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# A General Practitioner Multicenter Study: Fosfomycin Trometamol Single Dose versus Pipemidic Acid Multiple Dose

**Summary:** In order to evaluate the efficacy and safety of fosfomycin trometamol as single dose oral treatment for acute cystitis in women, an open, multicenter comparative study was carried out in general practices in France. 386 women, aged 16 to 75 years, with clinical symptoms of acute cystitis were enrolled in the study to receive either a single 3 g oral dose of fosfomycin trometamol or a five-day course of 400 mg pipemidic acid twice daily. The diagnosis of cystitis was based on clinical symptoms and significant bacteriuria ($\geq 10^5$ cfu/ml midstream urine). Follow-up examinations were carried out five to ten and 28 days after the end of treatment. 289 and 244 patients, respectively, were available for clinical and bacteriological evaluation at short-term (five to ten days) and medium-term (28 days) post-treatment follow-up. Both regimens were comparable for clinical and bacteriological efficacy with short-term eradication rates of 122/146 in the fosfomycin trometamol group and 130/143 in the pipemidic acid group. The results of medium-term follow-up were 113/122 and 114/122 for the eradication rates of the respective groups. Both drugs were well tolerated. Side effects were mild and of significantly shorter duration in the fosfomycin trometamol group.

**Zusammenfassung:** *Einmaldosis-Therapie mit Fosfomycin Trometamol im Vergleich zu Mehrfachdosierung mit Pipemidsäure: Multicenterstudie in Allgemeinpraxen.* Zur Prüfung der Wirksamkeit und Sicherheit von Fosfomycin Trometamol in Einzeldosis-Therapie der akuten Zystitis bei der Frau wurde in Frankreich in Allgemeinpraxen eine offene Multicenter-Vergleichsstudie durchgeführt. Einbezogen in die Studie wurden 386 Frauen im Alter von 16 bis 75 Jahren, mit klinischen Symptomen einer akuten Zystitis; sie erhielten entweder eine einmalige Einzeldosis von 3 g Fosfomycin Trometamol per os oder über fünf Tage 400 mg Pipemidsäure zweimal täglich. Die Diagnose Zystitis beruhte auf den klinischen Symptomen und einer signifikanten Bakteriurie ($\geq 10^5$ KBE/ml Mittelstrahlurin). Fünf bis zehn und 28 Tage nach Behandlungsende wurden Kontrolluntersuchungen durchgeführt. Für die Kurzzeit-Beurteilung (nach fünf bis zehn Tagen) und die mittelfristige Verlaufskontrolle (nach 28 Tagen) waren jeweils 289 und 244 Patienten für die klinische und bakteriologische Untersuchung verfügbar. Kurz nach Therapieende waren die klinischen und bakteriologischen Ergebnisse in den beiden Gruppen vergleichbar; unter Fosfomycin Trometamol waren 122/146 Patientinnen und unter Pipemidsäure 130/143 Patientinnen von ihrer Infektion befreit. Nach 28 Tagen lagen die Erreger-Eradikationsraten in den jeweiligen Gruppen bei 113/122 und 114/122. Die Verträglichkeit war bei beiden Medikamenten gut. Es traten nur leichte Nebenwirkungen auf, die in der Fosfomycin Trometamol-Gruppe signifikant kürzer anhielten als in der Vergleichsgruppe.

## Introduction

Fosfomycin trometamol is a new, orally absorbed fosfomycin salt. Fosfomycin is a non-toxic bactericidal antibiotic with activity against a broad spectrum of gram-positive and gram-negative bacteria including the causative agents of urinary tract infections. Fosfomycin has a unique chemical structure. So far no cross-resistance with other antibacterials has been observed.

Fosfomycin is not metabolized in the body. It is eliminated in its active form through the urinary tract. Serum and urinary concentrations yielded after a single oral dose of 3 g fosfomycin trometamol are as high as 30 mg/l and 2,500 mg/l, respectively. Antibacterially active urinary levels of the drug persist for at least 48 hours. Due to these characteristics, fosfomycin trometamol appears very well suited to treat urinary tract infections. As preliminary European studies have shown, fosfomycin trometamol provides sufficient activity for single dose treatment of acute cystitis in women [1–5].

Cystitis is a frequent cause of consultation in general practice. Sexually active women present a yearly incidence of acute cystitis of up to 20% [6]. Single dose treatment is an attractive alternative to standard regimens. Major advantages are assured compliance, lower toxicity with reduction of side effects, possibly less intensive selective pressure for the emergence of resistant organisms in gut, urinary or vaginal flora and reduced cost.

