iMedPub Journals
Our Site: http://www.imedpub.com/

THE INTERNATIONAL ARABIC JOURNAL OF ANTIMICROBIAL AGENTS

2012
Vol. 2 No. 1:3
doi: 10.3823/707

Fosfomycin Trometamol in Patients with Renal Insufficiency and in the Elderly

Kurt G. Naber[1], Petra Thomas[2], Reinhard Fünfstück[3]

1 Prof. Kurt G. Naber, MD. PhD Karl-Bicklederstr. 44c D-94315 Straubing, Germany Tel +49-9421-33369
E-mail: kurt@nabers.de

2 Petra Thomas
Head of Medical Service
PIERRE FABRE PHARMA GmbH
Jechinger Strasse 13 D-79111 Freiburg, Germany
E-Mail: petra.thomas@pierre-fabre.de

3 Prof. Reinhard Fünfstück, MD, PhD Department of Internal Medicine I Sophien- and Hufeland-Hospital POBox 2017 D-99401 Weimar, Germany

Correspondence:
r.fuenfstueck@klinikum-weimar.de
Phone: +49-3643-57.1100 (Sekretariat)

Abstract

Single oral dose therapy with fosfomycin trometamol (FT) 3 g is recommended in the treatment of uncomplicated urinary tract infection (UTI) not only in premenopausal, but also in postmenopausal elderly, otherwise healthy women. It can also be used as reapplication every 10 days for prophylaxis of recurrent uncomplicated cystitis. FT 3 g has also been used with two oral doses of 3 g (on two consecutive days) for perioperative prophylaxis in transurethral interventions or with three doses (every other day, three times) for treatment of complicated lower UTI including many elderly patients. The tolerance and safety in the patients above 65 years of age did not differ from younger ones. Therefore, there is also an indication to administer oral FT 3g in adults above 65 years of age for treatment or prophylaxis of uncomplicated UTI.

Patients with renal insufficiency up to a creatinine clearance of 20 ml/min can be expected to have still sufficiently high urinary concentrations of fosfomycin, that treatment of cystitis should be justified from pharmacokinetic/pharmacodynamic point of view. From preliminary clinical results there is also an indication to use oral FT 3 g in adults with renal insufficiency up to a creatinine clearance of 20 ml/min, with single dose for treatment of lower uncomplicated UTI with otherwise normal urinary tract or with repeated doses (every second or third day according to the degree of renal insufficiency) for treatment of lower complicated UTI caused by fosfomycin susceptible pathogens resistant to other oral antimicrobial drugs.

Introduction

In recent international and national guidelines the single oral therapy with fosfomycin trometamol (FT) is recommended as one of the first line empiric therapy of uncomplicated cystitis in women (1-3). Although this kind of short term therapy is well established in otherwise healthy premenopausal women (4-6), sometimes questions arise whether FT could also be used for the treatment of uncomplicated cystitis in elderly women, for prophylaxis of recurrent cystitis and prevention of postsurgical infections after urological interventions and probably with modified dosages also for the treatment of more complicated lower urinary tract infection (UTI) in male and female patients with and without reduced renal function.

The interest in the antibiotic therapy with FT was constantly raised, because there are only very few oral antimicrobials available which can be used empirically for the treatment

and prophylaxis of lower UTI in areas with a high incidence of ESBL-producing, fluoroquinolone and/or cotrimoxazole resistant uropathogens (7-8).

Aim of the review

The aim of this review is to investigate whether the single dose therapy of FT is also justified in elderly patients with and without reduced renal function, its use for prophylaxis of recurrent cystitis and postsurgical infections after urological interventions and whether FT could also be used for more complicated lower UTI in male and female patients.

Three main questions have to be considered concerning usage of FT in renal insufficiency and in the elderly:

1. What is the role of possible drug accumulation in patients with renal insufficiency after single dose therapy of 3 g FT in regard to adverse events?
2. Are urinary concentrations in patients with renal insufficiency still sufficiently high enough that single dose therapy of 3 g FT is justified for treatment of acute uncomplicated urinary tract infections in women with renal insufficiency?
3. What is the indication and clinical experience in patients with renal insufficiency with single dose therapy of 3 g FT?
4. Is there a role of multiple oral doses of FT for the treatment of male and female patients with more complicated cystitis due to fosfomycin susceptible uropathogens, which are resistant against other oral antimicrobial substances?

Methods

Literature search was performed in Medline and other sources concerning pharmacokinetics, pharmacodynamics and clinical studies with FT in younger and older adult subjects with normal and impaired renal function.

Results

Fosfomycin compounds

According to Della Bella & Ferrari (9) fosfomycin is a natural compound with a small molecular size (MW 138.06), presence of a carbon-phosphorus bond, and asymmetric carbon atom adjacent to an epoxide bridge. After stereo-specific binding to the target macromolecule, the oxygen bonds open into a reactive intermediate that irreversibly alkylates the nucleophilic active site of the bacterial membrane enzyme responsible for transforming N-acetyl-glucosamine into N-acetyl-muramic acid (Kahan et al. (10). The synthesis of the acetyl-muramyl pentapeptide "Park nucleotide" – the building block for the peptidoglycan polymer – is thus prevented.

Fosfomycin, a strong phosphoric acid, is quite unstable. Therefore, it only can be administered in the form of some sort of salts. Fosfomycin sodium (FS) is used for parenteral administration. Fosfomycin calcium (FC) - used e.g. in Japan also for oral administration - is characterized by a fairly low water solubility and therefore poor bioavailability.

Of several diverse organic cations fosfomycin trometamol (FT) was proved preferable for oral therapy and is registered as "Monuril 3000" (Zambon/Pierre Fabre Pharma) corresponding to 3.0 g fosfomycin and 2.631 g trometamol (total 5.631g). FT is better water soluble, chemically stable at physiological pH and has much better oral bioavailability than FC and thus higher serum and urinary concentrations after oral administration of the same dose (11).

