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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

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Abstract

This study is a comparison of the microbiological and clinical efficacy of single-dose fosfomycin trometamol therapy and a 5 day course of trimethoprim in the treatment of uncomplicated urinary tract infection in female patients. Urine dip-slide samples were obtained from 547 female patients aged 18–65 by 22 General Practitioners (GPs) participating in the study from 21 centres in the UK. All patients were diagnosed as having a urinary tract infection by their GP on the basis of history and clinical examination. Patients were randomised to receive either single dose fosfomycin trometamol or a 5 day course of trimethoprim in a 2:1 ratio. Patients who had significant bacteriuria ($\geq 10^5$ c.f.u /ml) at the first visit (300) were included in the microbiological analysis. The two commonest urinary pathogens isolated were *Escherichia coli* and *Staphylococcus saprophyticus*. Trimethoprim resistance was more frequent amongst *E. coli* isolates whereas fosfomycin trometamol resistance was more common amongst *S. saprophyticus* isolates. Microbiological cure was demonstrated in 83.3% of the trimethoprim treated group and 83% of the fosfomycin trometamol treated group. Persistence of the infecting bacteria was seen in 17% of each treatment arm. © 1998 Elsevier Science B.V./International Society of Chemotherapy. All rights reserved.

Keywords: Single-dose fosfomycin trometamol; Trimethoprim; *Escherichia coli*; *Staphylococcus saprophyticus*

1. Introduction

Urinary tract infections (UTIs) are common. Most present as bacterial cystitis in healthy women with structurally normal urinary tracts and intact voiding mechanisms. It has been estimated that as many as 20–30% of adult women have one or more attacks of UTI yearly [1]. In recurrent UTIs which are usually due to reinfection with different organisms [2], urinary tract abnormality needs to be excluded.

The length of treatment recommended has varied. Therapy for up to 14 days has been given because of fear of kidney damage. Certainly if the kidneys are clearly involved (loin pain, fever) extended therapy is needed. However in many patients infection appears to be confined to the lower urinary tract. In such patients shorter courses have been used [3], including single dose therapy. Because of the superficial nature of cystitis, short term therapy has gained wide acceptance as the preferred method of treatment and many studies have confirmed that single dose therapy can be as effective as conventional treatment [4].

More recently, a fosfomycin salt, fosfomycin trometamol (FMT) was noted to have pharmacological properties suggesting that single dose therapy could be satisfactory [5–16].

Fosfomycin was discovered in Spain in 1969 (Hendlin et al.) [17]. The chemical structure; (−)-*cis*-1,2-epoxypropyl phosphonic acid, combines two unusual features, an epoxide ring, rare among antibiotics

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and a carbone-phosphorus bond [18]. It inhibits bacterial cell wall synthesis by acting as a phosphoenol pyruvate analogue, irreversibly inhibiting enolpyruvyl transferase, an enzyme that catalyzes the first step in the biosynthesis of peptidoglycan [19,20].

Early in vitro studies of fosfomycin antimicrobial activity, showed high activity against the majority of Enterobacteriaceae. The activity against *Enterobacter* spp. and *Pseudomonas* spp. was not as high as against the other Gram-negative rods. Gram positive bacteria were found to be less sensitive than were Gram-negative bacteria. [22].

Various clinical trials have indicated that fosfomycin is a suitable antibiotic for lower urinary tract infection [10,11,32], being relatively free from side effects. Less than 6% of patients may report side effects of gastrointestinal nature, predominantly diarrhoea (3.7%) followed by nausea ($< 1\%$) [21]. A 3 g oral single dose can deliver and maintain urine levels which exceeds 128 mg/l for 24–36 h and it is suggested that these high levels are enough to prevent emergence of resistant strains [23].

Trimethoprim is a common first-line treatment for uncomplicated UTIs but increasing resistance has been observed in several localities. One study of trimethoprim resistance in urinary isolates at the Royal Free Hospital in 1981 and 1985, showed a rise in resistance from 11.1 to 23% amongst isolates of *E. coli*, *Proteus mirabilis*, *Staph. epidermidis* and faecal streptococci [24].

Most urinary tract infections (UTIs) present as bacterial cystitis in healthy women. Bacteria causing infection are limited to a few species, the commonest pathogen being *E. coli* which is present in 80–90% of the cases [25], most of the remainder being due to *S. saprophyticus* which accounts for as many as 10–20% of the UTIs in young adult women during late summer and autumn months [25]. Other responsible microorganisms include other Enterobacteria (*Klebsiella*, *Proteus*, *Enterobacter* and *Citrobacter* species) and *Enterococcus faecalis* in a small minority of cases.

