ORIGINAL PAPERS

Adv Clin Exp Med 2007, **16**, 6, 777–784
ISSN 1230-025X

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The Efficacy of Chronic Therapy of Recurrent Lower Urinary Tract Infections with Fosfomycin and Nitrofurantoin in Type 2 Diabetic Patients

Skuteczność przewlekłej terapii nawracających zakażeń dolnych dróg moczowych za pomocą fosfomycyny i nitrofurantoiny u chorych na cukrzycę typu 2

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Abstract

Background. Recurrent lower urinary tract infections (RUTIs) are one of the most frequent and arduous complications of diabetes. The aim of this study was to evaluate the efficacy of fosfomycin and nitrofurantoin in the treatment of RUTIs in type 2 diabetic women.
Material and Methods. The study comprised 100 post-menopausal type 2 diabetic women. All patients suffered from RUTIs and presented clinical signs of this disease and positive urine cultures (isolated bacterial uropathogen sensitive to fosfomycin and nitrofurantoin). The women were divided into two groups of similar size. Group 1 patients received fosfomycin every 30 days for 12 months and group 2 patients received nitrofurantoin every 12 hours before meals for 7 days and then every evening for 12 months. The patients remained under regular medical supervision in a diabetic outpatient clinic for the 12 months. Therapeutic success was established when both clinical cure and bacteriological eradication of the uropathogens were achieved at specified time points (3, 6, and 12 months) from the study begin.
Results. The percentage of patients effectively treated did not differ significantly at 3, 6, and 12 months between the studied groups ($p > 0.05$). Signs of urinary tract infection were absent in 89% and 91% after 3 months, 90% and 92% after 6 months, and 88% and 88% of patient groups after 12 months of the study duration 1 and 2, respectively.
Conclusions. Fosfomycin and nitrofurantoin are effective drugs for the treatment of recurrent uncomplicated lower urinary tract infections in type 2 diabetic patients (**Adv Clin Exp Med 2007, 16, 6, 777–784**).

Key words: fosfomycin, nitrofurantoin, diabetes mellitus, lower urinary tract infections.

Streszczenie

Wprowadzenie. Chorzy na cukrzycę typu 2 są często narażeni na występowanie nawracających zakażeń dolnych dróg moczowych (NIDDM).
Cel pracy. Porównanie skuteczności przewlekłej terapii fosfomycyną i nitrofurantoiną w leczeniu NIDDM u kobiet chorujących na cukrzycę typu 2.
Materiał i metody. Obserwacją objęto 100 kobiet w okresie postmenopauzalnym z objawami dyzurycznymi wskazującymi na NIDDM, u których wyhodowano w badaniu bakteriologicznym moczu patogen wrażliwy na badane leki. Chore podzielono na dwie grupy. Grupę 1 stanowiły chore leczone fosfomycyną, a grupę 2 – nitrofurantoiną. Czas obserwacji badanych chorych wynosił 12 miesięcy. Skuteczność leczenia przeciwbakteryjnego określano wówczas, gdy stwierdzono całkowite ustąpienie objawów dyzurycznych i eradykację uropatogenu w kontrolnych badaniach bakteriologicznych moczu.
Wyniki. Odsetek chorych bez zakażeń dróg moczowych po 3, 6 i 12 miesiącach leczenia nie różnił badanych grup (NS). Objawów klinicznych NIDDM po 3 miesiącach stosowania chemioterapeutyków nie obserwowano u 89%

kobiet w grupie leczonej fosfomycyną i 91% w grupie leczonej nitrofurantoiną. NIDDM po 6 miesiącach badania nie stwierdzono u 90% kobiet w grupie 1 i 92% w grupie 2. Objawy kliniczne NIDDM po 12 miesiącach przyjmowania badanych leków nie występowały u 88% kobiet w grupie leczonej fosfomycyną i 88% w grupie leczonej nitrofurantoiną.

Wnioski. Nitrofurantoina i fosfomycyna są skutecznymi chemioterapeutykami w leczeniu nawracających NIDDM u kobiet chorujących na cukrzycę typu 2 (**Adv Clin Exp Med 2007, 16, 6, 777–784**).

Słowa kluczowe: fosfomycyna, nitrofurantoina, cukrzyca typu 2, zapalenie dolnych dróg moczowych.