Pharmacokinetics of fosfomycin and trometamol in healthy subjects

After oral administration of 1.8 g of FT (equivalent to 1 g of acid fosfomycin) in 6 healthy subject two hours after oral administration the mean peak serum concentration of fosfomycin was 11.22 mg/l and that of trometamol 10.83 mg/l and 12 hours after oral administration 1.68 mg/l and 1.33 mg/l, respectively. Thus, the serum concentrations and serum half lives of the two moieties, fosfomycin and trometamol, are very similar (Lodola and Longo, personal communication, 1986, cited according to Della Bella & Ferrari (9). Since the two substances also have a similar molecular size (138.06 and 121.14, respectively), the authors concluded that the two moieties may move across the intestinal barrier by the same kinetics. Whether this occurs in the form of the whole molecule or after dissociation is an open question. Unfortunately trometamol concentrations were only measured in healthy subjects and not in patients with renal impairment.

Absorption, pharmacokinetics and urinary antibacterial activity of FT as compared to FS and FC

Bergan (11) compared the absorption, pharmacokinetics and the urinary antibacterial activity of fosfomycin after i.v. administration of fosfomycin sodium (FS) (50 mg/kg BW), after oral administration of FC (50 mg/kg BW), and after oral administration of FT (25 mg/kg and 50 mg/kg BW) in eight healthy volunteers (cross over study). In the following only the equivalent doses of 50 mg/kg BW of FS, FT and FC are discussed:

1. After i.v. bolus (5 min) administration of FS and oral administration of FT the peak serum concentrations are about 10 times higher after i.v. (276 + 80 mg/l) as compared to that after oral administration (about 26 + 2.5mg/l) of FT. But about 4 hours after administration the serum concentrations after i.v. FS and after oral FT are already similar (about 18 mg/l, presented only in figure 1). The peak serum concentration after oral administration of FC was only 6.5 + 3.2 mg/l.
2. A mean serum half life was calculated for i.v. FS, oral FT and FC of 3.4 h, 3.6 h and 5.6 h, respectively. The longer apparent half life of FC as compared to FT is explained by the delayed absorption indicated by the delayed Tmax.
3. The amount of drug absorbed from the oral doses is discernible from comparisons of the total areas under the serum concentration curves (AUC) compared to the same dose administered i.v. The mean bioavailability for FT was 41 % and that of FC only 12 %.
4. The mean urinary excretion up to 48 h after i.v. FS, oral FT and FC were 87 %, 43 % and 18 %, respectively.
5. The mean urinary concentrations at 24 h, 36 h, and 48 h after administration were highest for oral FT (about 480, 220, 110 mg/l, respectively), followed by oral FC (about 260, 120, 100 mg/l, respectively) and lowest for i.v. FS (about 110, 25,<10 mg/l, respectively).
6. The bacteriostatic titers were studied in urine samples taken after 24, 36 and 48 h. The urine samples were diluted in nutrient broth to detect what dilution (titer) still had a concentration of fosfomycin that was sufficient to inhibit the growth of a selected strain each of *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis* and *Pseudomonas aeruginosa*. Unfortunately the author did not mention the MIC of the tested strains. It is also not clear, whether the same results would have been achieved, if the urine samples would have been diluted with urine instead of nutrient broth, because the inhibitory and bactericidal activity depends also on the medium the study is performed. Nevertheless the results showed, that the urinary bacteriostatic titers at 24, 36 and 48 h for all strains were highest for oral FT, followed by oral FC and lowest for i.v. FS. For oral FT even after 48 h the bacteriostatic titer for *E. coli* was still about 1:256, *for P. mirabilis* 1:>64, for *E. faecalis* 1:>8, and for *P. aeruginosa* 1:>64 demonstrating that the urinary concentrations up to 48 h after administration are still high enough to well inhibit growth of urinary pathogens (susceptible to fosfomycin).

Antibacterial activity of FT in an in vitro bladder model

Wiedemann & Gross (12) performed bacterial elimination studies. The urinary concentrations as obtained by volunteers were simulated in the in vitro model according to Grasso et al (1978-see in references). As nutrient broth in the model, N II Bouillon (Merck, Darmstadt) with an addition of 10 mg/l glucose-6-phosphate was used. The following bacterial strains were tested: *E. coli* (MIC 1 mg/l), *K. pneumoniae* (MIC 4 mg/l), E. cloacae (MIC 8 mg/l), *S aureus* (MIC 2 mg/l), *S. faecalis* (MIC 16 mg/l). According to the authors this implies that the concentration of the drug during a 1-day period is high enough to prevent the development of resistant mutants in all these strains.

A single oral dose of 0.5 g FT eliminated *E. coli* (MIC 1 mg/l) effectively without regrowth after 23 h. Other bacterial strains have been eliminated less effectively or showed regrowth often with increased MIC. A 3-gram dose, however, was most effective and showed no regrowth of the strains tested after 23 h, although the effect on *E. faecalis* was still marginal. With this dosage no resistant mutants were obtained from the test cultures.

Pharmacokinetics of FT in young and elderly adults.

Borsa et al. (13) performed a comparative pharmacokinetic study after oral administration of FT and FC in 5 young and healthy men (26-33 years) and in 8 elderly adults (65-82 years) at a dose of 25 mg/kg body weight (BW) (corresponding to fosfomycin). The young men had a mean (SD) endogenous creatinine clearance (Cl-Cr) of 127 + 20 ml/mim per 1.73 m^2 and the elderly adults that of 78 + 22 ml/min per 1,73 m^2. The maximal plasma concentration (Cmax) was reached on average in younger men/elderly adults at 1.61/2.16 hours after administration and amounted to 18.5/22.0 mg/l (differences not statistically significant). The plasma half life was 5.37 h and 8.28 h, respectively, and the apparent volume of apparent distribution was 2.42 l/kg and 1.47 l/kg, respectively; both parameters also not statistically significant different. The urinary elimination of fosfomycin was on average in the younger 57.7% and in the elderly 27.5% (about half). The plasma clearance of fosfomycin was calculated on average as 324 ml/min per 1,73 m^2 and 161 ml/min per 1,73 m^2 and the renal clearance of fosfomycin as 180 ml/min per 1,73 m^2 and 49 ml/min per 1,73 m^2.