This study was conducted to assess the microbiological efficacy of fosfomycin trometamol as a first-line single dose therapy. The microbiological and clinical efficacy of a single 3 g oral dose of fosfomycin trometamol was compared with a conventional 5 day course of an oral dose of trimethoprim 200 mg twice daily.

2. Materials and methods

2.1. Selection of subjects

The inclusion criteria consisted of females of any race, aged between 18–65 years with uncomplicated lower urinary tract infection. The diagnosis of infection was based on symptoms (dysuria, frequency, urgency) and a microbiologically significant count ($\geq 10^5$ colony forming units (cfu)) in urine. The symptoms had to be present for less than 48 h before entering the trial.

Patients presenting with signs and symptoms of upper urinary tract infection (loin pain, fever > 38.5°C, rigor and vomiting) were excluded on clinical grounds.

The exclusion criteria also included pregnant or lactating women or women taking inadequate precautions against pregnancy, presence of urinary tract abnormalities that can predispose to infection and or presence of calculi, intravenous drug users, patients on antibacterial therapy in the previous 2 weeks or steroids, patients with chronic gastro-intestinal disorders, renal impairment, folate deficiency or megaloplastic anaemia, malignancies, HIV infection, hypersensitivity towards the agents being tested, any condition requiring treatment with any agent that could interact with the study drugs (i.e. antibacterials, antineoplastic drugs, sulphasalazine, metoclorapramide, oral therapy for vaginitis), unwillingness to participate or comply with the protocol requirements and any subject who was otherwise considered unsuitable.

2.2. Clinical trial design

This study was carried out in a comparative, randomised design. Patient randomization was performed in groups of nine, two thirds of subjects receiving a single 3 g oral dose of fosfomycin trometamol supplied as FMT (Monuril, Zambon Group, 3 g sachet) and one third receiving a 5 days course of trimethoprim 200 mg twice daily supplied as TMP 200 mg unitary dose tablets (10 tablets per bottle).

2.3. Collection of urine specimens

Mid-stream urine specimens were collected in a sterile 20 ml universal container at the GP surgery before treatment. A dipslide with a layer of McConkey agar and a layer of CLED agar on either side of the plastic strip (Unipath, Basingstoke, Hants., UK) was dipped into the urine to ensure adequate coverage of the entire agar surface and then removed and replaced in its own sterile universal container. For surgeries within two miles of the laboratory, the dipslides were directly delivered and for surgeries outside this range, dipslides were posted for processing and assessment.

2.4. Microbiological evaluation and assessment

The dip-slides were incubated for 24 h at 37°C and the amount of bacteriuria was assessed using standard pictures (Unipath) of bacterial colony growth within the agar rectangle.

Urine dip-slides reflecting a bacteriuria of $>10^5$ cfu/ml of urine were regarded positive (significant). Positive urine samples were subcultured onto blood and McConkey agar, the identification of organisms was based on morphology, lactose fermentation, haemolysis, oxidase, catalase and coagulase testing. Further biochemical identification was performed using the API system (Bio Merieux, France), API 20 E strips for the oxidase negative gram negative rods and API 20 NE for the oxidase positive gram negative rods. Catalase and coagulase testing was performed for the gram positive cocci, novobiocin sensitivity testing for staphylococci and aesculin hydrolysis for suspected enterococci.

Patients providing culture positive urine samples were asked to provide two further samples at day 7–9 and 28–30 for follow-up and these were tested in a similar manner to above.

The bacteriological efficacy was graded at each follow-up visit, using the following criteria: cured (bacterial growth $<10^4$ cfu/ml at each follow-up visit), persistence (growth of original bacterial strain $>10^5$ cfu/ml at the first follow-up visit), relapse (growth of the original bacterial strain $>10^5$ cfu/ml only at the second follow-up visit with no significant growth at the first follow-up visit) and reinfection (growth of a new bacterial strain $>10^5$ cfu/ml at any follow-up visit).

2.5. Antimicrobial susceptibility testing

The minimum inhibitory concentrations (MICs) for TMP and FMT were determined on Iso-sensitest agar (Unipath) supplemented with glucose-6-phosphate (25 mg/l) using an agar dilution method. After making a correction for the potency of fosfomycin trometamol, (1g of fosfomycin trometamol was equivalent to 0.53 g of fosfomycin) a concentration range of 0.12–256 mg/l was used, with a range of 0.06–28 mg/l for trimethoprim.

