Single-dose and seven-day trimethoprim and co-trimoxazole in the treatment of urinary tract infection

R. H. JONES, MRCP, MRCGP

General Practitioner, Andover

SUMMARY. One hundred and sixteen adults with symptoms of acute urinary tract infection were randomly collected into four groups and given single-dose or seven-day treatment with trimethoprim or co-trimoxazole. Of the 105 patients who completed the study, bacterial urinary infection was present in 70 patients (67 per cent). The rates for symptomatic and bacterial cures were high and indistinguishable between the groups, and there was no difference in the rate of recurrence of urinary infection in the six weeks after treatment. Side effects were lower in the group receiving single-dose trimethoprim ($P=0.09$).

Introduction

URINARY tract infection (UTI) is common in general practice, with an annual incidence of 26 per 1,000 patients.[1] Single, relatively large doses of sulphonamides,[2] co-trimoxazole[3] and amoxycillin[4] have been shown to be effective in treating uncomplicated UTI. Because trimethoprim alone has been found to be as effective as co-trimoxazole in conventional doses for treating UTI,[5,6] it is logical to assume that single-dose trimethoprim will be equally effective; two recent studies support this assumption.[7,8] The present study was designed to compare efficacy and incidence of side effects in single-dose and seven-day treatment regimes for UTI using co-trimoxazole and trimethoprim.

Method

Patients. One hundred and sixteen adult patients with symptoms of UTI (frequency and dysuria with or without urgency and haematuria) seen in a group practice of six general practitioners were studied. The patients were selected on the basis of a clinical diagnosis of UTI requiring antibiotic treatment, and their informed consent was obtained. Patients with known sulphonamide or trimethoprim hypersensitivity, renal failure and blood dyscrasias, pregnant women and those who had received antibiotics within the previous two weeks were excluded from the study. Eleven patients failed to complete the study, leaving 105—97 women and eight men—whose mean age was 41.8 years, and age range 14–71 years.

At entry to the study, the general practitioner administered a questionnaire which asked for details of urinary symptoms and specific gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhoea, dyspepsia, sore mouth), skin rash, headache and dizziness. Each patient was then randomly allocated to one of four treatment groups, as follows:

Group A: Trimethoprim 100 mg tablets (Monotrim, Duphar Laboratories), two twice daily for seven days.

Group B: Trimethoprim 100 mg tablets, four as a single dose.

Group C: Co-trimoxazole (Septrin, Wellcome Medical Division), two tablets twice daily for seven days.

Group D: Co-trimoxazole, four tablets as a single dose.

Each co-trimoxazole tablet contained trimethoprim 80 mg and sulphamethoxazole 400 mg.

Allocation was double-blind with respect to drug therapy, although the patients were evidently aware of the duration of the treatment.

A midstream specimen of urine (MSU) was obtained before starting treatment and a dip-slide technique was used for culture. The specimens of urine were examined microscopically in the laboratory for the presence of pus cells. The dip-slide cultures were examined the following day, and a colony count of 100 or more was taken as equivalent to a bacterial count of, or greater than, 10^8 organisms/litre. Urinary tract infection was defined as the presence of 10^8 organisms/litre in the presence of pyuria. Antibiotic sensitivity testing on lysed blood agar was performed on direct cultures from pyuric specimens or subcultures from the dip-slide.

During the study period the patient was free to consult his or her general practitioner about persistence of symptoms or side effects of therapy.

One week after treatment began, the patient was again asked to provide an MSU and to complete another questionnaire. The MSU was examined in the same way as before. The second questionnaire enquired after the same symptoms as in the first questionnaire, but was expressed in lay terms.

Bacteriological cure was interpreted as eradication of significant bacteruria in the second MSU. Symptomatic cure was judged to have been achieved when the patient recorded resolution of the previous urinary symptoms. Side effects were said to have occurred when the second questionnaire indicated an unwanted symptom not present at the start of treatment.

Six weeks after completion of the study the case notes of all participants were reviewed to check for recurrence of UTI or the development of moniliasis requiring further contact with the general practitioner. Where there was recurrence of UTI, the notes were studied in more detail with regard to previous UTI and, at a second review six weeks later, the development of further urinary infection was investigated.

Differences between groups were analysed using a chi-squared test.

