Florian M.E. Wagenlehner^a
Petra M. Thomas^b
Kurt G. Naber^c

^aKlinik und Poliklinik für Urologie, Kinderurologie und Andrologie, Universitätsklinikum Giessen und Marburg – Standort Giessen, Giessen, ^bPierre Fabre Pharma GmbH, Freiburg, and ^cTechnical University of Munich, Straubing, Germany

Fosfomycin Trometamol (3,000 mg) in Perioperative Antibiotic Prophylaxis of Healthcare-Associated Infections after Endourological Interventions: A Narrative Review

Key Words

Fosfomycin trometamol · Perioperative antibiotic prophylaxis · Healthcare-associated infections · Endourological interventions

Abstract

Introduction: Increasing antibiotic resistance also has an impact on perioperative antibiotic prophylaxis (PAP). This narrative review evaluates fosfomycin trometamol (FT) as PAP in endourological interventions. **Materials and Methods:** Nine clinical studies including 4 randomized comparative studies were analyzed. A total of 1,614 patients received FT as PAP for different endourological procedures and extracorporeal shock wave lithotripsy [ESWL; i.e. cystoscopy (n = 498), urodynamic studies (n = 39), ureteropyeloscopy (n = 10), urethrotomy (n = 20), lithotripsy (n = 15), transurethral resection of bladder tumors (n = 139), transurethral resection of the prostate (n = 843), ESWL (n = 20), ureterorenoscopic lithotripsy (n = 18), percutaneous nephrostomy lithotripsy (n = 12)]. **Results:** In 8 clinical studies, FT was shown to be effective in preventing healthcare-associated urinary tract infections (HAUTIs). One study showed no benefit. The usual dosage regimen was oral administration of 3 g of FT 3 h before and 24 h after the procedure. In 1 randomized comparative study investigating HAUTIs after diagnostic cystoscopy, it could also be shown that a single oral dose of 3 g of FT 3 h before cystoscopy was as effective as a double dose. **Conclusion:** According to the published re-

sults, for traumatic endourological interventions and surgical procedures, an oral dosage of 3 g of FT 3 h before and 24 h after the procedure and only 1 (prior) oral dosage for diagnostic procedures might be an alternative if PAP is indicated. Limitations of the studies are the low numbers of patients included for most indications. © 2013 S. Karger AG, Basel

Introduction

Healthcare-associated infections (HCAIs) are universal and complicate patient care with a daily prevalence of 1.4 million patients worldwide [1]. Healthcare-associated urinary tract infections (HAUTIs) are the most frequent HCAIs [2].

Perioperative antibiotic prophylaxis (PAP) is widely used in urology to prevent infectious complications. The aim of PAP in urological surgery is to prevent infective complications that result from diagnostic and therapeutic procedures [3]. However, PAP is only one of several measures to prevent infections and can never compensate for poor hygiene and operative technique.

The risk of postinterventional HCAIs and HAUTIs depends on the physical status of the patient, the endogenous and exogenous bacterial colonization and the type of intervention, in terms of invasiveness and surgical field contamination adapted from the surgical wound infection classes (e.g. clean, contaminated).

Prevention of Infectious Complications after Endourological Interventions

The endourological interventions investigated comprise diagnostic procedures (e.g. urethroscopy, urodynamic investigations), transurethral surgery [e.g. transurethral resection of bladder tumors (TURB) or the prostate (TURP)], ureterorenoscopic or percutaneous nephrostomic interventions, e.g. for removal of ureteral stones (ureterorenoscopic lithotripsy, URSL) or kidney stones (percutaneous nephrostomic lithotripsy, PCNL), as well as extracorporeal shock wave lithotripsy (ESWL) in a broader sense.

Indications for PAP in endourological interventions are discussed in the European Association of Urology guidelines, updated 2013 [3].

The antibiotic for PAP can be given either parenterally or orally. The administration route depends on the type of intervention and patient characteristics. Oral administration requires drugs that have good bioavailability.

Aim

Resistant uropathogens causing HAUTIs and consequent high antibiotic usage is a major concern [4]. As a consequence, classical smaller-spectrum antibiotics, such as co-trimoxazole and 2nd-generation cephalosporins, and in some areas even fluoroquinolones, can no longer be recommended for PAP because of increasing frequency of resistant uropathogens. In order not to use the classical broad-spectrum antibiotics, such as 3rd-generation cephalosporins, piperacillin/tazobactam and carbapenems, alternative antibiotics, such as fosfomycin trometamol (FT), should be considered for PAP and the evaluable data analyzed.

