V. I. Velichko, V. I. Synenko, D. O. Lagoda.
Odessa National Medical University, Odessa, Ukraine

THE RATIONALITY OF USING NOKAMEN IN A FAMILY PRACTICE DOCTOR

Summary. *General practitioners and family doctors most often face the problem of comorbidity of patients. Polypharmacy, as a consequence of polymorbidity, leads to an increase in the probability of systemic and undesirable effects due to drugs intake as a result the compliance between the doctor and the patient reduces. Kidney pathology is one of the common comorbid diseases. Urolithiasis takes the second place in prevalence, the third place in mortality and the fourth place in disability among urological diseases. The modern medicine must solve the problems of treating the patient by using drugs containing many components in order to simultaneously affect various links of the pathogenesis of the disease. One of such remedies on the Ukrainian market is the herbal-mineral complex Nokamen. The composition of Nokamen includes eight plant components and two minerals, which together produce a nephroprotective effect.*
Keywords: *family doctor; kidneys; urolithiasis; nephroprotection; prevention*

Modern Ukrainian medicine is undergoing rationalization changes. Today these changes have mostly affected primary care doctors - general practitioners and family doctors. General practitioners and family doctors most often face the problem of comorbidity of patients. A number of studies have shown that patients with chronic and comorbid diseases more often turn to primary care doctors, and the costs of their treatment constitute a significant amount both from the budget of the country in which the patients live and from the patient's own funds [1 - 3].

It has been established that in the USA more than 80% of insurance funds are spent on providing medical care to patients who have more than 4 diseases with a chronic course [4]. The study by H.S. Kim et al. has shown a correlation between a visit to a doctor and the appointment of treatment and the presence and number of concomitant diseases in patients who were diagnosed with diabetes. That is, the more comorbid diseases, the more visits to the doctor and the more prescribed drugs [5].

Polypharmacy is another problem faced by doctors and patients. Polypharmacy, as a consequence of polymorbidity, leads to an increase in the probability of systemic and undesirable effects due to drugs intake as a result the compliance between the doctor and the patient reduces [6, 7].

Among comorbid diseases, the most common are ischemic heart disease, dyscirculatory encephalopathy, arterial hypertension, chronic obstructive lung diseases, neoplastic processes, chronic gastritis with secretory insufficiency, chronic pyelonephritis, prostate adenoma, diabetes mellitus and spinal osteochondrosis, arthrosis.

Most of the listed diseases are systemic. They affect target organs, one of which is the kidneys. Treatment of kidney diseases is a long process, and drugs have side effects on other organs. It is expedient to use herbal preparations for the treatment of polymorbid patients.

According to the National Registry of the Netherlands, patients with such a threatening disease as diabetes mellitus also have a comorbid disease in 44% of cases [8]. It is well known that, in addition to comorbid diseases, patients with diabetes have problems with target organs. In our article, we will focus on the kidneys.

Even before the clinical symptoms occur, the presence of proteinuria and other changes in the analysis of urine indicate that kidney function is impaired. This is a stage when the therapy is needed to prevent kidney disease. If the clinical symptoms occur, a more severe course of the disease should be prevented. The study by R.G. Singh has shown a comparative analysis of the effectiveness of Punarnava, containing Boerhavia diffusa root and ACE inhibitor (ramipril), in patients with diabetic nephropathy [9].

Punarnava is a herbal Ayurvedic remedy. The product has an antiproteinuric effect and a number of other additional effects. It prevents the development of infection, and has antilytic, diuretic and renoprotective properties. All these effects are achieved with the help of the main component of the remedy, namely Boerhavia diffusa. This natural component contains a large amount of biologically active substances (flavonoids, alkaloids, steroid compounds, triterpenes, lipids, proteins, etc.), which exhibit antibacterial and hypoglycemic effects. Also they have anti-inflammatory, immunomodulatory and antispasmodic effects, and prevent the crystallization of calcium oxalates in urine. By reducing the level of protein in the urine, the product has a nephroprotective effect in disorders of carbohydrate metabolism.

The study by R.G. Singh involved patients with stage IV diabetic nephropathy. The study lasted six months. The patients were divided into two groups, the main group received Punarnava and ACE inhibitor, the comparison group received only ACE inhibitors.

The most common symptom in patients was a subjective feeling of weakness – in 60-90% of patients in both groups. Other common symptoms were anorexia, oedema, and vomiting. The main positive effect of the remedy containing Boerhavia diffusa, was an oedema reduction, which was observed in 28.57% of patients in the main group, while in the ramipril group, oedema reduction occurred in 14.28% of patients ($p < 0.05$). Therefore, it can be concluded that the remedy containing Boerhavia diffusa has diuretic properties in

this group of patients. In addition, the Indian Pharmacopeia classifies Punarnava as a diuretic and recommends it to patients who have problems with kidney function as monotherapy or in complex treatment [10].

Urolithiasis is another common disease faced by family doctors. Urolithiasis takes the second place in prevalence, the third place in mortality and the fourth place in disability among urological diseases. It should be noted that urolithiasis most often occurs in young people and has an acute course affecting the quality and lifestyle of the patient, significantly. It is well known that the threatening consequences of urolithiasis can and must be prevented. This can be done with the help of preparations containing herbal ingredients.

The properties of Dolichos biflorum as a litholytic agent are known. Thus, it has been found that the plant contributes to the dissolution of urinary stones formed by calcium oxalates. Dolichos biflorum is an annual plant with small leave. When the plant ripe it forms pods that have seeds inside. When analyzing the seeds of Dolichos biflorum, a number of substances were identified, in particular carotene, which is the international unit of measurement of vitamin A, and a very important enzyme – urease. At the same time, the seeds of Dolichos biflorum contain streptogenin, beta-sitosterol, phytohemagglutinin, beta-X-acetylglucosaminidase, α- and β-galactosidases, α-manosides and β-glycosides.

Studies show that patients with urolithiasis are more likely to have oxalate stones. In the United States of America, according to statistics, 75% of patients have oxalate stones. A similar trend is observed in Asian countries. Thus, the majority of patients also have oxalate stones in India [11]. Such a high incidence rate for oxalate stones is associated with the dietary habits of patients. A high intake of cereals such as millet and an animal proteins deficiency are one of the predictors of kidney stones disease with oxalate stones.

It should also be noted that this type of urolithiasis often has a relapsing course: 30% of patients may experience a new episode of urolithiasis in the next 10 years.

The study by R.G. Singh has found more significant litholytic properties of the preparation containing Dolichos biflorum compared to potassium citrate. The study lasted for 6 months; the patients were divided into two groups. The first group received the herbal preparation Dolichos biflorum, the second group – potassium citrate.

At the end of the study, a significant litholytic effect was found in the Dolichos biflorum group. Thus, a decrease in the size of stones was reported during 3 months of observation from 5.42 ± 1.55 mm to 4.26 ± 1.20 mm ($p<0.05$). Also in the first group, a decrease in the number of relapses of urolithiasis was found ($p<0.05$). However, despite the reduction in relapses, levels of serum calcium, phosphorus and uric acid, and urinary excretion of these substances did not differ between the two groups. Therefore, the preparation containing Dolichos biflorum can be used as a prophylactic agent to prevent relapses in patients with urolithiasis who turn to a family doctor.

Modern fashion trends in the diet of young people often involve the use of large amounts of protein supplements, which have a negative effect on the body in general and the kidneys in particular. The therapeutic effects of the alcoholic extract of Crataeva nurvula are known. At doses of 200, 400 and 600 mg, it is useful as a laxative and is used in the treatment of the urinary tract infections. At the same time, Crataeva nurvula extract is very useful as an anti-inflammatory agent for arthritis, and it effects on the female reproductive function as a contraceptive.

A study was carried out at the Charak College of Pharmacy and Research. The study has shown the effect of Crataeva nurvula on kidney function in cancer patients treated with cisplatin. Cisplatin is a potent antitumor agent, but its clinical use is limited by its toxic effects on the kidneys. The nephrotoxic effect of cisplatin includes increased renal generation of reactive oxygen metabolites and lipid peroxidation caused by a decrease in the level of antioxidants and antioxidant enzymes. In the course of the study, it was confirmed that Crataeva nurvula has a nephroprotective effect; in particular, Crataeva nurvula improves the function of nephrons, reducing the negative effect of the anticancer drug [12].

Another plant that affects kidney function is Butea frondosa. The study by Amit Gupta has found that Butea frondosa leaf aqueous extract has anti-inflammatory and antimicrobial properties. In addition, the plant itself has antioxidant and nephroprotective properties [13].

In our article, we have already mentioned the modern problem of polymorbidity and polypharmacy. Modern medicine must solve the problems of patient treatment with drugs containing many components with different medicinal properties. Considering this, it is possible to achieve a complex effect on various pathogenetic links of the disease. Nokamen is one of such remedies on the Ukrainian market. Together with the above plants, Nokamen contains ten natural components that give a nephroprotective effect.

Domestic studies indicate the effectiveness of Nokamen in patients with renal pathology. The article by E.A. Litvinets shows a comparative study of the effectiveness of Nokamen and the phytopreparation "Kidney" in women with exacerbation of chronic recurrent cystitis. According to the results of the study, it has been found that the use of Nokamen within 3 months after the treatment of the last episode of exacerbation of chronic cystitis significantly reduces the frequency of relapses compared to phytopreparation "Kidney". In the main group of patients taking Nokamen, exacerbation of chronic cystitis over the next 6 months was reported in 10.0% of patients, while in the comparison group taking phytopreparation "Kidney"- in 60.0% of patients. Therefore, Nokamen can be recommended for widespread use in order to prevent relapses of chronic cystitis [14].

A study of the effect of Nokamen on patients with urolithiasis with stones up to 55 mm in size has been carried out by V.P. Stus et al. A number of positive effects have been found. It has been found that Nokamen has a lithokinetic effect, which was manifested in the independent stones excretion in 12% of patients. Moreover, in several patients, the stones excreted imperceptibly. At the same time, Nokamen has bactericidal properties, for example, a decrease in bacteriuria from 22 to 12.5% ($p<0.05$) was reported in patients. In addition, it was confirmed that the plant components, included in Nokamen's composition, effect on the concentrations of calcium, uric acid in the blood and urine. Due to this fact Nokamen can be used as a remedy to prevent stone formation [15].

Therefore, based on domestic and international experience, Nokamen can be recommended to primary care physicians as a source of biologically active substances of natural origin, which has a positive effect on the functioning of the kidneys in conditions accompanied by the formation of stones and inflammatory processes in the kidneys and urinary tract.

Conflict of interests. Not declared.