Urinary tract infections are one of the most common bacterial diseases in humans. They are a major medical problem for outpatients, particularly women, result in frequent office visits, and often require the use of antimicrobial prophylaxis. [1–3]. In diabetic patients, recurrent lower urinary tract infections (RUTIs) are one of the most frequent and arduous complications of this disease. Patients with diabetes mellitus (DM) have asymptomatic bacteriuria (ASB), symptomatic urinary tract infections more often than patients without DM. It is well known that decisions concerning therapeutic strategy in RUTIs should be made on the basis of urine examination as well as the results of clinical examination and ultrasound procedures [4, 5]. Certain recommendations suggest that UTIs in diabetic patients should be treated in the same way as complicated UTIs in non-diabetic subjects [6]. In diabetic pregnant women with recurrent uncomplicated UTIs, antimicrobial prophylaxis is recommended [7]. However, it is still unknown how best to cure and prevent recurrences of UTIs in other diabetic subjects. The agents most commonly used in the treatment of urinary tract infections include nitrofurantoin (NF) and other nitrofuran derivatives, ciprofloxacin, norfloxacin, ofloxacin, ampicillin, cotrimoxazole, and fosfomycin trometamol (FT) [8, 9].

Nitrofurantoin (NF) has bacteriostatic and bacteriocidal activity against Gram-positive and Gram-negative bacteria such as *Escherichia coli*, *Klebsiella* spp., and *Staphylococcus aureus*. NF rarely leads to adverse effects such as nausea, vomiting, diarrhea, allergy, increased activity of serum aminotransferases, and symptoms of peripheral polyneuropathy [10–12]. Fosfomycin trometamol (FT) is an inhibitor of enolpyruvate transferase which exerts its bactericidal action by inhibiting the pathogen's cell-wall synthesis. FT demonstrates anti-adhesive effects which prevent the bacteria from adhering to the walls of the urinary tract. It has a broad spectrum of activity that includes *Escherichia coli*, *Citrobacter* spp., *Klebsiella* spp., *Proteus* spp., *Staphylococcus* spp., *Salmonella* spp., *Streptococcus faecalis*, *Pseudomonas aeruginosa*, and *Serratia spp*. Adverse reactions to FT are rare and develop in 1–8% of all patients, the most common being diarrhea, nausea, vomiting, skin rash, heartburn, vaginitis, headache, chills, and asthenia [13–17].

The aim of this study was to evaluate the efficacy and safety of fosfomycin trometamol and nitrofurantoin in the treatment of recurrent uncomplicated lower urinary tract infections in type 2 diabetic women.

Material and Methods

The study comprised 100 post-menopausal type 2 diabetic women under medical supervision at the outpatient clinic of the Department of Diabetology of the Medical University of Łódź. All the patients suffered from recurrent uncomplicated bacterial lower urinary tract infections.

The inclusion criteria were postmenopausal female, 50–70 years of age, with type 2 diabetes mellitus for at least five years without chronic diabetic complications. All the patients suffered (having had at least four UTIs episodes last 18 months, the last one 3–6 months previously) and presented clinical signs of UTIs and a positive urine culture (an isolated bacterial uropathogen sensitive to fosfomycin and nitrofurantoin). No treatment with antimicrobial agents was underway nor any pathologies of the kidney and urinary tract morphology were found earlier by abdominal ultrasonography. Exclusion criteria were asymptomatic bacteriuria and pyelonephritis, renal diseases (creatinine > 1.5 mg/dl), hepatic disorders (increased serum alanine (ALT) and aspartate (AST) aminotransferase levels twice the reference range or total serum bilirubin > 1.3 mg/dl), diseases connected with damage to the hematopoietic system, any allergies to medication and alcoholism.

At the beginning of the study, the following laboratory measurements were made: fasting serum glucose, $HbA_{1c,}$ electrolytes, kidney function tests (urea, creatinine), ALT, AST, bilirubin, and urinalysis. When urinary tract infection was determined on the grounds of medical history (dysuria) and urinalysis (leukocyturia/pyuria, proteinuria, and/or bacteriuria), then a bacteriological urine culture was made. If there was significant bacteriuria (> 10^5 CFU/ml) in the finding of the bacteriological culture and the pathogen was sensitive to fosfomycin and nitrofurantoin, the patient had abdominal ultrasonography and, if there were no pathologies, they were enrolled into the study.

All the patients had a physical examination, including gynaecological consultation.