Pharmacology of FT

Fosfomycin is a phosphonic acid derivative. It acts by inhibiting pyruvyl transferase, a cytoplasmic enzyme that catalyzes the first step in the biosynthesis of peptidoglycans. Since the early 1980s, the salt FT has been available. It is highly water soluble and thus more reliable than other salts, e.g. calcium, for oral administration due to its improved bioavailability [5].

After a single oral dose of FT (3 g of fosfomycin), mean peak plasma concentrations ranged from 22 to 32 mg/l

and were reached 2–2.5 h after administration. Fosfomycin is primarily excreted unchanged in the urine by glomerular filtration. The percentage of an oral dose which is excreted in the urine in the 48 h following administration ranges from 32 to 43%, of which about 85–95% is excreted in the first 24 h. The mean peak of urinary concentrations of fosfomycin, ranging from 1,053 to 4,415 mg/l, was recovered within the 4 h following the administration of a single oral dose. Only advanced renal insufficiency significantly affects the pharmacokinetics of fosfomycin. Dose modifications are not required for mild and moderate renal insufficiency.

Microbiology of Fosfomycin

Fosfomycin has a broad antibacterial spectrum of activity against the most common Gram-positive and Gram-negative bacteria responsible for urinary tract infections (UTIs). Fosfomycin has proved to be active against *Escherichia coli*, *Enterobacter* spp., *Citrobacter* spp., *Klebsiella* spp., *Proteus* spp., *Staphylococcus* spp. (including methicillin-resistant strains) and streptococci [5]. According to the European Committee on Antimicrobial Susceptibility Testing, the minimum inhibitory concentration breakpoints are <32 mg/l (susceptible) and >32 mg/l (resistant).

In a comparative study, 90% of strains of *E. coli*, *Citrobacter* spp., *Enterobacter aerogenes*, *Klebsiella* spp., *Serratia* spp., *Hafnia alvei* and *Proteus vulgaris* were sensitive to fosfomycin with a minimum inhibitory concentration required to inhibit the growth of 90% of organisms of 32 mg/l [5]. No increase in the rate of *E. coli* resistance from urine of patients with uncomplicated UTI has been observed during a period of 8 years throughout Europe, and it has remained below 3% [6]. Cross-resistance between fosfomycin and quinolones is quite rare [5]. Fosfomycin also usually remains active in the presence of extended-spectrum beta-lactamase-producing *E. coli* [7–9].

Safety of FT

Results of clinical trials have demonstrated that FT, administered as a single oral dose, is generally safe and well tolerated. In the overall evaluation of patients who received FT, the most frequently observed adverse events were diarrhea (4%), headache (2%), nausea (2%) and epigastric/abdominal pain (1.3%). The incidence of diar-

Table 1. Published studies of FT for PAP in endourological interventions and surgical procedures

Reference	Year	Indication	Study design	Comparator	Patients, n
Periti et al. [10]	1988	TURP	randomized	AMX, CTX	900
Periti et al. [10]	1988	TURB/cystoscopy	open	–	283
Di Silverio et al. [12]	1988	ESWL, URSL	open	–	30
Baert et al. [13]	1990	TURP	randomized	placebo	61
Di Silverio et al. [14]	1990	TURP, TURB etc.	open	–	712
Selvaggi et al. [15]	1992	TURP	open	–	70
Nicoletti et al. [16]	1994	cystoscopy	randomized	placebo	174
Szopinski et al. [17]	2002	TURP, PCNL, URSL	open	–	80
Jimenez-Pacheco et al. [18]	2012	cystoscopy	randomized	placebo	60

AMX = Amoxicillin; CTX = co-trimoxazole.

rhea, the most frequently reported adverse event, increased with multiple doses of FT. Serious adverse events occurring subsequent to FT treatment were rare [5].

FT for PAP in Endourological Interventions and Surgical Procedures

A total of 9 published studies (4 randomized and 5 open studies) could be identified (table 1) and will be discussed in more detail according to the year of publication.

