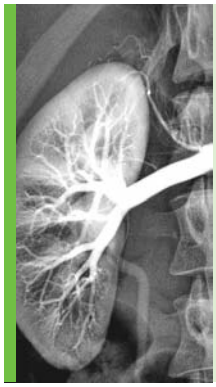

Effects of the herbal combination Canephron® N on urinary risk factors of idiopathic calcium urolithiasis in an open study

Asilbek A. Gaybullaev[1], Saidakhror S. Kariev[1]

Urolithiasis is the formation of calculi or concrements (kidney or urinary stones) in kidney and efferent urinary passages, often associated with typical spastic pain attacks. In industrialized countries such as Western Europe, the prevalence is above 10% and the recurrence rate is up to 50%, occurring more frequently in men than in women. Thus, urolithiasis has an important economic effect on healthcare systems (34, 37, 38, 45).

The main metabolic anomaly in idiopathic calcium urolithiasis is hypercalciuria, which is present in 30–40% of patients (17, 19, 29, 33). Another risk factor of stone formation is urinary oxalate. Citric acid is able to form complexes with calcium in urine, thereby decreasing the Ca-concentration. It also inhibits spontaneous and heterogenic nucleus formation of calcium oxalate. Under physiological conditions >50 % of urinary ionized calcium is bound by citrate in the body. Analytical investigations revealed that stone formers possess a low (decreased) level of urinary citrate, resulting in an increased urinary Ca-level (13, 27, 41). Idiopathic calcium urolithiasis is found in approx. 70–80% of patients with an age range between 30 and 50 years (9, 12, 24, 30, 32).

Therapy or prevention of urolithiasis depends on size of stones, their location in the urinary tract, etiology of stone formation and stone composition. Smaller concrements and stones might be treated sufficiently with lifestyle measures and medical treatment, whereas bigger stones require procedures such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), or percutaneous nephrolithotomy (PNL) (39).

SUMMARY

Purpose of our study was to investigate the effects of the herbal combination Canephron® N (Bionorica SE, Germany), an approved herbal medicinal product with a fluid extract of Centaurii herba, Levistici radix and Rosmarini folium, on urinary risk factors and on the activity of stone formation in patients with urolithiasis. Patients with uncomplicated calcium urolithiasis were treated over 2 (n = 32) or 4 months (n = 18). The use of Canephron® N resulted in an almost continuous decrease of urinary markers of lithogenesis, such as Ap[CaOx] risk index and the rate of crystalluria (CU), paralleled by increases of diuresis and pH-value of urine. After 4 month therapy these parameters were even more improved than after 2 months. Adverse effects were not observed. We consider the herbal combination as a promising agent for patients with urinary risk factors of idiopathic calcium urolithiasis and encourage ongoing clinical research.

Key words

Calcium urolithiasis, Canephron® N, herbal therapy, urinary risk factors, open study

Why should we look for herbal therapies?

Especially with the mechanistic therapies the probability of recurrent urolithiasis is high, as the underlying causes are not addressed. Also standard pharmacological agents such as thiazides have disadvantages in the sense of adverse effects and tolerability (39).

Therefore, traditional herbal therapies are considered being an alternative in the primary and secondary long-term prophylaxis and treatment of stone formation in patients with high risk of lithogenesis. Butterweck and Khan (10) concluded in a review on published data, that results from in vitro, in vivo and clinical studies reveal that herbal medicinal products could be useful as either an alternative or a complementary therapy in the management of urolithiasis. They identified data suggesting possible mechanisms (mode) of action including an increased excretion of urinary citrate and decreased excretion of urinary calcium and oxalate.

Overall, a goal of herbal therapy should include a reduction of lithogenetic urinary factors in addition to an increase of diuresis.

Effects of the study medication

The herbal combination product Canephron® N, available on the market since more than 35 years, has diuretic, spasmolytic, anti-inflammatory, antimicrobial and nephroprotective effects (1, 4, 8, 14, 15, 16, 18, 21, 22, 23, 26, 31, 40, 43,

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44). In Uzbekistan it is approved as herbal medicinal product for sole or adjuvant treatment of acute and chronic infections of urinary bladder (cystitis) and kidneys (pyelonephritis), for chronic non-infectious diseases of the kidneys and for prevention of (recurrent) urolithiasis.