From the study using an oral dose of 25 mg/kg[1] BW of FT in younger and elderly it can be concluded:

- T-max and C-max in younger and elderly are similar indicating about the same bioavailability in both groups
- the apparent volume of distribution of fosfomycin is about 2 l/kg BW (2.4 in younger and 1.5 l/kg BW in elderly) which indicates a good tissue penetration. This is also shown in the study by Scaglione et al. (14) who found at 6 hours

and thereafter concentrations of fosfomycin in the bladder mucosa in the same range as in the serum.
- the renal clearance of fosfomycin is higher than the corresponding Cl-Cr indicating that fosfomycin is eliminated by the kidneys by glomerular filtration and tubular secretion
- the terminal plasma clearance of fosfomycin is much higher than the renal clearance in both populations indicating that fosfomycin also has a considerable extra renal clearance (on average 196 ml/min per 1,73 m^2 in the younger and 112 ml/min per 1,73 m^2 in the elderly without statistical significant difference)
- since fosfomycin is mainly excreted by the kidneys, elderly adults with Cl-Cr moderately reduced to about 80 ml/min per 1,73 m^2 show an increased plasma half life of about 50% (increase from 5.4 h to 8.3 h).

Fosfomycin concentration after administration of FT in serum, urine and bladder mucosa in elderly patients.

Scaglione et al. (14) performed a pharmacokinetic study in 30 patients (17 males, 13 females, mean age 60.4 + 4.7 years) with normal renal and hepatic function undergoing open surgery because of bladder or prostate carcinoma. The patients received a single oral dose of 3 g FT. Serum, bladder mucosa tissue and urine concentrations were measured microbiologically until 24 h, 36 h, and 48 hours, respectively (**table 1**).The study shows that in patients with a mean age of about 60 years of age the serum concentration is slightly higher than the maximal serum concentration of younger men (Borsa et al. (13) and in the range of that of elderly patients. The bladder mucosa tissue concentrations, which at 6 hours and thereafter were in the range of the serum concentrations demonstrating good tissue penetration as expected from the high apparent volume of distribution.

Table 1. Fosfomycin concentrations in serum, bladder mucosa and urine after oral administration of FT 3 g (according to Scaglione et al. 1994)

Time (h)	Serum (mg/l)	Bladder Mucosa (mg/kg)	Urine (mg/l
3	24.5 + 4.3	13.0 + 5.1	2428 + 466
6	17.0 + 0.1	17.2 + 3.5	1906 + 172
12	6.7 + 1.7	7.3 + 2.1	1023 + 228
24	2.3 + 0.8	3.5 + 2.5	490 + 116
36		0.4 + 0.3	168 + 35
48			31 + 10

Pharmacokinetics in patients with different grades of renal insufficiency and on hemodialysis as compared to healthy adults with normal renal function

Fillastre et al. (15) investigated the pharmacokinetics of FT in patients with different grades of renal insufficiency:

- group I: 7 patients with Cl-Cr between 30 ml/min and 80 ml/min.
- group II: 6 patients with Cl-Cr between 10 ml/min and 30 ml/min.
- group III: 5 patients with Cl-Cr between 2 ml/min and 10 ml/min.
- group IV: 5 patients on hemodialysis for 4 hours (Travenol CF.1511 with an surface of 1.20 m^2).
- and a control group: 5 male adults (26-33 years) with normal Cl-Cr (127 ml/min + 20 ml/min).
- The control group was obviously the same 5 younger men as in the former study comparing younger and elderly adults (13) Borsa et al., 1988).

The subjects received after overnight fasting 25mg/kg^2 FT and remained in fasting stage for further 3 hours. The mean results are shown in **table 2**.

The study shows that after oral administration of about 2 g of FT (25 mg/kg BW):

- in healthy young men the mean Cmax (18.5 mg/l) is reached after 1.6 h and fosfomycin is excreted with a terminal plasma half life of 5.4 h.
- with increasing renal insufficiency (from group I to group III) the Tmax is delayed with up to 5.1 h in group III and Cmax is increased up to about twice the normal.
- with increasing renal insufficiency (from group I to group III) the renal clearance of fosfomycin decreases according to the Cl-Cr and the urinary excretion within 24 h decreases accordingly. Unfortunately, urinary excretion was not measured longer than 24h (see Jangknecht et al. (16) with increasing renal insufficiency (from group I to group III) the terminal plasma half life increases to up to about 10 times in patients with severe renal insufficiency.

During hemodialysis Cmax was elevated as in patients with severe renal insufficiency and the plasma half life prolonged like in patients with severe renal insufficiency. It should, however, be noted that the pharmacokinetic during hemodialysis may depend very much on the type of dialysator used as well as on the dialysis regime (time, ultrafiltration).

Table 2. Pharmacokinetic parameters of fosfomycin in patients with various degrees of renal insufficiency after oral administration of FT (25mg/kg BW[1]) – according to Fillastre et al. 1988.