In order to investigate the clinical and bacteriological efficacy and tolerance of fosfomycin trometamol in general practice, a multicenter trial was conducted in France. Women with uncomplicated urinary tract infection were treated either with a single 3 g dose of fosfomycin trometa-

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mol or five days of pipemidic acid, 400 mg twice daily which can be regarded as the standard reference treatment most widely used by general practitioners in France. According to calculations, a minimum of 200 patients were required for this comparative study.

## Patients and Methods

The study was designed as an open multicenter study to include a minimum of 200 patients. 88 investigators participated in the study which was coordinated by 13 supervisors (see Table 10).

*Inclusion criteria:* Only female outpatients exhibiting clinical signs and symptoms of uncomplicated lower urinary tract infection (UTI) and significant bacteriuria were enrolled in the study. Oral informed consent was obtained from all patients.

At the initial visit the patient was assigned to treatment with either a single dose of fosfomycin trometamol (Monuril®, batch no. 105/F/223), a 3 g sachet to be taken with a glass of water in the evening after emptying the bladder, or with a five-day course of 400 mg pipemidic acid (Pipram®) twice daily. Compliance was checked by counting the unused samples.

*Exclusion criteria:* Patients were excluded from the study if they were pregnant at enrollment or if they had a known nephropathy or severe concomitant disease such as diabetes which could compromise urinary excretion and/or favour infection; patients were also excluded if they had a history of hypersensitivity to one of the study drugs. Any associated antibacterial treatment other than the study drug was considered a cause for exclusion. Patients with clinical symptoms of acute UTI were excluded after enrollment if their urinary culture was negative or exhibited less than $10^5$ cfu/ml of midstream urine.

*Clinical evaluation:* When patients were first seen by their physicians, a careful clinical history was taken and a physical examination carried out. Patients were questioned for previous episodes of cystitis and pyelonephritis (or both) and for symptoms of the acute episode (dysuria, frequency, cystalgia and haematuria). Exclusion of upper UTI was by clinical criteria (loin tenderness, elevated temperature $\geq$ 38.5°C).

*Follow-up examinations:* The patients saw their physicians for a second clinical and microbiological examination five to ten days after the end of treatment (short-term follow up). A final follow up which also included urine culture was carried out 28 days after the end of treatment. However, it was up to the patient to visit her physician or send the urine sample directly to the laboratory and have the questionnaire completed by telephone call.

*Clinical response to treatment:* Clinical symptoms were rated as cured, improved, unchanged or worse. The evaluation was carried out by both the patient and the physician. Patients who had not responded to treatment by day 3 were classified as failure and treated with alternative treatment after another urine sample was collected.

*Biochemical and bacteriological urine tests:* Midstream urine was collected under the usual aseptic conditions. Urine was immediately tested for protein, glucose, acetone, blood, nitrites and pH using Labstix strips. A specimen was then promptly sent to the laboratory for cytological and bacteriological examination. Isolation and speciation was performed by standard methods. Patients were diagnosed as having cystitis if significant bacteriuria ($\geq 10^5$ cfu/ml urine) was detected.

*Bacteriological response to treatment:* Bacteriological cure was defined as eradication of the causative organism or reduction of colony counts to less than $10^5$ cfu/ml urine.

Reinfection was diagnosed if the patient had a different strain in her urine at $10^5$ cfu/ml or more at the first or second follow-up examination.

Relapse after cure was the reappearance of the initial isolate at $10^5$ cfu/ml urine or more after eradication.

*Side effects:* Side effects were recorded by the patient following a scheduled form which contained a list of expected side effects (diarrhoea, nausea, vomiting, cutaneous rash, abdominal pain, neurosensory disturbance).

The degree of side effects was rated as low, moderate or high if the side effects were reported to the physician upon questioning, spontaneously by the patient or if they had caused interruption of treatment.

Overall tolerability was rated as excellent, good, fair or poor. The duration of side effects was also recorded. The physician in charge decided if the undesired effects were unrelated, possibly or certainly related to therapy.

*Statistical analysis:* Statistical analysis was undertaken for inter- and intragroup variations using the Chi-square test, the Mann-Whitney test, other rank order tests and the tests of *McNemar* and *Friedmann* [6, 7].

## Results

*Homogeneity of Treatment Groups*

A total of 386 female patients aged 16 to 75 years with uncomplicated lower UTI were included in the study. Almost all of the patients had a history of cystitis whereas pyelonephritis, and cystitis plus pyelonephritis were rare events. 206 patients were assigned to oral treatment with a single 3 g dose of fosfomycin trometamol, and 180 patients to a five-day course of oral pipemidic acid, 400 mg twice daily. 90 patients were excluded from the evaluation mainly for not complying with the inclusion criteria (significant bacteriuria).

