Trimethoprim and co-trimoxazole in the treatment of acute urinary tract infections: patient compliance and efficacy

D. A. ANDREWES, MB, BS, DRCOG, P. J. CHUTER, MA, BM, B.CH, MRCP, M. J. DAWSON, MA, MB, B.CH, DRCOG, B. W. EDEN, MB, CH.B, MRCGP, R. M. A. MOORE, MB, B.CH, MRCGP, DRCOG, D. S. FREESTONE, MB, BS, DLO, DRCOG, C. A. MORRIS, B.SC, MD, DipBact

SUMMARY. Patient compliance and drug efficacy and side-effects were compared in two groups of patients with symptoms of acute lower urinary tract infections. One group was treated with trimethoprim, one tablet (300 mg) once a day, and the other with co-trimoxazole, two tablets (160 mg trimethoprim, 800 mg sulphamethoxazole) twice a day; both treatments were prescribed for seven days. Patient compliance was significantly greater with trimethoprim: corrected percentage compliance rates were 97·5 per cent for trimethoprim and 79·1 per cent for co-trimoxazole ($p<0·05$). Trimethoprim and co-trimoxazole were of equivalent effectiveness in the control of symptoms. Side-effects were more frequent with co-trimoxazole, but the difference was not significant.

Introduction

PATIENT compliance with prescribed treatment for acute illness depends on a number of factors: the presence of symptoms (Mohler *et al.*, 1955; Charney *et al.*, 1967; Drury *et al.*, 1976), the occurrence of side-effects (Wynn-Williams and Arris, 1958), the number of drugs administered concurrently (Malahy, 1966), the number of treatments required in a day (Blackwell, 1972), the comprehension of the patient (Parkin *et al.*, 1976), the clarity of treatment instructions (Wandless and Davie, 1977) and convenience of administration (Porter, 1969). Treatment that is highly effective in the control of an acute infection may lead to poor compliance during the last days of the treatment course (Mohler *et al.*, 1955; Charney *et al.*, 1967; Drury *et al.*, 1976), and paradoxically a less effective treatment may enjoy better compliance in these circumstances. Compliance may also influence the occurrence of side-effects, since a higher level of compliance leads to larger doses of the drug being taken. Alternatively, amalgamation of the daily dose of a drug into a single tablet, while facilitating patient compliance, may cause more side-effects, particularly for drugs prone to cause gastro-intestinal irritation and if side-effects are related to peak drug plasma concentrations.

In our study we compared compliance of drug regimens of a single daily tablet of trimethoprim and two tablets twice daily of co-trimoxazole, both prescribed as seven-day courses for women with symptoms of acute lower urinary tract infections. The study also gave an opportunity to compare efficacy and the occurrence of side-effects associated with these two regimes.

Method

Fifty-three female patients aged over 18 years with symptoms of acute lower urinary tract infections (dysuria and/or frequency) attending group practices in Telford or Shrewsbury were included in this investigation. Patients who were pregnant, those with known abnormalities of the urinary tract, with a history of urinary calculus, a history of urinary tract infection within the preceding month, any severe chronic disease requiring treatment with prescription-only medicines or evidence of impaired renal or hepatic function or blood dyscrasias were excluded.

Mid-stream samples of urine were collected, dipspoons inoculated and transported to the Public Health Laboratory for incubation at 37°C for 18 hours. Sensitivities were determined by a diffusion test on solid

D. A. Andrewes, P. J. Chuter and M. J. Dawson, General Practitioners, Telford; B. W. Eden and R. M. A. Moore, General Practitioners, Shrewsbury; D. S. Freestone, Wellcome Research Laboratories, Beckenham, Kent; C. A. Morris, Director, Public Health Laboratory, The Royal Shrewsbury Hospital (Convenor).

Table 1. Age, symptomatology, past history and bacteriology of patients treated for urinary infections.