	Control	Patients with renal insufficiency				p	
		Group I	Group II	Group III	Group IV		
Cl-Cr (ml/min)	127 + 20	30 - 80	10 - 30	2 - 10	hemodialysis		
Dose (mg)	2032	1792	1667	1811	1836	>0.1	NS
Cmax (mg/l)	18.5	26.0	35.7	27.4	37.9	0.02	S
Tmax (h)	1.61	2.38	4.58	5.06	7.92	<0.001	S
AUC (mg x h/l)	103	389	1267	2109	2367	<0.001	S
T1/2 elim (h)	5.37	10.8	24.5	50.3	39.6	<0.001	S
Urine 24h %	58	32	24	11	-	0.004	S
CR-F (ml/min)	180	43	10	5.4	-	<0.001	S

Cl-Cr – endogenous creatinine clearance; Cmax – maximal serum concentration; Tmax – time, when maximal serum concentration is reached; AUC – area under the time serum concentration; T1/2 – terminal half life; Urine 24h % - urinary excretion within 24 h as % of administered dose; CR-F – renal clearance of fosfomycin.

Urinary concentrations elderly female patients with renal function impairment after oral administration of FT.

Jangknecht et al. (16) investigated the urinary concentrations in seven elderly female nursing-home patients aged 71 to 90 years with renal function impairment indicated by an estimated Cl-Cr (Jeliffe Nr.4) between 21 and 72 ml/min. After oral administration of 3 g FT urine was collected in 12 h periods up to 84 h. The total urinary excretion of fosfomycin showed a fairly high range between 15 % and 60 % of administered dose: The higher the total urinary excretion the higher the urinary concentrations within in first 0-12h and 12-24 h and vice versa the lower the urinary concentrations 24-36 and 36-48 h, respectively.

In the three patients with the lowest Cl-Cr (21-28 mg/ml) the total urinary excretion were between 33 % and 57 % of administered dose. The urinary concentrations of these three patients were in the 12-24 h period between 328 and 1600 mg/l and in the 36-48 h period between 122-365 mg/l.

From the results of this study it can be concluded that also in patients with severe renal insufficiency (Cl-Cr 20-30 ml/min) the urinary concentrations after oral FT of 3 g are still sufficiently high and far above the MIC for susceptible pathogens with a breakpoint of <64 mg/l according to CLSI (17) or <32 mg/l according to EUCAST (18). In a European/Brazilian study with 2315 strains of *E. coli* collected from women with uncomplicated cystitis up to a breakpoint of <32 mg/l 96.5 % of the *E. coli* strains were included (19). For the 243 *E. coli* strains from Germany the corresponding percentage was 95.1 %. The MIC-90% for *E. coli* was 8 mg/l for the total study and 16 mg/l for Germany.

Clinical experience with single dose therapy of FT in women with acute uncomplicated UTI.

A metanalysis of 15 comparative studies and two additional large comparative studies published later showed an equivalent clinical and bacteriologic efficacy and tolerance between 3 g as single dose and comparative drugs (4-6). Therefore, FT can be recommended as a drug of choice in countries where it is available for the empiric therapy of uncomplicated cystitis in women (21).

Clinical experience with single dose therapy of FT in elderly patients with UTI

Rudenko & Dorofeyev (here the paper of Rudenko & Dorofeyev should be cited) Rudenko N, Dorofeyev A, 2006. Treatment of acute non complicated cystitis in elderly women. Giornale Italiano di Microbiologia Medica Odontoiatrica e Clinica 10:3-10. Treated 140 otherwise healthy postmenopausal women (mean (SD) age 70.6 (2.95) years) with symptoms of acute uncomplicated cystitis such as frequency, dysuria, urgency (suprapubic pain was also present in 20 % of the patients) with a single oral dose of 3 g FT. The bacterial spectrum consisted of: *E.coli* (in 72,14% of the patients), *E. faecalis* (10,70%), *S. saprophyticus* (4.29%), E. cloacae (2.86%), *P.mirabilis* (2.86%), *K. pneumoniae (*2.86%) , other pathogens (4.29%). 90% of the *E. coli* strains were susceptible to fosfomycin.

2012
Vol. 2 No. 1:3
doi: 10.3823/707

At the control visit, performed 7 days after the drug administration, 113 out of 126 (90%) patients were free of symptoms, in 8 (6%) there was an improvement, and in 5 (4%) the clinical pattern was unchanged. A bacterial cure was achieved in 110 out of 126 patients (87.3%); *E. coli* was eradicated in 90 out of 91 (99%) patients.

In the total population admitted to the study (n=140 patients), 15 adverse events were reported, however only 2 (allergic reactions of moderate severity) were judged possibly related to the treatment.

MacGowan et al. (23) treated 20 hospitalized patients (median (range) age: 72 (47-88) years; only 6 patients were <65 years) with UTI. A satisfactory bacteriological outcome was recorded in 11/17 of patients with susceptible pathogens and a satisfactory clinical outcome in 12/16 symptomatic patients. Three patients complained of possible adverse reactions: two had loose bowel motions 3 and 13 days after treatment, and one became drowsy, uncooperative and incontinent 60 min. after therapy. In this patient, tolerance was classified as poor, but the relationship of these reactions to fosfomycin is uncertain.

Clinical experience with single dose therapy of FT in pregnancy

Bayrak et al. (24) treated 84 pregnant women in the second trimester of pregnancy with asymptomatic bacteriuria with single dose of 3 g FT as compared to cefuroxime axetile 250 mg bid for 5 days. The microbiological elimination 7 days after therapy was 93.2 % with FT and 95 % with cefuroxime axetile. Both treatments were tolerated well. Only with cefuroxime axetile 2 cases (5 %) with vulvovaginitis were observed.

In three controlled studies a total of 250 pregnant women with asymptomatic bacteriuria were treated with a single oral dose of 3 g FT. The comparative substances were pipemidic acid 800 mg per day for 7 days in 156 patients, nitrofurantoin 200 mg per day for seven days in 10 patients and amoxicillin 3 g single dose in 31 patients (25).