References:

1. *StmfieldB., Lemke K.W., Herbert R., Pavlovich W.D., Anderson G. Comorbidity and the Use of Primary Care and Specialist Care in the Elderly. Annals of Family Medicine. 2005. 3(3). 215-222. doi: 10.1370/afm.307.*
2. *Wolff J.L., Starfield B., Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Archives of internal medicine. 2002. 162(20). 2269-2276.*
3. *Starfield B., Forrest C.B., Nutting P.A., von Schrader S. Variability in physician referral decisions. The Journal of the American Board of Family Practice. 2002.15(6). 473-480.*
4. *Valderas J.M., Starfield B., Sibbald B., Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Annals of family medicine. 2009. 7(4). 357-363.*
5. *Kim H.S., ShinA.M., Kim M.K., Kim Y.N. Comorbidity study on type 2 diabetes mellitus using data mining. The Korean journal of internal medicine. 2012. 27(2). 197-202.*
6. *van Weel C., Schellevis F.G. Comorbidity and guidelines: conflicting interests. Lancet. 2006. 367(9510). 550-551.*
7. *Valderas J.M., Starfield B., Sibbald B., Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Annals of family medicine. 2009. 7(4). 357-363.*
8. *Struijs J.N., Baan C.A., Schellevis F.G., Westert G.P., van den Bos G.A. Comorbidity in patients with diabetes mellitus: impact on medical health care utilization. BMC health services research. 2006. 6.84.*
9. *Singh R.G., Govind Kumar, Singh S.K., Tripathi Y.B., Singh R.H. Evaluation of antiproteinuric and renoprotective effect of punamava (boerhavia diffusa linn.) in diabetic nephropathy. Journal of Research and Education in Indian Medicine. 2010. 16(1-2). 45-48.*
10. *Singh R.H., Udupa K.N. Studies in Indian indigenous drug, Punamava (Boerhaavia diffusa, Linn.). Part I. Identification and pharmacognostical studies. The Journal of research in Indian medicine. 1972. 7(3). 1-12.*
11. *Ansari M.S., Gupta N.P., Hemal A.K., Dogra P.N., Seth A., AronM., Singh T.P. Spectrum of stone composition: structural analysis of 1050 upper urinary tract calculi from northern India. International journal of urology. 2005. 12(1). 12-16.*
12. *Shelkea T.T., Bhaskarb V.H., Adkara P.P., Jhaa U., Oswa- la R.J. Nephroprotective activity of ethanolic extract of stem barks of crataeva nurvula buch hum. International journal of pharmaceutical sciences and research. 2011. 2(10). 2712-2717.*
13. *Gupta A., Chaphalkar S.R. Anti-inflammatory and anti-microbial activities of aqueous leaves extract ofButea frondosa. Journal of Herb Med Pharmacology. 2016. 5(2). 85-88.*
14. *Литвинець Є.А., Литвинець В. Є. Порівняльне дослідження ефективності Нокамену в запобіганні загострень хронічного рецидивного циститу у жінок. Здоровье мужчини. 2018. 3(66). 1-3.*
15. *Стусь В.П., Моисеенко И. И., Шевченко Ю.Л., Лисицкая Л.А., Гузман С.Т., Панченко А. С. Применение фитотерапии в лечении камней почек небольших размеров. Урологія. 2018. 22(3). 58-64.*

Получено/Received	**29.01.2020**
Рецензировано/Revised	**03.02.2020**
Принято в печать/Accepted	**07.02.2020**

UDK 616.61-003.7-08:615.322.03 DOI: 10.26641/2307-5279.22.3.2018.143275

THE USE OF HERBAL MEDICINE FOR TREATING SMALL KIDNEY STONES

V.P. Stus, N.N. Moiseenko, Yu.L. Shevchenko, L.A. Lisitskaya, S.T. Guzman, A.S. Panchenko
SI «Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine»

Introduction. The proportion of urolithiasis in the structure of the incidence is 10-15% in the world and 5-9% in Europe. In the USA 13% of men and 7% of women suffer from urolithiasis [2]. In Ukraine, the incidence of urolithiasis in the structure of urological diseases is 27.4% to 32.7% [7, 8]. Every year the number of patients increases. Most working-age men and women (30–50 years) have a tendency to this disease.

Urolithiasis is endemic. Here is a list of regions where urolithiasis is most common: Asia Minor with Arabian Peninsula, southern and eastern regions of Asia, India, China (southern regions), Indonesia, North Australia, Northeastern Africa, southern regions of North America, east and west coasts of Southern America, Scandinavia , The Netherlands, Southeastern France, the southern regions of Spain, Italy, the southern regions of Germany and Austria, Balkan Peninsula, the Altai Territory, Ukraine (Dnipropetrovsk and Donetsk regions). In each endemic region, there are localities where the incidence is highest (i.e. Solonyansky region of Dnipropetrovsk oblast) [3].

The composition of stones is different in different endemic regions. In India, more than 80% of the stones consist of calcium oxalate; in Sudan, oxalates are about 75% of the stones; in Iraq, calcium oxalates are only 2-3%; in Israel - 5%. Many countries (Norway, USA, Israel, Iraq, Austria, Sweden) have a large percentage of mixed calcium oxalate and calcium phosphate stones (50-60%). Struvites (magnesium phosphates - ammonium) are common in Belarus - 28%, England - 20%, Belgium - 15%, USA - 15%. Uric acid stones are more common in Iraq - 40%, Belarus - 30%, Jordan - 30%, Israel - 28%, Austria, France - 23%. Cystic stones are rarely found, 1-2% of all stones (Belgium, USA). Pure phosphates were most common in Belgium - 21%, England, Austria, Sudan - 8-9% (Fig. 1). But considering the different number of stones studied in different countries of the world (USA - 10,000 stones, Sudan - 32 stones), the incidence of different composition of stones may be different [3].

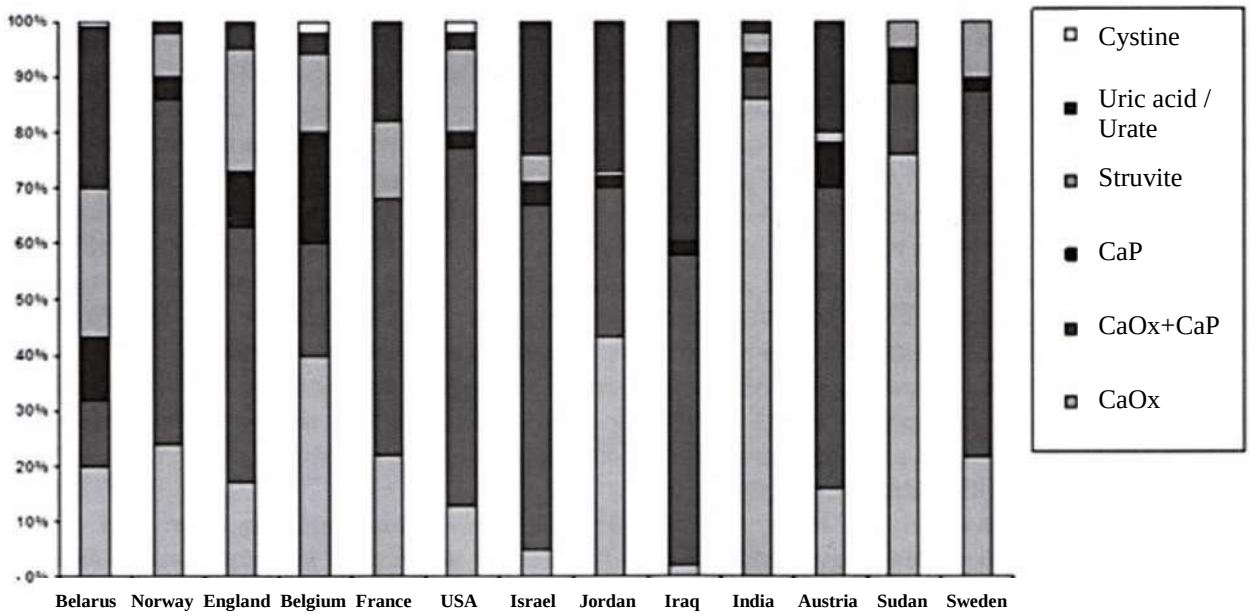

Fig. 1. Composition of stones in different countries

The diagram is based on the results of kidney stones analysis obtained after stone elimination in patients with urolithiasis; Belarus (151 stones), Norway (500 stones), England (243 stones), Belgium (239 stones), France (322 stones), USA (10 000 stones), Israel (1000 stones), Jordan (128 stones), Iraq (146 stones), India (431 stones), Austria (226 stones), Sudan (32 stones), Sweden (623 stones). All these stones were distributed according to the chemical composition in the following categories: Ca-Ox – pure calcium oxalate, Ca-Ox+CaP - mixed oxalate and phosphate calcium stones, CaP - pure calcium phosphate, struvite stones, uric acid stones and urate stones, and cystine stones.

Among the numerous etiological factors of urolithiasis, the main ones can be distinguished [4, 14]:

1. Impairment of urine outflow at any level of the urinary tract.
2. Metabolic disorders.
3. Infection.

The presence of more than one factor in a patient is likely to lead to stone formation. Stone is not formed overnight. A matrix is necessary for its formation. This matrix may be located in the collecting tubules and on the papilla of the kidney (most likely). The deposits of salt in the papilla and the collecting tubules, described by Randall, are likely the site of stone formation. According to the observations of Spanish urologists, such as Sabete Arrouya. H.A., Peras Ayala et all. (2018) the papillae damages may be in the form of deposits of Rendal plaques, tubular calcifications and papillary craters. Tubular calcifications are the most common injuries in patients with renal urolithiasis. Tubular calcifications were determined in patients with the increased urine calcium concentration. In patients with Rendal's plaque, hypocitraturia was observed. Hypoxaluria was observed more frequently in patients with papillary craters [11].

Currently, urolithiasis is not difficult to diagnose. After renal ultrasound examination, native computed tomography is performed. In 99–100% of cases it answers the following questions: whether stones are available, its localization, size and density, and whether urine outflow is impaired. In rare cases there may be the doubts regarding the localization of a small stone in the pelvic ureter and the absence of urine stasis. However, the presence of an appropriate clinic in a patient and ureteroscopy, which can be a diagnostic and, likely, a therapeutic measure, will give answer to question whether it is a stone or phlebolith [14].

Currently, the treatment of urolithiasis is rarely pathogenetic and not timely. We must honestly admit that unfortunately urologists are not able to treat urolithiasis, but they know well how to remove stones. The stones that have already “freed” from fixation on the papilla and are freely located in the pyelocus-pelvis system or ureter, can be removed. But removing is not a cure for urolithiasis [1].

In stone formation, urine pH plays an important role (its norm is 6.2–6.4). We all know the recommendations for its (pH) measurement for dissolving stones. But determining urine pH using litmus strips is not an accurate method. It is necessary to use pH-metry. Maybe this is the reason for the failed conservative therapy?

In practice the role of urine stabilizing protein – uromodulin is not yet used.

Attempts to dissolve stones are successful only in the presence of urate stones, and only in 55-60% of patients [1, 10]. In our practice, we have one (but proven) case of dissolving a urate stone sized of 2 cm (reception of blemaren within five months). It was proved by using computed tomography performed before and after blemaren treatment. However, both doctors and patients still want to dissolve stones by using modern therapeutical methods, but not only by eating eggshell with garlic [2, 5, 6].

Phytopreparations are used to treat various diseases, including kidney disease, but their use remains at the level of the Middle Ages or even worse. Only in rare studies we find attempts to scientifically explain a possible mechanism of action. For example, the study by N.G. Chaban et al., (2014), where the purpose of collecting herbs in two stages (immediately loosen, then dissolve) is experimentally proved [9,11].

In this study, we studied the effectiveness of phytocomplex Nokamen®, produced by the pharmaceutical company Ananta Medicare for patients with urolithiasis.

Since Nokamen contains mineral substances and 10 herbs most commonly used in urology, these results can also be interpolated to other phytopreparations containing these components (Table 1).

The purpose of this study: to study the effectiveness of Nokamen in patients with urolithiasis with stones sized of up to 55 mm.

Objectives:

1) to study the litholytic properties of Nokamen;
2) to study the lithokinetic properties of Nokamen;
3) to study the changes in the clinical and biochemical properties of blood and urine in the course of receiving Nokamen;
4) to study the antibacterial properties of Nokamen.