Efficacy and safety

Efficacy and safety have been investigated in several studies (5, 6, 7, 20, 25, 28, 42). Most of these studies included patients with urinary tract infections, but some of them involved also patients with nephrolithiasis or urolithiasis. Hitherto already 3 studies have been conducted in Uzbekistan, all revealing clinically relevant effects in patients with urolithiasis: Alyaev et al. (2) enrolled 48 women with chronic cystitis and urolithiasis, Chernenko et al. (11) enrolled 135 patients with urolithiasis after surgical removal (n = 31), ESWL (n = 32) and patients with uric hyper-crystalluria (n = 47) and Amosov et al. (3) performed early post-operative metaphylaxis in 79 patients after ESWL. At the end of the therapy documentation most patients reported partial or complete relief from dysuric complaints including decreased or absent pain previously existing in the renal region.

About the preparation

The aim of our study was to gain information on urinary risk factors and activity of stone formation in patients with idiopathic calcium urolithiasis during treatment with Canephron® N. The preparation contains in 100 g of the liquid 29 g of an aqueous-alcoholic extract (extracting agent ethanol 59% by volume) of 0.6 g Centaurii herba (Common Centaury herb), 0.6 g Levistici radix (Lovage root) and 0.6 g Rosmarini folia (Rosemary leaves).

Methods

The open uncontrolled prospective study was conducted at the Urologic Clinic of Tashkent Postgraduate Medical Education Institute. From a collective of more than 250 patients with calcium urolithiasis visiting the urologic clinic, patients with uncomplicated idiopathic calcium urolithiasis were selected and asked for study participation as outpatients. In all 50 patients agreed to the study participation and gave written consent. The patients were diagnosed according to the 3 types of calcium urolithiasis: *So* (first-time stoner without residual stone or fragments), *Sres* (first-time stoner with residual stone or fragments), and *Rmo* (recurrent stone former with mild disease and without residual stone(s) or fragments (36). The study was approved by the local ethics committee.

In a first setting (group 1) 32 adult patients (mean age 36.2 ± 2.8 years) suffering from idiopathic calcium urolithiasis were included and treated with the herbal combination for 2 months in the winter period 2008/2009. The second setting (group 2) includes 18 calcium urolithiasis patients (mean age 36.6 ± 3.3 years), treated for 4 months in the period winter 2009/spring 2010. Each study part included a follow-up investigation 1 month after discontinuation of herbal therapy.

All patients were exclusively treated with Canephron® N at a daily dose of 3 × 50 drops.

Each participant was given verbal and written instructions about study and method of urine collection. Diuresis was determined by patients themselves with diaries on daily urine volume; patients with improper collection of urine were excluded. They also were instructed to remain with their usual diet and to avoid any medical therapy with effects on diuresis. The daily fluid intake of every patient (via diary) was also taken into consideration.

Indices of the rate of crystalluria (CU, as a function of the CaOx molar product and urinary citrate concentration in mmol/l) and ionic activity index of CaOx – Ap(CaOx) were used as criteria for stone formation activity. The Ap[CaOx] index was derived with the formula Ap[CaOx] index = $1.9 \times Ca^{0.84} \times Citr^{-0.22} \times Mg^{-0.12} \times$ urinary volume $^{-1.03}$ (Ca, Mg, Ox, and Citr expressed in µmol/24 h, urinary volume in litre) according to the EAU (35). Further parameters were daily diuresis (ml/24 h), urinary pH and urinary excretion of calcium (Ca; µmol/24 h), magnesium (Mg; mol/l), oxalate (Ox; mg/100 ml) and citrate (Citr; µmol/l).

For the evaluation of tolerability, patients were asked at each follow-up visit for the occurrence of adverse events.

The outcome of all parameters was evaluated by descriptive statistics. Statistical significance was evaluated exploratively on the 5% level compared to baseline; primary and secondary outcome parameters had not been defined before starting the study.

Results

Ap[CaOx]-Index

In group 1 the factor Ap[CaOx] as index for the risk of stone formation was decreased significantly ($p < 0.05$) as compared to the baseline within 4 weeks of therapy and remained decreased after a further month of treatment. It was still decreased one month after therapy discontinuation. During the 4 month therapy (group 2) the index decreased until the 4-month visit, it was still below baseline 1 month after discontinuation (**Fig. 1**).