A multicenter randomized trial enrolling 900 patients (24 Italian centers) was carried out by Periti et al. [10] in 1988 to compare the prophylactic efficacy of a double dose (3 h before and 24 h after surgery) of 3 g of FT (329 patients) versus a double dose of 3 g of amoxicillin (283 patients) versus a double dose of 1,920 mg of co-trimoxazole (288 patients) in patients undergoing TURP [11]. The results for the 675 patients of the controlled study published earlier [11] are included in the 1988 publication [10]. The incidence of significant postoperative bacteriuria, assessed within 2 weeks, was found to be significantly lower in the FT group (16.4%) in comparison to the other 2 groups (24.7% for amoxicillin and 27.4% for co-trimoxazole). The prophylaxis was also effective in reducing the incidence of postoperative symptomatic infections. The incidence was significantly lower in patients treated with FT (3.3%) than in those in the other 2 treatment groups (8.1% for amoxicillin and 8.3% for co-trimoxazole). The incidence of side effects, mainly gastrointestinal related, was lower in FT-treated patients (3.6%) than in the other 2 groups (6.4 and 8.3%) (table 2).

In an open study [10] including a total of 283 patients (52 females and 231 males; mean age 62.7 ± 12.5 years),

Table 2. Outcome of PAP in 900 patients in the 1988 study by Periti et al. [10]

	AMX	CTX	FT
Total TURP, n	283	288	329
Fever >38° C on 1st postoperative day	6.0%	4.9%	3.0%
Fever >38° C on 6th–8th postoperative day	3.5%	3.8%	0.3%
Bacteriuria >10 ⁵ CFU/ml within 2 weeks	24.7%	27.4%	16.4%*
Symptomatic infection within 1 week	8.1%	8.3%	3.3%*
Adverse events	6.4%	8.3%	3.6%

Outcome of PAP in 900 patients undergoing TURP in 24 Italian urology wards with 2 doses each (3 h before and 24 h after the procedure) of either 3 g of FT, 3 g of amoxicillin (AMX) or 1.92 g of co-trimoxazole (CTX). *p < 0.01: significantly lower than the results for AMX and CTX. CFU = Colony-forming units.

76 patients (26.9%) underwent cystoscopy (group A) and 207 patients (73.1%) underwent transurethral resection of vesical or urethral papillomas (TURB; group B). The prophylactic efficacy of a double dose (3 h before and 24 h after the procedure) of 3 g of FT was analyzed. The results for the 233 patients in the open study published earlier [11] are included in the 1988 publication [10]. Significant postoperative bacteriuria was observed in 5 of 76 patients (6.6%) who underwent cystoscopy (group A) and in 35 of 207 patients (16.9%) who underwent TURB (group B). None of the group A patients developed postoperative symptomatic infections, while in group B patients, symptomatic infections (positive bacteriuria and fever >38°C) occurred in 5 cases (2.4%). Mild, moderate and transient side effects, primarily involving the gastrointestinal tract, occurred in 24 out of 283 patients (8.5%),

with no significant differences based on gender or between groups.

In 1988, Di Silverio et al. [12] evaluated FT for prevention of UTI in 30 patients (21 males, 9 females) with a mean age of 42 years (range 22–76) and a mean weight of 71.3 kg (range 60–90) undergoing ESWL ($n = 20$) and ureteropyeloscopy ($n = 10$). Fourteen patients had a single stone, 9 had bilateral stones and 7 had ureteral stones. Patients who had been given antibiotics within 3 days preoperatively, had a positive urine culture within 48 h of surgery and were not in good general condition were excluded from the study. The patients received 2 doses of 3 g of FT, 3 h before and 24 h after the procedure. Urine cultures were performed before and 24 h, 1 week and 2 weeks after the procedure. Significant bacteriuria (colony-forming units 10^5 /ml within 5 days after treatment) with postoperative fever greater than 38°C was observed in 2 out of 30 patients (6%), who thereafter received a different antibiotic therapy.

A double-blind, parallel-group controlled trial of FT versus placebo was carried out in patients undergoing TURP [13], comparing 31 patients treated with a double dose of FT (3 g per os each) on the evening before and after TURP versus 30 patients treated with placebo. After removal of the catheter (day 5), the first midstream urine was collected for culture, and from that moment on all patients were treated with a nitrofurantoin derivative for 2 weeks. Significant early bacteriuria occurred in 6 of the 30 patients treated with placebo and in 0 of the 31 who received FT. None of the patients suffered from a major symptomatic or complicated infection. However, all patients received nitrofurantoin 100 mg twice daily for 2 weeks starting the day of catheter removal (5th day after surgery).