Materials and methods. The study was carried out on the clinical base of the Department of Urology of the State Institution “DMA of MoH of Ukraine” in “Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov". Clinical and biochemical studies were carried out in the certified laboratory of the State Institution "Dnipropetrovsk Medical Academy of MoH of Ukraine". In total, 32 patients with urolithiasis were involved in the study. The stones were localized in the kidneys. The maximum stone size did not exceed one centimetre, namely 69% in men and 31% in women. The age distribution was as follows: up to 20 years old –

4.5%; 20-39 years old – 4.5%; 30-39 years old – 13.7%; 50-69 years old – 27%.

In the left kidney, the stones were localized in 17 patients (53.1%), in the right kidney - in 4 (12.5%), in both kidneys - in 11 (34.4%). Some patients had a few stones.

The composition and properties of the components of Nokamen Table 1

Plant name	Active ingredients	Properties
Crataeva nurvala bark, 100 mg	Saponins (diosgenin), flavonoids, plant sterols (lupeol), tannins and glucosinolates (glucaparin)	• litholytic (oxalates) • anti-inflammatory • antispasmodic
Saxifraga ligulata rhizome, 60 mg	Furocoumarins (about 0.5% pimpineline, isopimpineline and isoberganten), isocoumarins (bergenin), 0.3-0.5% volatile oils and saponins	• litholytic (all types of stones due to the effect on the crystal-colloid ratio) • antibacterial • reduces irritation of the urinary tract
Butea frondosa flowers, 40 mg	Flavone glycosides (butein, butrin), chalcones, triterpenes and sterols	• anti-inflammatory • diuretic • litholytic (oxalates)
Dolichos biflorus seed, 40 mg	Phenolic compounds, flavonoids, unsaturated fatty acids, steroids and saponins	• antispasmodic • antioxidant • litholytic (oxalates, urates)
Sodium carbonate, 20 mg	Sodium hydrocarbonate	• litholytic (oxalates, urates)
Tribulus terrestris fruit, 100 mg	Steroid saponins, flavonoids, alkaloids and tannins	• litholytic (oxalates) • angiobacterial • improving the reproductive system tonus
Rosmarinus officinalis extract, 20 mg	Alkaloids (rosemarycin), tannins, flavonoids, resins, bitters	• antispasmodic • anti-inflammatory • natibacterial
Rubia cordifolia root extract, 20 mg	Anthraquinone glycosides (purpurin and munjistin), ruberitrinic acid	• litholytic (oxalates) • diuretic properties
Boerhavia diffusa root , 70 mg	Phytoecdysones, calcium salts and alkaloids, including punarnavin	• stimulation of metabolism • diuretic • litholytic (oxalates, urates)
Asphaltum, 70 mg	Oxidized alpha-pyrones, triterpenes, phenolic lipids, gum, albuminoids , gum and fatty acid traces, large amounts of benzoic and hippuric acids and their salts	• anti-inflammatory • immunostimulating • reparative

The native computed tomography was performed in patients for verification of the diagnosis. Ultrasound examination is not an absolutely reliable method for detecting stones. According to EAU clinical recommendations, ultrasound sensitivity is 32–70%, and specificity is 70–97%. Before the start of the study, the patients underwent urine and blood test, urine culture test and antibiotic sensitivity test, biochemical blood analysis (creatinine, urea, uric acid, calcium concentrations), urine biochemical analysis (calcium, uric acid concentrations). Patients took Nokamen 2

capsules twice a day for 6 months. It was recommended to take fluid, allowing to maintain diuresis at the level of 1.5-2 litres per day. After 6 months of taking Nokamen, complete blood and urine tests, urine culture test and antibiotic sensitivity test, biochemical blood analysis (creatinine, urea, uric acid, calcium concentrations), and urine biochemical analysis (calcium, uric acid concentrations) were repeated. Also, native computed tomography was re-performed for all patients.

After three months one patient stopped taking Nokamen on his own for domestic reasons.

Results and discussions.

In the course of the study, in 4 patients (12.5%) the calculi sized of 5-6 mm were discharged, independently. In 3 patients, the stones discharge was not accompanied by pain sensations. In one patient, the stones discharge was accompanied by renal colic, which required additional prescription of antispasmodics (baralgin).

According to the results of computed tomography, it was found that due to Nokamen activity, the growth of kidney stones was suspended.

Urine culture test has shown that out of 32 patients, bacteriuria was initially found in 7 patients. *Enterococcus faecalis* was found in 4 patients (in 2 patients – a concentration of $5x10^5$ mt/ml, in 2 patients – $5x10^3$ mt/ml). In 3 patients, *Escherichia coli* was found (in one patient – concentration of $5x10^6$ mt/ml, in 2 – $5x10^3$ mt/ml), in addition, one of them had associated with *Enterococcus faecalis* – $5x10^3$ mt/ml. *Pseudomonas aeroginosa* $5x10^6$ mt/ml was found in 1 patient. After treatment, the concentration of *Escherichia coli* $5x10^6$ mt/ml was decreased to $5x10^4$ mt/ml. There was no increase of *Escherichia coli* after 6 months of taking Nokamen in a patient with an initial concentration of *Escherichia coli* $5x10^3$ mt/ml. In one patient with a concentration of *Enterococcus faecalis* $5x10^5$ mt/ml, bacteriuria was not detected after treatment. In a patient with the original association of *Escherichia coli* and *Enterococcus faecalis*, *Ecinetobacter baumanti* $5x10^3$ mt/ml was found after treatment. In the patient who stopped treatment after 3 months (initially *Enterococcus faecalis* $5x10^8$ mt/ml), the type and concentration of the pathogen remained the same. In patients with *Pseudomonas aeruginosa*, the type and concentration of the pathogen is not changed after treatment (Table 2).

In 28.6% of patients in the general urine test, crystalluria (mainly oxaluria) was determined before taking Nokamen.

Effect of Nokamen on bacteriuria **Table 2**

Sr.No	Type of pathogen	Before treatment	After treatment
1.	Enterococcus faecalls	$5xl0^5$	No growth
2.	Enterococcus faecalls	$5x10^5$	Growth (2^{nd} patient stopped treatment after 3 months)
3.	Enterococcus faecalls	$5x10^3$	No growth
4	Escherichia coli	$5x10^6$	$5x10^4$
5.	Escherichia coli	$5x10^3$	No growth
6.	Enterococcus faecalis + Escherichia coli	$5x10^3$	Ecinetobacter baumanti $5x10^3$
7.	Ps. aeruginosa	$5x10^6$	$5x10^6$ Ps. aeruginosa

After 6 months of taking Nokamen, only one patient had salt crystals in the urine (oxalates) (Table 3), that attests to the litholytic properties of Nokamen.

The blood calcium concentration in the patients before Nokamen treatment was about 2.44 mmol/L. After 6 months, the calcium concentration decreased to 2.34 mmol/L (the change is statistically significant $p < 0.05$).

The blood uric acid concentration was also decreased from 268.0 mmol/L to 311.1 mmol/L (the change is statistically significant $p < 0.05$).

The blood creatinine concentration was not changed significantly in the course of the study in patients taking Nokamen® (104.3 mmol/L before treatment and 98.4 mmol/L after treatment) (Table 4).

The urine uric acid concentration before the start of the study was about 2.56 ± 0.12 mmol/L. After 6 months, the excretion of uric acid in the urine was

increased to 3.02 ± 0.14 mmol/L (the change is statistically significant p <0.05).

The urine calcium concentration was initially 3.66 + 0.05 mmol/L. After 6 months of taking Nokamen, the urinary calcium concentration was increased to 4.79 + 0.15 mmol/L (the change is statistically significant p <0.05) (Table 5).

Crystalluria severity **Table 3**

Parameters	Before treatment	After treatment
Crystalluria (Oxaluria)	28.6 %	3%

Effect of Nokamen on blood calcium, uric acid, creatinine concentrations **Table 4**

Parameters	Before treatment	After treatment
Ca	2.44 ± 0.15 mmol/L	2.34 ± 0.17 mmol/L
Uric acid	268.0 ± 49.2 mmol/L	311.1 ±58.1 mmol/L
Creatinine	104.4 ± 18.1 mmol/L	98.4 ± 16.5 mmol/L

Effect of Nokamen on urine calcium, uric acid concentrations **Table 5**

Parameters	Before treatment	After treatment
Ca	3.66 ± 0.15 mmol/L	4.79 + 0.15
Uric acid	2.56 ± 0.12 mmol/L	3.02 + 0.14

Conclusions

1. Nokamen® has a litokinetic effect. In 12% of patients, stones discharge has occurred, independently. In addition, in 3 patients the stones excreted without any pain (according to CT results the amount of kidney stones has decreased).
2. Nokamen® has a bactericidal effect. Bacteriuria has decreased from 22% to 12.5%.
3. Nokamen® effects on the blood and urine calcium, uric acid concentrations. This may contribute to the dissolution of calculi (Rendal plaques, etc.) or contribute to the prevention of stone formation.

References:

1. *Аляев Ю.Г. Современные аспекты медикаментозного лечения больных мочекаменной болезнью / Ю.Г. Аляев, В.И. Руюенко, Е.В. Философова // Рус. мед. журн. — 2004. — Т. 12, № 8. — С. 534-540.*
2. *Борисов В.В., Дзеранов Н К. Мочекаменная болезнь. Терапия больных камнями почек и мочеточников. — М.: Изд-во Российского общества урологов, 2011. — 88 с.*
3. *Вощула В.И. Мочекаменная болезнь. — 2006. — 268 с.*
4. *Дзеранов Н.К., Бешлиев Д.А. Лечение мочекаменной болезни — комплексная медицинская проблема // Consilium Medicum: приложение. Урология. — 2003. — С. 18—22.*
5. *Корсун В.Ф., Корсун Е.В., Суворов А.П. Клиническая фитотерапия в урологии. — М.: МК, 2011. - 336 с.*
6. *Мирошников В.М. Лекарственные растения и препараты растительного происхождения в урологии. — М.: МЕДпресс, 2005. — 240 с.*
7. *Полиенко А. К., Севостьянова О.А., Мосеев В.А. Влияние некоторых причин на распространение мочекаменной болезни в мире // Урология, — 2005. — № 1. — С. 74—78.*
8. *Сайдакова Н.О., Старцева Л.М., Кравчук Н.Г. Основш показники уролог1чно! допомоги в Украш за 2005—2006роки (eidoM4e видання). — К., 2007.*
9. *Чабан Н.Г., Степанов А.Е., Рапопорт Л.М., Цариченко Д.Г., Подволоцкий Д.О. Фитохимические основы создания препаратов для литолиз оксалатных конкрементов // Вестник МИТХ. — 2014. - Т. 9, № 2. - С. 37-45.*
10. *Micali S., Grande M., Sighinolfi M.C. et al. Medical therapy of urolithiasis // J Endourol. — 2006;20(11):841~847.*
11. *Sabate Arroyo, Pieras Ayala, G rases Frexedas, Tubau Vi dan a et al. Relationship of endoscopic lesions of the renal papilla with type of renal stone and 24 h urine chemistry. — EAU 18, Copenhagen, 16-20 March, 2018.*
12. *Soygur T., Akbay A., Kupeli S. Effect of potassium cirate therapy on stone recurrence and residual fragments after shockwave lithotripsy in caliceal calcium urolithiasis: A randomized controlled trial // J. Endourology. — 2002. — V. 16(3). — P. 149—152.*
13. *Shoag* JTasian *G.E., Goldfarb D.S., Eisner B.H. The New Epidemiology of Nephrolithiasis // Advances in Chronic Kidney Disease. — 2015. — Issue 4. — P. 273—278.*
14. *Turk C., Knoll T, PetrikA., Sarica K, Skolaricos A., Straub M., Seitz C. Guidelines on Urolithiasis. — Europian Association of Urology, 2015.*

Hoshenko Y.A., ** Rossihin V.V., *Osipov P.G., ** Bukhmin A.V.