Rate of crystalluria (CU)

In group 1 there was a remarkable decrease of the rate of crystalluria (function of the

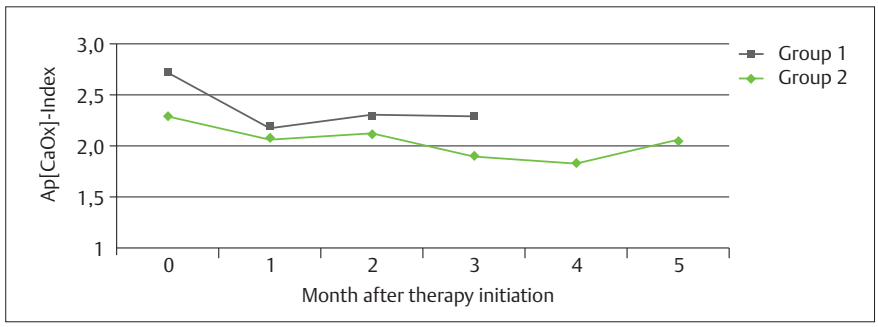

Fig. 1: Risk index AP(CaOx) for stone formation. Group 1: 2 months treatment with Canephron® N and 1 month follow-up; group 2: 4 months treatment and 1 month follow-up.

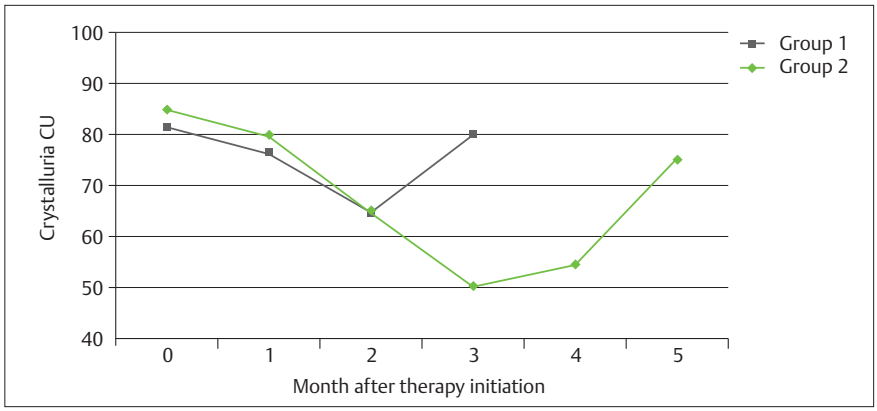

Fig. 2: Effects on rate of crystalluria in group 1 (2 months of therapy) and group 2 (4 months of therapy) and after 1 month of follow-up.

CaOx molar product and urinate citrate concentration in mmol/l): the effect found after 1 month of therapy was further increased after the second month of treatment. At the follow-up visit 1 month after the end of therapy it still was below baseline. In group 2, there was a continuously decrease of CU during the first 3 months followed by a slight increase within the last month of therapy and a strong return nearly to baseline at 1 month of follow-up (**Fig. 2**).

Diuresis

In both groups there was a remarkable increase of diuresis already 1 month after therapy onset, with a drop to baseline (group 1) or in direction of baseline (group 2) after one further month. In group 2, the prolonged treatment again favoured diuresis. After discontinuation of treatment diuresis was reduced in both groups (**Fig. 3**).

Laboratory parameters

In both groups, during herbal therapy the pH shifted to more alkaline values and remained elevated during therapy. After discontinuation of treatment pH dropped to baseline values again (**Fig. 4**).

Tables 1 and **2** list the effects of the herbal therapy on further parameters relevant for urolithiasis. In both groups urinary calcium, oxalate and citrate decreased, whereas magnesium was elevated. A small sustained effect was seen nearly for all of these parameters 1 month after therapy discontinuation. Presumably the small samples are the reason that only some of these parameters at distinct time points were changed significantly.

Tolerability

In both study settings the administration of Canephron® N revealed an excellent tolerability. The patients did not report any therapy-related adverse reactions.