	Patients presenting with bacteriuria		Patients presenting without bacteriuria	
	Treated with co-trimoxazole (n=15)	Treated with trimethoprim (n=14)	Treated with co-trimoxazole (n=9)	Treated with trimethoprim (n=10)
Average age	32.7 yrs	29.9 yrs	31.7 yrs	27.8 yrs
(Range)	24-69 yrs	18-68 yrs	20-45 yrs	18-47 yrs
Duration of symptoms before start of treatment in days	5.5	4.3	7.0	6.2
(Range)	1-35	1-8	1-21	1-15
Percentage of patients with symptoms before treatment (average symptom score in brackets)†				
Dysuria	*93* (2.20)	*100* (2.00)	*89* (1.78)	*80* (1.50)
Frequency	*100* (2.50)	*100* (1.93)	*89* (2.00)	*90* (2.30)
Chills	*80* (0.93)	*57* (0.64)	*44* (0.33)	*0* —
Haematuria	*27* (N.C.)	*29* (N.C.)	*33* (N.C.)	*10* (N.C.)
Past history				
Cystitis	12 *(80%)*	9 *(64%)*	4 *(44%)*	6 *(60%)*
<4 attacks	6	4	2	3
4-10 attacks	3	2	1	1
>10 attacks	3	2	1	2
Pyelonephritis	1††	1	—	—
Culture				
E. coli	12ø	11□		
S. albus	1*	1		
S. aureus	1	—		
Proteus spp.	—	1		
Mixed	1x	1**		

* Resistant to trimethoprim and sulphafurazole.
x *E. coli* and *S. faecalis* resistant to sulphafurazole; *S. albus* sensitive to trimethoprim and sulphafurazole.
** *E. coli* and *S. faecalis* resistant to sulphafurazole.
ø 3 isolates resistant to sulphafurazole.
N.C. = not calculated.
† 3-point scale: mild 1.0, moderate 2.0, severe 3.0.
□ 2 isolates resistant to sulphafurazole.
†† Also had attacks of cystitis.

media against trimethoprim (1·25 μg), sulphafurazole (100 μg) and other antibiotics. Urine was tested for the presence of albumin and glucose and the centifuged deposit examined microscopically.

Immediately following collection of the first urine sample, patients were allocated by random selection for treatment with either co-trimoxazole 960 mg (equivalent to two tablets, each containing 80 mg trimethoprim and 400 mg sulphamethoxazole) twice daily, or trimethoprim 300 mg (equivalent to a single tablet) daily for seven days. Drugs were supplied in identical code-numbered amber glass jars, labelled with directions for use and shielded by corrugated cardboard sleeves to conceal the identity of the contents. Each jar contained either 32 tablets of co-trimoxazole or eight tablets of trimethoprim. Each patient was asked to return to the doctor if symptoms failed to regress within 72 hours.

Patients were asked to complete a card each day for seven days from the start of treatment to record details of the occurrence and severity of symptoms of dysuria, frequency, fever, malaise, rash, nausea, vomiting, indigestion and sore mouth/tongue. Fourteen days after the start of treatment, patients provided a second mid-stream urine sample for microscopy and culture, returned their symptom card and their treatment jar for assessment of compliance and were questioned about any other symptom events occurring in the interval. Recurrence of infection within six weeks of entry into the study was recorded.