Belgorod State National Research University *, Kharkiv Medical Academy of Postgraduate Education **

CLINICAL EFFICACY OF USE OF PHYTOPREPARATION "NOKAMEN" IN THE COMPLEX TREATMENT OF PATIENTS WITH UROLITHIASIS

According to data of different authors, patients with urolithiasis make a large part of (30 to 45%) patients in urology hospitals, and their amount continues to grow [1,2,3]. In Ukraine, over the past decade, the incidence of urolithiasis has been increased from 305.6 cases per 100 000 of adults in 1989 to 535.8 cases in 2009 [4,5].

The introduction of lithotripsy into the urological practice has fundamentally changed the approaches for urolithiasis therapy, and opened new prospects to decrease morbidity and disability, allowing to refuse a surgery and an anesthesia [6,7].

The ultimate success of lithotripsy is determined by auxiliary therapeutic measures aimed at acceleration of the discharge of fragments, as well as the prevention of stone formation, that allows to avoid re-lithotripsy and other endoscopic procedures.

The herbal complex Nokamen manufactured by the pharmaceutical company "Ananta Medicare", United Kingdom, is registered and approved for use as a food supplement in Ukraine. Nokamen is an uroprotector with an accent on litholytic effect. The Nokamen's copmosition contains the following active ingredients: Crataeva nurvala bark - 100 mg, Saxifraga ligulata rhizomes - 60 mg, Butea frondosa flowers - 40 mg, Dolichos biflorus seeds - 40 mg sodium bicarbonate - 20 mg, Boerhavia diffusa roots - 70 mg, Asphaltum - 70 mg, Tribulus terrestis fruits - 100 mg, Rozmarinus officinalis extract - 20 mg, Rubia cardifolia extract - 20 mg.

The purpose of study is the determination of the possibility of use of Nokamen phytopreparation in the complex treatment of patients with nephrolithiasis treated with remote lithotripsy. In the period from November 2014 to February 2015 were examined and treated 42 patients with calculi in the kidneys and ureters. Nokamen was indicated in 2 tablets, 2 times a day after meal. The course of treatment made 45 days.

Research tasks:

1. To assess the Nokamen's effectiveness for the prevention of infectious and inflammatory complications after remote lithotripsy.
2. To assess the Nokamen's effect on the time limits of the discharge of calculi after lithotripsy.
3. To study the possibility of Nokamen's effect on microcirculation of renal parenchyma to reduce trauma risks in remote lithotripsy.

Complex examination of patients with nephrolithiasis was carried out with the use of modern methods of diagnosis:

1. Plain and excretory urography (to confirm the presence of calculi and determine the functional state of the kidneys). 2. Renal ultrasound with Doppler sonography (to determine the blood flow state in the parenchyma) before and at different stages after lithotripsy. 3. General analysis of blood and urine (detection of hidden leukocyturia). 4. Bacteriological urine examination. 5. Biochemical blood tests.

The comparative analysis of the results of the treatment of the patients with nephrolithiasis was carried out in two groups of patients. First, the control group, consisted of 20 patients with localized calculi in the renal pelvis of the ureter, was treated with remote lithotripsy followed by conventional post-operative conservative therapy. The second group was the main group consisted of 22 patients with comparable localization and clinical disease. But unlike the first group of patients, after lithotripsy therapy these patients were administered with Nokamen only in the dose of 2 tablets 2 times a day after meal. Dynamic observation was carried out for 45 days. The main group consisted

of 9 men (41%) and 13 women (59%). The average age of patients was 42 years (16 to 71 years). According to calculi localization the patients were classified as follows (Table 1.)

Table 1. Classification of patients of the main group in accordance with localization of concrements:

Localization of concrements	Amount of patients	
	Persons	%
Pelvis and calyx	11	50
Ureter	9	41
Ureteropelvic junction	2	9
TOTAL	22	100%

The sizes of calculi in the kidneys fluctuate between 6 and 24 mm, ureters - between 6 and 9 mm. According to the data of excretory urography and ultrasound a moderate ureteropyelectasis was revealed in all patients with ureteral calculi, and in 2 patients with calculi in the UPJ.

Out of the total amount of patients of the main group (22) complaints on renal colic were observed in 18 (81.8%), leukocyturia of different severity was revealed in 19 patients (86.4%). According to the urine culture results bacteriuria from 10_3 to 10_5 cfu/ml, was revealed in 11 (50%) of 22 patients in the main group. The characteristic of obtained microflora was presented in Table 2.

Table 2. The characteristic of obtained microflora in the patients of the main group before start the treatment.

Microlfora	Amount of patients	
	Persons	%
Ecoli	5	45,4
Pseudomonas aerug.	1	9,1
Proteus mirabilis	2	18,2
Providencia rettgeri	1	9,1
Enterococcus	2	18,2
TOTAL	11	100%

Remote lithotripsy was carried out according to the indications for all 22 patients in compliance with necessary conditions for the operation. The only one lithotripsy session has been enough for the fragmentation of calculi in the prevailing number of patients (21 pers.). 3 lithotripsy procedures were performed for only one patient with localization of 25 mm stone in the pelvis.

The assessment criterions of the treatment efficiency were: frequency of renal colic occurrence, the time of clearance of urinary tract from all fragments after lithotripsy, the dynamics of changes in urine results (leucocyturia, bacteriuria), the dynamics of changes in Doppler parameters and tolerability. Doppler ultrasound was carried out before lithotripsy and right after lithotripsy, and then in 7 days, in 2 weeks and in 7 weeks after starting the treatment. X-ray was performed when indicated.

The analysis of clinical observation has shown that from the 22 patients treated with Nokamen on the background of lithotripsy, in the postoperative period a renal colic occurred only in 2 patients, and it makes 9% from the total number of the patients of the main group. In this case, these 2 patients had calculi of significant sizes (> 20 mm), and after lithotripsy the steinstrasse occured and it was the indication for additional therapy. In the control group of patients treated without Nokamen, the renal colic was observed in 57%. The results show pronounced antispasmodic properties of Nokamen preparation.

The positive dynamics of urinalysis has been recorded. Before starting the treatment, leukocyturia of different severity (from 4500 to 28000 in 1ml on Nechiporenko) occurred in 19 (86.4%) of 22 patients of the main group. In a week after starting the treatment with Nokamen the leukocyturia's severity was significantly reduced (up to 8000 in 1 mL) in most patients. The results of urine were

normalized in 7 of 19 patients with leukocyturia, thereby the total amount of patients with leukocyturia has been reduced down to 54.5% (12 patients). These results confirm the anti-inflammatory properties of the Nokamen. The follow-up (2 weeks) for patients treated with Nokamen, allowed to confirm the effectiveness of the drug regarding the infectious-inflammatory process. Thus, the number of patients with leukocyturia was reduced down to 8 (36.4%) in three weeks. The patients, who had a stable leukocyturia, were treated with antibiotic therapy according to the sensitivity of the urine microflora. 4 weeks later in the group of patients treated with Nokamen, 4 patients still had leukocyturia (18%) and for these patients the antibiotic therapy was continued with medications in combination with Nokamen. After 7 weeks of treatment the number of patients with bacteriuria was reduced. If there are 11 patients with bacteriuria in the main group before staring the treatment, then in a month after the treatment, bacteriuria 10 CFU / ml was revealed in 3 (13.6%) patients only. There were not revealed any changes of electrolytic composition of blood serum (Na +, K +, Ca ++, Mg ++) in 7, 14 and 45 days.

The time of discharge of calculi has been significantly reduced in the patients after remote lithotripsy during the treatment of Nokamen. The urinary tracts were cleaned from fragments by the end of the first week survey. The lithotripsy, followed by traditional drug therapy, was carried out in the group of patients with the similar localization of the calculus, and the urinary tracts were completely cleaned from the fragments in two - three weeks. The re-lithotripsy sessions should be carried out for two of these patients. Thus, Nokamen promotes more rapid discharge of calculi from the urinary tract after lithotripsy.

Ultrasonography with dopplerography was performed in the postoperative period after remote lithotripsy in the control group (without Nokamen) and in the main group (with Nokamen) in terms, such as: before lithotripsy, right after lithotripsy, in 2 days, 7 days, 2 weeks, 4 weeks after starting the treatment of Nokamen . The blood flow condition was evaluated by the pulsatility index (P_1) at the level of the renal artery and segmental vessels.

The analysis of the dynamics of Doppler ultrasonography indicators in the patients of the control group showed a significant increase of the pulsatility and resistivity indices: right after lithotripsy and during the early postoperative period. They became normal only in 7 days (Table. 3).

In patients after lithotripsy the disorder of renal blood flow occurs due to shock wave, and the severity and the damage mode depends on the initial state and the urodynamics behavior [3].

Due to the fact that in patients with pyeloectasia the pulsatility and resistivity indices had high values: $P_1 = 1,23 \pm 0,06$ ($P < 0.05$) and $Cl = 0,72 \pm 0,03$ ($P < 0, 05$), we divided the main group into two subgroups. The first one consisted of 11 patients with calculi in pelvis and calyx without ectasia, the second one - 11 patients with ureteropyeloectasia.

Table 3. The dynamics of dopplerography indices in patients of the control group (without Nokamen)

Index	Before lithotripsy	Indices after lithotripsy		
		Right after	In 2 days	In 7 days
P_1	1,1 ± 0,02	1,3 ± 0,04 P <0,01	1,14 ± 0,013 P <0,01	1,04 ± 0,036 P <0,05
Cl	0,66 ± 0,01	0,75 ± 0,023 P <0,01	0,68 ± 0,02 P <0,05	0,63 ± 0,02 P <0,05

P – in comparison with indices before lithotripsy.

Table 4. The dynamics of dopplerography indices after lithotripsy with Nokamen treatment.

Index	Before lithotripsy	Indices after lithotripsy				
		Right after	In 2 days	In 7 days	In 2 weeks	In 7 weeks
P_1	1,03 ± 0,08	1,3 ± 0,04 P <0,005	0,94 ± 0,05 P <0,01	0,96 ± 0,09 P <0,01	0,95 ± 0,06 P <0,01	0,96 ± 0,03 P <0,01

Cl	0,63 ± 0,02	0,75 ± 0,023 P <0,01	0,6 ± 0,016 P <0,01	0,61 ± 0,03 P <0,01	0,6 ± 0,02 P <0,01	0,55 ± 0,05 P <0,01

P – in comparison with indices before lithotripsy.

In order to define the effect of the Nokamen preparation on the state of renal blood flow after lithotripsy, we have carried out the comparative analysis of pulsatility and resistivity indices in the equal groups of patients (in 11 patients), while maintaining the urine outflow. Table 3 shows the patients' indices after lithotripsy without using Nokamen, and Table 4 - indices after lithotripsy in patients treated with Nokamen.

It was found that in the group of patients who underwent lithotripsy without using Nokamen, the restoration of renal hemodynamics occurred only on the 7^{th} day after lithotripsy. Normalization of hemodynamics after lithotripsy in patients treated with Nokamen, was more rapid, and in 2 days after lithotripsy the pulsatility and resistivity indices corresponded to indices before the intervention. These indices were not varied for the entire observation period, regardless of the number of lithotripsy sessions (Table. 4).