Discussion

Both study parts revealed a remarkable and increasing effect with respect to the Ap[CaOx]- und CU-indices of lithogenesis. After cessation of therapy, the Ap[CaOx]-index remained almost decreased at the follow-up after 1 month. The CU-index was in the baseline range after 1 month of therapy cessation.

The results of both studies revealed a strong effect on diuresis within 1 month of therapy, which is considered to be remarkable, as the therapy was initiated to expel concrements in the urinary tract. In group 1, this enhancement disappeared until the visit after 2 month and dropped below baseline value, while in group 2 diuresis remained elevated with a second peak at the 3-month visit. In this group diuresis remained elevated, even in the month after the end of therapy. The differences of the effects on diuresis between both studies cannot be explained so far.

In healthy individuals on normal diet, urinary pH ranges between 4.6 and 7.5, depending on the amount of ingested animal proteins and vegetables. In patients with calcium oxalate urolithiasis (as enrolled in our study), urine pH should be elevated to prevent the risk of lithogenesis. In both study cohorts, during the use of the herbal medicinal preparation the pH shifted to

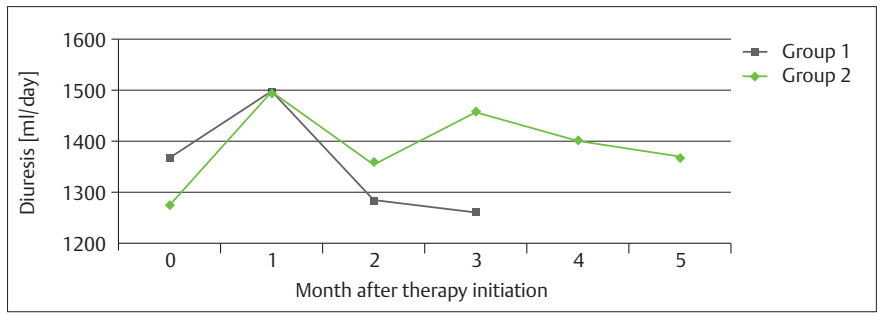

Fig. 3: Effect on diuresis (ml/24 h) in group 1 (2 months of therapy) and group 2 (4 months of therapy), and after 1 month of follow-up.

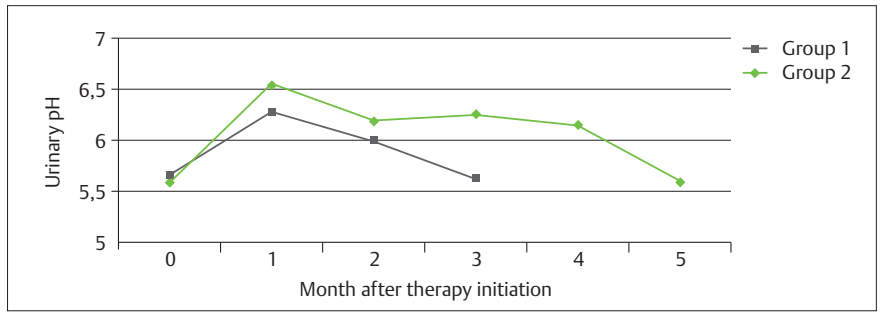

Fig. 4: Effect on pH-value in group 1 (2 months of therapy) and group 2 (4 months of therapy), and 1 month of follow-up.

Table 1: Parameters of urinary function in group 1 (n = 32) during 2 months of therapy and at 1 month of follow-up.

Parameter	Baseline	1 month of therapy	2 months of therapy	1 month after therapy
pH-value	5.64 ± 0.04	6.25 ± 0.03*	5.99 ± 0.03*	5.60 ± 0.03
Calcium [µmol/24 h]	140 ± 2.09	136 ± 3.38	130 ± 3.13*	140 ± 2.87
Oxalate [mg%]	77 ± 1.55	62 ± 2.73*	71 ± 2.12*	66.2 ± 2.42*
Magnesium [mol/l]	58 ± 2.51	69.5 ± 2.31*	71 ± 2.00*	62 ± 2.09
Citrate [µmol/l]	1.80 ± 0.24	1.80 ± 0.02	1.71 ± 0.03	1.74 ± 0.02

*significant at $p < 0.05$ (month of therapy vs. baseline)

more alkaline values significantly as compared to baseline.