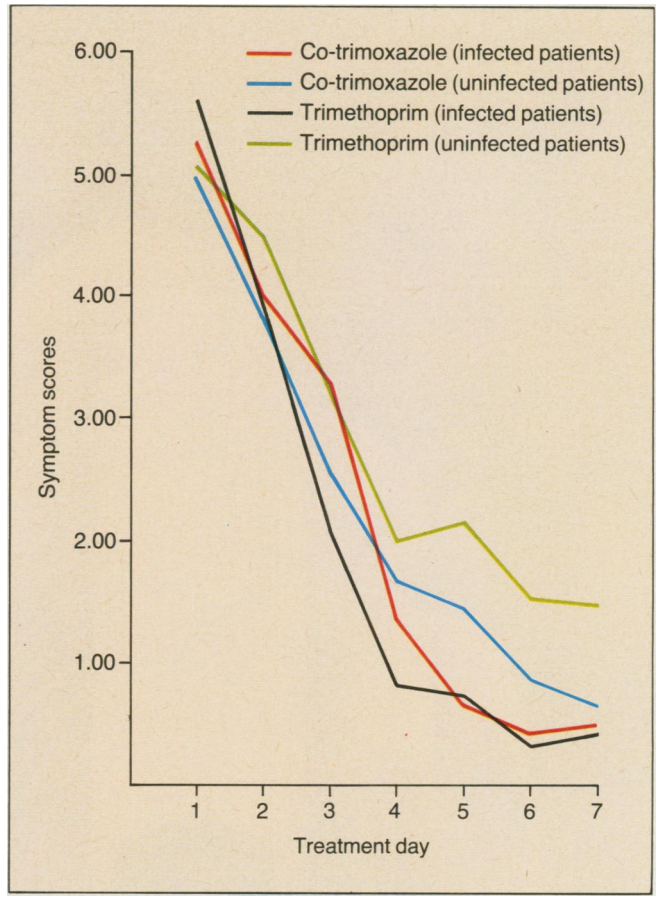
Results

Of the 53 patients entered into the study, 27 were treated with co-trimoxazole and 26 with trimethoprim. Five patients (three issued with co-trimoxazole and two with trimethoprim tablets) failed to return treatment jars, symptom cards, provide a second urine sample or attend for follow-up. The remaining 48 patients comprised 29 with bacteriuria, 24 of whom also had pyuria and 19 whose first urine sample was bacteriologically sterile. At entry into the study, the urines of 26 of 29 patients with bacteriuria contained $>10^5$ organisms/ml. Two patients were included with $10^{4.7}$ organisms/ml of urine, and one with $10^{4.6}$ organisms/ml of urine. The urines of all three of these patients contained pus cells. Details of the age, duration of symptoms before treatment, presenting symptomatology and previous history of urinary infections are shown in Table 1. These groups did not differ

Table 2. Patient compliance with treatment prescribed assessed by tablet counts.

	Co-trimoxazole	Trimethoprim
Number of patients assessed	22	23
Number of patients removing prescribed quantity of tablets from treatment jar	7 (32%)	15 (65%)
Number of patients removing tablets in excess of the prescribed quantity	4 (18%)	5 (22%)
Number of patients removing:		
1 to 2 days' treatment less than prescribed	3 (14%)	2 (9%)
3 to 5 days' treatment less than prescribed	2 (9%)	0 (-)
>6 days' treatment less than prescribed	6 (27%)*	1 (4%)
Percentage compliance $\frac{\text{Number of tablets removed}}{\text{Number of tablets prescribed}} \times 100$		
All patients	73.9%	97.5%
Corrected by exclusion of patients where treatment was interrupted by side-effects*	79.1%	97.5%

*Course of treatment interrupted by side-effects in two patients.



Symptoms and day of treatment. Average summated symptom scores per treatment day.

significantly (five per cent level), comparisons being made by t-tests, appropriately modified where necessary, to account for inequality of variance.

Bacteriology

Escherichia coli was isolated from 23 (79 per cent) of the 29 infected urines, of which five (22 per cent) isolates were resistant to sulphafurazole. All isolates of *E. coli* were sensitive to trimethoprim. *Staphylococcus albus* and *S. aureus, Streptococcus faecalis* and *Proteus* species were isolated from the other six infected urines. The spectrum of infecting organisms was similar in the two groups of patients (Table 1).

Second urine samples were collected from 27 of the 29 patients with bacteriuria. All 12 patients who received trimethoprim, and 12 of 15 patients treated with co-trimoxazole, were bacteriologically cured, regardless of the infecting species of bacteria or its antibiotic sensitivities. In three patients who failed to respond bacteriologically to treatment with co-trimoxazole, there was persistence or recurrence of symptoms, and in one patient in the group treated with trimethoprim, whose urine no longer contained bacteria following treatment, symptoms continued until therapy was changed to talampicillin.

Patient compliance

Three patients did not return their treatment jars. Patient compliance was therefore assessed in 22 patients treated with co-trimoxazole and 23 treated with trimethoprim alone. The correct number of tablets was removed from the treatment jars by 15 (65 per cent) of those treated with trimethoprim but by only 7 (32 per cent) of those prescribed co-trimoxazole, a difference which is statistically significant ($p<0.05$). Compliance assessments (Table 2) showed the generally superior compliance associated with the single tablet daily dosage regimen. Percentage compliance rates were 97·5 per cent for trimethoprim and 73·9 per cent for co-trimoxazole ($p<0.05$). Even if we exclude from the analysis two patients in whom treatment with co-trimoxazole was interrupted by side-effects, the percentage compliance rate for co-trimoxazole remained at less than 80 per cent.