In study 1, the microbiological elimination rate 25-30 days after therapy with FT and pipemidic acid was 94% for both treatments. The rate was 77% and 68% for FT and amoxicillin at four weeks in study 2. 15 days after therapy, the eradication rate was 84% and 90% with FT and nitrofurantoin (study 3). FT showed comparable results as with longer treatment using nitrofurantoin or pipemidic acid and showed better results than single dose therapy with amoxicillin. FT did not show any adverse events during pregnancy. The results also suggested that FT is safe in pregnancy from the point of view of foetal toxicity. Since treatment for asymptomatic bacteriuria is likely to be given only after the first trimester, thus it should be unlikely to have any influence on major malformations and chromosomal abnormalities (25).

Clinical experience with two doses of FT for perioperative prophylaxis in transurethral interventions.

Periti et al. (26) used a double oral dose of 3 g FT for the perioperative prophylaxis in patients undergoing transurethral surgery: 3 g were administered 3 h before and 3 g 24 h after the intervention. The FT regimen was compared with two other regimens: amoxicillin 2 x 3 g, and cotrimoxazole 2 x 1.92 g. A total of 675 patients undergoing TURP with a mean (SD) age of 63.3 (14) years were evaluated from 24 Italian centres. All three groups of patients were comparable concerning demography and intervention conditions. The patients had a postoperative indwelling urinary catheter on average for 3-5 days. The results (**table 3**) showed a significantly better outcome with two doses of 3 g FT about one day apart in regard to bacteriuria and symptomatic infections as compared to two doses of amoxicillin 3 g and cotrimoxazole 1.92 g.

Baert et al (27) performed a double-blind study in 61 patients undergoing TURP. 31 patients (mean (SEM) age: 69 (1.45)) received 3g FT orally on the evening before and after the operation and 30 patients (mean (SEM) age: 66.1 (1.37)) received placebo. After removal of the transurethral catheter on the 5th day 0/31 in the FT group and 6/30 of the placebo group acquired UTI. There were no side effects registered.

Table 3. Infectious complications and adverse events in patients with perioperative prophylaxis with two doses of fosfomycin tometamol (FT) 3 g and compared with two doses of amoxicillin (AMX) 3 g and cotrimoxazole (CTX) 1.92 g.

	AMX	CTX	FT
Patients (n)	207	212	256
Fever >38oC on 1st postop. day	5.3 %	4.2 %	1.5 %
Fever >38oC on 6th – 8th postop. day	4.3 %	4.2 %	0.4 %
Bacteriuria >105 CFU/ml	24.6 %	25.0 %	14.8 %*
Symptomatic infection	8.6 %	8.4 %	1.9 %*
Adverse events	8.2 %	7.5 %	4.7 %

* significantly (p<0.01) lower than with AMX and CTX.

Di Silverio et al (28) included a total of 712 patients (521 men and 191 women >14 years of age) undergoing transurethral diagnostic and/or therapeutic manoeuvres. The oral dosage for perioperative prophylaxis was 3 g FT 3 h before and 3 g FT 24 h after the intervention. Out of 618 patients with sterile urine or with bacteriuria <10^5 CFU/ml on baseline screening, 20 (3.2 %) developed UTI on the 2nd day and 22 (3.6 %) on the 7th day after treatment. Overall, a total of 24 side effects were observed (3.3 %): nausea/vomiting 7, pyrosis 5, diarrhoea 5, constipation 1, skin rash 3, headache 3. 16 (2.2 %) of which were considered by the authors FT treatment associated.

Clinical experience with multiple doses of FT 3 g in patients with complicated cystitis

Pulluku et al. (29) treated 52 patients (aged 55.0 + 18.3, rage 19-85; 25 males, 27 females) with clinical symptoms of cystitis with dysuria, frequency or urgency, with pyuria with >20WBC/mm^3 in urine and an ESBL-producing E. coli (>10^5 CFU/ml); no leukocytosis or fever; 36 of them had complicating factors such as indwelling catheter-7, hemi- or quadriparesis -2, malignancy of the urinary tract – 4, other malignancies – 4, diabetes mellitus - 5, nephrolithiasis – 3, recent urological interventions – 6, and were diagnosed complicated cystitis. All patients received FT (3 g every other night, three times). Overall clinical and microbiological success was 94.3 % (49/52) and t8.5 % (41/52), respectively, at 7 to 9 days after therapy. Relapse and reinfection rates were 0 % (0/28) and 10.7 % (3/28), respectively. None of the patients stated any side effect.

Senol et al (30) treated in an observational prospective comparative study 47 patients with complicated lower UTI caused by ESBL-producing E. coli. 27 patients (13 males, 14 females, aged 57.5 + 15.3 years), of whom 19 had complicating factors, were treated orally with FT 3 g every other night three times. 20 patients (7 males, 13 females, aged 57.5 + 20.7 years) were treted with meropenem (1 g tid i.v.) or imipenem (500 mg four times daily) for 14 days. Clinical and microbiological success in the FT and carbapenem groups was similar (21/27 vs 19/20 and 16/27 vs. 16/20, p>0.05). Although it was not a randomised controlled study, according to the authors the data show that FT may be a suitable, effective and cheap alternative in the treatment of ESBL-producing *E. coli*-related complicated lower UTI.

Shrestha et al (31) treated a 85 year old man with complicated UTI due to a vancomycin-resistant *Enterococcus spp*. with FT 3 g orally every 3 days for 3 weeks. In the history the patient had a renal insufficiency (CL-Cr 25 ml/min), obstructive urogenital symdrome with BPH, several times transurethral catheterisations, TURP, epididymo-orchitis and recurrent chills and shiverings. After the 2nd dose of FT the symptoms disappeared. The patient had no clinical recurrence until 2 years after therapy.