Overall, our study confirmed previous results seen in studies conducted in Uzbekistan in patients with urolithiasis (2, 3, 11).

In our studies the excretion of calcium, oxalate and citrate decreased more or less during therapy, and was paralleled by an increase of magnesium excretion. Comparing both studies obviously the extended therapy duration results in a prolonged retaining of salt excretion. Urinary magnesium can prevent urinary stone formation, being at the same time a complex former and an inhibitor of stone formation. In both study parts magnesium excretion was increased and remained on elevated levels even at until the follow-ups.

Regarding the multifactorial pathogenesis of stone formation, the herbal combination Canephron® N seems to be able to effect more than one condition in (calcium) urolithiasis. In comparison to the 2-month treatment, a prolongation of therapy to 4 months showed a reliable further decrease in calciuria and oxaluria. After discontinuation of the 4-month treatment, calcium and oxalate excretion remained lower as compared to baseline as was seen in the 2-month course of therapy.

After end of therapy, diuresis was higher in comparison to baseline in both study groups. Such a prolonged diuretic effect is characteristic for herbal diuretics and has been proposed numerously. To achieve a sustainable increase of diuresis in patients with urolithiasis it might be indicated to conduct therapy in intervals, with some distinct breaks in between. This additional positive effect suggests a repeated therapy after a period of cessation, which might improve the efficacy and definitely reduces therapy costs.

Based on the results of our study, long-term administration of the herbal preparation seems to affect several marked factors promoting stone formation. Such a multifactorial influence might be relevant for the prophylaxis of recurrences of urolithiasis. We therefore recommend an interval therapy with Canephron® N in patients with calcium urolithiasis of all types.

The efficacy of Canephron® N should be evaluated upon prolongated follow-up of the results of metaphylaxis. As uncontrolled studies have limitations, it would be interesting to confirm the results in further studies in order to gain more details about the relevance and meaning of the effects of Canephron® N in patients with lithogenesis. Under the settings and conditions of our study, we consider the study results as very promising.

Conflict of interests

The study was conducted as investigator initiated study without financial support. The study medication was provided by Bionorica SE.

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REFERENCES

1 Abdul-Ghani AS, El-Lati SG, Sacaan AI et al. Anticonvulsant effects of some Arab medicinal plants. Int J Crude Drug Res 1987; 25: 39–43
2 Alyaev YG, Amosov AV, Grigoryan VA et al. A phytogenic drug Kanefron in patients with chronic cystitis and urolithiasis. Urologiia 2005; (4): 29–33
3 Amosov AV, Alyaev YG, Saenko VS. Herbal drug Kanefron H in postoperative metaphylaxis of urolithiasis. Urologiia 2010; (5): 65–71
4 Aqel MB. A vascular smooth muscle relaxant effect of *Rosmarinus officinalis*. Int J Pharmacogn 1992; 30: 281–288

Table 2: Parameters of urinary function in group 2 (n = 18) during 4 months of therapy and at 1 month of follow-up.

Parameter	Baseline	1 month of therapy	2 months of therapy	3 month of therapy	4 month of therapy	1 month after therapy
pH-value	5.58 ± 0.65	6.51 ± 0.08*	6.19 ± 0.05*	6.22 ± 0.08*	6.16 ± 0.06*	5.6 ± 0.05
Calcium [µmol/24 h]	135 ± 3.46	130 ± 3.23	126 ± 2.69*	122 ± 2.89*	123 ± 4.14*	128 ± 3.31
Oxalate [mg%]	67.7 ± 3.34	60.9 ± 2.81	64 ± 3.48	58.9 ± 3.91	56.8 ± 2.22*	61.9 ± 2.37
Magnesium [mol/l]	61.4 ± 3.08	69.1 ± 3.44	67.5 ± 3.35	73 ± 3.55*	70.5 ± 3.22*	63.1 ± 3.70
Citrate [µmol/l]	1.86 ± 0.04	1.78 ± 0.03	1.69 ± 0.03*	1.73 ± 0.02*	1.71 ± 0.02	1.78 ± 0.02

*significant at $p < 0.05$ (month of therapy vs. baseline)

