Treating Acute Urinary Tract Infections

An RCT of 3-day versus 7-day Norfloxacin

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SUMMARY

A randomized, controlled trial was carried out to compare two courses of treatment in women with acute urinary tract infection in general practice. The 3-day course of treatment was found to be as effective as, and cheaper than, the 7-day therapy.

RÉSUMÉ

On a procédé à un essai randomisé et contrôlé dans le but de comparer deux régimes thérapeutiques chez les femmes atteintes d'infection urinaire aiguë dans un contexte de médecine familiale. Les résultats révèlent que le traitement de trois jours est aussi efficace et moins coûteux que le traitement de sept jours.

Can Fam Physician 1993;39:514-518.

UNCOMPLICATED URINARY TRACT infection (UTI) is common in women, especially in general practice.[1,2] The length of treatment of uncomplicated UTI, ie, 3 days versus 7 to 10 days, has been a hot topic during the past 10 years.[3-10]

Both treatment schedules have their benefits. Advantages of short-term treatment are better patient compliance, lower cost, and less frequent adverse effects.[11] An advantage of long-term treatment is the reduced possibility of recurrent infections.[12] Although some studies promote 3-day treatment, most have not had a sufficient number of patients to support their conclusions.[8,10,11,13,14]

Recently, a new group of antimicrobial agents has been developed, of which norfloxacin is often prescribed for the treatment of UTI.[15,16] Many papers have been published on the clinical efficacy of different lengths of treatment with norfloxacin for UTI.[17-19] Although a 3-day course of trimethoprim-sulfamethoxazole is now accepted as adequate for the treatment of UTI, no extrapolations from one antibiotic to another should be made.[8,20]

In this study, a 3-day course of norfloxacin was compared with a 7-day course for the treatment of women visiting their family physicians in the southern part of The Netherlands with complaints of acute uncomplicated UTI. End points of evaluation were the clinical and bacteriologic outcome, the number of adverse effects, and cost.

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METHODS

Included in the survey were women who were not pregnant aged 18 to 65 years consulting their general practitioners with complaints of at least one of the following symptoms during the last 24 hours: dysuria, strangury, and frequent or urgent urination. Excluded from the survey were patients who had signs and symptoms of pyelonephritis, known abnormalities of the renal tract, or diabetes. Also excluded were patients who had received either chemotherapy or antibiotics during the past month, patients who were known to be hypersensitive to nalidixic acid derivatives, and patients who had had a UTI within the last 3 months. General practitioners

(n = 12) from the southern The Netherlands were asked to participate in this study.

The protocol was approved by the Medical Ethics Committee of Maastricht University Hospital. All patients received oral and written information and all gave informed consent. They were allocated to one or the other course of treatment in a double-blind, randomized way by means of the double dummy technique. The two strategies were 400 mg of norfloxacin twice daily for 7 days or 400 mg of norfloxacin twice daily for 3 days followed by 4 days of placebo twice daily.

A fresh urine sample was requested from all patients before the start of the medication, at the end of the medication (7 days later), and at least 6 weeks later. Patients were also asked to complete a questionnaire on compliance, relief of symptoms, and side effects. Patients were told to return to their general practitioners if symptoms did not disappear or if side effects occurred. Uropathogens were isolated and identified by standard microbiologic methods using API 20E (API Montalieu, Vercieu, France) for Enterobacteriaceae.

Cultures of 10^5 colony forming units (cfu)/mL or more were considered to be positive. Cultures with two or more pathogens were regarded as mixed cultures. To evaluate patient compliance 1 week after starting medication, the presence of growth-inhibiting factors was tested. Clinical outcome was evaluated 1 and 6 weeks after starting medication through the questionnaire and data from the general practitioners. If patients returned to their physician with persistent complaints of UTI, the therapy was considered a failure.

