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EFFECTIVENESS OF CANEPHRON® N IN THE COMPLEX MANAGEMENT OF SUBCLINICAL GOUTY NEPHROPATHY

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Background. *The risk of chronic kidney failure increases by 3-10 times with the steady increasing of uric acid level in the blood. It is known that the protein fractions is closely correlated with the level of uric acid.*

Objective. *Microalbuminuria and microglobulinuria are predictors of kidney damage. The study involved 50 patients with gout who had never received preventive treatment of gouty nephropathy. We choosed Canephron N (Bionorica, Neumarkt, Germany) as a combined phytodrug with nephroprotective effect. All studied patients were men with obesity.*

Results. *According to standard examination kidney damage haven't been found, but laboratory tests on microproteinuria showed that the vast majority of patients have signs of subclinical gouty nephropathy.*

Conclusions. *Canephron N in complex gout treatment helps to decrease uric acid level in the blood and increase its excretion.*

KEY WORDS: **gout, chronic kidney disease, hyperuricemia, Canephron N**

Introduction

The term "gouty nephropathy" (GN) comprises all renal pathology that may occur in patients with gout, including urate nephrolithiasis, tophi in the renal parenchyma, glomerulosclerosis, arteriosclerosis with subsequent nephrosclerosis, interstitial nephritis and chronic renal failure. Moreover, the use of non-steroidal anti-inflammatory drugs (NSAIDs) for symptomatic treatment of patients with gout is associated with nephrotoxicity and may result in acute tubular necrosis, acute interstitial nephritis, proteinuria, hypertension, hyperkalemia [6, 13]. The prevalence of kidney damage in patients with gout ranges from 30 to 70%. Hence it is essential that patients with chronic gout receive therapy for prevention of GN without any (or with minimal) side effects and contraindications. For this purpose we have chosen a herbal based medicine – Canephron® N (Bionorica, Neumarkt, Germany) which is an approved medicinal product containing a fixed combination of centaury herb (*Centaurium* sp.), lovage root (*Levisticum officinale* Koch), and rosemary leaves (*Rosmarinus officinalis* L.) [19]. It has been available on the European market for more than 40 years. The drug has diuretic [12, 33], spasmolytic [1, 32], anti-inflammatory

[11, 23, 29], antimicrobial [7, 8, 17], nephroprotective [18] and hypouricemic [25] effects. Some clinical studies show a therapeutic benefit in patients with urinary tract infections [9, 21, 26] and diabetic nephropathy [19].

Materials and Methods

We examined 50 patients with gout (all men), who were hospitalized in the Department of Rheumatology of Ternopil University Hospital. The patients were not previously diagnosed or tested for GN, nor were previously tested for GN. All the patients underwent main laboratory and instrumental methods of investigation and some additional tests for microalbumin and microglobulin levels in morning urine performed by means of ELISA method. Microproteinuria means any manifestation of microalbuminuria (MA), microglobulinuria (MG) or their combinations. The patients were divided into 2 groups: the patients of group I (n=25), the study group, received standard urate lowering therapy (Allopurinol), NSAIDs for pain control and Canephron® N; the patients of group II (n=25), the control group, received only Allopurinol and NSAIDs. Body mass index (BMI), plasma and urine uric acid (UA) levels, blood creatinine, urea and glomerular filtration rate (GFR) were tested. Kidney ultrasound and joint x-ray were also performed. Canephron® N was prescribed, 2 tablets 3 times per day for 6 weeks. After 6 weeks patients' microalbumin, microglobulin levels in urine and UA levels in plasma and urine were re-examined.

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Continuous variables are expressed as mean±standard error of the mean. Differences between the variables were determined by unpaired or paired t-test, as appropriate. A value of $p < 0,05$ was considered to be statistically significant.

Results and Discussion

Baseline indicators of the examinations are presented in Table 1. Due to the BMI, the majority of patients in both groups were diagnosed with obesity. Blood creatinine level, urea and GFR were uninformative, because the findings were normal in both groups. Also nephrolithiasis was found in both groups. Laboratory and instrumental investigations showed that a significant proportion of the patients had subclinical GN (fig. 1).

In the study group 48% patients had MA and 60% of them had MG. In the control group 44% patients had MA and 52% of them had MG. The patients from the study group received a combined treatment (Allopurinol, NSAIDs + Canephron N) and had better test results than the group which received standard treatment (Allopurinol, NSAIDs) (Table 2).