5 Barsom S. Behandlung von Nierenerkrankungen. Canephron® in der urologischen Praxis. Z Allg Med 1979; 55: 997–1000
6 Bauer KM, Nappert H. Klinische Erfahrungen mit Canephron bei der Behandlung von Nierenerkrankungen. Med Welt 1976; 27: 265–268
7 Berger M. Die Bedeutung von Canephron® bei der Behandlung chronischer Harnwegsinfektionen. Therapiewoche 1977; 27: 1739–1742
8 Berkan T, Üstünes L, Lermioglu F, Özer A. Antiinflammatory, analgesic, and antipyretic effects of an aqueous extract of *Erythraea centaurium*. Planta Med 1991; 57: 34–37
9 Bijarnia RK, Kaur T, Singla SK, Tandon C. A novel calcium oxalate crystal growth inhibitory protein from the seeds of *Dolichos biflorus* (L.). Protein J 2009; 28: 161–168
10 Butterweck V, Khan SR. Herbal medicines in the management of urolithiasis: alternative or complementary? Planta Med 2009; 75: 1095–1103
11 Chernenko VV, Savchuk VI, Zheltovska NI, Shtilvaser LM. Peculiarities in correction of urinary pH and hypercristalluria in patients. Men's Health: Ukrainian Scientific Magazine 2003; (2): 68–71
12 Dallera JE, Chandhoke PS. Epidemiology and Incidence of Stone Disease. In: Stoller ML, Meng MV, eds. Current Clinical Urology, Urinary Stone Disease: The Practical Guide to Medical and Surgical Management. Totowa, NJ: Humana Press Inc; 2007: 27–34
13 Feil G, Bichler KH, Lahme S et al. Citrate load test for detection possible disordered citrate metabolism in stone formers. Eurolithiasis. 9th European Symposium on Urolithiasis. Rotterdam, September 14–16, 2001: 1–3
14 Gracza L, Koch H, Löffler E. Isolierung von Rosmarinsäure aus *Symphytum officinale* und ihre anti-inflammmatorische Wirksamkeit in einem In-vitro-Modell. Arch Pharm 1985; 318: 1090–1095
15 Haloui M, Louedec L, Michel JB, Lyoussi B. Experimental diuretic effects of *Rosmarinus offinalis* and *Centaurium erythraea*. J Ethnopharmacol 2000; 71: 465–472
16 Horiuchi K, Shiota S, Kuroda T et al. Potentiation of antimicrobial activity of aminoglycosides by carnosol from *Salvia officinalis*. Biol Pharm Bull 2007; 30: 287–290
17 Khaskhali MH, Byer KJ, Khan SR. The effect of calcium on calcium oxalate monohydrate crystal-induced renal epithelial injury. Urol Res 2009; 37: 1–6
18 Klancnik A, Guzej B, Kolar MH et al. In vitro antimicrobial and antioxidant activity of commercial rosemary extract formulations. J Food Protect 2009; 72: 1744–1752
19 Konstantinova OV. Estimation the efficiency of medicamentous methods of metaphylaxis on urolithiasis metabolic risk factors [Masters (PhD) thesis]. 2nd Moscow Medical Institute; 1990
20 Kopp H. Zur Behandlung von Nierenerkrankungen mit Canephron. Physikal Med Rehab 1975; 16: 78–80
21 Kumarasamy Y, Nahar L, Cox PJ et al. Bioactivity of secoiridoid glycosides from *Centaurium erythraea*. Phytomedicine 2003; 10: 344–347
22 Kumarasamy Y, Nahar L, Sarker SD. Bioactivity of gentiopicroside from the aerial parts of *Centaurium erythraea*. Fitoterapia 2003; 74: 151–154
23 Mounchid K, Bourjilat F, Dersi N et al. The susceptibility of *Escherichia coli* strains to essential oils of *Rosmarinus officinalis* and *Eucalyptus globulus*. African J Biotechnol 2005; 4: 1175–1176
24 Ochmański W, Kmiecik J, Sułowicz W. Analysis of chemical composition of urinary stones. Int Urol Nephrol 1999; 31: 743–750
25 Pessler G, Wagner W. Die Behandlung akuter und chronischer Harnwegsinfektionen mit einem Phytopharmakon. Therapiewoche 1979; 29: 2406–2410
26 Rampart M, Beetens JR, Bult H et al. Complement-dependent stimulation of prostacyclin biosynthesis: inhibition by rosmarinic acid. Biochem Pharmacol 1986; 35: 1397–1400
27 Sallis JD, Parry NF, Meehan JD et al. Controlling influence of phosphocitrate in vitro and in vivo on calcium oxalate crystal formation and growth. Scanning Microscopy 1995; 9: 127–136
28 Schleicher K, Schleicher B. Klinische Erfahrungen mit Canephron® in der Frauenheilkunde, insbesondere während der Schwangerschaft. Therapiewoche 1977; 27: 9411–9413
29 Schwille PO. A Survey of calcium urolithiasis in normocalcemic hypercalciuria: Possible role of nutrients and diet-mediated factors. Urol Res 1979; 7: 149–155
30 Spirnak JP. Renal Calculi. In: Resnik MI, Novick AC, eds. Urology Secrets. 2nd ed. Philadelphia: Hanley & Belfus; 1999: 271–291
31 Sterner W, Heisler E, Popp HO, Fischer H. Studien über die Canephron-Wirkung bei chronischen Nierenerkrankungen. Physikal Med Rehab 1973; 14: 239–258
32 Stoller ML, Boulton DM. Urinary Stone Disease. In: Tanago EA, McAninch JW, eds. Smith's General Urology. 15th ed. New York: Lange Medical Books/McGraw-Hill; 2000: 291–320
33 Straub M, Strohmaier WL, Berg W et al. Diagnosis and metaphylaxis of stone disease. Consensus concept of the National Working Committee on Stone Disease for the upcoming German Urolithiasis Guideline. World J Urol 2005; 23: 309–323
34 Strohmaier WL. Volkswirtschaftliche Aspekte des Harnsteinleidens und der Harnsteinmetaphylaxe. Urologe A 2000; 39: 166–170
35 Tiselius HG, Ackermann D, Alken P et al. EAU Guidelines on urolithiasis. European Association of Urology 2005: 1–50; http://www.uroweb.org/guidelines/
36 Tiselius HG, Alken P, Buck C et al. EAU Guidelines on urolithiasis. European Association of Urology 2009: 1–116; http://www.uroweb.org/guidelines/
37 Tiselius HG. Epidemiology and medical management of stone disease. BJU Int 2003; 91: 758–967
38 Trinchieri A. Epidemiological trends in urolithiasis: impact on our health care systems. Urol Res 2006; 34: 151–156
39 Türk, C, Knoll T, Petrik A et al. EAU Guidelines on urolithiasis. European Association of Urology 2011: 1–104; http://www.uroweb.org/guidelines/

