A comparative study of pipemidic acid and nitrofurantoin in the treatment of uncomplicated urinary tract infections

E. C. MEYER, H. S. SCHOEMAN

Summary

In an open uncontrolled trial 60 women with confirmed uncomplicated urinary tract infections were randomly allocated to receive either pipemidic acid (Septidron; Ethimed) or nitrofurantoin for 10 days. Urine cultures were done on day 1 and day 10. No statistical difference was found in the subjective and objective assessments of the response to the two medications and it is concluded that pipemidic acid is a satisfactory and effective alternative to nitrofurantoin in the treatment of uncomplicated urinary tract infections in women.

Patients and methods

Sixty white women over 16 years of age who presented in private practice with symptoms of a lower urinary tract infection were entered into the study. Symptoms included frequency, dysuria, pain, nocturia, haematuria, and general malaise. Criteria for exclusion were pregnancy, allergy to the medication, need for hospital admission or an inability to return for follow-up. Patients with signs of an upper urinary tract infection or those with a documented urinary tract abnormality were excluded. Informed signed consent was obtained. A complete medical history was taken.

Special note was taken of previous urinary tract infections and treatment. The intensity of symptoms pertaining to the present infection was recorded on a linear scale of 0 - 4. The results of a complete medical and pelvic examination were entered on a standard form. A cervical smear was taken. Any vaginal discharge was examined microscopically by saline and potassium hydroxide wet-slide preparation. Two clean-void midstream urine specimens were collected. The first was examined by 'dipstick' semiquantitatively for protein and haematuria (N-Multistix; Ames). Both Gram-smear and wet-smear slides were made and examined microscopically. The second specimen was submitted for bacterial culture and sensitivity studies.

All but 3 of the patients admitted to the trial had symptomatic bacteriuria defined as > 100 000 colonies/ml of a single organism in bacterial culture and the presence of at least one of the following: dysuria, frequency, urgency, abdominal pain, enuresis or a temperature of > 38°C orally. The other 3 patients who were entered into the trial had more than one of the above signs and very high pus cell counts and haematuria. Multiple Gram-negative bacteria were present on their initial Gram smears.

All patients were entered into the trial according to the objective results of the initial Gram smear. They were assigned randomly to receive either capsules containing nitrofurantoin macrocrystals 50 mg 6-hourly or pipemidic acid 400 mg 12-hourly. The women were given specific treatment instructions. After the results of the bacterial culture became available, the patients remained in their original treatment group despite infections with organisms unsusceptible to the particular antibiotic. If a patient's condition deteriorated, she was dropped from the study.

Of the 52 women who finally completed the trial, 26 received nitrofurantoin and 26 pipemidic acid (Table I). The patients were followed up on day 5 and day 10. On return visits a detailed history was obtained with regard to compliance, duration of symptoms and occurrence of side-effects related to the medication. Intensity of symptoms, signs and side-effects were entered on a linear scale from 0 to 4. The women were examined and the results of the examinations entered on a standard form. Wet- and Gram-smear slides were repeated on both occasions, and bacterial culture and sensitivity tests repeated on day 10.

Results

Of the 60 women who were originally entered into the trial, 52 completed the study. Of the 8 drop-outs, 4 did not return for follow-up examinations, and 2 did not comply with medication instructions. The 4 patients who did not return were contacted telephonically and reported feeling well. Two patients who were infected with organisms resistant to their assigned medication were dropped from the study. Women in the two treatment groups of 26 patients each were similar in age, history of previous...
infections and duration of symptoms. For statistical analysis Student's \( t \)-test and the chi-square test were used. Bacterial pathogens were as listed in Table 1.

### TABLE 1. URINARY PATHOGENS CULTURED

<table>
<thead>
<tr>
<th>Urinary pathogens</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>E. coli</td>
<td>13</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>3</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>3</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>3</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>1</td>
</tr>
<tr>
<td>Proteus</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>1</td>
</tr>
<tr>
<td>Negative cultures</td>
<td></td>
</tr>
<tr>
<td>(unidentified Gram-negative bacilli on smear)*</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26</strong></td>
</tr>
</tbody>
</table>

*Case 1 = + blood, 288 pus cells, 6 erythrocytes; case 2 = + blood, 27 pus cells, 2000 erythrocytes; case 3 = + blood, 10 pus cells, 30000 erythrocytes. Multiple Gram-negative bacilli were present on the smears of these 3 patients. They had very explicit signs and symptoms which improved after treatment.