Clinical experience with multiple doses of FT 3 g in patients with recurrent UTI

Rudenko & Dorofeyev (22) Rudenko N, Dorofeyev A, 2005. Prevention of urinary tract infections by long-term administration of fosfomycin trometamol. Arzneim.-Forsch,/Drug Res. 55:420-7. Performed a double-blind, randomised prospective placebo-controlled study in 317 women with recurrent cystitis. The patients received every 10 days FT 3 g orally or placebo for 6 months. The follow-up was until 12 months. 302 patients stayed throughout the study which represents a good compliance. The number of UTI per patient year was 0.14 in the FT group and 2.97 in the placebo group, which was statistically significant different (p<0.001). FT was tolerated well.

Ruxer et al. (32) included 50 women with recurrent UTI and type 2 diabetes mellitus into their study. 25 patients (aged 57.8 + 7.6 years) received every 30 days FT 3 g orally and 25 patients (aged 60.0 + 7.9) received notrofurantoin retard 100 mg bid for 7 days and thereafter 100 mg qd for 6 months. There was no significant difference between the study group in whom no UTI was seen at 3 and 6 month of long-term treatment. No clinically relevant adverse reaction or significant laboratory abnormality were observed in the FT group. In the nitrofurantoin group only one patient reported vertigo of several days that was most likely related to the study drug.

Discussion

According to the recently published German guidelines on management of uncomplicated UTI (3), uncomplicated cystitis can be observed in the following patients' groups:

- otherwise healthy non pregnant premenopausal women.
- otherwise healthy pregnant women.
- otherwise healthy postmenopausal women.
- otherwise healthy younger men.
- otherwise healthy patients with diabetes mellitus and stable metabolism.

Fünfstück et al (34) reported that a lower UTI (cystitis) in patients with mild and moderate renal insufficiency (without oliguria) and with normal urinary tract can also be classified as uncomplicated, because such an infection has no adverse impact on renal function.

The single oral dose therapy with FT 3 g is established in acute uncomplicated cystitis in women. This was mainly investigated in a variety of studies with several comparators in premenopausal otherwise healthy women (4,5,6,18). In the meantime, clinical studies also have shown that the single dose therapy with FT 3 g can also be used in otherwise healthy pregnant women (24-25) and in otherwise healthy postmenopausal women (22) . Many of these women were older than 65 of years. In addition, MacGowan et al. (23) treated 14 hospitalised patients aged above 65 years with mainly complicated UTI also with the single dose therapy with FT 3 g with satisfactory results. For perioperative prophylaxis for transurethral interventions two doses of FT 3 g one day apart were used (26-28). In these 3 studies a total of 905 patients treated with two doses of FT 3 g were analysed; many of them, especially in the two studies on perioperative prophylaxis in TURP were males and above the age of 65 years(26-27). Further more, in these two studies and the one case report, in which FT 3g was administered every other or third (one case) day three times or in the case report for 3 weeks, most of the patients were above 65 years of age.

All these clinical studies found no evidence that the tolerance and safety of single dose or multiple doses of oral FT 3 g were different compared to single dose of oral FT 3g in premenopausal younger women. Therefore, based on clinical safety and tolerance there is no reason to restrict the use of oral FT 3 g therapy to the age until 65 years.

It can also be expected that some of the patients above 65 years of age had already at least a moderate renal insufficiency. Therefore, it is important to consider the use of FT also from this point of view.

The pharmacokinetic studies show that at least above a renal insufficiency with an endogenous creatinine clearance of 20 ml/min the urinary concentrations on the first and second day after oral administration of FT 3 g are still sufficiently high and above the MICs of susceptible uropathogens. Therefore, the urinary antibacterial activity should also be sufficient to eliminate susceptible uropathogens. Although there are no data on urinary concentrations in patients with a Cl-Cr lower than 20 ml/min, it sill can be postulated that in patients with any amount of urine production the urinary concentration of fosfomycin will be at least as high as the plasma concentration because FT is practically not protein bound and filtered by the glomeruli. Therefore, the urinary concentrations may also be effective to some extent in such situations considering a MIC-90% of 8-16 mg/l for *E. coli*, as found in the ARESC study (19).

Since fosfomycin is mainly excreted by the kidneys by glomerular filtration and tubular secretion, it can be expected that the plasma half life will be prolonged in patients with renal insufficiency. In patients with Cl-Cr between 10-30 ml/min an 5 times increase and in patients with Cl-Cr between 2-10 ml/min a 10 times increase of plasmy half life as compared to subjects with normal renal function was observed on average (15). After a single dose of FT 3 g, however, the peak plasma concentration is only doubled in patients with Cl-Cr between 10-30 ml/min as compared to subjects with normal renal function. There is no reason to anticipate that the doubling of peak plasma concentration should create any problems in regard to safety and tolerance, if these peak plasma concentrations are compared with peak plasma concentrations after i.v. administered of FS (same dose). After i.v. administration the peak plasma concentration is 10 times higher as compared to oral administration in subjects with normal renal function of the same dose (11).

Therefore, Dose modification according to the grade of renal insufficiency should be performed beginning from GFR < 60 ml/min (Hartmann et al. (35). In general, this can be done either by reducing the dose (Dettli 1, cited according to Hartmann et al. (35) or by prolongation of the dosing interval (Dettli 2, cited according to Hartmann et al. (35). If it is necessary to obtain less fluctuation of the peak concentration, the modification according to Kunin (cited according to Hartmann et al. (35) should be used; after the first normal dose every half life half of the initial dose is repeated. However, what ever dosing modification is used for antibiotic therapy always the first dose should be the normal dose as in patients with normal renal function. Therefore, a dose reduction of a single dose therapy even in patients with severe renal impairment is obsolete in any case.

For repeated dosing the prolongation of half life has to be considered. Almost no accumulation of the drug will occur if the drug is administered every 3 half lives. Since in younger patients with normal renal function the plasma half life is about 5 h, a once daily administration should not cause any drug accumulation. To use two doses (one day apart) as for perioperative prophylaxis should not cause any drug accumulation in patients with a creatinine clearance above 80 ml/min and cause only slight accumulation in patients with creatinine clearance of 30-80 ml/min. In patients with renal insufficiency with creatinine clearance between 10-30 ml/min, the second dose should either be administered every second or third day or the daily dose should be reduced after the first regular dose to 1/3 of the normal dose at the following days.

