng/ml	IL-1β, pg/ml	IL-6, pg/ml	TNF-α, pg/ml
I group (n=30) BT CPN and HTN	before treatment	7,44±0,69	525,19±76,32	33,38±3,47	32,54±3,41	17,05±2,97
	after 10 days of treatment	5,24±0,82*	379,14±28,12*	21,59± 2,49**	21,39± 2,16**	10,55±**1,11***
	after 1 month of treatment	5,23±0,94	374,55±31,11*	18,64±**2,02****	17,93±**2,04****	10,31±**1,07***
	after 12 months of treatment	6,16±0,92	380,09±28,76*	19,89±**2,53****	18,01±**2,01****	10,32±1,34*
II group (n=30) BT CPN and HTN + Meldonium	Before treatment	7,21±0,68	541,09±70,96	34,67±3,66	33,76±2,96	15,68±2,39
	after 10 days of treatment	5,03±0,71*	382,34± 52,05*	20,19±2,92**	21,31±**1,62****	9,13±**1,07***
	after 1 month of treatment	4,95±0,45**	334,21±**24,07****	18,72±2,34****	18,75±**2,32****	8,67±**0,85****
	12 months after treatment	5,11±0,51*	335,75±**43,33***	18,80±2,11****	17,91±**2,41****	8,62±**0,91****
III group (n=30) BT CPN and HTN + Canephron N	Before treatment	6,96±1,17	493,19±53,42	29,78±3,31	28,26±2,49	16,63±2,35
	after 10 days of treatment	4,88±0,30*	354,12±**41,08***	18,84±**2,17****	18,24±**2,54****	10,82±**1,61***
	1 month after treatment	4,84±0,36*	351,87±**42,23***	17,92±**2,65****	16,51±**2,01****	9,98±**1,32***
	after 12 months of treatment	5,33±0,47	352,06±**41,09***	17,76±**2,32****	15,53±**2,18****	9,97±**1,43***
IV group (n=30) BT CPN and HTN + Meldonium + Canephron N	before treatment	7,57±1,34	502,34±49,87	35,64±3,78	32,11±2,73	16,39±2,15
	after 10 days of treatment	4,91±0,42*	312,05±**35,04****	21,05±**2,49****	19,23±**2,16****	9,04±**1,43****
	after 1 month of treatment	4,37±0,33**	304,11±**33,74****	19,17±**2,23****	17,48±**2,39****	8,86±**1,04****
	after 12 months of treatment	4,40±0,29**	304,07±**28,15****	19,14±**2,27****	17,01±**2,37****	8,29±**1,54****

Notices. CRP - C-reactive protein, sICAM-1 - soluble intercellular adhesion molecule-1, IL-1β - interleukin-1β, IL-6 - interleukin-6, TNF-α - tumor necrosis factor-alpha, * - p<0,05, ** - p<0.01, *** - p<0.001 - value of the difference data in comparison with the values before treatment.

Endothelial function was studied over the content of endothelin-1 in serum (ELISA). PWV evaluated by rheoplethysmography with synchronous recording rheo plethysmohram brachial and ankle arteries. CAVI is determined by the following formula [6]: CAVI = 2ρ × In (Ps / Pd) × PWV2/ΔP, where PWV - pulse wave velocity in the interval "shoulder - *ankle",* Ps - systolic arterial blood pressure, Pd - diastolic blood pressure, P - pulse blood pressure, ρ - blood viscosity.

ASI determined by the values of pulse pressure and stroke volume. TIMC set by dopplerography on the machine "Logiq 500" (Kranzbuhler, Germany) on an empty stomach, at room temperature 22°C, with the patient lying on his back after 10-15min rest. To determine endothelin dependent vasodilation (EDVD) and endothelin independent vasodilation (EIVD) measured the diameter of the brachial artery on an empty stomach (at rest), and then 90 seconds after decompression artery (EDVD) and 5 minutes after administration of 0.5 mg nitroglycerin (EIVD) method on D.S. Celermajer (1992) in the modification O. Ivanov (1998) [3].
Statistical processing of the results was performed using Microsoft Exel 2010 and standard software package "Statistica 8.0 for Windows" ("Stat Soft", USA). Results are presented as mean (M) and average error (m). Chance of differences between dependent and independent options evaluated using Student t-test (the difference was considered significant at $p<0.05$).