### Efficacy of treatment

All patients in both groups reported symptomatic relief by day 5. The mean day of improvement of symptoms in the pipemidic acid group was day 2.96, and the mean for the nitrofurantoin group was day 3.12. These results did not differ significantly.

Of the pipemidic acid group, 1 patient still had microscopic signs of infection consisting of > 20 pus cells on wet smear and Gram-negative bacteria on Gram smear on day 5. On day 5 of the trial 2 of the 26 women in the nitrofurantoin group still had microscopic signs of infection. These results did not differ significantly.

On day 10 of the trial 3 patients in the pipemidic acid group had microscopic signs of infection (pus cells > 10 on high-field microscopy) and significant bacteruria. One patient had an *Escherichia coli* infection which was resistant to pipemidic acid. Her original culture had shown *E. coli* which was susceptible to pipemidic acid. It was impossible to determine whether this was a case of superinfection or resistance developing during therapy. The other 2 patients were superinfected with *Streptococcus faecalis* resistant to pipemidic acid. There were no cases of relapse during treatment in the pipemidic acid group.

Of the nitrofurantoin group, 5 patients had microscopic signs of infection after 10 days' treatment. Two had cultures positive for the initial organism, which was sensitive to nitrofurantoin. Her original culture had shown *E. coli* which was susceptible to pipemidic acid. It was impossible to determine whether this was a case of superinfection or resistance developing during therapy. The other 2 patients had superinfection with an organism sensitive to nitrofurantoin and 1 patient was superinfected with a resistant *Pseudomonas*. All 3 of these patients' urine was free of the initial infecting organism which had been nitrofurantoin-sensitive.

### Summary of day 10 results

Of the 26 patients admitted to each of the treatment groups, 23 in the pipemidic acid group and 21 in the nitrofurantoin group were free of lower urinary tract infection on day 10. These results do not differ statistically. In the pipemidic acid group there were 2 cases of superinfection with a resistant organism and 1 case of either superinfection or resistance developing during treatment. In the nitrofurantoin group there were 2 cases of relapse and 3 cases of superinfection. These results do not differ significantly.

### Complications

The incidence and intensity of side-effects in the two groups were similar, and did not differ significantly. Two patients in each group complained of slight nausea lasting for the first 4 days of pipemidic acid treatment and the first 2 days of nitrofurantoin treatment. Two patients in the pipemidic acid group and 1 patient in the nitrofurantoin group complained of abdominal discomfort lasting 2 - 5 days.

Two patients in each group complained of vertigo or headache. The vertigo lasted significantly longer in the nitrofurantoin group (10 days compared with 4.5 days in the pipemidic acid group \( P < 0.05 \)). One patient in the nitrofurantoin group had a moderate skin rash which lasted 5 days.

### Discussion

The results of this study indicate that pipemidic acid is an acceptable alternative to nitrofurantoin in the treatment of uncomplicated lower urinary tract infections in women. There were no cases of relapse in the pipemidic acid group. The 2 cases of relapse in the nitrofurantoin group were evaluated cystoscopically and by retrograde pyelography after completion of the trial. No significant urinary tract abnormality was diagnosed in these volunteers. Previous authors have found a correlation between relapse with the same strain and bacteruria localised in the upper collecting systems. Most authors agree that if the same organism sensitive to the same drug recurs after discontinuation of therapy, the dose or duration of therapy was inadequate.