An inoculum of 10^4 cfu/spot, was applied to antibiotic-containing plates with a multipoint inoculator (Mast Diagnostic, Bootle, Merseyside, UK) MICs were determined after incubation at 37°C for 24 h as the lowest antibiotic concentration completely inhibiting growth (one colony ignored).

Escherichia coli strain NCTC 10418 was used as a control strain for the susceptibility testing of both agents, (MIC for TMP was 0.12–0.25 mg/l and FMT 2–4 mg/l).

3. Results

A total of 547 female patients attending general practitioners clinics with symptoms of urgency, frequency or dysuria of less than 48 h duration were recruited into the study. All of them provided urine samples and 530 (350 treated with FMT and 180 with TMP) had a full clinical evaluation.

A total of 22 General Practitioners provided specimens and information from these 547 patients. About 30% of the patients were recruited in Scotland, 29% in the Midlands (9% in Northern England), 16% in the East London area and 16% in North London.

In both treatment groups (TMP and FMT) the population was homogeneous regarding age, height, weight and race. Most patients were Caucasian (97%) and the mean age was 40 years. A total of 237 (68%) of the FMT treated group and 117 (65%) of the TMP treated group who had full clinical evaluation, gave history of previous UTI.

Of the 547 first time urine culture samples received, 535 samples were suitable for microbiological evaluation, 12 samples were excluded for the following reasons: immersion of dipslide in urine [5], broken and dried-up dipslides [3], dipslide lost in the post [2], dipslide lost in the lab [1] and male gender [1].

A further 26 samples were excluded from the study due to heavy mixed growth ($>10^5$ cfu/ml with more than three bacterial species present in significant numbers). Out of the remaining 509 patients, 300 patients had positive urines with significant bacteriuria, all but two with a single bacterial species. A total of 204 patients were treated with FMT and 96 treated with TMP.

After processing the samples from the first visit (day 0), the frequency of infection by different bacterial species showed that 298 (99.3%) of the positive samples were due to single bacterial species and 2 (0.7%) had dual infection (*E. coli* plus *S. saprophyticus* and *E. coli* plus *Enterococcus faecalis*). Bacteria isolated were *E. coli* in 235 (77.8%), *S. saprophyticus* 24 (7.9%), *P. mirabilis* 20 (6.6%), *E. faecalis* 9 (3%), *Klebsiella* sp. 4 (1.3%), *Citrobacter* sp. 3 (1%), *Enterobacter sp.* 2 (0.7%), *S. aureus* 2 (0.7%), *S. epidermidis* 2 (0.7%) and *Xanthomonas* sp. 1 (0.3%).

The frequencies of responsible pathogens isolated from patients with significant bacteriuria in this study agrees with previous documented studies [25].

Table 1, shows the results of the first follow-up urine cultures on day 7–9. Of the 300 patients who had positive urines with significant bacteriuria on the first visit (day 0), 26 patients (8.6%) failed to provide a follow-up (day 7–9) urine sample (19 (9%) in fosfomycin treated patients and 7 (7%) in trimethoprim treated patients). Unsatisfactory samples were received from 5 (5.2%) patients treated with TMP and from 8 (3.9%) patients treated with FMT. Of the 261 evaluable patients (177 treated with FMT and 84 treated with TMP) on the first follow up visit (day 7–9), microbiological cure from the infecting organism was observed in 70 patients (83.3%) of the trimethoprim treated group and 147 patients (83%) of the fosfomycin treated group.

Table 1
Microbiological evaluation of outcome of treatment as judged by urine culture of the first follow up visit at day 7–9

Patient treatment group	Significant bactiuria day 0	Microbiological evaluation of the first follow up visit at day 7–9							
		Exclusion			Evaluable samples	Eradication rate		Persistence	
	Number	Sample not received	Unsatisfactory sample	Total	Number	Number	%	Number	%
FMT	(204)	(19)	(8)	(27)	(177)	(147)	(83)	(30)	(16.9)
	195	*19*	*8*	*27*	*168*	*139*	*82.7*	*29*	*17.3*
TMP	(96)	(7)	(5)	(12)	(84)	(70)	(83.3)	(14)	(16.6)
	96	*9*	*5*	*14*	*82*	*69*	*84.1*	*13*	*15.9*
Total	(300)	(26)	(13)	(39)	(261)	(217)	(83.1)	(44)	(16.9)
	291	*28*	*13*	*41*	*250*	*208*	*83.2*	*42*	*16.8*

The data in brackets refer to patients with microbiological evaluation (300 pts) of outcome of treatment as judged by urine culture of the first follow up visit at day 7–9.
The data in italics referred to the subset of patients with both microbiological and clinical evaluation (291 pts).