Clinical response

The severity of symptoms (dysuria, frequency, fever and malaise) was assessed daily by the patient for seven days from the start of treatment using an arbitrary scale rising from 0 (no symptoms) to 3 (severe). The figure shows the average rated symptom scores per treatment day for infected and uninfected groups of patients treated with trimethoprim and co-trimoxazole. In infected patients, symptoms resolved at least as rapidly with trimethoprim as with co-trimoxazole. Average symptom scores also fell in patients for whom bac-

teriuria was not demonstrated, although the falls were somewhat less rapid.

Side-effects

Daily diary recording of side-effects provides a sensitive monitoring system which is useful in comparative studies but tends to inflate the number of side-effects reported. Diary records were completed by 23 of the 24 patients in each treatment group. Side-effects were documented by 15 (61 per cent) of patients treated with trimethoprim and 17 (70 per cent) of those treated with co-trimoxazole, and were of sufficient severity for treatment to be stopped in two of these patients. The predominating side-effects were nausea and indigestion, which were of similar frequency in both groups. Two and five patients treated respectively with trimethoprim and co-trimoxazole recorded that they had a sore mouth, and a rash occurred in another patient receiving co-trimoxazole. In general, somewhat fewer side-effects occurred in the group treated with trimethoprim, but the differences did not achieve statistical significance.

Discussion

Our tablet counts showed that patients complied better with the single daily tablet dose regime of trimethoprim than with the four tablet daily dose regime of co-trimoxazole. No indications were given to patients that compliance assessments were being carried out and we do not believe that patients adjusted the number of tablets remaining in returned treatment jars. The results of treatment with trimethoprim and co-trimoxazole do not differ significantly, either in the percentage of patients cured or the speed of resolution of symptoms. Thus, the different compliance cannot be explained by differences in efficacy. Indeed, the marginal superiority of trimethoprim may perhaps relate to the superior compliance associated with this simpler regime.

Side-effects were somewhat more frequent following administration of co-trimoxazole than trimethoprim, but these differences were not significant and it seems likely to be only a minor factor in the different compliance of the two treatments. Brumfitt and Pursell (1972) and Lacey and colleagues (1980) reported over twice as many side-effects with co-trimoxazole as with trimethoprim in their comparative trial where both drugs were given twice daily. The difference in incidence of side-effects is less in our study, but it is possible that a greater difference might have been evident if the compliance of the two treatments had been equivalent.

Gatley (1968) showed a direct relationship between the number of tablets prescribed daily and non-compliance. A tablet of co-trimoxazole ('Septrin') weighs 505 mg, while that of trimethoprim ('Syraprim') weighs 350 mg. The daily ingestion of the single smaller tablet is probably an important factor and it seems that the differences in compliance between the two treatment regimes may relate to their relative convenience and acceptability.

It is suggested that trimethoprim and a sulphonamide act synergistically and that their concurrent administration, by inhibiting successive stages in the formation of tetrahydrofolate by bacteria, would be likely to delay the emergence of resistant organisms (Darrell *et al.*, 1968). In this study, over 20 per cent of isolates of *E. coli* were sulphonamide resistant and the sulphonamide component of co-trimoxazole may contribute little to the control of infection in these patients. Nevertheless, evidence has been presented which indicates possible synergy between trimethoprim and sulphonamides, even for the sulphonamide-resistant strains of *E. coli* (Sourander *et al.*, 1972; Grüneberg 1975). Trimethoprim should be prescribed for patients known to be hypersensitive to sulphonamides, but for others the doctor must decide whether to prescribe co-trimoxazole, which may give rise to more side-effects, or to favour trimethoprim alone, which might speed the appearance of trimethoprim-resistant organisms. Trimethoprim resistance can be expected to pose a greater threat in hospital patients than in the community (Huovinen and Toivanen, 1980), perhaps because of the increased risk of cross-infection or greater use of trimethoprim alone in hospitals.

The use of trimethoprim has been the subject of recent editorials in the *Lancet* (1980) and the *British Medical Journal* (1980); these include helpful summaries of the literature and also define some areas in which our present knowledge of the relative merits of trimethoprim alone and of co-trimoxazole is incomplete and in need of further appraisal.

References

Blackwell, B. (1972). The drug defaulter. *Clinical Pharmacology and Therapeutics,* **13**, 841-848.

