Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women

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Introduction
Acute uncomplicated urinary tract infection is a common disease in women, with an incidence of 25 to 70 per 1,000 women per year [1-2]. The duration of treatment ranges from a single dose to 10-day courses and several types of antibiotics are being used. In spite of many comparative studies with different antibiotics in varying treatment lengths in the past 20 years, the optimal treatment remains disputable. Shorter courses of one or three days offer advantages over courses of the conventional longer duration, namely giving fewer side-effects, better patient compliance, less selection of resistant microorganisms and lower costs. Apart from these advantages several studies suggest that single-dose treatments are as effective as the conventional treatments [3-5]. Most of these studies, however, included too few patients to prevent the statistical type II error (no difference detected, while there is in fact a difference) [6-7]. Pooling the data from those small studies and performing studies with sufficient numbers of patients gave the following results [7-11]:

- single-dose amoxicillin is significantly less effective than conventional multi-dose therapy;
- a single-dose treatment with trimethoprim–sulfamethoxazole is (almost) as effective as multi-dose therapy and causes fewer side-effects;
- recurrence rates at 4 to 6 weeks are sometimes the same and sometimes higher with single-dose therapy.

The appropriate antimicrobial agent for single-dose treatment should have a broad spectrum against both Gram-negative and Gram-positive uropathogens and be preferably bactericidal. The preferred pharmacokinetic profile of the drug used as a single-dose agent in urinary tract infection is one with high concentrations in the urine and a slow excretion rate, which will guarantee a level of the antimicrobial agent above the minimal inhibitory concentration (MIC) for uropathogens for a prolonged period of time [12].

In the Netherlands in 1990 the trometamol salt of fosfomycin (Monuril® 3000) has been introduced for the use in lower urinary tract infections. The drug has a favourable pharmacokinetic pattern, it shows antibacterial activity against uropathogens like Escherichia coli (MIC < 2 mg/l), Proteus mirabilis (MRC50 2.8 mg/l) and Staphylococcus saprophyticus (MRC50 32-128 mg/l) [13], and it penetrates into leucocytes and shows no cross-resistance with other antibiotics because of its unique chemical structure [14].

Until now not many comparative trials have been done on this drug with sufficient numbers of patients in general practice. In two recent studies in general practice a single dose of fosfomycin trometamol appeared to be as effective as conventional treatments with norfloxacin and clavulanate-potenti­ated amoxicillin, respectively [12,14].

In 1989 one of the favourite treatments for acute urinary tract infections in general practice in the Netherlands was nitrofurantoin 50 to 100 mg four times daily for seven days [15]. Nitrofurantoin has been in clinical use for over 35 years for the treatment of urinary tract infections. It is a synthetic nitrofuran and is effective against many Gram-positive and Gram-negative organisms, and is bactericidal against most common urinary tract pathogens, including Escherichia coli, enterococci, Klebsiella and Enterobacter [16].

In this study the efficacy and tolerability of orally administered fosfomycin trometamol in a single dose of 3 g versus nitrofurantoin in a dose of 50 mg four times daily for seven days were compared.
Methods

Patients
Non-pregnant female patients over 18 years who presented themselves in general practice with acute dysuria, stranguria and/or urinary frequency were included in the study. Patients were excluded if they had signs and symptoms of a complicated or higher urinary tract infection, had diabetes, known liver or kidney disease, known anatomic abnormalities of the urinary tract, an indwelling catheter, known allergy to nitrofurantoin or fosfomycin, recent use of immunosuppressive drugs, antibiotic treatment in the previous 2 weeks, were not able to read or write the Dutch language or were not suitable according to the general practitioner.

The study was conducted according to the Declaration of Helsinki, issued by the World Medical Associations in 1960 and revised in 1975 and 1983. Approval for the study had been obtained by the Ethical Review Board of Leiden University. The patients were given verbal and written information, and entry into the study required their verbal consent.

