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Fosfomycin tromethamine as second agent for the treatment of acute, uncomplicated urinary tract infections in adult female patients in The Netherlands?

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ABSTRACT

Background: Uncomplicated urinary tract infections (UTIs) are common among female patients. According to the national guidelines of the Dutch College of General Practitioners (GPs), the drugs of first and second choice as therapy for UTIs are nitrofurantoin and trimethoprim with resistance percentages of 2% and 23%, respectively. The third choice is fosfomycin tromethamine for which no current resistance data from The Netherlands are available. The aim of this study was to determine these resistance percentages.

Methods: During 2003–04, urine samples were collected from a representative sample of 21 general practices spread over The Netherlands, the Sentinel Stations of The Netherlands Institute for Health Services Research (NIVEL). *Escherichia coli* isolated from female patients visiting their GP with symptoms of an acute, uncomplicated UTI were used. Fosfomycin tromethamine susceptibility was determined by Etests. An MIC of fosfomycin tromethamine of 64 mg/L or lower was considered to indicate susceptibility, and MIC values of 96 mg/L or higher were considered to indicate resistance. *E. coli* ATCC 25922 was used as a reference strain.

Results: In total, 1705 *E. coli* strains were tested, of which 11 (0.65%) were resistant to fosfomycin tromethamine. The MIC_{50} and MIC_{90} values for this population were 1 and 4 mg/L, respectively. Within the inhibition zone of 162 susceptible *E. coli*, resistant mutant colonies were observed, of which after

repetition of the susceptibility testing 68 were resistant. In total, 79 (5%) strains were resistant to fosfomycin tromethamine. There was no cross-resistance observed between fosfomycin tromethamine and other antimicrobial agents tested previously.

Conclusions: The high *in vitro* susceptibility to fosfomycin tromethamine in this population and the lack of cross-resistance between fosfomycin tromethamine and other agents together with the extensive global clinical experience support the choice of the national guidelines of the Dutch College of GPs to include fosfomycin tromethamine as a therapeutic option in general practice for uncomplicated UTIs.

INTRODUCTION

Acute, uncomplicated urinary tract infections (UTIs) are a very common disease among female general practice patients. In The Netherlands, the incidence in women between 16 and 65 years of age is 26 per 1000 inhabitants per year. In almost 80% of the urine samples of these patients, *Escherichia coli* has been isolated as the causative uropathogen.[1,2] According to the national guidelines of the Dutch College of General Practitioners (GPs),[3] nitrofurantoin and trimethoprim are the drugs of first and second choice in The Netherlands, with resistance percentages of 2% and 23%, respectively.[4–6] The third choice for empirical therapy is fosfomycin tromethamine for which unfortunately no current resistance data from The Netherlands are available. The ECO-SENS project, testing over 3278 uropathogens isolated in 17 countries between January 1999 and December 2000 including 195 *E. coli* isolates from The Netherlands, showed a resistance percentage to fosfomycin tromethamine of 0.5% (95% CI 0.01–2.8).[2]

Fosfomycin tromethamine is a phosphonic acid, cell-wall-active antimicrobial agent effective against Gram-positive and -negative microorganisms. In clinical practice, the compound is used for the treatment of uncomplicated UTIs caused by *E. coli* and *Enterococcus faecalis*.[7,8] In The Netherlands, fosfomycin tromethamine can be used in the treatment of UTIs caused by microorganisms susceptible to fosfomycin tromethamine in young women over the age of 12 years. It can be administered as a single daily dose and has been shown to be safe even after long-term administration.[9,10]

According to the recommendations of the Infectious Diseases Society of America (IDSA), there is a need for current information on local susceptibility percentages. Knowledge of current bacterial susceptibility data and time trends are important when making optimal empirical choices.[11] The present study was undertaken, because no current data were available in The Netherlands concerning the susceptibility of uropathogenic *E. coli* to fosfomycin tromethamine.

MATERIALS AND METHODS

Patients

From January 2003 until December 2004, GPs (n = 21) spread over The Netherlands participating in the Sentinel Stations project of The Netherlands Institute for Health Services Research (NIVEL) were asked to include all non-pregnant, female patients presenting in their practice with symptoms suggestive of an acute, uncomplicated UTI (i.e. urgency, dysuria, urinary frequency or stranguria without fever >38°C). The patient population of this network accounts for ≈1% of the Dutch population and is designed to be representative for age, regional distribution and degree of urbanization.[12] A urine dipslide was performed for all

enrolled patients and sent to the Medical Microbiology Laboratory in Maastricht as described previously.[5,6]

The fosfomycin tromethamine susceptibility of uropathogenic *E. coli* isolated from these patients was determined and compared with the susceptibility data for several other antimicrobial agents determined in our previous studies.[5,6] The general practices located all over The Netherlands were designated according to the NIVEL Sentinel Station Network as region 1 for the Northern part, region 2 for the Eastern part, region 3 for the Western part and region 4 for the Southern part of The Netherlands.