Bacteriologic outcome was scored as the elimination, persistence, or recurrence of the same or a different microorganism.[11] No distinction was made between relapse and reinfection because, from the standpoint of the patient (and the physician), this distinction is unimportant.[8]

The short-term cure rate was defined as the number of patients from whom the initial pathogen was eliminated, compared with the number of evaluable patients. The accumulated cure rate was defined as the number of patients in whom cure was noted at the last control visit, compared with the number of evaluable patients.[14]

Adverse effects were also evaluated on the basis of the data on the questionnaire and information supplied by the physicians. If medication was stopped because of side effects, the therapy was considered a failure.

Statistical significance was calculated by means of χ^2 analysis.

For an evaluation of the cost, it was assumed that a 3-day course was cheaper unless there was a statistically significant increase in the number of recurrences or a worse clinical outcome in this group. On the other hand, the shorter period of medication could be expected to produce fewer side effects in the 3-day treatment group. Therefore, the number of failures and the number of patients with additional visits to their general practitioners or to the urologist were compared in both groups. Assuming a short-term cure rate of 95% with 7 days of treatment, a type I error (α) of 0.05, a type II error (β) of 0.20, and a clinically important difference between treatments (δ) of 10%, 140 patients in each group are required.[8,11,13,21]

The randomization was done by Merck Sharp & Dohme (Haarlem, The Netherlands), which also supplied the medication. The code was not known to the investigators, the physicians, or the patients. It was kept at the laboratory in a sealed envelope and was broken 6 weeks after the last patient was included.

Table 1. **Microorganisms isolated in treatment groups**

MICROORGANISMS	TREATMENT GROUP N (%)*	
	3 DAYS	7 DAYS
Escherichia coli	104 (73)	111 (79)
Proteus sp	16 (11)	6 (4)
Staphylococcus sp	15 (10)	16 (11)
Other Enterobacteriaceae	9 (6)	5 (4)
Streptococcus sp	—	3 (2)

**Percentage of positive urine samples.*

Table 2. **Relief of symptoms 1 week and 6 weeks after initiation**

OUTCOME	TREATMENT GROUP N (%)* 3 DAYS	7 DAYS	*P* VALUE
1 WEEK AFTER INITIATION	175	173	0.13
Relief of symptoms	166 (95)	155 (90)	
Same or worse complaints	9 (5)	18 (10)	
6 WEEKS AFTER INITIATION	141	137	0.8
Relief of symptoms	131 (93)	127 (93)	
Same or worse complaints	10 (7)	10 (7)	

** % of total number of patients.*

RESULTS

From April 1989 to October 1990, 395 patients were randomized to one of the two groups. One hundred ninety-nine patients were allocated to the 3-day treatment group and 196 were allocated to the 7-day treatment group. Eleven patients (six in the short-term and five in the long-term group) did not return at all, so 384 patients (193 and 191, respectively) were evaluable. A bacteriologically positive urine sample was obtained from 144 and 141 patients, respectively. Escherichia coli was the most frequently isolated organism (104 and 111, respectively), followed by *Staphylococcus* sp and *Proteus* sp. No differences between the two treatment groups were observed (*Table 1*).

Patient compliance was recorded by using the answers provided by the patients on the questionnaire and assessing the presence of growth-inhibiting factors in the urine 1 week after starting medication. The patients reported 96% compliance; however, in only 76% of the urine samples of the 7-day treatment group was the presence of a growth-inhibiting factor demonstrated.

For the clinical outcome 1 week after starting medication, 348 patients were evaluable, 175 in the short-term treatment group and 173 in the long-term treatment group. No significant differences in clinical outcome were observed between the groups (*Table 2*). Twenty patients (10 in each group) still had complaints of dysuria; 15 of these (seven and eight patients in the short-term and long-term groups, respectively) returned to their family doctors. Another antibiotic was prescribed to four out of the seven in the first group and to seven out of the eight in the second group. Trimethoprim-sulfamethoxazole for 5 to 7 days was then the drug of choice. After the first week without any treatment, three patients in the 3-day treatment group and eight in the 7-day group recovered. Some patients had symptoms only after the first week (but not at the first control visit).