Since FT is mainly used for the treatment of lower UTI, because the plasma concentrations after 3 g single dose are not high enough in younger patients with normal renal function for treatment of systemic infections, the limiting factor in renal insufficiency might be the urinary concentrations reached.

Unfortunately no data on urinary concentrations are available below a creatinine clearance of 20 ml/min. But for this degree of renal insufficiency the urinary concentrations seem to be sufficiently high that at least from pharmacokinetic/pharmacodynamic point of view a single dose of FT 3 g could be used for the treatment of lower UTI also in these patients if there are no abnormalities within the urinary tract. For complicated cystitis repeated doses of FT have shown already good results in preliminary studies. In elderly patients in patients with reduced renal function the repeated dose should be given every second or in patients with more severe renal impairment every third day.

In patients with normal renal function it was shown that fosfomycin and trometamol are absorbed and eliminated in the same range (Lodola and Longo, personal communication, 1986, cited according to Della Bella & Ferrari(9). For patients with renal insufficiency the pharmacokinetic data concerning global body clearance and urinary excretion are also very similar (15, 33). Therefore all considerations regarding fosfomycin can be translated cum grano salis also to trometamol assuming that the degree of renal function has no major influence an the gastrointestinal absorption of trometamol. Trometamol has been used as organic base as a buffer for metabolic acidosis also in patients with severe renal insufficiency and even in anuric patients. Since a single 3 g oral dose of FT corresponds to less than 1/4-1/5 of the lowest dose of i.v. dose of trometamol in patients with renal insufficiency to correct metabolic acidosis, no additional side effects in patients with renal insufficiency may have to be expected from the trometamol moiety except if there is a hypersensitivity to trometamol. Even a 4 to 5 times repeated 3g dose of FT would only amount to the lowest recommended i.v. dose in patients with renal insufficiency to correct metabolic acidosis.

Conclusion

Single oral dose therapy with FT 3 g is recommended for treatment and prophylaxis of uncomplicated UTI not only in premenopausal, but also in postmenopausal elderly, otherwise healthy women above 65 years of age, because tolerance and safety of FT did not differ from younger ones. FT 3 g has also been used with two oral doses of 3 g (on two consecutive days) for perioperative prophylaxis in transurethral interventions or with three doses (every other day, three times) for treatment of complicated lower UTI including many elderly patients. Up to a creatinine clearance of 20 ml/min urinary concentrations of fosfomycin can still be expected to be sufficiently high for single dose therapy of UTI caused by fosfomycin susceptible uropathogens even in cystitis of elderly patients with otherwise normal urinary tract.

References

1. Grabe M, Bjerklund Johansen TE, Botto H, Wullt B, Cek M, Naber KG, Pickard RS, Tenke P, Wagenlehner FME. 2011. Guidelines on urological infections. European Association of Urology, Arnhem, The Netherlands, ISBN/EAN: 978-90-79754-96-0.
2. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE. 2011. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. CID: 52: e103-e120 .
3. Wagenlehner FME, Schmiemann G, Hoyme U, Fünfstück R, Hummers-Pradier E, Kaase M, Kniehl E, Selbach I, Sester U, Vahlensiek W, Watermann D, Naber KG. Epidmiology, diagnostics, therapy and management of uncomplicated bacterial community acquired urinary tract infections in adults (short version 17 June 2010). Chemother J. 2011, 20:158-168.
4. Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, Athanasiou S. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother 2010, 65: 1862–1877.
5. Lecomte F, Allaert FA,. Single-dose treatment of cystitis with fosfomycin trometamol: analysis of 15 comparative trials on 2.048 patients. Gior. It. Ost. Gin. 1997, 7-8
6. Minassian MA, Lewis DA, Chattopadhyay D, Bovill B, Duckworth GJ, Williams JD. A comparison between single-dose fosfomycin trometamol (Monuril) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women. Int J Antimicrob Agents. 1998, 10:39-47.
7. Azap OK, Arslan H, Serefhanoglu K, Colakoglu S, Erdogan H, Timurkaynak F, Senger SS. Risk factors for extended-spectrum b-lactamase positivity in uropathogenic Escherichia coli isolated from community-acquired urinary tract infections. Clin Microbiol Infect. 2010, 16: 147–151.
8. Lee S-J, Lee DS, Choe HS, Shim BS, Kim CS, Kim ME, Cho Y-H. 2011. Antimicrobial resistance in community-acquired urinary tract infections: results from the Korean Antimicrobial Resistance Monitoring System. J Infect Chemother . 2011, 17:440–446.
9. Della Bella D, Ferrari V, 1988. Monuril: historical background. In Neu, Williams (eds), New Trends in Urinary Tract Infections. Int. Symp., Rome 1987, pp 116-120 (Karger, Basel)
10. Kahan FM, Kahan JS, Cassidy PJ, Kropp H, 1974. The mechanism of action of fosfomycin (phosphonomycin). Ann NY Acad Sci. 1974, 235:364-85.
11. Bergan T, 1990. Degree of absorption, pharmacokinetics of fosfomycin trometamol and duration of urinary antibacterial activity. Infection 18, Suppl 2:S65-S69
12. Wiedemann B, Gross M. Antibacterial activity of fosfomycin trometamol in the urine after simulation of oral doses in a pharmacokinetic in vitro model. Eur Urol 1987, 13 Suppl 1:76-9.
13. Borsa F, Leroy A, Fillastre J-P, Godin M, Moulin B. Antimicr Agents Chemother 1988, 32 :938-41.
14. Scaglione F, Cicchetti F, Demartini G, Arcidiacono M. Fosfomycin distribution in the lower urinary tract after administration of fosfomycin trometamol salt. Int J Clin Pharm Res.1994, 14:107-9.
15. Fillastre JP, Leroy A, Josse S, Moulin B. Étude pharmacocinétique du trométamol-fosfomycine chez les malades insuffisants rénaux. Pathologie Biologie.1988, 36 :728-30.
16. Jangknecht R, Hooymans PM, Fabius GTJ, Nohlmans-Paulssen MKE, Machielsen C, Boogaard-van den Born J, Rang J, Smits CAM, Willems-Thissen ME, Krommenhoek A. Pharmacy World & Science. 1994, 16:149-53.
17. Clinical and Laboratory Standards Institute, 2009. Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement M100-S19 Wayne, PA, USA: CLSI.
18. European Committee on Antimicrobial Susceptibility Testing (EUCAST), 2010. Available at http://www.eucast.org