The received data allow to draw a conclusion that the prescription of Nokamen for the patients with urolithiasis before lithotripsy allows to restore a renal blood flow more rapidly, to reduce the trauma of parenchyma as a result of the shock wave impact to a minimum level and to reduce the period between sessions down to 2 days, if necessary.

As mentioned above, during the disorder of urine outflow from the upper urinary tract, the disorder of renal blood flow at the level of vessels of renal hilum was observed. And this disorder consisted in a significant increase of pulsatility index: 1,5 ± 0,4 (p> 0.001). The last one remained significantly increased, and it testified to the decrease of blood velocity in the parenchyma.

In a week P_1 and Cl indices in the Nokamen's group were 0,96 ± 0,1 (P> 0.01) and 0,6 ± 0,03 (P> 0.01) respectively. It testifies to the normalization of blood velocity. The study of hemodynamics in patients with urolithiasis has revealed a significant increase of P_1 and Cl indices when ureteropyeloectasia. It is connected with the increase of intrapelvis pressure, leading to disorder of blood flow in the parenchyma.

For a more detailed study of the change of blood velocity P_1 and Cl indices were determined at the segmental level of the vascular bed. Analysis of the results showed that in the group of patients who did not receive Nokamen, P_1 and Cl indicators were increased up to 1,43 ± 0,07 and 0,76 ± 0,01, respectively. At that time the patients treated with Nokamen, hemodynamic changes were expressed slightly - 1.11 ± 0.06 and 0.64 ± 0.02, respectively.

Thus, the efficacy of Nokamen in improvement of blood flow not only at the level of the renal arteries, but also at the level of microcirculation was confirmed.

Conclusions

These results confirm the effectiveness of the herbal remedy Nokamen in patients with urolithiasis in combination with the remote lithotripsy:

1. Nokamen is effective in the prevention and treatment of infectious and inflammatory complications, reducing the severity of leukocyturia and bacteriuria.
2. The terms of the discharge of fragments from the urinary system after lithotripsy are reduced in two times. Nokamen reduces the frequency of renal colic and the risk of formation of steinstrasse after remote lithotripsy.
3. Nokamen improves renal blood flow and reduces the risk of traumatic parenchymal damage due to shock wave during lithotripsy.
4. Nokamen should be prescribed one week before the planned lithotripsy followed by the administration in the postoperative period to prevent possible vascular and Infectious complications.

UDC 616.63-074:612.46:613.2 DOI: 10.26641/2307-5279.24.4.2020.224412

EFFECT OF ALIMENTRAL FACTORS ON URINE pH

V.P. Stus, N.N. Moiseenko, M.V. Zhbakov, V.V. Ehalov

SI « DMA of the Ministry of Health of Ukraine »

Introduction. Modern medicine is moving towards minimization of invasiveness, improvement and development of prevention of the most common urological diseases that do not involve any surgical intervention. In the development of the most common both urological and general diseases, the alimentary factor is of great importance. It is possible to trace its effect on the body by many laboratory parameters, but this article will talk specifically about the acid-alkaline balance of urine.

The normal environment for the human body is neutral one: the intracellular pH is 6.8, and the blood plasma pH is 7.33 to 7.45. As a result of everyday chemical processes occurring in our body, acidic and alkaline metabolites are formed. In addition, acidic metabolites are formed 20 times more than alkaline metabolites. The body has protective systems aimed primarily at neutralization of acidic decay products and their elimination from the body. Mechanisms for maintaining pH stability are divided into physical-chemical and physiological ones. The acidity of the blood is adjusted in the greatest way, therefore the buffer systems of the blood are the first link of the body's defense against acidity fluctuations. Buffer systems are alkaline and acidic substances that neutralize products and metabolites of the opposite nature that enter the blood [1]. The advantage of buffer systems is the ability to instantly react to pH changes and quickly neutralize a small amount of strong acids and bases. However, the buffer reserves in the blood are quite limited, and due to a strong acid load these reserves begin to be extracted from other organs and tissues, the acidity of which is less critical. Accordingly, in case of a constant acid load, even though the blood pH remains stable, the tissues of other organs undergo pathological acidification causing many chronic diseases. In addition to the fact that buffer systems are able to correct pH shifts limited by their capacity, which is determined by the number of equivalents of a strong acid or base, there is a second drawback of the first line of defense, which lies in its inability to remove metabolic products from the body. In this case, there are second and third physiological lines of defense (respiratory and urinary systems, the liver, gastrointestinal tract, and sweat glands) [2].

The respiratory system is the body's second line of defense against acidity fluctuations. It starts to act 3-12 minutes after the pH drop. The excretion of metabolites occurs quickly, but in case of a strong acid load, the respiratory mechanisms are able to remove only 50-70%, and they are ineffective in case of an excess of alkalis [2].

The mechanisms of the urinary system are the third link in the acidity regulation. In contrast to the buffer and respiratory mechanism, the renal mechanism is not able to affect the pH drop in a short time, but it acts for several days. However, at the same time, up to 500 mmol/day of acids or bases are excreted from the body in the urine, and the urine pH with a strong acid or alkaline load can vary from 4.5 to 8 [3].

In ordinary mixed food and normal drinking regime in a healthy person the excretion of acids exceeds the excretion of bases, therefore urine has a slightly acidic reaction (pH 5.3-6.5) and the concentration of hydrogen ions is about 800 times higher than in the blood. The role of the kidneys in compensating for metabolic and respiratory acidosis is to increase the excretion of hydrogen ions. The kidneys produce and excrete in the urine the amount of hydrogen ions equivalent to their amount continuously entering the plasma from the cells of the body, while replacing the hydrogen ions secreted by the epithelium of the tubules with sodium ions of the primary urine [3]. A stable deviation of urine acidity from the norm can be observed in some urological diseases, such as metabolic disorders, urolithiasis and urothelial tumors [4].

Alimentary factor. The level of acidity of the biological environment of the body is most affected by the diet. All products in the disintegration process form acid and alkaline metabolites.

Human metabolic processes were formed over many centuries and corresponded to different lifestyles at different times.

The history of the nutritional regime of mankind is divided into three large time stages:

— B.C.;
— Agrarian culture;
— Modern humanity.

For most of their lives, humans have been hunters and gatherers. One-third of the diet consisted of low-fat bushmeat and two-thirds of plant products. This diet was completely alkaline, with an average acid load of minus 78 mEq per day.

The situation fundamentally changed with the emergence of an agrarian civilization, when a person began to eat a lot of grain crops, dairy products and fatty meat of domesticated animals [5].

In addition, the regimen of physical activity has changed significantly. Physical activity has a significant effect on urine acidity. After average work intensity, the acidity of urine changed by 0.5 ± 0.67 c.u. towards the oxidation, but after a significant and large load, this figure reached 1.0 + 0.001 c.u. towards oxidation [6]. Thus, the rapid development of civilization has led to abrupt changes in the metabolism formed over millions of years.

The food of modern humans, which has changed especially over the past 20 years and which people began to consume in the last 100 years, does not meet the genetic needs of the body, as it has a sharp acidic character [7]. Moreover, the industrialization of agriculture over the past two centuries has led to significant mineral depletion of soils. As a result, there was not only an imbalance between positively charged ions (anions) and negatively charged ions (cations), but also an imbalance between the cations themselves. If earlier the ratio of K/Na was about 10/1, then the modern diet has a ratio of about 1/3, that is, it has changed 30 times and reversed.

There was also an increase in the chloride/bicarbonate ratio. Edible salt (NaCl), presented in large quantities in our food, only exacerbates the situation. Thus, food ceased to provide the required level of cations and their balance.

Modern food, compared with Paleolithic Ages, is poor not only in potassium, but also in magnesium, as well as dietary fiber, but it is rich in saturated fats, simple sugars, sodium and chlorine.

This contributes to a painful chronic state of acidification of organs and tissues - metabolic acidosis. Unfortunately, acidification of tissues has affected the majority of the population of developed countries, and its degree is increases. What we used to consider natural age-related diseases (urolithiasis, caries, osteoporosis, gout) often turns out to be the direct consequences of mineral depletion [7].

Fundamental factor. At the beginning of the 21st century, a study of the human diet was carried out in America. The another characteristic of food, important from the point of view of health, has been found in this study (in addition to calorie content, saturation with proteins, carbohydrates, fats and vitamins) [8].

Net acid excretion (NAE). It is the sum of urinary excretion of organic acids (OAs) and potential renal acid load (PRAL). OAs is mainly determined by body surface area and it can be estimated by using anthropometric measurements (OAs (meq/d) = body surface area of the individual x 41 / 1.73) [9].

PRAL is the dietary acid load. It consists of the ratio in food of components forming either an acid or an alkali during metabolism. This is an indicator of the acid-forming ability of food products, which allows to consider not only the chemical composition of food products, but also the bioavailability of macro- and microelements, and other nutrition-independent metabolic processes in the body. The greater its positive value, the higher the acidifying effect of the product, and the greater its negative value, the higher its alkalizing effect. When food is dominated by acid-forming components, the acid load is positive. If there are more alkali-forming components in the food (organic salts of potassium and magnesium), then the acid load is a negative value.

To calculate PRAL, the average net absorption of the relevant nutrients must be considered, including protein, the degree of dissociation of phosphate at pH 7.4, and the ionic valence of magnesium and calcium.

Based on these factors determining PRAL (after taking into account the appropriate atomic weights), nutrient-specific conversion factors are obtained that allow to calculate PRAL directly from diets: PRAL (meq/d) = 0.49 x protein (g/d) + 0.037 x phosphorus (mg/d) – 0.021 x potassium (mg/d) – 0.026 x magnesium (mg/d) – 0.013 x calcium (mg/d).

To estimate total urinary NAE, it is necessary to add OAs and PRAL (NAEs = PRAL + OAs) [9].

It is important to understand that if OAs for a healthy person is a relatively stable value, then PRAL is an indicator that varies greatly depending on the menu and can be adjusted by the person himself. This is extremely important for some groups of people, for example, patients with urolithiasis, because with the help of just adjusting your diet, you can prevent the recurrence of urolithiasis. For ease of calculation, an extensive PRAL table of various products was formed (Table 1).

It is important to consider that the figures given in the table are approximate, since many factors affect the acidic properties of the product. The composition of plant food depends on the chemical composition of the soil on which it was grown, as well as belonging to one of the many varieties.