Bacterial strains

After isolation and identification, the *E. coli* strains were kept at –20°C in peptone/glycerol (30% w/v), and before susceptibility testing, the strains were purified twice on blood agar plates.

Antimicrobial susceptibility

Susceptibility to fosfomycin tromethamine was determined by Etest (AB BIODISK, Sweden) according to the manufacturer's instructions. Briefly, Mueller–Hinton agar plates were inoculated with the bacteria to be tested using an inoculum size of 10^5 cfu/mL. Etest strips were applied on the agar plates and read according to the instructions of the manufacturer after overnight incubation at 37°C.

Susceptibility to amoxicillin, co-amoxiclav, trimethoprim ± sulfamethoxazole, gentamicin, norfloxacin, ciprofloxacin and nitrofurantoin was determined according to the recommendations of the CLSI[13] using a microbroth dilution method as described previously.[5,6] The MIC (in mg/L) of each antibiotic was defined as the lowest concentration of the antibiotic agent that inhibited bacterial growth after overnight incubation at 37°C. MIC values of fosfomycin tromethamine of 64 mg/L or lower were considered to indicate susceptibility, and MIC values of 96 mg/L or higher were considered to indicate resistance. *E. coli* ATCC 25922 was used as a quality control reference strain.

RESULTS

A total of 3141 women with suspected UTI were enrolled in the study by the GPs. Of these women, 231 were 0–11 years, 1993 were 12–70 years and 917 were over the age of 70 years. Positive urine cultures were found in 67%, 79% and 88% of the women for the three age groups, respectively. *E. coli* was isolated in 1705 patients: 100 (43%) in the children, 1109 (56%) in the women aged 12–70 years and 496 (54%) in those aged >70 years. The number of *E. coli* isolated for each geographical region (1–4) was 74 (4%), 363 (21%), 916 (54%) and 352 (21%), respectively.

The determination of the fosfomycin tromethamine resistance of the 1705 isolates using the Etest resulted in 0.64% (95% CI 0.36–1.15) resistant strains. The MIC_{50} and MIC_{90} values for all strains tested were 1 and 4 mg/L, respectively. Of the 11 strains considered resistant, 2 strains had an MIC of 96 mg/L, 3 an MIC of 128 mg/L, 2 an MIC of 256 mg/L, 2 an MIC of 512 mg/L and 2 an MIC of 1024 mg/L. Of the resistant isolates, two were found in the age group 0–10 years (MICs of 256 and 1024 mg/L), one was found in the group aged 21–50 years (MIC of 512 mg/L), one was found in the patients aged 51–70 years (MIC of 128 mg/L) and seven were found in the oldest patients (MICs of 96–1024 mg/L). Also, there was no relation between fosfomycin tromethamine resistance and the age of the patients.

Within the zone of inhibition of 162 susceptible *E. coli* strains, resistant mutant colonies were observed. Purification of these mutated isolates on blood agar plates and repetition of the susceptibility testing resulted in 68 (42%) strains with an MIC of 96 mg/L or higher which were thus also considered resistant. These mutant strains comprised 4% (95% CI 3.2–5.0) of the total population tested.

Neither the MIC distribution curve of fosfomycin tromethamine for the original 1705 isolates nor that for the resistant mutant colonies ($n = 68$) showed significant differences across the four geographic regions ($P > 0.05$; data not shown).

Of the 79 (4.6%; 95% CI 3.7–5.7) strains isolated that were resistant to fosfomycin tromethamine (original isolates and mutants), the numbers of strains (%) with co-resistance to the following antimicrobials were: trimethoprim ± sulfamethoxazole, 15 (19%); amoxicillin, 17 (22%); co-amoxiclav, 6 (8%); gentamicin, 3 (4%); both quinolones, 4 (5%); and nitrofurantoin, 2 (3%). Multidrug resistance, i.e. resistance to three or more groups of antimicrobial agents, was observed in four strains.

The antimicrobial agents recommended as first and second choice by the Dutch College of GPs for the empirical treatment of acute (uncomplicated) UTIs are nitrofurantoin and trimethoprim. Resistance to these agents was found in 2% and 23%, respectively, of all isolates tested.[5,6] Cross-resistance between fosfomycin tromethamine and other antimicrobial agents tested was not observed.

DISCUSSION

We found a high *in vitro* susceptibility to fosfomycin tromethamine and a lack of cross-resistance between fosfomycin tromethamine and other antimicrobial agents in the uropathogenic *E. coli* tested from urine samples in female general practice patients in all age groups. The results of this study are consistent with the results of studies from other countries.[2,7,14] The high *in vitro* susceptibility of the isolates tested to fosfomycin tromethamine was not surprising, as in countries where fosfomycin tromethamine has been used for many years in the treatment of UTIs the resistance level is still low.[2,15] This low resistance prevalence may be related to its restricted use for the treatment of acute, uncomplicated UTIs.