The women were divided into two groups of similar size. Group 1 comprised patients who were to receive fosfomycin (Monural, granulated mass, Zambon, Italy). The fosfomycin was applied orally after dissolution in a boiled water glass at 10 p.m. at least 2 hours after the last meal and after emptying the bladder. Fosfomycin was given every 30 days for the next 12 months. Group 2 comprised patients who were to receive nitrofurantoin (Nifuratio retard, tablet, 0.1 g, Ratiopharm, Germany). The nitrofurantoin was applied orally at 0.1 g every 12 hours before meals for 7 days and then 0.1 g. every evening for the next 12 months. The characteristics of the subjects are shown in Table 1.

No fungi were cultured in the urine. Only one bacterial strain was isolated in each patient's urine sample. The isolated bacterial strain before the study and after 12 months are shown in Tables 2 and 3.

The general study design was identical in the two groups. The patients remained under regular medical supervision in the diabetic outpatient clinic for the 12 months of the study. For one year the patients were treated with the antimicrobial agents. Throughout this time the patients had clinic visits every three months, during which routine laboratory tests, including fasting serum glucose, kidney and liver function tests, urinalysis, and bacteriological urine culture were monitored. The biochemical parameters of the studied groups before the study and after 12 months are shown in Tables 4 and 5.

Therapeutic success (efficacy of treatment) was established when both clinical cure and bacteriological eradication of the uropathogens were achieved at specified time points (3, 6, and 12 months) from the beginning of the study. Safety and tolerability of the drugs were assessed with clinical evaluations which included a regular physical examination and laboratory assessment. Adverse effects were monitored throughout the study to stop the therapy in the event any serious side effect developed. Patients with manifestations of urinary tract infection (dysuric symptoms and the presence of a pathogen in the urine culture) were excluded from the study. All the patients were informed of the aim and methodology of the study and gave their voluntary written consent. The study was approved by the Ethics Committee for Research at the Medical University of Łódź and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

The results were analyzed according to well-known statistical methods using StatSoft Statistica for Windows, release 6.0 (StatSoft, Inc., Tulsa, USA). To determine differences between and within the groups, the two-sided test for propor-

Table 1. Characteristics of subjects

Tabela 1. Charakterystyka badanych grup

	Group 1 (Grupa 1)	Group 2 (Grupa 2)	*p*
Number of subjects (Liczba chorych)	50	50	NS
Mean age* – years (Średni wiek* – lata)	60.1 ± 7.2	61.2 ± 8.1	NS
Duration of diabetes mellitus* – years (Czas trwania cukrzycy* – lata)	8.7 ± 4.2	8.1 ± 3.8	NS
BMI* – kg/m^2	27.4 ± 1.8	28.1 ± 2.2	NS
HBA_{1c} value* (Wartość HBA_{1c}*) %	6.4 ± 1.2	6.2 ± 1.0	NS
Mean fasting glycemia* – mmol/l (Średnie stężenie glukozy na czczo* – mmol/l)	7.1 ± 2.1	7.3 ± 1.9	NS
Number of patients with clinical symptoms of dysuria (Liczba chorych z objawami dyzurycznymi)	50	50	NS
Number of patients with: – significant bacteriuria (> 10^5 CFU/ml) – proteinuria – leukocyturia or pyuria – in urinalysis at the study beginning (Liczba chorych ze zmienną bakteriurią – > 10^5 CFU/ml)	 50 46 50	 50 44 50	NS

* x ± SD

Table 2. Type and number of isolated bacterial strains in urine in group treated with fosfomycin

Tabela 2. Rodzaj i liczba wyhodowanych w moczu szczepów bakterii w grupie chorych leczonych fosfomycyną

Type of isolated bacterial strains (Rodzaj wyhodowanego szczepu bakterii)	Number of subjects in group 1, n = 50, in which one selected bacterial strain type was isolated – before the study (Liczba chorych w grupie 1, n = 50, u których wyhodowano dany szczep bakterii – przed rozpoczęciem badania)	Number of subjects in group 1, n = 21, in which one selected bacterial strain type was isolated – after one year (Liczba chorych w grupie 1, n = 21, u których wyhodowano dany szczep bakterii – po roku badania)
Escherichia coli	39	17
Enterobacter spp.	3	1
Enterococcus spp.	6	3
Staphylococcus spp.	2	0

Table 3. Type and number of isolated bacterial strains in the group treated with nitrofurantoin

Tabela 3. Rodzaj i liczba wyhodowanych szczepów bakterii w moczu w grupie chorych leczonych nitrofuratoiną