Table 1

Acid load parameters [5]

Product	PRAL (mEq/100g)	Product	PRAL (mEq/100g)	Product	PRAL (mEq/100g)
Vegetables		*Cereals and flour products*		*Meat products*	
Pumpkin	-5,6	Boiled white rice	1,7	Milk sausage	6,7
Beet	-5,4	Whole buckwheat	3,7	Pork sausage	7,0
Carrot	-4,9	Whole corn	3,8	Smoked pork sausage	7,7
Zucchini	-4,6	White rice	4,6	Lean beef	7,8
Potato	-4,0	Coarse rye flour	5,9	Lean pork	7,9
Cauliflower	-4,0	Oat flakes	10,7	Lean chicken	8,7
Red radish	-3,7	Oat	13,3	Lean turkey	9,9
Aubergine	-3,4	*Pasta*		*Seafood*	
Tomato	-3,1	Macaroni	6,1	Pike, walleye	6,8
White cabbage	-2,8	Noodles	6,4	Atlantic herring	9,1
Cucumber	-2,4	White flour spaghetti	6,5	Shrimps	10,5
Garlic	-1,7	*Bakery products*		*Eggs*	
Onion	-1,5	Wheat bread	3,7	*and dairy products*	
Ordinary mushrooms	-1,4	Rye bread	4,1	Fat cottage cheese	0,0
Sweet pepper	-1,4	Rusks	5,9	Whole milk	1,1
Fruits and berries		*Sweets*		Whole milk yogurt	1,5
Avocado	-8,2	Honey	-0,3	Chicken egg, whole	8,2
Banana	-5,5	White sugar	0,0	Hard cheese	19,2
Apricot	-4,8	Bitter chocolate	0,4	Cheddar cheese	26,4
Melon	-4,5	Milk ice cream	0,6	*Oils*	
Kiwi	-4,1	Milk chocolate	2,4	Margarine	-0,6
Grape	-3,9	*Beverages*		Olive oil	0,0
Pear	-2,9	Carrot juice	-4,8	Sunflower oil	0,0
Orange	-2,7	Orange juice	-3,7	Butter	0,6
Pineapple	-2,7	Red wine	-2,2	*Nuts*	
Lemon	-2,6	Coffee	-2,3	Hazelnut	-2,8
Plum	-2,6	Mineralized water	-1,8	Walnut	6,8
Peach	-2,4	Indian tea	-0,3	Pistachios	8,5
Apple	-2,2	Green tea	-0,3	*Herbs and seasonings*	
Watermelon	-1,9	Beer	0	Parsley, greens	-12,0
		Vodka	0,1	Cider vinegar	-2,3
		Coca Cola	0,4	Mayonnaise classic	0,6

The properties of products of animal origin will also depend on the environment, the nature of food, health and many vital factors of the animal. Therefore, these tables do not allow for accurate calculation, but they are sufficient for daily monitoring of nutrition.

Effect of medications on urine pH. The pH level of the medium affects the rate of dissolution of most drugs. Many drugs have the ability to change the acidity of urine, so they can affect the rate of excretion of other medicinal substances. Some sulfonamides are acetylated in the body, and their acetyl derivatives can cause crystalluria with kidney damage due to poor solubility in an acidic medium. Therefore, the use of drugs that increase the acidity of urine is not recommended [10].

Antibiotics, uroseptics, and phytopreparations are the most common groups of drugs in the treatment of patients with a urological profile.

Italian and American researchers carried out a study to identify the connection between the use of antibacterial drugs and the development of urolithiasis [11].

The results have shown that women, who used antibiotics for a total of 2 months or more in the first (40-49 years) and the second age groups (40-59 years), have a higher risk of symptomatic urinary stone disease compared to the patients who did not use antibiotics in this same age group.

Urine composition was generally similar across the groups of women treated with antibiotics, with the exception of slightly lower urine pH and urinary citrate levels in patients treated with antibiotics for 2 or more months [11].

Both the effect of antibiotics on the acidity of urine, and the effect of acidity on the pharmacological action of drugs are important. It has been established that there are many factors that affect the effectiveness of antibiotics in urinary tract infections (UTIs), and pH is one such factor. Due to the fact that the pH of human urine varies over a very wide range – from acidic (pH 4.5) to alkaline (pH 8), and this factor is quite easy to manipulate, this can be a significant advantage for a better understanding of the role of pH in the efficacy of antibiotics in UTIs.

Representatives of the Department of Surgery, Department of Urology of China and Canada in 2014 carried out a study, the purpose of which was to determine the effect of pH on the activity of clinically significant antibiotics against major bacterial uropathogens [11].

An *in vitro* study has studied the activity of 24 commonly used antimicrobials against bacterial strains belonging to 6 major uropathogens (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis, Staphylococcus saprophyticus* and *Staphylococcus epidermidis*) at various pH values (from 5 up to 8).

To assess the activity of antibiotics, the standard disk diffusion method and the method of serial microdilutions were used. As it turned out, for 18 of the 24 studied antibiotics, the pH value played a significant role in the overall inhibitory activity of the drug. Although most of the tested drugs have shown similar activity against most or almost all pathogens, several antibiotics had pH-dependent activity against certain pathogens.

Fluoroquinolones, cotrimoxazole, aminoglycosides and macrolides were more active in an alkaline environment, while tetracyclines, nitrofurantoin and many beta-lactams showed the highest activity in an acidic environment. The activity of sulfamethoxazole, oxacillin, amoxicillin, clavulanic acid, vancomycin, imipenem, and clindamycin was largely independent of the pH of the medium [12].

Along with antibiotic therapy, uroprotectors and diuretics based on medicinal plants are used in the treatment of inflammatory diseases of the urinary tract and urolithiasis. The advantage of herbal remedies over antibiotics is less hepatotoxicity and the absence of acquired resistance by microorganisms. [13]

Purpose of the study: establishing the relationship between changes in the pH of urine from the human diet, as well as determining the effect of medications (Nokamen) on the acidity of urine.

Materials and methods of research. We carried out a study to confirm the dependence of the actual indicators of urine acidity and the above calculations.

The study of urine pH was carried out by using a pH meter PCT-407pH manufactured in Taiwan. To achieve maximum accuracy, the instrument was calibrated every 10 measurements using standard solutions.

The study involved 53 students of the SI "Dnepropetrovsk Medical Academy of the Ministry of Health of Ukraine" (aged 20-21 years). Every day for a week, the students recorded their diet, after which every morning they gave a second portion of urine for analysis of the pH level.

The study was carried out with different groups of students throughout the year and continues to this day. All subjects can be divided into two approximately equal groups: “Students with a stable pH level” and “Students with a sharply changing pH level”. First of all, the diets of those who showed stable results were analyzed, after which it became obvious that absolutely all students who consistently show a slightly acidic pH adhere to a healthy diet, with a predominance of vegetables, fruits, fish and cereals, boiled meat, as well as fried food in a small quantity. The participant, who followed a strict diet, ate low-calorie foods daily and in small quantities for three consecutive days, showed the pH of 5.56; 5.57; 5.56. For the rest of participants, acidity fluctuated within three tenths. In general, we can say that slightly acidic urine is formed with such a diet, when each meal in total gives an indicator of acid load in the range from +15.0 mEq to +28.0 mEq. The diets of the participants with neutral urine pH cannot be considered as unhealthy. Often their diets were even balanced, but there was one thing in common: no meat. The students, who neglect meat products, but at the same time consume enough cereals, fish and nuts, excreted neutral urine. The acid load of one meal ranged from +7.0 mEq to +10.0 mEq in these participants. It can be calculated that a difference of 10 mEq in acid load corresponds approximately to a difference in acidity of 0.6. (Fig. 1).

In general, we can say that the dependence of urine acidity on food consumed is quite clearly traced in people with a stable urine pH.

Acidic, slightly alkaline and alkaline environments were not encountered in these participants, even in cases where they once neglected proper nutrition and ate fast food, fatty and high-calorie foods. This suggests that the acidity of urine is a fairly stable indicator, which is difficult to change with one or two meals.

The rations of students, who showed sharp drops in urine acidity in the range from acidic 4.7 to slightly alkaline 7.8, have been studied. In this group, the correlation of acid load and urine pH was less obvious because when acidifying foods were consumed for several days, the acidity level of urine was more than 7.4, and, conversely, when a sharply acidic diet was abandoned, the acidity level of urine became slightly acidic 5.3–5.5. But with a detailed study of the diet, it was possible to reveal that all participants with sharp changes in pH have the wrong, unbalanced diet. All students who eat a lot of fast food (including sushi), and those who prefer fatty and fried home cooking, had daily acidity spikes. It should be noted that the participants who do not consume “harmful” foods at all, but at the same time eat irregularly, without a certain portion, also have an unstable level of acidity. People who drink only coffee in the morning, have "snacks" at lunch and have a hearty dinner in the evening, as a rule, show an acidic pH of 4.7-5, and those who generally severely restrict themselves in food and have several cups of coffee, a sandwich and fruits a day, show a slightly alkaline pH of 7.8-8.2.

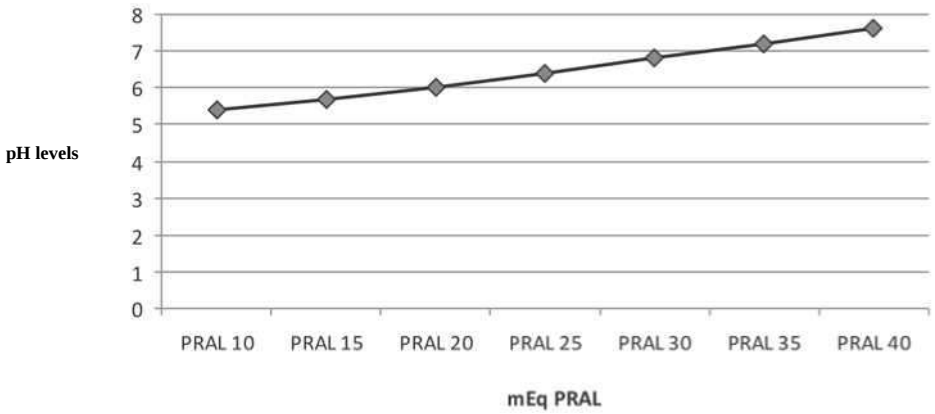

Fig. 1. Dependence of pH on the dietary acid load

The participants in the second group experienced sharp pH spikes by several units at least once every 3 days. The following important observation has been made: all the participants in the second group, unlike the first one, did not maintain the proper level of water balance. The people on the balanced diet consumed at least 1.5 liters of fluid daily (most of which was plain water), and most of the participants in the second group consumed a few cups of coffee or tea with little plain water.

Some participants were asked to adjust their diet, normalize portion sizes and meal times, and refuse fast food, fried and fatty foods. The result was not immediately observed, but within three days the level of urine acidity began to stabilize and moved into the range from slightly acidic 5.5 to neutral 7.1 (Fig. 2). This confirms the statement that the urinary system responds to an increase in acid metabolites within a few days.

Separately, we would like to note the effect of sweets and alcoholic beverages on the acidity of urine. The fact that some participants ate candy and sugary drinks daily did not affect their results in comparison with people who did not abuse sugar. Several participants drank 0.5 to 1.0 liters of beer almost daily, but they fell into the group of people with a stable neutral pH, apparently the principle of drinking enough liquids worked.

The effect of the phytopreparation Nokamen on changes in the pH level of urine has been studied (Fig. 3). The study involved 13 people with initially high acidity of urine. Each subject took Nokamen 2 tablets twice a day for 6 months. As a result of this therapy, during the first month, the pH level of the patients stabilized and was close to the average normal values (Table 2).