Persistence of infection was seen in 14 (16.6%) TMP treated patients and 30 (16.9%) in the FMT treated group and reinfection with new organism was seen in 5 (5.9%) TMP treated patients and 18 (10.3%) of the FMT treated group.

A total of 44 patients with persistent infection were followed up for a second time (day 28), 12 failed to provide a sample (nine in FMT and three in TMP treated group), one unsatisfactory specimen was received in the FMT group, microbiological cure was observed in 11 patients (seven in the FMT and four in the TMP treated group), 18 (40.9%) persisted (11 in the FMT and seven in theTMP treated group) and two (4.5%) patients were reinfected with a new organism in the FMT group.

Of the 194 patients (132 treated with FMT and 62 treated with TMP) who had negative cultures on day 7–9, 122 patients (82 treated with FMT and 40 treated with TMP) had negative cultures on the second follow up visit (day 28), 51 failed to provide a urine sample (31 of the FMT and 19 of the TMP treated group), six unsuitable samples (five of the FMT and one of the TMP treated group), six of the FMT treated group showed reinfection with a different organism and ten patients had relapse of infection (eight of the FMT and two of the TMP treated group).

Of the 23 patients who showed reinfection on day 7–9 (18 of the FMT and five of the TMP treated group), microbiological cure was observed in ten patients (eight of the FMT and two of the TMP treated group), two patients had reinfection (one in each group), six failed to provide a urine sample (four of the FMT and two of the TMP treated group), four patients of the FMT treated group had persistent infection and one patient of the FMT treated group had relapse of infection.

3.1. Sensitivity of isolated pathogens to FMT and TMP related to response to treatment.

E. coli was the most common pathogen comprising 235 (77.8%) of the strains. MICs were performed on 224 strains, eleven failed to grow on subculture. With TMP the susceptible population (up to 4 mg/l) were clearly separated from a more resistant population (> 16 mg/l). The FMT results show the major number of strains falling between 0.25–4 mg/l and a small tail (5.7% of strains) extending up to 64 mg/l (Fig. 1a,b). The histogram for 21 strains of *S. saprophyticus* is shown in Fig. 2a,b. Three strains only (14%) had low MICs to FMT with the majority MICs between 16–512 mg/l. The TMP results showed one population with all strains having MIC 2 mg/l or less. The relationship of response to therapy and the MIC was clear in patients receiving TMP. Ten (71%) of the 13 resistant *E. coli* treated were not eradicated whereas all of the six sensitive *S. saprophyticus* treated were eradicated. Failure of therapy was found in ten strains of *E. coli* with a TMP MIC > 32 mg/l, two strains of susceptible *E. coli* (MIC 0.25 and 0.5 mg/l) and two strains of *Proteus mirabilis* (MIC 0.5 mg/l). There was no relationship between the MIC of FMT and eradication of organisms. With *E. coli* 18 (12%) of the 150 susceptible strains were not eradicated and one (12%) of eight resistant strains were not eradicated. Similarly with *S. saprophyticus* where the three susceptible strains were eradicated as were 60% of the resistant strains. All 13 strains of *Proteus mirabilis* were eradicated although one had a raised MIC (32 mg/l).

Other isolates which persisted were two *Klebsiella* spp. of which one strain was sensitive FMT in vitro (MIC 8 mg/l) and one was resistant (MIC 64 mg/l), *E. faecalis* (both sensitive) and one of *Citrobacter* spp. Further details of failed treatment appears in Table 2.

There was no change in antimicrobial resistance as judged by MIC data for the post-treatment urinary isolates.

4. Discussion

The total microbiological cure rates were similar for both trimethoprim and fosfomycin trometamol (83% for FMT treated group and 83.3% for TMP treated group).

The cited cure rates [15,27–31] in uncomplicated UTI patients receiving similar doses range from 100% (Corte et al. 25/25) to 70% (Naber and Thyroff-Friesing 103/150). Variations in cure rates demonstrated in various studies could have been due to the large difference between the number of patients enrolled and the number evaluated. In the study by Cooper et al. [30], for example, 141 patients were enrolled and 33 patients on fosfomycin were evaluated (including male patients) whereas Naber and Thyroff-Friensing enrolled 446 evaluable patients [15]. Most of data in previous studies with very high cure rates have been collected from sample sizes of less than 100 evaluable patients, hence they were liable to statistical errors.

Another factor influencing the clinical and microbiological outcome is the causative bacteria. In this study, results suggest that FMT is more efficacious than TMP in the treatment of *E. coli* UTIs than those caused by *S. saprophyticus* and *E. faecalis*.