Type of isolated bacterial strains (Rodzaj wyhodowanego szczepu bakterii)	Number of subjects in group 1, n = 50, in which one selected bacterial strain type was isolated – before the study (Liczba chorych w grupie 1, n = 50, u których wyhodowano dany szczep bakterii – przed rozpoczęciem badania)	Number of subjects in group 1, n = 20, in whom one selected bacterial strain type was isolated after one year (Liczba chorych w grupie 1, n = 20, u których wyhodowano dany szczep bakterii – po roku badania)
Escherichia coli	38	15
Enterobacter spp.	4	2
Enterococcus spp.	3	1
Staphylococcus spp.	5	2

Table 4. Biochemical parameters in the group treated with fosfomycin before and after 12 months of the study duration. Values are x ± SD

Tabela 4. Biochemiczne parametry w grupie chorych leczonych fosfomycyną przed i po 12 miesiącach. Wartości podano jako x ± SD

	Before the study (Przed badaniem)	After one year (Po roku)	*p*
Na^+ – mmol/l	139.8 ± 7.2	136.7 ± 9.1	NS
K^+ – mmol/l	4.23 ± 0.72	4.37 ± 0.69	NS
Creatinine (Kreatynina) µmol/l	94.0 ± 21.8	98.8 ± 19.6	NS
Urea (Mocznik) mmol/l	6.2 ± 2.8	5.8 ± 3.6	NS
Alanine aminotransferase (Aminotransferaza alaninowa) U/l	33.4 ± 9.2	36.2 ± 8.8	NS
Aspartate aminotransferase Aminotransferaza asparaginowa U/l	31.7 ± 8.1	26.2 ± 9.7	NS
Total bilirubin (Bilirubina całkowita) µmol/l	12.6 ± 5.5	14.1 ± 6.0	NS

tions was used. The differences were considered significant if $p < 0.05$.

Results

Forty-seven patients treated with FT and 46 with NF attended the first follow-up visit after three months of antibacterial treatment (3 patients in group 1 and 4 in group 2 did not attend this follow-up visit). The percentage of patients effectively treated for three months did not differ significantly between the two groups ($p > 0.05$): signs of urinary tract infection were absent in 89% (n = 42) and 91% (n = 42) of the patients in groups 1 and 2, respectively (Fig. 1).

The second follow-up visit, after six months of antibacterial treatment, was attended by 41 patients

Table 5. Biochemical parameters in the group treated with nitrofurantoin before and after 12 months of the study duration. Values are x ± SD

Tabela 5. Bichemiczne parametry w grupie chorych leczonych nitrofurantoiną przed i po 12 miesiącach badania. Wartości podano jako x ± SD

	Before the study (Przed badaniem)	After one year (Po roku)	*p*
Na^+ – mmol/l	135.2 ± 8.1	134.9 ± 5.8	NS
K^+ – mmol/l	4.35 ± 0.69	4.39 ± 0.73	NS
Creatinine (Kreatynina) µmol/l	97.0 ± 25.2	93.9 ± 21.9	NS
Urea (Mocznik) mmol/l	6.0 ± 3.1	5.4 ± 3.4	NS
Alanine aminotransferase (Aminotransferaza alaninowa) U/l	32.4 ± 8.5	33.9 ± 8.7	NS
Aspartate aminotransferase (Aminotransferaza asparaginowa) U/l	36.0 ± 6.9	29.8 ± 8.6	NS
Total bilirubin (Bilirubina całkowita) µmol/l	13.5 ± 6.4	13.9 ± 6.7	NS

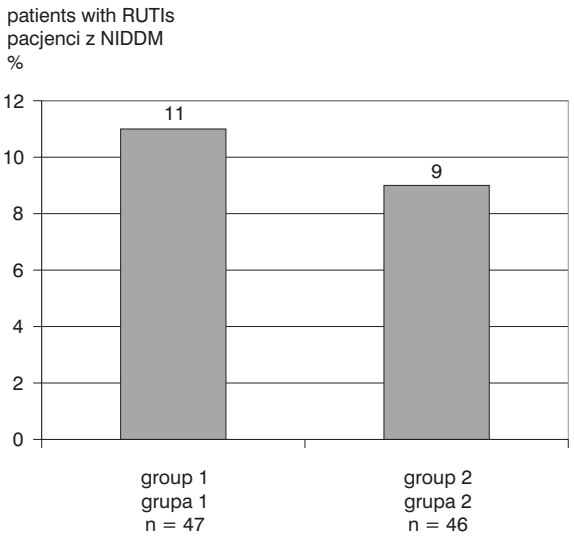

Fig. 1. Percentage of patients with recurrent lower urinary tract infections in the studied groups after 3 months of antibacterial treatment