The pathogenesis of GN is associated with hyperproduction of UA and imbalance between

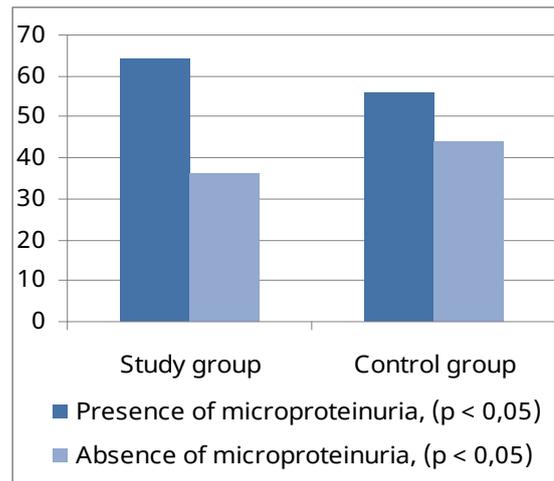


Fig. 1. Microproteinuria in patients suffering from gout.

the processes of its tubular secretion and reabsorption. But currently there is not enough evidence that hyperuricemia (HU) is a marker of renal dysfunction or a risk factor for kidney disorders. The controversial results of the impact of HU on development of chronic kidney disease (CKD) are, partly, due to difficulties in diagnosis of GN at the early stage because of a long subclinical period [5, 10, 24, 27].

Hyperproduction of UA and its excretion decrease leads to HU. The risk of chronic kidney

Table 1. Baseline indicators

Markers	Study group (n=25)			Control group (n=25)			p-value
Age, (yrs)	54,98±1,22			50,63±1,19			<0,05
Disease duration, (yrs)	8,96±0,57			7,42±1,43			>0,05
BMI	28,64±0,61			30,62±1,37			>0,05
Creatinine, (mmol/L)	72,12±0,39			78,31±1,21			>0,05
Urea, (mmol/L)	5,05±0,65			4,96±0,27			>0,05
GFR, ml/min	130,88±1,22			129,64±0,31			>0,05
Uric acid in plasma, (mcmol/L)	0,556±0,08			0,552±0,12			>0,05
X-ray stage, (%)	I	II	III	I	II	III	-
	11,4	79,5	9,1	11,8	76,5	11,7	
Nephrolithiasis, (%)	28			36			-

p – significant differences between the baseline indicators of the study and control groups.

Table 2. Dynamics of changes at the beginning of the study and after 6 weeks of combined treatment with Canephron N and standard therapy (the study group), and standard therapy only (the control group)

Markers	Study group (n = 25)		Control group (n = 25)		p-value
	Baseline	After treatment	Baseline	After treatment	
Microalbuminuria, (mg/L)	131,81±3,45	62,38±2,99*	114,72±3,91	122,19±2,11	<0,05
Microglobulinuria, (mg/L)	20,08±2,06	13,37±3,32*	22,36±3,12	21,19±2,94	<0,05
Uric acid in plasma, (mcmol/L)	0,556±0,08	0,457±0,06*	0,562±0,12	0,498±0,23**	<0,05
Uric acid in urine, (mmol/L/day)	5,21±1,18	6,72±1,34*	5,02±1,09	5,08±1,02	<0,05

p – significant differences between the post-treatment markers of the study and control groups;

* – after treatment in comparison with baseline markers of the study group ($p < 0,05$);

** – after treatment in comparison with baseline markers of the control group ($p < 0,05$).

failure (CKF) rises in 3–10 times caused by increase in UA in blood. Every 4th patient has CRF as a gout complication [3, 4, 5, 22]. Several studies have shown relations of HU to the signs of kidneys damage [30, 31]. Also UA can affect renal hemodynamics due to vasoconstriction in cortical layer and increase the expression of renin. An additional mechanism in kidneys damage is the UA impact on the formation of the endothelial dysfunction by increasing monocyte chemoattractant protein-1 (MCP-1) in vascular smooth muscle fibres and cells of the proximal renal tubules. MCP-1 is a main pathogenetic chemokine of CKD and atherosclerosis [16].

It is established that the protein fraction is closely correlated with the level of UA in blood; that is why HU causes endothelial dysfunction and MA [2]. If albumins and other highmolecular weight proteins are found in urine, glomerular injury is present. Microglobulins (β_2 -, α_1 - and retinol-binding protein), MG, are tubular disorders characterized by low-molecular weight proteins in urine. MA and MG are predictors of kidneys damage [14, 15, 19, 20, 28]. Reference limits of MA and MG are presented in table 3.

Conclusions

Microalbuminuria and microglobulinuria are the main early symptoms of renal damage in patients with gout. The prevalence of kidney

Table 3. Reference limits of microalbuminuria and microglobulinuria

Type	Indicators (mg/L)
Normoalbuminuria	<20
Microalbuminuria	20–200
Macroalbuminuria	>200
Normoglobulinuria	<12
Micro- and macroglobulinuria	>12

damage is significantly ($p < 0,05$) higher than the incidence of gouty nephropathy in clinical practice. Blood creatinine level, urea and GFR are uninformative at the stage of GN formation, which is asymptomatic. GN was diagnosed in 64% patients of the study group and in 56% ones of the control group according to the levels of MA and MG. Uncontrolled hyperuricemia, which does not reach the target level, is a major risk factor for development of GN. The group of the patients who received Canephron N as a standard gout treatment had better results after re-examination. This herbal based medicine has uricosuric effect because it decreases UA level in plasma. Microproteinuria decreased in 2 times after the combined treatment with Canephron N. Also we did not detect any side effects during 6 weeks of the study. So, Canephron N is recommended for treatment of subclinical gouty nephropathy.

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Received: 2016-02-10