British Medical Journal (1980). Bacterial resistance to trimethoprim. **281**, 571-572.

Brumfitt, W. & Pursell, R. (1972). Double-blind trial to compare ampicillin, cephalexin, co-trimoxazole and trimethoprim in treatment of urinary infection. *British Medical Journal,* **2**, 673-676.

Charney, E., Bynum, R., Eldredge, D., *et al.* (1967). How well do patients take oral penicillin? A collaborative study in private practice. *Pediatrics,* **40**, 188-195.

Darrell, J. H., Garrod, L. P. & Waterworth, P. M. (1968) Trimethoprim: laboratory and clinical studies. *Journal of Clinical Pathology,* **21**, 202-209.

Drury, V. W. M., Wade, O. L. & Woolf, E. (1976). Following advice in general practice. *Journal of the Royal College of General Practitioners,* **26**, 712-718.

Gatley, M. S. (1968). To be taken as directed. *Journal of the Royal College of General Practitioners,* **16**, 39-44.

Grüneberg, R. N. (1975). The use of co-trimoxazole in sulphonamide-resistant *Escherichia coli* urinary tract infection. *Journal of Antimicrobial Chemotherapy,* **1**, 305-310.

Huovinen, P. & Toivanen, P. (1980). Trimethoprim resistance in Finland after five years' use of plain trimethoprim. *British Medical Journal,* **1**, 72-74.

Lacey, R. W., Lord, V. L., Gunasekera, H. K. W. *et al.* (1980). Comparison of trimethoprim alone with trimethoprim/sulphamethoxazole in the treatment of respiratory and urinary infections with particular reference to selection of trimethoprim resistance. *Lancet,* **1**, 1270-1273.

Lancet (1980). Trimethoprim, **1**, 519-526.

Malahy, B. (1966). The effect of instruction and labelling on the number of medication errors made by patients at home. *American Journal of Hospital Pharmacy,* **23,** 283-292.
Mohler, D. N., Wallin, D. G. & Dreyfus, E. G. (1955). Studies in the home treatment of streptococcal disease. I. Failure of patients to take penicillin by mouth as prescribed. *New England Journal of Medicine,* **252,** 1116-1118.
Parkin, D. M., Henney, C. R., Quirk, J. *et al.* (1976). Deviation from prescribed drug treatment after discharge from hospital. *British Medical Journal,* **2,** 686-688.
Porter, A. M. W. (1969). Drug defaulting in a general practice. *British Medical Journal,* **1,** 218-222.
Sourander, L., Saarimaa, H. & Arvilommi, H. (1972). Treatment of sulfonamide-resistant urinary tract infections with a combination of sulfonamide and trimethoprim. *Acta Medica Scandinavica.* **191,** 1-3.
Wandless, I. & Davie, J. W. (1977). Can drug compliance in the elderly be improved? *British Medical Journal,* **1,** 359-361.
Wynn-Williams, N. & Arris, M. (1958). On omitting P.A.S. *Tubercle,* **39,** 138-142.

Acknowledgement

We are grateful to Mr P. R. O. Smith for carrying out the statistical analyses.

Address for reprints

Dr C. A. Morris, Public Health Laboratory, The Royal Shrewsbury Hospital, Mytton Oak Road, Shrewsbury SY3 8XH.

Family practice in Massachusetts

An analysis of data collected from a one-year survey of the activities of seven residency trained family physicians practising in Massachusetts was carried out. These data were compared to a study of activities of Massachusetts general practitioners done in 1967-1968, and to the Virginia Study of 1976. Both hospital and health centre encounters were analysed.

The age distribution of the practices paralleled that of the general practitioners, particularly the younger general practitioners. The sex distribution was also comparable. However, over one third of all health problems recorded during the study were for preventive or non-illness visits. This represented a significant percentage increase over the general practitioners as well as the family physicians in the Virginia Study. The site of activity was also different in showing a 10 per cent increase in office visits over 1967-1968. Women's health issues, which include maternity and family planning care, represented a larger percentage of the practices of the residency graduates than was the case in the Virginia Study. Educational and health manpower implications of the study are discussed.

Source: Frey, J. J. & Rice, C. A. (1980). Family practice in Massachusetts: a comparison of residency trained family physicians with the general practitioner experience of 1967-1968. *Journal of Family Practice,* **10,** 663-671.