The largest trial [14] was conducted as an open study in 72 urological surgical centers in Italy on 712 (mainly male) patients undergoing different transurethral interventions, i.e. surgical procedures, such as TURP (31.2%) and TURB (19.5%), in 53.5% of the patients and other endoscopic (mainly diagnostic) procedures in 46.5% of the patients, such as cystoscopy (38.9%), urodynamic studies (5.5%), lithotripsy (2.1%) and urethrotomy (2.8%). The patients received a double dose of 3 g of FT, 1 dose 3 h before and 1 dose 24 h after the intervention. Of the 712 patients included in the study, 94 (13.2%) already had significant preoperative bacteriuria, mainly *E. coli* (56.4%), *Proteus* spp. (17.0) and *Enterobacter* spp. (10.6%). These patients were excluded from further microbiological evaluation. Of the 618 patients suitable for microbiological evaluation, 20 (3.2%) had bacteriuria on

the second day and 22 (3.6%) on day 7 after the procedure. Overall, the treatment was well tolerated. Only 24 (3.3%) mild and transient adverse events were recorded, none requiring treatment. According to the physician, 16 of the events (2.2%) were associated with FT treatment.

In an open study in 1992, Selvaggi et al. [15] evaluated 70 patients undergoing TURP. The patients received 3 g of FT 3 h before and 24 h after the procedure. Seven out of 70 (10%) developed fever $\geq 38^\circ\text{C}$. In 3 patients, the fever was due to catheter obstruction; the urine culture was negative and because of prompt resolution of the symptoms, no treatment was administered. In the remaining 4 (5.7%), a positive urine culture with pathogens resistant to fosfomycin required a different antibiotic therapy. At the 2-week follow-up, another 5.7% showed a symptomatic UTI with a cumulative infection rate of 11.4%. Moreover, asymptomatic bacteriuria occurred within 2 weeks in 17.1% of patients. However, these patients were not treated, and repeated urine cultures became negative. A low incidence (4.2%) of adverse events was observed, mainly related to the gastrointestinal tract.

In 1994, Nicoletti et al. [16] investigated a total of 174 patients (2 Italian centers; 78.4% males; age 45–81 years) undergoing transurethral cystoscopy in a prospective, randomized, double-blind clinical trial with 3 groups. Patients in group 1 ($n = 57$) received 3 g of FT 3 h before and 24 h after the procedure; in group 2 ($n = 58$), patients received 3 g of FT 3 h before and placebo 24 h after the procedure, and in group 3 ($n = 59$), patients received placebo 3 h before and after the procedure. On day 3 after the procedure, significant bacteriuria (colony-forming units $\geq 10^5$ /ml) was found in 2 patients (3.5%) in group 1, 3 (5.2%) in group 2 and 15 (25.4%) in group 3, with mainly Gram-negative uropathogens. The results of both groups treated with FT were similar (not significantly different), but they were significantly ($p < 0.01$) better than those of the group treated only with placebo (group 3). The cumulative incidence of (mainly gastrointestinal) adverse events was 7.0% in group 1 (double dose of FT), 5.2% in group 2 (single dose of FT) and 3.4% in group 3 (only placebo).

In an open study in 2002, Szopinski et al. [17] investigated a total of 60 patients after perioperative prophylaxis with 3 g of FT. (It could not be determined if a single or a double dose was given. In Poland, the double dose is registered for perioperative prophylaxis.) The patients were divided into 2 groups, as follows: group 1 with 30 men undergoing TURP and group 2 with 30 patients (11 males and 19 females) undergoing PCNL (12 patients) and URSL (18 patients). Negative urine cultures were ob-

served in 57 patients (95%) immediately after the procedure and in 85% 2–3 weeks later. Adverse events (diarrhea) occurred in 13.3%.

In 2012, Jimenez-Pacheco et al. [18] performed a randomized clinical trial of antimicrobial prophylaxis for flexible urethroscopy, with 30 patients receiving 3 g of FT and 30 receiving placebo. Follow-up was performed after 10 days by a site visit and urine culture and after 30 days by telephone interview. The incidence of bacteriuria, pyuria and microhematuria was 10, 23.3 and 26.7%, respectively, in the control group and 11.1, 37.0 and 29.6%, respectively, in the FT group; these results were not significantly different [18].