MIC data demonstrate that FMT has good in vitro activity against 95% of *E. coli* (MIC 4 mg/l), whereas a significant resistant population (15%) to TMP (MIC 128 mg/l) was found in the same species which is likely to be associated with clinical failure of TMP as a therapeutic agent. MIC data also indicated that TMP

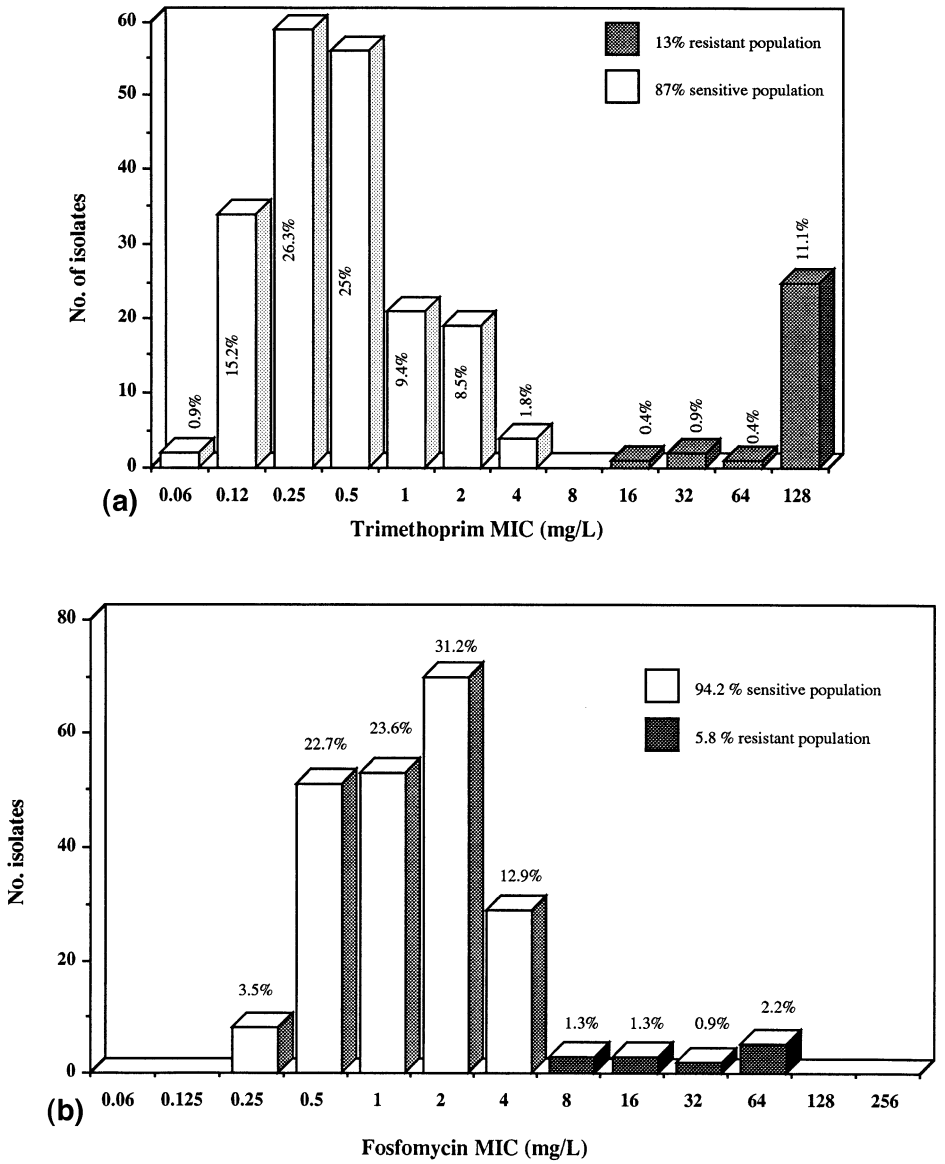

Fig. 1. (a) Susceptibility of *E. coli* isolates ($n = 224$) to trimethoprim (TMP). (b) Susceptibility of *E. coli* ($n = 224$) to fosfomycin (FMT).

has higher activity than FMT against *S. saprophyticus* and *E. faecalis*. In the first follow-up post-treatment visit, persistence of infection due to the same bacterium was identical for both treatment groups (17%). Treatment failure in the TMP treated group correlated clearly with the MICs of the isolates. A total of 13 strains of *E. coli* were resistant to TMP, ten (77%) of which were responsible for treatment failure. All *S. saprophyticus*, were susceptible and were cleared.