Study design
After giving informed consent patients were assigned in a random and double-blind way to receive one of two regimens:
• group A: one sachet with 3 g fosfomycin trometamol and 28 capsules of placebo four times daily for seven days (single-dose regimen);
• group B: one sachet with placebo and 28 capsules of nitrofurantoin 50 mg four times daily for seven days (seven-day regimen).

The treatments were strictly randomized, within blocks of six consecutive patients stratified for each general practitioner. Blinding was achieved with the double-dummy technique, using two placebos. Fosfomycin trometamol and placebo sachets were supplied by Zambon Nederland BV (Amersfoort, the Netherlands). The Department of Pharmacy of the University Hospital Leiden (Leiden, the Netherlands) prepared the nitrofurantoin and placebo capsules and randomized the study medication.

On day 1, at the study entry, both patient and general practitioner filled in a questionnaire about the presence of symptoms, urinary history, comorbidity and co-medication. Clean voided urine specimens were obtained from all patients for dipslide culture tests (Uricutt®, Orion Diagnostica, Espoo, Finland). This test has a sensitivity of 95% and a specificity of 99% [17]. The dipslide was incubated in a Cultura® incubator (Mediost medical products, Doesburg, the Netherlands) at 37°C overnight and read by the general practitioner or practice nurse by comparing it with the reference chart.

All patients were asked to return on day 4, day 9 and day 42 after enrollment. On return visits both patient and general practitioner filled in a questionnaire about (relief of) the symptoms and possible side-effects. In addition, a clean voided urine specimen for dipslide culture was obtained and read by the general practitioner or practice nurse. At the end of the study all dipslides were collected and read by the study co-ordinator (E. Van Pienbroek).

If a patient returned with symptoms of a urinary tract infection between day 9 and day 42, that visit replaced the follow-up visit of day 42. The patient and general practitioner filled in the questionnaires of day 42, a dipslide was made and the patient was withdrawn from the study.

Clinical efficacy
The patients gave their opinion on the efficacy of the treatment in two ways. At each return visit they recorded the presence or absence of the symptoms that had been used as inclusion criteria. In addition on day 4 and day 9 they judged their urinary tract infection as being cured, improved, unchanged or worsened. The clinical cure rates were based on this second outcome measure.

On day 42 the general practitioners gave their opinion on the overall efficacy of the treatment in terms of cure, improvement, failure (=persistence) or relapse/reinfection.

Bacteriological efficacy
The dipslide results were interpreted as positive (=significant bacteriuria) if > 10⁵ colony-forming units/ml (cfu/ml) were counted. The bacteriological cure rates were based on these results. The following definitions were used [18]:
• short-term cure: < 10⁵ cfu/ml at day 9;
• long-term cure: < 10⁵ cfu/ml at day 9 and day 42;
• persistence: ≥ 10⁵ cfu/ml at day 9;
• relapse or reinfection: < 10⁵ cfu/ml at day 9 and ≥ 10⁵ cfu/ml at day 42.

Side-effects
Side-effects were registered at each return visit. The patient was asked about any possible side-effect on the questionnaire. The general practitioner was asked to evaluate all adverse reactions the patient named as to their severity (mild or severe) and relation to the study drug (none, possible, probable, certain, unknown).

Number of patients needed
Based on the literature we expected a urinary tract infection to be (short-term) eradicated in about 90% of the patients treated with nitrofurantoin 50 mg four times daily for seven days [16]. We considered a 10% decrease in short-term effectiveness of the fosfomycin trometamol treatment (80% eradication) to be still acceptable, taking into account the reduced development of resistant micro-organisms, greater compliance and fewer side-effects of the single-dose therapy [12]. We expected the long-term effectiveness to be the same for both treatments. With α=0.05 (one-sided) a number of 156 patients per treatment group were required to detect the difference between 90% and 80% efficacy with a power (=1–α) of 0.75 [19]. These numbers were the aim of the trial.

Analysis of data
The data were analysed blind by means of the computer program SPSS-PC 3.0. First the two treatment groups were compared with regard to their baseline characteristics.

To evaluate the differences between the treatments two analyses were performed. First an end-point analysis was done, in which the clinical and bacteriological response and side-effects were compared by means of chi-square.