Results

Seventy patients (67 per cent) were found to have urinary tract infection as defined above; the pathogens isolated from their MSUs are shown in Table 1.

Of the 74 cultures of pathogens, 34 (46 per cent) were fully sensitive to antibiotics on testing. Twenty-two (50 per cent) of the 44 cultures of *Escherichia coli* showed a variety of patterns of resistance, with 15 being sulphonamide-resistant, nine ampicillin-resistant and four resistant to cephalosporins. Although fully sensitive to ampicillin, five out of six cultures of *Streptococcus faecalis* were resistant to co-trimoxazole, sulphonamides, and cephalosporins. Ampicillin and sulphonamide resistance was found in one each of the cultures of *Proteus* species. Overall the incidence of ampicillin resistance was 10 out of 74 cultures (14 per cent) and co-trimoxazole resistance five out of 74 (7 per cent).

Bacteriological cure was achieved in all but two patients: a female patient with an infection from a fully sensitive strain of *Staphylococcus albus* treated with co-trimoxazole for seven days still had the organism in pure culture after therapy, although her symptoms had resolved and pyuria was virtually abolished; a second female with a mixed growth of a co-trimoxazole-sensitive strain of *Proteus* sp. and a strain of *Strep. faecalis* had persisting infection from *E. coli* and *Proteus* after a single dose of co-trimoxazole, although her symptoms had also resolved and there was no pyuria.

Symptomatic cure was achieved in all four groups, ranging from 85 per cent to 92 per cent of patients, with no significant differences between treatment groups. Failure to relieve symptoms occurred in 13 patients, only six of whom had proven UTI. Five of these 13 patients were subject to recurrent UTI.

Recurrence of symptoms of UTI occurred within six weeks in eight patients, five of whom went on to develop further UTIs requiring investigation of their renal tracts, with anatomical abnormalities being found in two patients. There was no significant difference in recurrence rate between the single-dose and seven-day groups; although six of these patients had received trimethoprim (three single-dose and three seven-day treatment), and two had had co-trimoxazole (one single-dose and one seven-day treatment), there was no significant difference between drug therapies ($P=0.10$). Four patients developed vaginal moniliasis requiring treatment. These results are summarized in Table 2.

Side effects of treatment occurred in 21 patients, with several patients developing more than one unwanted effect. The incidence of side effects was lower in the single-dose trimethoprim group but this difference was not quite significant ($P=0.09$). The pattern of side effects is shown in Table 3.

Table 1. Pathogens in urinary tract infections.

	Positive cultures	
	Number	Percentage
Escherichia coli	44	*60*
Staphylococci (coagulase-negative)	8	*11*
Other coliforms	6	*8*
*Streptococcus faecalis**	6	*8*
Proteus spp.	6	*8*
Mixed growth	3	*4*
Other streptococci	1	*1*
Total	74	*100*

*With *Proteus* spp. in two MSUs and with *E. coli* in two MSUs.

Discussion

The finding of bacterial infection in two thirds of the patients admitted to the study is higher than the 40–50 per cent usually reported[1,9] and may reflect awareness on the part of the prescribing doctors of patients in whom frequency-dysuria is likely to be non-infective.

There was an expected predominance of coliform organisms in the infected urines[1,10] but with coagulase-

Table 2. Results of treatment.

Treatment	Number of patients	UTI		Bacteriological cure		Symptomatic cure		Recurrence of UTI		Moniliasis	
		n	%	*n*	%	*n*	%	*n*	%*	*n*	%
A. Trimethoprim 7 days	27	18	*67*	18	*100*	23	*85*	3	*17*	2	*7*
B. Trimethoprim single-dose	25	15	*60*	15	*100*	23	*92*	3	*20*	1	*4*
C. Co-trimoxazole 7 days	28	19	*68*	18	*95*	24	*86*	1	*5*	1	*4*
D. Co-trimoxazole single-dose	25	18	*72*	17	*94*	22	*88*	1	*6*	0	*4*

*Percentage of patients with confirmed UTI.

Table 3. Treatment groups and numbers of patients with side effects.