This correlation was not demonstrated in the FMT treated group. Resistant strains were not the prime cause of treatment failure with FMT. Of 15 strains of *S. saprophyticus* which were resistant, only six (40%) persisted. *E. coli* was responsible for persisting infection in 19/30 of the cases of which only one strain was resistant (MIC 128 mg/l).

It is not clear, why 18 susceptible strains persisted among this group of patients; a possible explanation is that there might have been an underlying pathology (complicated UTI) or kidney involvement. On the other hand, of eight resistant strains of *E. coli* seven strains (2 MIC 8 mg/l; 2, 16 mg/l; 1, 32 mg/l; and 3, MIC 64 mg/l) were eradicated.

Spontaneous cure could explain this finding [26]; alternatively these isolates were clinically susceptible. The findings overall suggest the break points of eight or 128 mg/l are unrelated to treatment failure. Overall treatment failure rate in this study was 17%. In a study by Naber and Thyroff-Friensing [15], enrolling similar size of patient population, treatment failure rate was 10%. The proportion of treatment failure in FMT group compared to TMP group were similar in both studies.

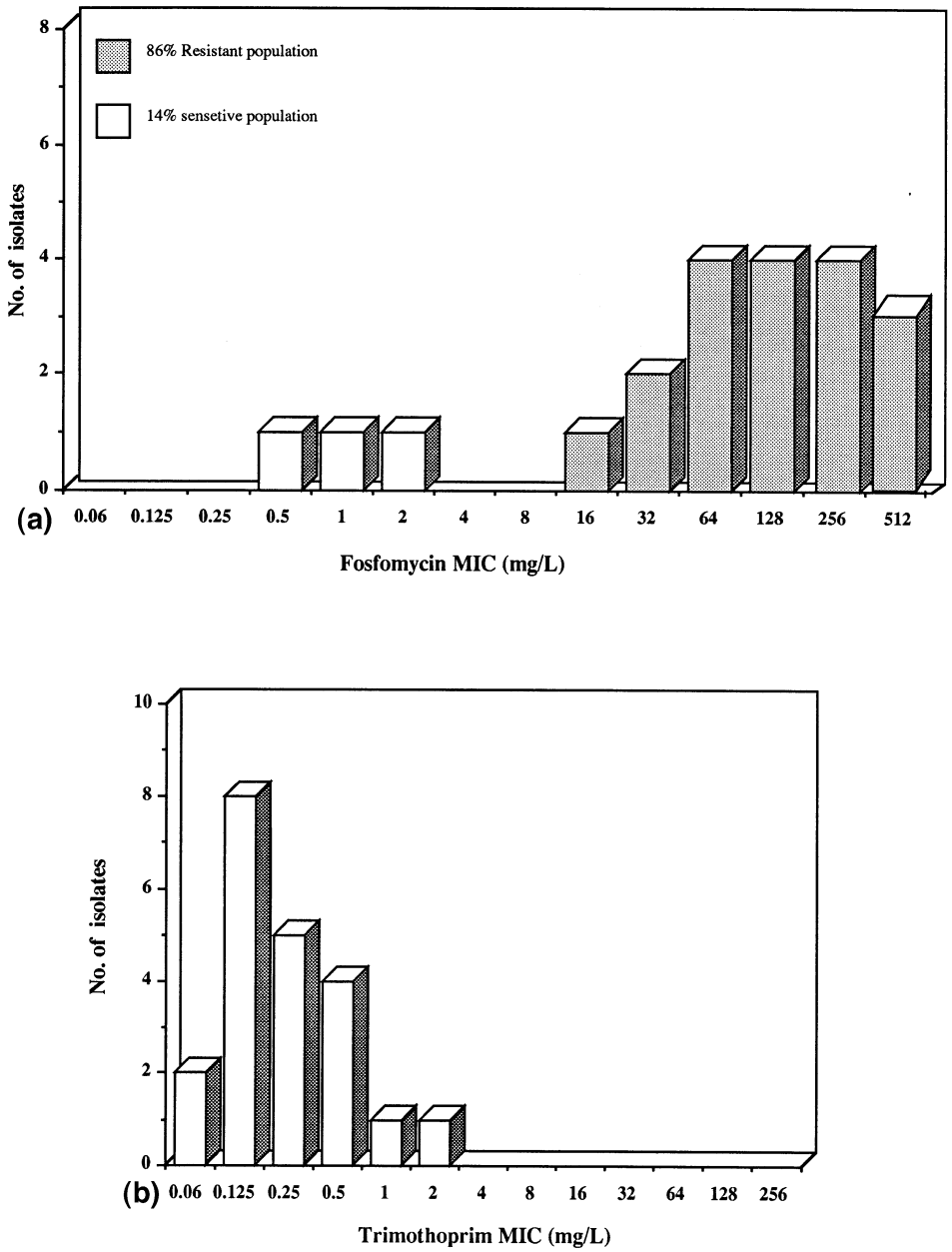

Fig. 2. (a) Susceptibility of *S. saprophyticus* ($n = 21$) to fosfomycin (FMT). (b) Susceptibility of *S. saprophyticus* ($n = 21$) to trimethoprim (TMP).