Final evaluation for efficacy and safety of the study drugs was possible for 150 patients in the fosfomycin trometamol group and for 146 patients in the pipemidic acid group. Patient characteristics are presented in Table 1. Statistical analysis confirmed that the two groups were comparable with respect to age, height and weight. There was also homogeneity when the urological history of the patients was compared, i. e. the number of previous episodes of UTI and clinical symptoms of the actual infection.

A slightly greater number of patients was enrolled in the fosfomycin trometamol group than in the pipemidic acid group during the warm months (June, July, August), i. e. 54.3% compared to 45.7%. This difference is not statistically significant (Chi-square test: $p = 0.247$). Thus, the two groups were considered comparable with regard to possible influences of heat on the onset and persistence of the infection. The most frequent urinary isolates were *Escherichia coli* and *Proteus* spp. (Table 2). The bacterial species were homogeneously distributed among the two groups. Five patients in each group had two isolates.

The two groups were also comparable for clinical signs and symptoms (diurnal and nocturnal pollakiuria, urgency, lumbar pain, haematuria, suprapubic pain). The same is true for the biochemical parameters (proteinuria,

glycosuria, ketonuria, haematuria, nitrite and pH).
These data allow the conclusion to be made that the two treatment groups were comparable on admission.

### Response to Treatment

*Bacteriological Evaluation*
As stated in the Methods section, results of treatment were evaluated twice: five to ten (short-term) and 28 days (medium-term) after the end of treatment.
Bacteriological findings were used as the main criteria of efficacy evaluation.
Short-term results are available for a total of 289 patients (Table 3). Eradication of the causative organism was reported for 122/146 patients treated with fosfomycin trometamol and for 130/143 patients treated with pipemidic acid (83.5% and 90.9%, respectively; Chi-square = 3.48; $p > 0.5$, i. e. non-significant difference).
Comparison by age group was carried out on the age groups determined when assessing homogeneity of the patients. As shown in Table 4, there was a decrease in short-term efficacy in the highest age group of each treatment group. Differences proved to be non-significant except in the age group 37 to 47 years where pipemidic acid appeared to be superior with an eradication rate of 100% compared to 81.2% with fosfomycin trometamol. A trend, however, non-significant, was observed in favour of pipemidic acid in the age groups 17 to 26, 58 to 68 and 69 to 75 years; the results were in favour of fosfomycin trometamol in the age groups 27 to 36 and 48 to 57 years. These results are similar when reinfections are included in the efficacy evaluation.
Medium-term results (28 days after the end of treatment) were available for a total of 244 patients since 52 patients did not show up for their last follow-up. 113/122 patients treated with fosfomycin trometamol (92.6%) and 114/122 patients treated with pipemidic acid (93.4%) were still free of significant bacteriuria. The differences are not significant (Chi-square = 0.06; $p > 0.05$) (Table 3).
These results demonstrate that the medium-term efficacy of the two drugs was comparable in the patient population studied.
As observed at the short-term evaluation, a lower eradication rate was observed in the highest age group (69 to 75 years) with both treatments.
There was a non-significant trend in favour of pipemidic acid treatment in the age groups 17 to 26, 37 to 47 and 69 to 75 years and in favour of fosfomycin trometamol in the age groups 27 to 36 and 58 to 68 years (Table 5).
The statistical analysis did not show any differences in the two treatment groups with respect to bacteriological efficacy at medium-term evaluation, regardless of the age groups.
When the two treatment groups were compared for modifications during the post-treatment follow-up, no significant differences between short-term and medium-term results were observed for the two groups. This confirms that single dose treatment does not lead to an increased number of late failures in the period up to 28 days post treatment.

### Clinical Evaluation

The overall clinical evaluation was assessed jointly by the patient and the physician during the two visits following treatment (end of treatment plus five to ten days, and end of treatment plus 28 days). In each group the physician's and the patient's opinion were comparable with respect to treatment response rated as cured, improved, unchanged or worsened.
During the initial visit and the two follow-up visits the patient was specifically questioned for symptoms such as pollakiuria, urgency, lumbar pain, haematuria, nycturia and suprapubic pain. The evolution of symptoms between day 0 and five to ten days after therapy is presented in Table 6.
The regression of symptoms was comparable for the two treatment groups. Both treatments achieved significant reductions in urinary excretion of proteins, blood and nitrites as assessed by comparison of the results of Labstick tests for the respective parameters before treatment and during follow-up.