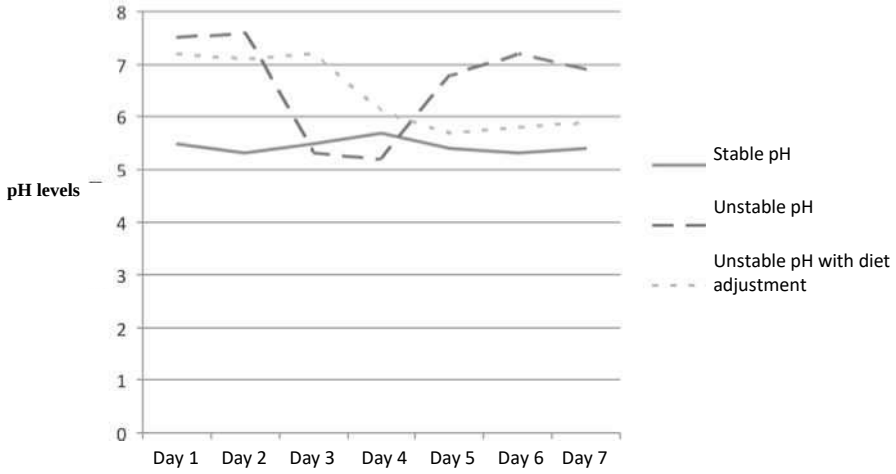

Fig. 2. Types of pH level progression

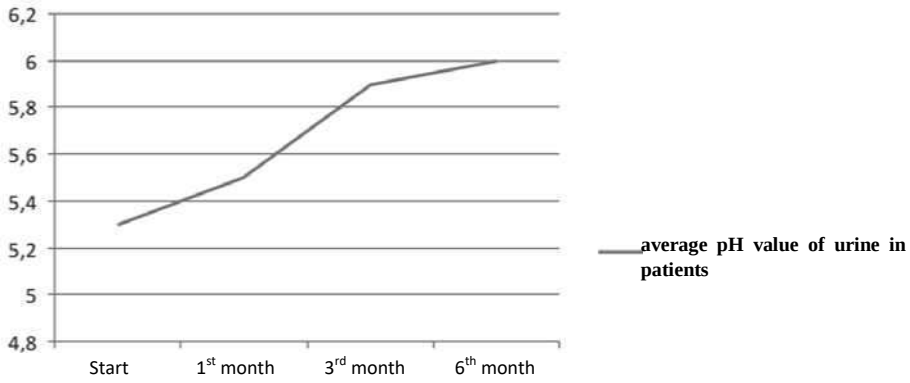

Fig. 3. Change in the acidity of urine during the reception of Nokamen

Table 2

Urine pH values at the stages of Nokamen therapy

No.	Urine pH during the first month	Urine pH after 3 months	Urine pH after 6 months
1	5,6	5,8	6,0
2	4,8	5,8	5,7
3	5,5	5,7	5,8
4	5,0	5,3	5,4
5	6,0	6,1	6,0
6	6,2	6,6	6,5
7	6,0	6,0	6,1
8	5,9	6,2	6,1
9	5,7	6,1	6,0
10	5,8	5,9	6,1
11	5,6	5,8	6,0
12	5,9	6,0	5,9
13	5,1	5,8	5,7

Conclusions

1. The acidity of human urine depends mainly on the diet. A characteristic, such as PRAL, is reliable and the acid load of 10 mEq gives a change in urine acidity of about 0.6.

2. It has been established that in order to maintain the urine pH in the natural slightly acidic range, it is necessary to regulate not only the diet, but also the diet timeliness and fragmentation.

3. The urinary system reacts to changes in the general acidity of the body within a few days, but not instantly.

4. An important role in stabilizing the level of acidity of urine is the maintenance of water balance in the body.

5. Medications can affect the acidity of urine.

6. Nokamen helps to maintain the normal pH level.

References:

1. Hartig, V. (1982). *Sovremennaya infuzionnaya terapiya. Parenteralnoepitanie [Modern infusion therapy. Parenteral nutrition]*. M.: Meditsina [in Russian].

2. Morrison, V.V., Chesnokova, N.P., & Bizenkova, M.N. (2015). Kislotno-osnovnoe sostoyanie. Regulyatsiya kislotno-osnovnogo gomeostaza (lektsiya 1) [Acid- alkali state. Regulation of acid-base homeostasis (lecture 1)]. *Mezhdunarodnyiy zhurnalprikladnyih i fundamentalnyih issledovaniy — International Journal of Applied and Basic Research, 3*, 270—273 [in Russian].

3. Kubarko, A. I., Pereverzev, V. A., & Semenovich, A. A. (2010). *Fiziologiya cheloveka [Humanphysiology]*. Minsk: Vyish. shk. [in Russian].

4. Golovanov, S.A., Sivkov, A.V., Polikarpova, A.M., Drozhzheva, V.V., Andryuhin, M.I., Prosyannikov, M.Yu. (2018). Metabolicheskie faktoryi riska i formirovanie mochevyih kamney. Issledovanie III: Vliyanie pH mochi. [Metabolic risk factors and the formation of urinary stones. Study III: Effect of urine pH]. Eksperimentalnaya i klinicheskaya urologiya — *Experimental and Clinical Urology, 1*, 84—90 [in Russian].

5. Pitanie i kislotno-schelochnoy balans [Nutrition and acid-alkali balance]. *hozar.livejournal.com.* Retrieved from https://hozar.livejournal.com/398205.html [in Russian].

6. Polulyaschenko, T.A. (2012). Biohimicheskiy metod kontrolya funktsionalnogo sostoyaniya organizma yunyih velosipedistov naetape nachalnoy podgotovki [Biochemical method for controlling the functional state of the body of young cyclists at the stage of initial training]. *Fizychne vykhovannya, sport i kultura zdorovya u suchasnomu suspilstvi — Physical education, sports and health culture in modern society.* (pp. 457—460). Lutsk [in Russian].

7. Entshura, P.V., Lokemper, I.B., & Galkin, A.A. Schelochnaya sistema ozdorovleniya [Alkaline Healing System]. *ekniga.org.* Retrieved from https://ekniga.org/dom-i-semya/zdorove/35669-schelochnaya-sistema- ozdorovleniya.html [in Russian].

8. Eaton, S.B., Eaton 3rd, S.B., & Konner, M.J. (1997). Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. *Eur J Clin Nutr,* 51(10), 715—716. Doi: 10.1038/sj.ejcn.1600471.

9. Remer, T., Dimitriou, T., Manz. F. (2003). Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. *Am J Clin Nutr, 77(5),* 1255—1260. Doi: 10.1093/ ajcn/77.5.1255.

10. Prokofeva, L.V., Kormishina, A.E., & Kormishin, V.A. (2017). *Kurs lektsiypo obschey farmakologii [Course of lectures on general pharmacology]*. Ulyanovsk: UlGU [in Russian].

11. Yang L., Wang K., Li H., Denstedt J.D., Cadieux P.A. (2014). The Influence of Urinary pH on Antibiotic Efficacy Against Bacterial Uropathogens. *Urology, 84(3),* 731.e1—731.e7. Doi: 10.1016/ j.urology.2014.04.048.

12. O vzaimodeystvii lekarstvennyih sredstv chast II [About drug interactions, part II]. www.remedium.ru. Retrieved from: https://www.remedium.ru/doctor/therapeutics/o-vzaimodeystvii-lekarstvennykh-sredstv- chast-ii/ [in Russian].

13. Gessnera, A. (2017). Vozdeystvie na mikrobiom: fitoterapiya v sravnenii s antibiotikami [Impact on the microbiome: herbal medicine versus antibiotics]. *Medychna hazeta «Zdorovya Ukrayiny 21 storichchya» — Medical newspaper "Health of Ukraine of the 21st century", 21(418),* 51.

COMPARATIVE STUDY ON THE EFFECTIVENESS OF NOKAMEN FOR PREVENTING EXACERBATIONS OF CHRONIC RECURRENT CYSTITIS IN WOMEN

Litvinec E.A., Litvinec V.E.

DVNZ "Ivano-Frankivsk National Medical University"

The purpose of the study: to study the efficacy and safety of using Nokamen phytocomplex for preventing exacerbations of chronic recurrent cystitis.

Materials and methods. We have carried out an open monocentric, comparative study which involved 60 women aged 20-65 years with chronic recurrent cystitis. In order to prevent the exacerbation of chronic recurrent cystitis based on a random sample, the patients were divided into II groups. Nokamen phytocomplex at a dose of 1 tablet 2 times a day for 3 months was intended to the main group (30 patients). The second group (30 patients) - the comparison group took an tincture of phytomixture "Kidney" at a dose of 50 ml 3 times a day for 3 months also.

Results. Analysis of the results has shown that the use of Nokamen phytocomplex within 3 months after the treatment of the last episode of exacerbation of chronic cystitis significantly reduces the incidence of relapses in comparison with phytomixture. Thus, in the main group of patients receiving Nokamen, an exacerbation of chronic cystitis was reported in 6 months - in 3 (10.0%) patients, while in the comparison group – in 18 (60.0%) patients.

Conclusion. This study has shown that the use of a balanced phytocomplex of Nokamen for 3 months compared with phytomixture is more effective in preventing exacerbations of chronic recurrent cystitis. So, it can be recommended for wide use as a highly effective and safe remedy.

Key words: chronic recurrent cystitis, Nokamen, phytomixture.

Cystitis is an infectious and inflammatory process in the wall of the bladder, which is localized predominantly in the mucous membrane [2, 5, 6]. The prevalence of acute cystitis in Ukraine is 314 per 100 thousand people, and chronic cystitis - 135 per 100 thousand people. Most patients are young women and women in the pre-menopausal period. If the infection of the bladder is constantly repeated (periodic relapse of its inflammation), the chronic cystitis, which has the ICD-10 code - N30.1-N30.2 can be diagnosed. Chronic recurrent cystitis or chronic cystitis with frequent exacerbations is the most common pathology diagnosed in women of reproductive age [1, 3, 5].

Based on the statistics, every third to fourth woman in the most active reproductive and working age (20-40 years old) experiences acute cystitis, and in one third it becomes recurrent. More often, recurrence occurs within the first three months after the first episode [2, 5]. Another study, which covered a wider age range of women (17-82 years), has shown even more global problem. Recurrent cystitis occurs in 45% of patients during the first year. Among the women 55 years of age and older, each second suffers from repeated exacerbations [10].

Women are highly susceptible to relapse of cystitis, which can be explained by such factors as: anatomical and physiological features of the female body (short and wide urethra, proximity to the reservoirs of opportunistic bacteria); gynecological diseases associated with inflammation and hormonal components that disturb vaginal dysbiosis; frequency of sexual acts, and contraception peculiarities. A significant factor of the bladder infection is a sexual intercourse. The variability of the location of the urethra outer opening creates a high probability of vaginal ectopia, while the urethra opens directly into the vestibule of the vagina. This results conditions for the retrograde passage of the vaginal contents into the bladder during sexual intercourse. In addition, the common "complication" of the onset of sexual activity is the formation of gimenouurethral conjunctions, resulting urethra hypermobility, which is displaced in the vagina during coitus. Non-observance of sexual hygiene causes a cystitis attack almost after every sexual intercourse [2, 3, 5].

Adhesion (sticking) of certain types of bacteria to the epithelium of the bladder plays the important role in the development of cystitis. Spicy food and prolonged retention of urination, which can lead to persistent functional disorders, in which the consistency between the bladder muscles are lost, also contributes to chronic cystitis [5, 6, 7].

Most relapses occur in the first 3 months after a treatment of the previous episode. Within 6 months after the first episode of urinary tract infection (UTI), 27% of young women develop at least one culture-confirmed relapse, and 2.7% have at least 2 relapses. After a treatment of an uncomplicated cystitis the disease recurs for 1 year in almost half of women [2, 5]. If the causative agent of cystitis was E. coli, relapses occur in 36% of women under 55 years of age and in 53% of women over 55 years of age within 1 year [6]. Frequent relapses of cystitis are found in 10-15% of women over 60 years of age [10].

The cystitis occurs due to the presence of pathogens and dystrophic congestive processes in the wall of the bladder. In most cases, cystitis is caused by gram-negative bacteria, about 80% of which is *Escherichia coli*. The second most common pathogen (11%) is *Staphylococcus saprophyticus*. The other causes are mainly *Enterococcus faecalis*, *Klebsiella spp*. and *Proteus spp*. In the etiology of cystitis, urogenital infections caused by *Chlamydia trachomatis*, *Ureaplasma urealiticum* and *Trichomonas vaginalis* play a significant role [4, 5].