A. Trimethoprim 7 days (n=8)		B. Trimethoprim single-dose (n=2)		C. Co-trimoxazole 7 days (n=6)		D. Co-trimoxazole single-dose (n=5)	
Anorexia	2	Nausea	2	Nausea	1	Nausea	1
Nausea	2			Nausea + dizziness	1	Nausea + dyspepsia	1
Rash	1			Nausea + anorexia	1	Nausea + anorexia	1
Sore mouth + rash	1			Nausea, sore mouth + dyspepsia	1	Nausea + dizziness	1
Sore mouth	1			Rash	1	Dyspepsia	1
General malaise: nausea, dizziness, lassitude leading to cessation of therapy	1			Dyspepsia + vomiting	1		

negative staphylococci contributing over 10 per cent of the positive cultures. The importance of these organisms has previously been pointed out by Maskell and her co-workers[11] and this study confirms their findings that the majority of patients with staphylococcal UTI are young women. Bacterial resistance to ampicillin was found in 14 per cent of positive cultures; this was twice as frequent as co-trimoxazole resistance, suggesting that co-trimoxazole or trimethoprim may be more appropriate first-line treatments for urinary infections.

Bacteriological cure rates were high in all groups and are comparable with previous reports of single-dose and conventional therapies. The symptomatic cure rate was also high in this study, and is higher than in a recent comparative trial[12] of daily trimethoprim and twice-daily co-trimoxazole, each given for one week, in which symptomatic cure rates were 67 per cent and 72 per cent respectively. The only other published work[7,8] on single-dose trimethoprim does not assess symptomatic responses to therapy. It is interesting to note that in the two patients where there was bacteriological failure of therapy, their symptoms had resolved after one week and also that, despite five other urine cultures being co-trimoxazole-resistant, symptomatic and bacteriological cures were achieved in all five episodes. These findings suggest that some bacterial UTIs are self-limiting. There was also no difference in symptomatic cure rate between patients on single-dose and patients on seven-day regimes: this suggests that placebo effect in their treatment was not particularly important, which is at odds with the contention that some patients 'prefer to continue treatment for a day or two while symptoms linger'.[10]

Recurrence of infection within six weeks was similarly evenly distributed between single-dose and seven-day treatment groups, and although six of the eight patients with recurrent infection had been treated with trimethoprim this was not quite significant. Four of these eight patients (one from each group) were subsequently investigated because of recurrent UTIs and two were found to have abnormalities of the urinary tract (a bladder tumour and a pelvic kidney). This study does not support the suggestion[13] that failure of single-dose treatment to clear infection is a useful indicator of patients who require further investigation.

Vaginal moniliasis was a problem in only four patients—6 per cent of those receiving trimethoprim and 2 per cent of those receiving co-trimoxazole; these figures are lower than the 18 per cent and 5 per cent respectively reported for seven-day courses of daily trimethoprim and twice daily co-trimoxazole.[12]

The major difference between the effects of treatment is in the frequency of side effects. The number of side effects produced by single-dose trimethoprim is considerably less than other regimes, as is the number of patients developing side effects (8 per cent on single-dose trimethoprim compared with 20–30 per cent on other regimes). This is in accordance with the findings of Harbord and Gruneberg[7] in which there were no side effects attributable to single-dose trimethoprim, and comparable with the study of Lacey and colleagues[8] in which only three out of 96 patients given a single dose of trimethoprim experienced side effects.

In summary, single dose trimethoprim and co-trimoxazole are as effective as seven-day courses of these drugs in the treatment of UTI in general practice, although trimethoprim produces less side effects. The advantages of single-dose therapy are chiefly that cure rates are high, side effects fewer and the costs lower. If every general practitioner were to treat one episode of UTI each week, the difference in cost of therapy between

single-dose and seven-day treatments would be approximately £1 million each year. These benefits support the wider use of single-dose regimes.

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Address for correspondence

Dr R. H. Jones, 56 Junction Road, Andover, Hampshire SP10 3QU.

Measles vaccine

Favourable attitudes in the 'health team' are fundamental to the achievement of adequate levels of immunization in vulnerable children. A study has shown wide variation in the views of professionals to immunization, suggesting that children are often denied protection because of exaggerated concern about adverse reactions to the vaccine.

Source: Berkeley MIK. Measles—the effect of attitudes on immunization. *Health Bulletin* 1983; **411:** 141-147.