### Tolerability

The overall tolerability (Table 7) was evaluated at the end of treatment and rated as excellent, good, fair and poor. Information was obtained from 288 patients, 144 in each group. The number of patients for whom tolerability was rated as good or excellent by the physician was slightly higher in the fosfomycin trometamol group: 138/144 (95.8%) than in the pipemidic acid group: 133/144 (92.4%). However, this trend is not significant.
Undesired effects were recorded by the patient on a questionnaire. 46 patients, 25 in the fosfomycin trometamol group and 21 in the pipemidic acid group reported adverse events. Some patients complained about more than one undesired effect with a total of 37 side effects being recorded for the fosfomycin trometamol group and 27 for the pipemidic acid group.
The main side effect with fosfomycin trometamol was diarrhoea (11/144; 7%) and with pipemidic acid nausea (16/144; 11%). None of the adverse events was rated as severe. 13 and 15 events in the fosfomycin trometamol and pipemidic acid groups, respectively, were rated as medium and 19 and 12, respectively, as slight. There was no significant difference in the two groups with regard to severity of adverse effects (Mann-Whitney test: $p = 0.352$).
Only four side effects were regarded by the physician in charge as certainly related to treatment with fosfomycin trometamol and seven to pipemidic acid (Table 8).
The duration of the adverse events reported was significantly lower with fosfomycin trometamol (mean 1.83 days) than with pipemidic acid (mean 3.32 days; Mann-Whitney test: $p = 0.002$) (Table 9). This is probably due to the

Table 1: Patients' characteristics.

| | FT (n = 150) | PA (n = 146) |
|---|---|---|
| Age (years) Mean ± SD | 39.1 ± 15.3 | 41.5 ± 15.9 |
| Weight (kg) Mean ± SD | 59.0 ± 10.2 | 59.4 ± 9.0 |
| Height (cm) Mean ± SD | 162.8 ± 5.5 | 162.5 ± 5.7 |

Table 2: Infecting pathogens from pretreatment urine cultures.

| Organisms | FT (n = 150) n | % | PA (n = 146) n | % | Total |
|---|---|---|---|---|---|
| *Escherichia coli* | 110 | 73.3 | 112 | 76.7 | 222 |
| *Proteus* spp. | 20 | 13.3 | 16 | 11.0 | 36 |
| *Klebsiella* spp. | – | – | 7 | 4.8 | 7 |
| Other | 20 | 13.3 | 11 | 7.5 | 31 |

Table 3: Overall bacteriological evaluation.

| Outcome | Treatment | Follow-up at 5–10 days n | % | 28 days n | % |
|---|---|---|---|---|---|
| Eradication | FT | 122 | 83.6 | 113 | 92.6 |
| | PA | 130 | 90.9 | 114 | 93.4 |
| Recurrence | FT | 1 | 0.6 | 5 | 4.0 |
| | PA | 1 | 0.7 | 3 | 2.5 |
| Reinfection | FT | 1 | 0.6 | 3 | 2.5 |
| | PA | 3 | 2.1 | 2 | 1.6 |
| Persistence superinfection | FT | 22 | 15.0 | 1 | 0.8 |
| | PA | 9 | 6.3 | 3 | 2.5 |
| Total | FT | 146 | – | 122 | – |
| | PA | 143 | – | 122 | – |

Table 4: Bacteriological results at 5–10 days of follow-up.

| Eradications | | | | |
|---|---|---|---|---|
| Age groups (years) | Fosfomycin trometamol | | Pipemidic acid | |
| | No. of patients | % | No. of patients | % |
| 17–26 | 28/33 | (84.8) | 32/35 | (91.4) |
| 27–36 | 38/44 | (86.4) | 20/26 | (76.9) |
| 37–47 | 26/32 | (81.2) | 27/27 | (100) |
| 48–57 | 13/14 | (92.8) | 22/24 | (91.7) |
| 58–68 | 11/13 | (84.6) | 24/24 | (100) |
| 69–75 | 6/10 | (60.0) | 5/7 | (71.4) |
| Total | 122/146 | (83.5) | 130/143 | (90.9) |

Table 5: Bacteriological results at 28 days of follow-up.