A slightly higher re-infection rate with different pathogens in the follow-up MSU was seen in the FMT treated group (10%) than in the TMP treated group (6%) but this difference was not significant. The re-infection rates were similar and comparable to those seen in previous studies [15].

Clinical and microbiological evaluation of fosfomycin trometamol for uncomplicated urinary tract infection based on comparative studies is difficult. Published studies show large variations in the number of patients enrolled and the number evaluated, variable comparative antibiotics were used in variable doses, there are no standardised definitions and terminologies, procedures of follow-up have varied and most of the studies excluded pregnant women, who present with a significant number of bacteriuria and UTIs to general practice.

Correlation of in vitro studies and clinical outcome produce difficulties in interpreting results; breakpoint concentrations of FMT varied amongst various studies ranging from 8–128 mg/l because of various factors such as type of media used, test conditions, the presence and concentration of G6P in the test media and decisions on where to draw the breakpoint in relation to the urine level of the drug. There are two populations of *E. coli* with regard to FMT, those with MIC 1–4 mg/l and those with MIC 8–64 mg/l. In our studies these showed no correlation to outcome which

Table 2
Persistent infection after therapy: organisms responsible

	Persistent infection	Organisms responsible	Resistant strains	MICs (mg/l)	Sensitive strains	MICs (mg/l)
TMP treated group $n = 84$	14	*E. coli* = 12	10	2(64)7(128) 1(>128)	2	1(0.25)1(0.5)
		Proteus mirabilis = 2	—	—	2	2(0.5)
FMT treated group $n = 177$	30	*E. coli* = 19	1	1(128)	18	(<8)
		Klebsiella = 2	1	1(64)	1	1(8)
		E. faecalis = 2	—	—	2	1(2)1(16)
		Citrobacter spp. = 1	—	—	1	1(1)
		S. saprophyticus = 6	6	2(64)1(128) 3(>128)	—	—

appears to be related to patient factors (probably, renal involvement) rather than to MICs. Similarly with *S. saprophyticus* 60% of strains (required high MICs of FMT 64–512) were eradicated.

In the absence of standardised methods and procedures, it is difficult to draw the lines between susceptibility and resistance.

The microbiological distinctions are clear cut but clinical results indicate that strains with high MIC can respond and strains with low MIC respond. There is a low prevalence of resistance to fosfomycin. Whether or not significant levels of resistance will emerge with widespread use of this agent in the UK remains to be seen. However, fosfomycin has an advantage in that it is unrelated to other agents used in the treatment of infection due to its unique mechanism of action. Therefore if resistance arises it is unlikely to lead to cross-resistance to other agents used for the treatment of UTI.

Overall in the treatment of lower urinary tract infections in general practice where the organism and susceptibility is initially unknown, single dose FMT 3 g showed microbiological and clinical efficacy comparable to a trimethoprim 5 day course. Some patients failed to respond even though the organism appeared to be fully susceptible. It is possible that more than one dose was needed by these patients.