For references 40–45 see online version at www.thieme-connect.de/ejournals.

ZUSAMMENFASSUNG

Wirkungen des pflanzlichen Kombinationsarzneimittels Canephron® N auf Risikofaktoren der idiopathischen Kalziumurolithiasis in einer offenen Studie

Ziel der Studie war es, die Wirkungen von Canephron® N auf Risikofaktoren der Steinbildung zu untersuchen. Das bewährte Präparat enthält Auszüge aus Centaurii herba, Levistici radix und Rosmarini folium. Patienten mit umkomplizierter Kalziumurolithiasis wurden über 2 (n = 32) bzw. 4 Monate (n = 18) mit Canephron® N behandelt. Es resultierte ein nahezu kontinuierlicher Rückgang der Marker im Harn für die Steinbildung wie das Aktivitätsprodukt Ap[CaOx] und die Rate der Kristallurie; parallel nahmen Diurese und pH-Wert des Harns zu. Diese Parameter waren nach der 4-monatigen Therapie stärker verbessert als nach der 2-monatigen. Unerwünschte Wirkungen wurden nicht beobachtet. Wir bewerten das pflanzliche Kombinationsarzneimittel als vielversprechenden Wirkstoff für Patienten mit Risikofaktoren der idiopathischen Kalziumurolithiasis. Die Ergebnisse rechtfertigen weitere klinische Forschung.

SCHLÜSSELWÖRTER

Kalzium, Urolithiasis, Canephron® N, pflanzliches Arzneimittel, Risikofaktoren, offene Studie