19. Schito GC, Gualco L, Naber KG, Botto H, Palou J, Mazzei T, Marchese A, 2010. Do different susceptibility breakpoints affect the selection of antimicrobials for treatment o uncomplicated cystitis? Journal of Chemotherapy 22: 345-55
20. Stein GE, 1998. Single-dose treatment of acute cystitis with fosfomycin tromethamine. Ann Pharmacotherapy 32:215-19.
21. Naber KG, Wullt B, Wagenlehner FME, 2011. Antibiotic treatment of uncomplicated urinary tract infections in premenopausal women. Int J Antimicr Agents Suppl 38S: 21-35.
22. Rudenko N, Dorofeyev A, 2005. Prevention of urinary tract infections by long-term administration of fosfomycin trometamol. Arzneim.-Forsch,/Drug Res. 55:420-7.
23. MacGowan AP, Bailey RA, Egner W, Picken DM, Reeves DS, 1990. An open study of the efficacy and safety of single dose fosfomycin trometamol in treatment of hospitalised patients with urinary tract infection (pilot study). Infection 18, Suppl 2: S107-S108.
24. Bayrak O, 2007. Is single dose fosfomycin trometamol a good alternative for asymptomatic bacteriuria in the second trimester of pregnancy. Int Urogynecol J Pelvic Floor Dysfunct 18:525-9.
25. Reeves DS, 1992. Treatment of bacteriuria in pregnancy with single dose fosfomycin trometamol: a review. Infection 20 Suppl 4:S313-6
26. Periti P, Novelli A, Reali EF, Lamanna S, Fontana P, 1987. Prophylactic chemotherapy with fosfomycin trometamol salt during transurethral prostatic surgery: a controlled multicenter clinical trial. Eur Urol 13 Suppl 1:122-31.
27. Baert L, Billiet I, Vandepitte J, 1990. Prophylactic chemotherapy with fosfomycin trometamol versus placebo during thransurethral prostatic resection. Infection 18, Suppl 2: S103-S106.
28. Di Silverio F, Ferrone G, Carati L, 1990. Prophylactic chemotherapy with fosfomycin trometamol during transurethral and urological manouvres. Results of a multicentre study. Infection 18, Suppl 2: S98-S102.
29. Pulluku H, Tasbakan M, Sipahi OR, Yamazhan T, Aydemir S, Ulusoy S, 2007. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. Int J Antimicr Agents 29:62-5.
30. Senol S, Tasbakan M, pullukcu H, Sipahi OR, Sipahi H, Yamazhan T, Arda B, Ulusoy S, 2010. Carbapenem versus fosfomycin tromethamol in the treatment of extended-spectrum beta-lactamase-producing Escherichia coli-related complicated urinary tract infection. J Chemother 22:355-7.
31. Shrestha MK, Amuh D, Goldman MP, Riebel WJ, Tomford JW, 2000. Treatment of a complicated vancomycon-resistant enterococcal urinary tract infection with fosfomycin. Infectious Diseases in Clinical Practice 9:368-71
32. Ruxer J, Mozdzan M, Siejka A, Loba J, Markuszewski L, 2006. Fosfomycin and nitrofurantoin in the treatment of recurrent urinary tract infections in type 2 diabetic women. A preliminary report. Diabetologia Doswiadczalna/Kliniczna 6(5):277-82.
33. Brasch H, Theis E, Iven H, 1982. Pharmacokinetics of TRIS (hydroxymethyl-)aminomethane in healthy subjects and in patients with metabolic acidosis. Eur J Pharmacol. 22: 257–64
34. Fünfstück R, Naber KG, Bishop MC, 2010. Urinary tract infections in patients with renal insufficiency and dialysis. Epidemiology, pathogenesis, clinical symptoms, diagnostics and treatment. pp 426-37. In: Naber KG, Schaeffer AJ, Heyns CF, Matsumoto T, Shoskes DA, Bjerklund Johansen TE (eds): Urogenital Infections. European Association of Urology -International Consultation on Urological Diseases, 1st edition 2010, Arnhem, The Netherlands, ISBN:978-90-79754-41-0.
35. Hartmann B, Czock D, Keller F, 2010. Arzneimitteltherapie bei Patienten mit chronischem Nierenversagen. Deutsches Ärzteblatt 107: 647-56.
36. Grasso S, Meinard G, Carneri I, Tamassia V, 1978. New in vitro model to study the effect of antibiotic concentration and rate of elimination on antibacterial activity. Antimicrob. Agents Chemother. 13:570-6
37. Gior. It. Ost. Gin. 1997, 7-8
38. Rudenko N, Dorofeyev A, 2006. Treatment of acute non complicated cystitis in elderly women. Giornale Italiano di Microbiologia Medica Odontoiatrica e Clinica 10:3-10.
39. Rudenko N, Dorofeyev A, 2005. Prevention of urinary tract infections by long-term administration of fosfomycin trometamol. Arzneim.-Forsch,/Drug Res. 55:420-7.