Three patients (11.5%) in the pipemidic acid group and 3 patients (11.5%) in the nitrofurantoin group were re-infected with new organisms. These patients were investigated for anatomical or functional abnormalities of the urinary tract, but no significant abnormalities were diagnosed. The single case of *E. coli* infection resistant to pipemidic acid is regarded as a case of re-infection rather than as one of resistance developing during treatment. R-plasmids do not confer 4-quinolone resistance and the only way bacteria can resist them is by mutation. The emergence of resistance by initially susceptible organisms during the course of therapy with pipemidic acid is significantly lower than with its parent compound nalidixic acid.

Cessation of symptoms was not a reliable guide to efficacy of treatment since all patients became asymptomatic within the first 5 days of treatment. Of these, 3 women (1 in the pipemidic acid group and 2 in the nitrofurantoin group) still had microscopic signs of infection. This confirms that there is a poor correlation between resolution of symptoms and duration of efficacy of treatment. In both groups 100% were symptom-free by day 5, while the cure rate was only 94%. At the end of the trial period, all women were symptom-free, but the cure rate was 88.5% in the pipemidic acid group and 81% in the nitrofurantoin group.

Adverse reactions were noted in 6 patients in both groups. None of the side-effects necessitated cessation of treatment. There were no patients with serious side-effects such as peripheral neuropathy or episodes of pleuroneumonic reactions in the nitrofurantoin-treated subjects.

We conclude that pipemidic acid is a satisfactory and effective urinary antiseptic. In a dosage of 400 mg twice a day it is comparable to nitrofurantoin 50 mg 4 times a day in the treatment of uncomplicated lower urinary tract infections in women.

We acknowledge the supply of Septidron by Noristan Laboratories (Pty) Ltd.
Mebendazole 500 mg for single-dose treatment of nematode infestation

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Summary

Single 500 mg doses of mebendazole (Vermox; Janssen) were administered to 211 children aged 5 - 16 years in a rural area for treatment of single and mixed infestations with Ascaris lumbricoides, hookworm and Trichuris trichiura; the majority of subjects had low egg counts. Treatment was particularly effective against Ascaris, less effective against hookworm and promising against Trichuris. In most refractory cases egg output was considerably reduced. Treatment resulted in fewer Ascaris (95%) and hookworm (84%) ova reaching the environment. The results compare well with those obtained elsewhere in the world. One case of Strongyloides stercoralis infestation appeared after treatment. The drug was well tolerated and no side-effects were observed.


Single and mixed helminth infestations are common in many rural areas of the eastern Transvaal. Besides the two schistosomes which infect humans, the nematodes Ascaris lumbricoides, hookworm and to a lesser extent Enterobius vermicularis, Trichuris trichiura, Strongyloides stercoralis and tapeworms, are the most prevalent.1

The treatment of subjects in rural situations poses two main problems: (i) until recently the use of broad-spectrum anthelmintics required repeated low-dose regimens for up to 3 or 4 days to effect a cure — this incurred extra cost, logistic inconvenience and reduced compliance by the last day; and (ii) the infested and thus the treated subjects live in a 'wormy' environment and soon become re-infested. The possible solution to the former problem lies in development of an effective broad-spectrum anthel­mintic which can be administered as a single dose with high cure and egg-reduction rates in all age groups. On the other hand, the problem of re-infestation means that preventive measures are required as a back-up to treatment, which may have to be repeated over a period of time.

In the past mebendazole (Vermox; Janssen) has proved effective in multiple low-dose and, more recently, in single high-dose regimens, giving high cure and egg-reduction rates in all age groups with single or mixed infestations.2 Two recent trials, one assessing single doses of 100, 200, 500 and 600 mg and another single 500 mg doses, demonstrated the efficacy of the drug and its lack of contraindications and side-effects.

The aim of the present study was to assess the efficacy of a 500 mg dose of mebendazole for single-dose treatment of children with single and mixed infestations with Ascaris, hookworm and Trichuris in the south-eastern Transvaal Lowveld. Mebendazole has not been used extensively on a 500 mg single-dose schedule in the RSA.

Subjects and methods

A group of 217 schoolchildren from three semi-intensive farming areas (Karino, Hazyview and Brondal) near Nelspruit in the eastern Transvaal were treated for helminth infestations. Of the 211 (121 males, 90 females) who were finally assessed, 147 (69,7%)...