4. RESULTS AND DISCUSSION:

The data Table 1 shows that patients with CPN and HPT developed ED, manifested as increased levels of ET-1 in serum, CAVI, PWV, ASI, TIMC and reduced EDVD, EIVD.
In the analysis of ET-1 treatment for the decrease of its content by 46.5% ($p<0.01$), 46.9% ($p<0.01$) at 1 and 12 months in patients who received the background BT Meldonium (II group). More significantly, this figure decreased (by 51,2%, $p<0.01$, 50.6%, $p<0.01$) after simultaneous administration Meldonium and Canephron N against BT (IV group). Adopting the same treatment regimen resulted in increased EDVD by 77.7% ($p<0.001$), 83.3% ($p<0.001$) and EIDV by 39.4% ($p<0.001$) and 39.3% ($p<0.001$) at 1 and 12 months of treatment, respectively. Along with improving ED observed positive changes in key markers of arterial stiffness vessels – CAVI and PWV. Thus, in the fourth group of patients who received Meldonium and Canephron N against BT, after 1 and 12 months of treatment, the expressed likely significant reduction CAVI - by 19.7% ($p<0.001$), 25.3% ($p<0.001$) and PWV - by 20.7% ($p<0.001$) and 23.4% ($p<0.001$). Also found that the value ASI during treatment positively changed and the best result was observed after 1 and 12 months in patients II and IV group. This decrease ASI was 21.1% ($p<0.01$) and 22.2% ($p<0.01$) and 23.9% ($p<0.01$) and 25.0% ($p<0,01$), respectively. As TIMC, then at 1 and 12 months after application Meldonium and Canephron N is decreased by 12.6% ($p<0.05$) and 15.8% ($p<0.01$).

Thus, antihypertensive treatment of CPN and HPT with the inclusion Meldonium and Canephron N improves ED.
In all patients with CPN and HPT to treatment found activation of systemic inflammatory response by increased levels of CRP, sICAM-1, IL-1β, IL-6 and TNF-a (Table 2).

Appointment of BT contributed to a significant reduction of CRP is a 10 day treatment (29.6%, $p<0.05$). But it is worth noting that in this group of patients during treatment at 1 and 12 months recorded inaccurate changes CRP ($p>0.05$), which prompted us to further prescribing potentiation basic treatment. Admission Meldonium (II group) led to a decrease in CRP at 31.4% ($p<0.01$) and 29.1% ($p<0.05$), Canephron N (III group) - by 30.5% ($p<0.05$) and 23.4% ($p>0.05$), and their combination to 42.3% ($p<0.01$) and 41.9% ($p<0.01$) after 1 and 12 months treatment, respectively. In patients of group II concentration of sICAM-1 decreased by 38.2% ($p<0.01$) and 38.0% ($p<0.05$) at 1 and 12

months of treatment, respectively. The best result is demonstrated in patients who received both Meldonium and Canephron H (IV group) - sICAM-1 decreased by 39.5% ($p<0.01$) and 39.5% ($p<0.01$), respectively. Simultaneous treatment Meldonium and Canephron N against BT helped reduce levels of proinflammatory cytokines. Thus, the content of IL-1β and IL-6 at 1 and 12 months of observation decreased by 46.2% ($p<0.001$) and 46.3% ($p<0.001$) and 45.6% ($P<0.001$) and 47.0% ($p<0.001$), respectively. Positive dynamics was observed and the content of TNF-α in the serum during treatment. Yes, his decline and approaching normal levels in healthy people is most pronounced observed in patients receiving combination Meldonium and Canephron N (IV group). After 1 and 12 months of such treatment, its level decreased in the lower side at 45.9% ($p<0.01$) and 49.4% ($p<0.01$), respectively.

Thus, antihypertensive treatment of chronic renal failure with hypertension to include Meldonium and Canephron N inhibits the activity of systemic inflammation.

5. CONCLUSIONS

1. Introduction to the basic therapy of chronic pyelonephritis and hypertension Meldonium and Canephron N can slow the progression of the endothelial dysfunction and improve the elastic properties of elastic arteries, particularly reduce endothelin, cardio-ankle vascular index, pulse wave velocity, aortic stiffness index, thickness intima - media complex and increase endothelium dependent vasodilatation and endothelium independent vasodilatation.
2. Patients with chronic pyelonephritis with hypertension receiving Meldonium and Canephron N potentiates the decrease in the intensity of systemic inflammation by positive dynamics of C-reactive protein, soluble intercellular adhesion molecule-1, interleukin-1β, interleukin-6 and tumor necrosis factor-α.

3. Application Meldonium and Canephron N in treatment of patients with chronic pyelonephritis with hypertension appropriate, effective and safe for prolonged use.

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