Until now, in The Netherlands, the use of fosfomycin tromethamine for the treatment of UTIs is limited but might increase for several reasons. First, the steady increase in resistance of uropathogenic *E. coli* to trimethoprim, amoxicillin and the fluoroquinolones[4–6] underscores the need for an alternative, effective oral compound for the treatment of UTIs. Secondly, the long-standing experience in many other countries showing no measurable increase in resistance[2,7,8] and the lack of cross-resistance with other compounds seem to justify an increase in clinical use of fosfomycin tromethamine. Also, fosfomycin tromethamine can be administered in a single daily dose, is known to be well tolerated even after long-term administration and has no effect on haematology and blood chemistry.[9,10] Finally, in the recent revision of the national guidelines of the Dutch College of GPs for the treatment of UTIs, fosfomycin tromethamine is mentioned as an effective therapeutic option.[3] Owing to the higher incidence of side effects of nitrofurantoin such as nausea and vomiting, and allergic and neurological reactions,[16] especially in the elderly population, fosfomycin tromethamine would be a good alternative agent for this patient group. However, more well-controlled intervention studies are necessary in the elderly. Furthermore, in children under the age of 4 years, it might be a good replacement for co-amoxiclav, which is known to cause diarrhoea,[17] and for amoxicillin for which the resistance percentage has increased to 40% (S. Nys, G. Donker, A. Bartelds, P. Nelemans, and E. Stobberingh unpublished data). However, this does not imply that we recommend the use of this agent in a paediatric population as there should first be more adequate and well-controlled studies performed. Short-term therapy with fosfomycin tromethamine is also not recommended for pyelonephritis.

Another possible indication in favour of the use of this agent is the treatment of the increasing numbers of UTIs caused by extended-spectrum β-lactamase (ESBL)-producing *E. coli*. Ellington *et al.*[18] examined the usefulness of fosfomycin tromethamine for these *E. coli* in lower UTIs. Strains producing this CTX-M ESBL are often resistant to multiple antibiotics, and only a few agents are still available for effective treatment. For the treatment

of acute, uncomplicated UTIs caused by these strains, fosfomycin tromethamine and nitrofurantoin are the only remaining oral options. Their *in vitro* study showed that among 230 CTX-M-producing *E. coli*, resistance to fosfomycin tromethamine was only 2%. However, the authors described a mutation frequency at 4 x MIC of $1.5 \pm 1.0 \times 10^{-4}$ for fosfomycin tromethamine resistance (MIC > 256 mg/L) and did suggest that resistance might arise rapidly by widespread clinical use of fosfomycin tromethamine. Although this is presently not (yet) the case, it remains to be seen whether these mutants predispose for selection of mutants resistant to fosfomycin tromethamine.

Despite the high mutation frequency *in vitro*, fosfomycin tromethamine resistance in clinical isolates is still rare. Several reasons have been suggested and some of them have been confirmed *in vitro*. First, mutants selected *in vitro* have a lower growth rate both in the absence and in the presence of fosfomycin tromethamine. These *in vitro* observations were supported by clinical data. In a treatment study, Neuman and Rufin[19] showed that strains resistant to fosfomycin tromethamine (MIC > 128 mg/L) could still be eradicated by fosfomycin tromethamine treatment. They suggested that the growth of these strains is sufficiently reduced to prevent establishment in the bladder. Secondly, fosfomycin tromethamine reduces the adherence of bacteria to uro-epithelial cells[15,20,21] and consequently prevents the endurance of the bacteria in the bladder. It has also been demonstrated that resistance mutations will also result in a reduction in pilus biosynthesis.[22] Finally, spread of strains resistant to fosfomycin tromethamine among people is hampered because of limited growth of these strains in the faeces.[23]

Furthermore, the antimicrobial susceptibility percentages presented in this study are those for unselected uropathogens. The numbers of patients who were eligible for the study, but not approached by the GPs, and the number of patients eligible and approached, but who declined participation, are not known.

In conclusion, the data presented in this study regarding the antibacterial activity of fosfomycin tromethamine against uropathogenic *E. coli*, isolated from female general practice patients all over The Netherlands, support the findings of studies performed worldwide. The extensive global clinical experience in combination with a still low prevalence of resistance to fosfomycin tromethamine among Dutch *E. coli* isolates appears to support the choice of the national guidelines of the Dutch College of GPs[3] for the treatment of uncomplicated UTIs to include fosfomycin tromethamine as a therapeutic option. Furthermore, we strongly suggest to introduce this agent as a drug of second (instead of third) choice in the next revision of the national guidelines of the Dutch College for the empirical treatment of acute, uncomplicated UTIs in adult females. Also, fosfomycin tromethamine might be an adequate equivalent for co-amoxiclav in children and for nitrofurantoin in the elderly due to less side effects after the appropriate clinical trials have been performed.

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TRANSPARENCY DECLARATIONS

None to declare.

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