| Eradication | | | | |
|---|---|---|---|---|
| Age groups (years) | Fosfomycin trometamol | | Pipemidic acid | |
| | No. of patients | % | No. of patients | % |
| 17–26 | 25/27 | (92.6) | 25/26 | (96.1) |
| 27–36 | 37/40 | (92.5) | 15/19 | (78.9) |
| 37–47 | 25/26 | (96.1) | 27/27 | (100) |
| 48–57 | 12/12 | (100) | 20/20 | (100) |
| 58–68 | 10/10 | (100) | 23/24 | (95.8) |
| 69–75 | 4/7 | (57.1) | 4/6 | (66.6) |
| Total | 113/122 | (92.6) | 114/122 | (93.4) |

Table 6: Treatment response by symptoms 5–10 days after therapy.

| Symptoms | FT n | % cured | PA n | % cured |
|---|---|---|---|---|
| Dysuria | 123 | 88.6 | 116 | 91.3 |
| Frequency | 136 | 88.2 | 135 | 86.6 |
| Cystalgia | 103 | 89.3 | 106 | 91.5 |
| Hematuria | 52 | 98.0 | 51 | 92.1 |

Table 7: Overall tolerability evaluation.

| | Excellent | | Good | | Fair | | Poor | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Fosfomycin trometamol | 107 | 74.3 | 31 | 21.5 | 6 | 4.2 | 0 | – |
| Pipemidic acid | 102 | 70.8 | 31 | 21.5 | 10 | 6.9 | 1 | 0.7 |

Table 8: Adverse events: imputability to treatments (physicians' evaluation).

| Imputability /treatment | Monuril | | Pipemidic acid | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Certainly related | 4/144 | 2.7 | 7/144 | 4.8 |
| Not related | 11/144 | 7.6 | 3/144 | 2.0 |

Table 9: Overall mean duration of adverse events.

| | Fosfomycin trometamol | Pipemidic acid | p* |
|---|---|---|---|
| Mean duration (days) | 1.83 | 3.32 | 0.002 |

* Mann-Whitney test.



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Table 10: List of local coordinators.

| | |
|---|---|
| Bordeaux | Pr *Conri* |
| Clermont-Ferrand | Dr *Hermabessiere* |
| Lyon | Dr *Lafuma* |
| Marseille | Dr *Arniaud*<br>Dr *Cassely* |
| Nancy | Dr *Franco* |
| Rennes | Pr *Allain* |
| Rouen | Pr *Humbert*<br>Dr *Vargues* |
| Strasbourg | Dr *Jacqmin*<br>Dr *Charton* |
| Toulouse | Dr *Desrus* |

Monitor of the study (on behalf of Zambon, France) *P. Auclair,* Ph. D.

short treatment with this drug. Systolic and diastolic blood pressures measured at first visit and controls did not show any significant differences between the treatment groups and during the follow-up period.

## Discussion

Many studies have shown that single dose treatment can efficiently eliminate bacteria from the urinary tract if the infection is limited to the superficial mucosal layers [8–23]. Lower toxicity with reduction of side effects, better treatment compliance, decreased risk of alterations of the intestinal and vaginal flora and of the emergence of resistance have been advocated as the main advantages of single dose treatment [4, 17, 18]. Failure to eradicate urinary tract infection after single dose treatment may indicate that deeper structures are involved. Thus, single dose treatment provides a useful test to identify those patients in whom further investigation should be considered. In some countries this regimen has become the standard treatment for acute cystitis in non-pregnant young women [11, 15–21].

Not all drugs used for treatment of urinary tract infections are as suitable for single dose treatment.

Fosfomycin trometamol yields high sustained concentrations in urine for at least 48 hours when given as a single dose. This is an advantage over many of the standard antibacterials used for acute lower UTI [9, 10, 22]. An evolving problem in using standard antimicrobials to treat urinary tract infections is increasing resistance development in urinary isolates, even from outpatients [23].

The present study corroborates the findings of previous European studies with respect to therapeutic efficacy and tolerability of fosfomycin trometamol in single dose treatment of uncomplicated lower urinary tract infection in women. 3 g fosfomycin trometamol given as a single dose proved to be as comparably effective as a five-day course of 400 mg pipemidic acid twice daily, the most frequently used standard treatment for uncomplicated UTI in France. This was true for both short-term and medium-term results assessed five to ten and 28 days after the end of treatment. Relapses and reinfection were not observed more frequently with the single dose regimen than the five-day standard treatment. Both drug regimens were well tolerated and were comparable for side effects which, however, lasted significantly shorter in patients treated with fosfomycin trometamol. The broad spectrum of activity of the drug against urinary pathogens, the long-lasting urinary concentrations and lack of toxicity appear to be advantageous for the use of this drug for single dose treatment of uncomplicated lower UTI in women.

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