Ryc. 1. Odsetek chorych w badanych grupach z nawrotem zakażenia dolnych dróg moczowych po 3 miesiącach przeciwbakteryjnego leczenia

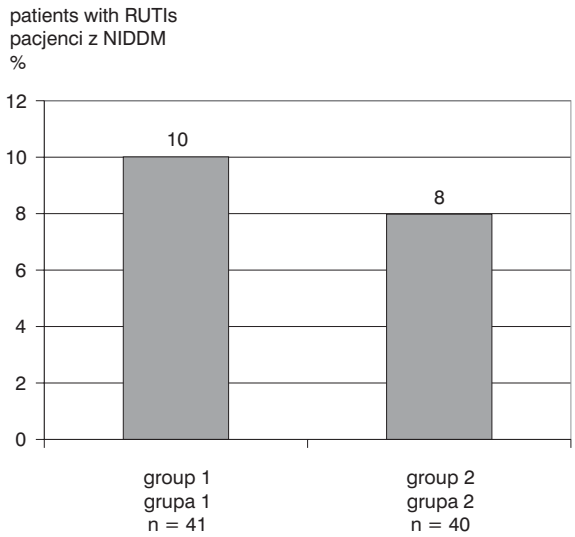

Fig. 2. Percentage of patients with recurrent lower urinary tract infections in the studied groups after 6 months of antibacterial treatment

Ryc. 2. Odsetek chorych w badanych grupach z nawrotem zakażenia dolnych dróg moczowych po 6 miesiącach przeciwbakteryjnego leczenia

managed with FT (5 had been excluded at the previous visit due to the diagnosis of recurrent UTI and 1 patient did not attend this follow-up visit) and 40 patients managed with NF (4 patients had been excluded due to the presence of signs of urinary tract infection confirmed at the previous visit and 2 did not attend this follow-up visit). The percentage of patients effectively treated for six months did not differ significantly between the two groups ($p > 0.05$); signs of urinary tract infection were absent in 90% (n = 37) and 92% (n = 37) of the patients in groups 1 and 2, respectively (Fig. 2).

The third follow-up visit, after 12 months of antibacterial treatment, was attended by 33 patients managed with FT (4 patients had been excluded at the previous visit due to the diagnosis of recurrent UTI and 4 did not attend this follow-up visit) and 34 patients managed with NF (3 patients had been

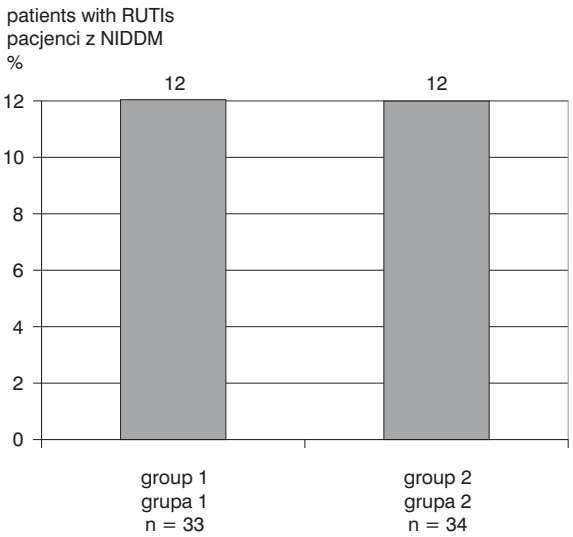

Fig. 3. Percentage of patients with recurrent lower urinary tract infections in the studied groups after 12 months of antibacterial treatment

Ryc. 3. Odsetek chorych w badanych grupach z nawrotem zakażenia dolnych dróg moczowych po 12 miesiącach przeciwbakteryjnego leczenia

excluded due to the presence of signs of urinary tract infection confirmed at the previous visit and 3 did not attend this follow-up visit). The percentage of patients effectively treated for twelve months did not differ significantly between the two groups ($p > 0.05$); signs of urinary tract infection were absent in 88% (n = 29) and 88% (n = 30) of the patients in groups 1 and 3, respectively (Fig. 3).

Reinfection was observed in 31% of the patients of group 1 (n = 13 subjects) during the study. Eight patients in this group did not attend visits. Reinfection was observed in 27% of patients of group 2 (n = 11 subjects) within one year. Nine did not attend the control visits.