Deformation and deep damages of the bladder wall layers cause a decreased capacity of the bladder and its partial dysfunction.

The diagnosis of recurrent cystitis is verified if within six months there were at least two exacerbations of the disease or three or more during the year. There are two cases for the development of relapse. 1) Persistence of infection. In this case, the infectious agent gets into the mucous membrane of the bladder or urethra and parasites it, causing the exacerbations regularly. 2) Reinfection. In this case, there is a repeated infection. The first exacerbation of the disease ends with complete elimination of the bacteria, but the cause of relapse is a new infectious agent. This

may be the same or another type of bacteria that has again entered the urinary tract [2, 10].

Prophylactic treatment is indicated to the patients with frequently recurrent cystitis (> 2 exacerbations for 6 months and > 3 exacerbations for 1 year). Such therapy involves several approaches: prolonged prophylactic administration of one of the antibiotics in low doses every 10 days for 3 months; for patients whose exacerbations are associated with sexual intercourse, the antibiotic after coitus with a gradual dose reduction is recommended [5, 7].

An analysis of 108 studies has shown that as a result of the prophylactic use of antibiotics, the probability of relapse decreased 8-fold, however, at the end of the course, in 3 months, 60% of patients again experienced exacerbations. In addition, side effects have been developed in the form of intestinal dysbiosis and oral and vaginal candidiasis [10].

At present, there is a certain opinion regarding this method of prevention: if it is possible to do other ways, antibiotics may not be used until reception.

This condition is associated with a significant proliferation of polyresistant bacteria, their increased virulence, the activation of their own conditionally pathogenic microflora in conditions of reducing the body's defence and infection with hospital bacteria. Other important components of the problem are that over the past 40 years, fundamentally new classes of antibiotics have not appeared in the pharmaceutical market and in clinical practice. In addition, the number of antibiotic therapy side effects increase [6].

Resistance of bacteria to antibacterial agents is the main factor limiting antibiotic therapy and one of the reasons for unsuccessful treatment with antibacterial drugs. Every year around 20,000 articles are published about the spread of antibiotic resistance, which indicates the relevance of this problem [7].

Thus, losing the fight against infections strategically, humanity is forced to resort to tactical maneuvering. In these conditions, the role of phytotherapy, directly aimed at suppressing the development of pathogenic microbial pathogens in the urinary tract, is increasing.

Also, the negative side of most pharmacological drugs is their nephrotoxicity, the ability to sensitize and allergenize the body, especially when prolonged use. Taking into account the mentioned above, the attention was paid to phytotherapy in the treatment of patients with chronic cystitis [6, 8, 9]. The advantages of phytotherapy in the treatment of this pathology are as follows:

- phytopreparations have a pronounced therapeutic effect and a much smaller spectrum of side effects;

- wide range of therapeutic effects and minor toxicity allow long-term use of phytopreparations without the risk of severe complications (hepatotoxic, nephrotoxic, inoculation);

- pharmacodynamics of phytopreparations is quite rich (antiseptic, anti-inflammatory, analgesic, antispasmodic, diuretic and others), which allows to influence on several pathological chains;

- the effect of phytocomplexes is more natural and "soft". There is a modulating effect of these drugs on the immune system and metabolism due to the presence of biologically active substances, vegetable oils, vitamins, antioxidants, etc.

That is why Nokamen, produced by ANANTA Company, due to its complex of the necessary pharmacological mechanisms with a multifaceted effect on the genitourinary system, is very interesting. However, the effectiveness of this remedy in preventing relapses of chronic cystitis was not studied.

The purpose of the study: to study the efficacy and safety of using Nokamen phytocomplex for preventing exacerbations of chronic recurrent cystitis.

Materials and methods.

We have carried out an open monocentric comparative study which involved 60 women aged 20-65 years with chronic recurrent cystitis. Each patient had at least 2 relapses of cystitis at intervals of 2-4 months. In most cases, the exacerbations were caused by hypothermia, a substitution for the sexual partner, frequent sexual contacts and acute infections. The episodes of exacerbation of chronic cystitis were treated on the eve in all the patients included in the study. In

order to prevent the exacerbation of chronic cystitis, the patients were divided into II groups on the basis of a random sample. The main group (30 patients) was treated with Nokamen at a dose of 1 tablet twice a day for 3 months. Nokamen phytocomplex has the following balanced composition of the active substances: Crataeva nurvala bark – 100 mg, Saxifraga ligulata rhizome – 60 mg, Butea frondosa flowers – 40 mg, Dolichos biflorus seed – 40 mg, sodium carbonate – 20 mg, Boerhavia diffusa root – 70 mg, Asphaltum – 70 mg, Tribulus terrestris fruit – 100 mg, Rosmarinus officinalis whole plant extract – 20 mg, Rubia cordifolia root extract – 20 mg.

The second group (30 patients) - the comparison group took a tincture of phytomixture "Kidney", at a dose of 50 ml 3 times a day for 3 months. The composition of this phytocomplex contains the following plants: field horsetail (*Equisetum arvense*), corn stigma, tickseed, knotweed (*Polygonum aviculare*), currant leaves, bearberry (*Arctostaphylos uva-ursi*).

The criteria for the patients' inclusion in the study were as follows: the diagnosis of chronic recurrent cystitis, the age of patients 20-65 years, the patient consent for the study.

The criteria for exclusion from the study were as follows: malformations of the urinary system; the presence of concomitant disease, which is not provided for in the protocol and can affect the pharmacokinetics and pharmacodynamics of the drugs used in the study, as well as affect the interpretation of data; the presence of neuropsychiatric pathology in patients, which may also affect the complicacy between the patient and the physician; patients intolerant to the drugs used in the study; refusal to participate in the study.

All patients involved in the study were examined using the following methods: examination of complaints and anamnesis, objective physical examination; clinical blood test; clinical urine analysis; Nechiporenko urine analysis; urine culture test; daily proteinuria; Zimnitsky test; biochemical blood test (urea, creatinine, liver tests); ultrasound examination of the abdominal cavity and genitourinary system.

Statistical comparison between groups was performed using t-test. Differences were considered as significant when $p < 0.05$.

During the study period, detection and registration of possible side effects were performed.

During the study the safety and tolerability evaluation, based on the study of the incidence of adverse events in the context of drug administration, was carried out. If there was a reasonable suspicion that an adverse event is associated with the study drug, it was considered as a side effect.

The criteria for assessing the tolerance were the patients' personal feelings in the background of using the study drug and the medical examination of possible allergic rash, peripheral edema, tachycardia and unforeseen adverse reactions.

Degrees of evaluation: good tolerance - the absence of side effects or insignificant severity side effects, which do not require the treatment cessation or change of the drug's dosage; satisfactory tolerance - the presence of adverse reactions that are mild or moderate, requiring the drug's reduction dose; poor tolerability - the presence of adverse reactions requiring the drug cessation. All patients involved in the study have completed the full course of the planned examination and treatment.

Patient groups were comparable in age, severity of clinical symptoms and concomitant pathology. Comparison of the initial data of laboratory studies has shown the uniformity of the main group and the comparison group.

Patient monitoring was carried out in order to determine the duration of remission within 6 months.

All patients were examined after their information consent in accordance with the GCP IHC requirements.

Results and Discussion.

The study was carried out at the urological department of the regional clinical hospital in Ivano-Frankivsk on the clinical basis of the Urology Department, DNEZ "Ivano-Frankivsk National Medical University". The age of the patients ranged from 20 to 65 years, on average 34.5 ± 2.6.

The analysis of the results has shown that the use of Nokamen phytocomplex within 3 months after the treatment of the last episode of exacerbation of chronic cystitis significantly reduces the incidence of relapses. Thus, in the main group of patients receiving Nokamen at a dose of 1 tablet twice a day for 3 months, any exacerbation of chronic cystitis was not reported. But in 4 months only 1 (3.3 %) patient experienced the exacerbation, in 5 months - 2 (6.6%) patients, and in 6 months - 3 (10.0%) patients. In the comparative group, after 2 months, the exacerbation of chronic recurrent cystitis was reported in 2 (6.6%) patients, in three months - in 5 (16.6%) patients, in four months - in 9 (30.0%) , in 5 months - in 12 (40.0%), and in 6 months - 18 (60.0%) patients experienced the exacerbation chronic recurrent cystitis (Table 1).

Table 1

Frequency of exacerbations of chronic recurrent cystitis during 6 months of observation

	1 month	2 months	3 months	4 months	5 months	6 months
Main group (Nokamen), n=30	0	0	0	1 (3.3 %)	2 (6.6 %)	3 (10.0 %)
Comparative group, n=30	0	2 (6.6 %)	5 (16.6 %)	9 (30.0 %)	12 (40.0 %)	18 (60.0 %)

Any adverse reaction has not been observed when using Nokamen and phytomixture "Kidney".

Thus, the obtained data demonstrate that Nokamen phytocomplex is an effective remedy for the prevention of exacerbations of chronic recurrent cystitis.

Conclusions

1. This study has shown that the use of Nokamen for 3 months compared with phytomixture is more effective for preventing exacerbations of chronic recurrent cystitis.

2. Nokamen has no side effects and is well tolerated by patients, so it can be recommended for wide use as a highly effective and safe remedy for preventing chronic recurrent cystitis.

References:

1. Vozianov S.O. Resources and main indicators of the urological service of Ukraine for 50 years / S.O. Vozianov, N.O. Saidakova, L.M. Startseva // Urology. - 2015 – No. 2. - P. 9-19.
2. Vozianov A.F. Atlas: guide on urology: 3 volume. / A.F. Vozianov, A.V .Lyulko. - Dnipropetrovsk: RIA "Dnepr-VAL", 2001 - P. 1905.
3. Acute uncomplicated cystitis in women. Primary care / S.P. Pasechnikovka // Series «Library of Health of Ukraine». - K .: LLC "Doctor-Media", 2012.- P. 64.
4. Pasechnikov S.P. Monitoring of the species spectrum of causative agents of urinary tract infections and their sensitivity to antibacterial drugs in the urological department / S.P. Pasechnikov, N.A. Saidakova, V.S. Gritsay, V.V. Kuznetsov // Urology. - 2011.- Volume 15, No.2.– P. 9-16.
5. Pasechnikov S.P. Nonspecific cystitis: modern principles of diagnosis and treatment / S.P. Pasechnikov, M.V. Mitchenko // Health of Ukraine 21st Century. - 2017. No.8 (405). – P. 50-51.
6. Shulyak O.V. Evaluation of the preventive potential of Kanefron N in the treatment of recurrent cystitis in women of reproductive age / O.V. Shulyak, M.E. Sabadash // Health of woman. - 2015 – No. 10. – P.51-55.
7. Bonkat G. Guidelines EAU: guide lines on urological infections / G. Bonkat, R. Pickard, R. Bartoletti [et al.]. – 2017. – P. 106.
8. Dingermann T., Loew D. Urologika // Phytopharmakologie. — Stuttgart. Wiss. Verlagsgesellschaft Stuttgart, 2003. — P. 250-258.

9. Naber K.G. Efficacy and safety of the phytotherapeutic drug Canephron® N in prevention and treatment of urogenital and gestational disease: review of clinical experience in eastern europe and central asia // Research and reports in Urology. — 2013. — No. 5. — P. 39-46.
10. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect. Dis.Clin.North. Am. – 2014. – No. 28. – P. 1-13.