The bacteriologic outcome was assessed as the short-term cure rate and the accumulated cure rate 1 week and 6 weeks after therapy, respectively. The short-term cure rates were 92% and 95% for the 3-day and 7-day groups, respectively ($P = 0.30$). The accumulated cure rates were 82% for the 3-day group and 88% for the 7-day group ($P = 0.30$) (*Table 3*). Adverse effects (gastrointestinal complaints, followed by headache and fatigue) occurred in 26 patients (13%) and 29 patients (15%), respectively ($P = 0.79$).

The 3-day course of treatment was cheaper. Seven patients from the 3-day group and eight patients from the 7-day group returned to their general practitioner. No difference was seen in the follow up of these patients; most received an antimicrobial agent and none were sent to a hospital for further examination. Attention was also paid to the period of sick leave granted. No sick leave was recorded for women without a paid job. No significant differences were found between the two treatment groups. In total, 28 patients had a period of sick leave. The mean number of days of absence from work was 2.8 days in the 3-day group and 2.6 days in the 7-day group. The mean number of days of sick

Table 3. **Short-term and accumulated cure rates:** *Assessment 1 week and 6 weeks after therapy.*

TIME AFTER START OF THERAPY	TREATMENT GROUP				P VALUE
	3 DAYS		7 DAYS		
	TOTAL	N (%)	TOTAL	N (%)	
1 week	169	155 (92)	169	161 (95)	0.30
6 weeks	152	124 (82)	144	126 (88)	0.30

leave per subject (patients without sick leave included) was 0.4 days.

DISCUSSION

This study observed the recommendations made by Fihn and Stamm[11] and the criteria suggested by the Working Party of the British Society of Antimicrobial Chemotherapy.[22] Even after 6 weeks, the number of patients with clinical symptoms of UTI and with a bacteriologically proven UTI was sufficient to avoid a type II error.

The difference between compliance levels reported by the patients on the questionnaires and those revealed by urinanalysis demonstrated that the patients' answers were not fully reliable. This was also mentioned by Urquhart and colleagues,[23] who tried to overcome this problem by developing a computerized pillbox to optimize the measurement of patient compliance.

Clinical outcome was considered the most important parameter for the patient. No difference in clinical failure rate was observed between the two treatment groups. Similar failure rates have been observed in other studies. Remarkably enough, when the patients (seven and eight in the short-term and long-term groups, respectively) returned to their general practitioner, a different medication was prescribed in four and seven cases, respectively, irrespective of the presence of significant bacteriuria. A positive urine culture was present in only two and five patients, respectively.

In the economic evaluation, no significant differences between the treatment regimens were observed, either in terms of return to the general practitioner or in terms of sick leave. The only difference, then, was the initial cost of the medication – which was, of course, lower in the shorter treatment course. It was significant that 76% of the patients in the 7-day treatment group (using data on growth-inhibiting factors in urine) complied. This means that 24% of patients do not complete their therapy. It is not known whether they stopped after 1 day or after 5 days, but the fact that so many patients did not complete their antibacterial course suggests that general practitioners could be misled about the efficacy of 7-day treatment programs for UTI.

CONCLUSION

The results of this randomized, double-blind study, conducted with a sufficient number of patients and adequate follow up, indicate a similar clinical and bacteriologic cure rate 1 week and 6 weeks after the start of the medication, the same number of adverse effects, and lower costs for the 3-day treatment. We can conclude from this that a 3-day course of norfloxacin is as effective as, and cheaper than, a 7-day course in the treatment of acute uncomplicated urinary tract infections in women who are not pregnant. ■

Acknowledgment

We thank general practitioners G.H.M.J. Beusmans, W.H.R. Croughs, H. van Hapert, M. Peeters, J.R.A.Y. van Rosy, J.A.G. Screever, A.J.M. Screever-Delahaye, J.J.M. Theunissen, F.E.G. Verhaegh, W.P.M. Vierhout, and F.W.A. Vissers for their cooperation in this study.

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