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References

[1] Hooton TM. The epidemiology of urinary tract infection and the concept of significant bacteriuria. Infection 1990;18(S2):40–2.
[2] Bailey RR. Review of published studies on single-dose therapy of urinary tract infection. Infection 1990;18(S2):53–6.
[3] Hooton TM, Stam WE. Management of acute uncomplicated urinary tract infection in adults. Med Clin North Am 1991;75(2):339–57.
[4] Bailey RR. Management of lower urinary tract infection (Review). Drugs 1993;45(3):139–44.
[5] Greenwood D. The trometamol salt of fosfomycin: microbiological evaluation. Eur Urol 1987;13(S1):69–75.
[6] Bergogne-Berezin E, Muller-Servieys C, Joly-Guillon ML, Brenne N. Trometamol-fosfomycin (Monuril) bioavailability and food-drug interaction. Eur Urol 1987;13(S1):64–8.
[7] Arion R, Fontana P. Single dose treatment of lower urinary tract infection with fosfomycin trometamol: preliminary experiences. Chemioterapia 1987;6(4):295–8.
[8] Andrews JM, Baquero F, Beltran JM, Canton E, Crokaert F, Gobernado M, Gomez-Ius R, Loza E, Navarro M, Olay T, et al. International collaborative study on standardization of bacterial sensitivity to fosfomycin). J Antimicrob Chemother 1983;12:357–61.
[9] Bergan T, Thorsteisson SB, Albini E. Pharmacokinetic prophile of fosfomycin trometamol. Chemotherapy 1993;39:297–301.
[10] Moroni M. Monuril in lower uncomplicated urinary tract infection in adults. Eur Urol 1987;13(S1):101–4.
[11] Grassi GG. Clinical development of fosfomycin trometamol. Infection 1990;18(S2):57–9.
[12] MacGowan AP, Bailey RA, Egner W, Picken DM, Reeves DS. An open study of the efficacy of single dose fosfomycin trometamol in treatment of hospitalised patients with urinary tract infection. Infection 1990;S2:S107–8.
[13] Capri S, Del-Bono GP, Dellamano R. Cost-effectiveness comparison of single dose antibiotic treatment of lower urinary tract infection. J Chemother 1992;4(3):171–5.
[14] Greenwood D. Fosfomycin trometamol activity in vitro against urinary tract pathogens. Infection 1990;18(S2):60–4.

[15] Naber KG, Thyroff-Friesinger U. Fosfomycin trometamol versus oflaxacin/co-trimoxazole as single dose therapy of acute urinary tract infection in females: a multicenter study. Infection 1990;18(S2):70–6.
[16] Bruffit W, Naber KG, Marget W, editors. Detection and management of lower urinary tract infection: The value of single dose therapy. Infection 1990;18(S2):33.
[17] Hendlin D, Stapley EO, Jackson M, et al. Phosphomycin: a new antibiotic produced by strains of Streptomyces. Science 1969;166:122–3.
[18] Christensen BG, Leanza WJ, Beatttle TR, Patchett AA, Arison BH, Ormond RE. Phosphomycin. Structure and synthesis. Science 1969;166:123–5.
[19] Kahan FM, Kahan JS, Cassidy JP, Kropp H. The mechanism of action of fosfomycin. Ann New York Acad Sci 1974;235:364–86.
[20] Minassian MA, Williams JD. The clinical Pharmacology of fosfomycin trometamol. Rev Contemp Pharmacother 1995;6:45–53.
[21] Zimmerman SB., Stapley E O., Wallick H, Baldwin R. Phosphomycin IV: Susceptibility testing method and survey, Proceedings from ICAAC 1969. Antimicrob Agents Chemother 1970:303–309.
[22] Naber KG, Johnson FN. The safety and tolerability of fosfomycin trometamol. Rev Contemp Pharmacother 1995;6:63–70.
[23] Bergan T. Pharmacokinetic of fosfomycin. Rev Contemp Pharmacother 1995;6:55–62.
[24] Hamilton-Miller JMT, Purves D. Trimethoprim resistance and trimethoprim usage in and around the Royal Free Hospital in 1985. J Antimicrob Chemother 1986;18:643–4.
[25] Kunin CM. Urinary tract infection in females. Clin Infect Dis 1994;18:1–12.
[26] Nicolle LE. The optimal management of lower urinary tract infections. Infection 1990;18(S2):50–2.
[27] Cortes R, Pascual T, Lou-Arnal S, et al. Single oral dose of phosphomycin trometamol versus pipemidic acid and norfloxacin in treating uncomplicated low-level urinary tract infections. Aten Primaria 1992;10:1007–112.
[28] Crocchiolo P. Single dose fosfomycin trometamol versus multiple dose cotrimoxazole in the treatment of lower urinary tract infections in general practice. Multicent Group Gen Practit Chemother 1990;36(S1):37–40.
[29] Elhanan G, Tabenkin H, Yahalom R. Single dose fosfomycin trometamol versus 5-day cephalexin regimen for treatment of uncomplicated lower urinary tract infections in women. Antimicrob Agents Chemother 1994;38:2612–4.
[30] Cooper J, Raeburn A, Brumfitt W, et al. Single dose and conventional treatment for acue bacterial and non-bacterial dysuria and frequency in general practice. Infection 1990;18:65–9.
[31] Ferraro G, Ambrosi G, Bucci L, et al. Fosfomycin trometamol versus norfloxacin in the treatment of uncomplicated lower urinary tract infection of the elderly. Chemotherapy 1990;36(S1):46–9.
[32] Naber KG. Fosfomycin trometamol in treatment of uncomplicated lower urinary tract infections in adult women—an overview. Infection 1992;20(S4):310–2.