All of the subjects in this study were included in the assessment of the safety and tolerability of the drug. No clinically significant changes in physical examination and laboratory tests were recorded. Mild headache was found in three patients treated with nitrofurantoin and in four treated with fosfomycin, nausea in one patient treated with nitrofurantoin, and mild epigastric pain in two patients treated with nitrofurantoin and three patients treated with fosfomycin. These mild undesirable experiences were most likely related to treatment, but were transient and retreated spontaneously.

Discussion

An increased prevalence of bacteriuria in diabetic patients can be the result of differences between the host responses in diabetic and non-diabetic patients. In type 1 DM the main risk factors for RUTIs include the duration of diabetes, peripheral neuropathy, and sexual intercourse. In type 2 DM, risk factors for RUTIs include advanced age of the subjects and asymptomatic bacteriuria (ASB). Poorly controlled diabetes mellitus and residual urine after urination are not supposed risk factors for ASB and RUTIs. This higher prevalence of RUTIs in patients with DM does not appear to be based on a difference in virulence.

Treatment based on the commonly used antibiotics or chemobiotics is usually connected with non-compliance and different side effects of the agents. These are the main reasons why the recurrence of urinary tract infections, mainly in diabetic subjects, remains an important medical problem. Clinical trials demonstrated that in patients with acute uncomplicated lower urinary tract infection, a single-dose fosfomycin trometamol therapy was effective and its efficacy was comparable to that of several other common antibacterial agents, e.g. β-lactams and fluoroquinolones, co-trimoxazole (trimethoprim + sulfamethoxazole), nitrofurantoin, and pipemidic acid [14].

Recently, a growing rate of resistance among common urinary tract pathogens such as *E. coli* to traditional antimicrobial therapies, including the gold standard, co-trimoxazole, has been demonstrated. Fluoroquinolone antimicrobial agents have thus taken on an expanding role in the management of RUTIs. They have demonstrated high bacteriologic and clinical cure rates as well as low rates of resistance among the most common uropathogens [18]. However, the treatment modality in diabetic patients with recurrent urinary tract infection remains unclear. There are different opinions on the problem of long-term treatment of RUTIs and the risk of its side effects. Elder [19] suggested that long-term therapy is indicated for women with complicated, prolonged, or recurrent UTIs. On the basis of these findings, the high clinical efficacy and safety of fosfomycin is worth emphasizing, indicating that it can be successfully applied in diabetic patients.

A high efficacy of a single dose of fosfomycin in the treatment of acute RUTIs has been reported [15–17]. Kremery et al. [7] compared a single dose of 3 g of fosfomycin with a three-day course of 400 mg of ceftibuten given orally in pregnant women suffering from acute symptomatic lower RUTIs. They showed that therapeutic success was achieved in 95.2% of the patients treated with fosfomycin trometamol versus 90.0% of those treated with ceftibuten (p was non-significant). There are also promising data on the application of fosfomycin in patients in the perioperative period (the

first dose given before and the second 24 hours after an operation) [20].

The efficacy and safety of chronic antimicrobial therapy in the treatment and prevention of uncomplicated lower RUTIs in patients with diabetes mellitus have not been studied so far. To the knowledge of the present authors, there have been no studies related to the efficacy of long-term fosfomycin application in the treatment and prevention of uncomplicated lower RUTIs, also in diabetic patients.

The present authors have observed that during both full and reduced-dose therapy, the efficacy of nitrofurantoin and fosfomycin seems comparable. There was no significant differences in the efficacy of these drugs during the treatment. It is therefore suggested that these drugs are similarly effective in the treatment of uncomplicated lower RUTIs during regular treatment.

On the grounds of this study, it can be concluded that the treatment of lower RUTIs in patients with DM should be systematic, always based on the application of antibiotics according to the results of an antibiogram. The aim of the treatment is not only to exclude the clinical signs of RUTIs, but mainly to eradicate the uropathogens. It is suggested that fosfomycin and nitrofurantoin should be applied not only in acute, but also in recurrent infections. Based on these results it is believed that treatment with these agents in type 2 diabetics with recurrent lower urinary tract infections can be continued for several months. Such therapy is associated with beneficial therapeutic effects and does not involve the risk of adverse reactions.

The authors conclude that fosfomycin and nitrofurantoin are safe and effective drugs in the treatment of recurrent uncomplicated lower urinary tract infections in type 2 diabetic patients.

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Conflict of interest: None declared

Received: 24.09.2007
Revised: 11.10.2007
Accepted: 28.11.2007