Discussion

In the studies analyzed, a total of 1,614 patients received FT as PAP for different endourological procedures, mainly as a double dose of 3 g, usually 3 h before and 24 h after the procedure, except in 88 patients who received only a single 3-gram dose 3 h before cystoscopy. PAP was performed with FT for the following endourological procedures in the lower urinary tract according to increasing invasiveness: cystoscopy (total, $n = 498$; $n = 145$ in 2 randomized comparative studies), urodynamic studies ($n = 39$), ureteropyeloscopy ($n = 10$), urethrotomy ($n = 20$), lithotripsy ($n = 15$), TURB ($n = 139$) and TURP (total, $n = 843$; $n = 314$ in randomized comparative studies); in the upper urinary tract it was performed for the following procedures: ESWL ($n = 20$), URSL ($n = 18$) and PCNL ($n = 12$).

According to the European Association of Urology guidelines, PAP is recommended for practically all patients undergoing TURP and PCNL [3]. In the other procedures, the indication for PAP depends on additional risk factors. For TURP, one of the most invasive surgical endoprocures in the lower urinary tract, it could clearly be shown that PAP with a double dose of 3 g of FT was significantly better in preventing postoperative bacteriuria and symptomatic UTI than PAP with a double dose of either amoxicillin or co-trimoxazole [10]. The placebo-controlled study by Baert et al. [13] can only be analyzed until the 5th day, when the catheter was removed, because all patients received a nitrofurantoin derivative for 2 weeks thereafter. Nonetheless, in this study also it could be shown that until the 5th day, patients who received PAP with FT showed a significantly lower rate of bacteriuria than the patients who received placebo. In the one double-blind randomized study comparing a double dose

versus a single dose versus placebo in patients undergoing cystoscopy, it could be demonstrated that a single dose is as effective as a double dose but significantly superior to placebo in preventing bacteriuria after cystoscopy. Thus, a single oral dose of 3 g of FT 3 h before an endourological diagnostic procedure may be considered if PAP is indicated. However, a recent study by Jimenez-Pacheco et al. [18] failed to show a benefit of FT in flexible urethroscopy.

In the 5 open studies including a fairly high number of patients undergoing different endourological diagnostic and surgical procedures, similar good results could be achieved and it could be shown that the safety and tolerability of FT as PAP was good, with a low number of mainly gastrointestinal adverse events only.

Analyzing especially the comparative study by Periti et al. [10] in patients undergoing TURP, it may be argued that today amoxicillin and co-trimoxazole would not be considered the preferred antibiotics for PAP. Nowadays, usually a fluoroquinolone or a cephalosporin are mostly recommended instead. However, it needs to be considered that the rates of resistant uropathogens (e.g. *E. coli*) against amoxicillin and especially against co-trimoxazole were low at the time these studies were performed. Unfortunately, there is now a worldwide variably steep increase in the rates of bacterial (especially *E. coli*) resistance also against fluoroquinolones and cephalosporins, with the consequence that in modern guidelines these two classes of antibiotics are no longer recommended as first-line drugs for the treatment of uncomplicated UTI [3, 19, 20]. The reason for that is not to unnecessarily increase the selection pressure for resistant pathogens. The same consideration holds true for PAP. According to general rules, broader-spectrum antibiotics should be used cautiously for PAP and reserved for treatment. Today, this consideration would certainly apply to fluoroquinolones and cephalosporins, in order not to select further fluoroquinolone-resistant and extended-spectrum beta-lactamase-producing Enterobacteriaceae, especially *E. coli*.

Since the rate of resistance against fosfomycin is still low despite its clinical usage for decades [6, 21], and since there is also no cross-resistance or parallel resistance against fosfomycin and other frequently used antibiotics, such as co-trimoxazole, cephalosporins and fluoroquinolones, FT could also be recommended in endourological diagnostic and surgical procedures if PAP is indicated. However, it must be noted that with the exception of cystoscopy and TURP, for the other indications low patient numbers were included in the studies.

Conclusion

In 8 clinical studies (3 randomized comparative studies), FT has been shown to be as effective as PAP in preventing HAUTIs following different endourological interventions and surgery. In 1 randomized study, no benefit was noted in comparison to placebo. The usual dosage regimen was oral administration of 3 g of FT 3 h before

and 24 h after traumatic endourological interventions and surgical procedures and only 1 (prior) oral dosage for diagnostic procedures.

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