

RESEARCH

Sulphadimidine, co-trimoxazole, and a placebo in the management of symptomatic urinary tract infection in general practice

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PAINFUL and frequent micturition are symptoms commonly encountered in general practice particularly in females. Examination of a mid-stream urine specimen reveals significant bacteriuria in about half the females with symptoms implying that bacteria are actually multiplying in the bladder urine. (Kass, 1956; Mond *et al.*, 1965). Prevalence figures vary according to the criterion of infection adopted, but using Kass' criterion a rate of 8.3 per 1,000 patients at risk per year has been reported. (Mond *et al.*, 1965). The condition is, however, five times commoner in females than in males (Loudon and Greenhalgh, 1962).

It is accepted practice to give patients with symptoms a sulphonamide or an appropriate antibiotic when significant bacteriuria is demonstrated but there is disagreement about the most suitable preparation. Sulphonamides are commonly favoured because of their effectiveness, lack of side-effects, and low cost (Fry *et al.*, 1962; Gallagher *et al.*, 1965; Brumfitt and Reeves, 1969). Other workers have disputed the value of using a sulphonamide as the drug of first choice because of increasing *in vitro* resistance (Robertson, 1968; Sleet, 1969; Milne *et al.*, 1969). This trial was designed to find out whether the superior *in vitro* effectiveness of co-trimoxazole over a sulphonamide alone (Darrell *et al.*, 1968) could also be demonstrated *in vivo* in the management of acute urine infection in general practice.

When significant bacteriuria is not isolated from females with symptoms the value of antibacterial therapy remains to be demonstrated. It may be beneficial; Fuller (1966) felt that it was impossible in the psychological situation of general practice not to give active treatment to this group. It may be wasteful; Mond *et al.* (1965) stopped therapy if significant bacteriuria was not found in their patients. It may actually be harmful; Moore (1968) suspected that high-powered antibiotic therapy could interfere with the normal symbiosis of resident urethral and perineal organisms. Watanabe (1963) has shown that pathogens carrying transfer factors for multiple resistance can be selected in the rectum of patients receiving antibiotic therapy. These might subsequently infect the urine in patients with recurrent symptoms.

It was, therefore, considered that useful information might result from the double-blind comparison of co-trimoxazole with a placebo when symptoms were not accompanied by significant bacteriuria.

Patients and methods

1 *Patients*

During a 12 month period from July 1969 to July 1970 all patients above 15 and under 75 presenting with dysuria and frequency were referred to one of us (D.B.). The practice consists of a partnership of three principals and one trainee caring for 7,500 patients in Middleton, a small town of 50,000 people situated on the northern fringe of the Manchester industrial conurbation.

In addition, there are 1,000 patients at a local teacher-training college for men who were excluded from the study. The practice population has been demonstrated to be representative of the population as a whole.

Some patients were excluded from the trial. Pregnancy was a contra-indication, as was known sensitivity to sulphonamides, the presence of cardiac, renal, or hepatic failure, or concurrent antibacterial therapy.

2 *Diagnosis and investigations*

A mid-stream urine specimen was passed into a wide-mouthed, waxed hospital container. The problem of transporting the specimen of urine to the laboratory was overcome by the use of the dip-spoon described by Mackey and Sandys (1965); this also acted as a semi-quantitative organism-counting technique. The spoons contained McConkey agar and were inoculated the moment the urine was passed. Females with an organism count in the urine of 10^5 or more (Brumfitt and Reeves, 1969) were considered to have infected urines and were included in the main study. Females with an organism count in the urine of 10^4 or below were included in a second study involving the double-blind comparison of co-trimoxazole and a placebo. Counts between 10^4 per ml. and 10^5 per ml. were considered equivocal and patients with such counts were excluded.

All patients had a blood count (performed by a Coulter counter) before and two days after therapy. The blood specimens and initial urine specimens were taken to the pathology laboratory the same day but follow-up urine specimens were occasionally posted.

All females who developed significant bacteriuria on follow-up had an IVP examination.

3 *Sensitivity testing*

After overnight incubation of the dip-spoon the urinary pathogens were isolated and identified by subculture onto a McConkey agar plate followed by conventional biochemical tests. Diagnostic Sensitivity Test Agar (D.S.T.) Oxoid Code No.C.M.261 was prepared and sterilized and lysed horse blood was added to make a final concentration of five per cent. Using a standard light inoculum the organism was spread all over this plate and the discs for sensitivity testing (Mast Laboratories Ltd) were added. The plates were left at room temperature to allow diffusion of the antibiotic after which they were incubated at 37°C overnight.

Zones of up to 3–4 mm. around the disc were reported as sensitive. Very small colonies appearing inside the zone of inhibition were ignored since their presence was considered to be due to substances in the medium inhibitory to the agents under test. Isolates were tested for sensitivity to sulphadimidine (200 mcg/disc), tetracycline (100 mcg/disc), ampicillin (25 mcg/disc), colomycin (200 mcg/disc), nalidixic acid (30 mcg/disc), streptomycin (10 mcg/disc), nitrofurantoin (200 mcg/disc), and co-trimoxazole (25 mcg/disc).

4 *Therapy*

Each infected patient admitted to the study was given a numbered bottle containing a seven day course (58 tablets) of either sulphadimidine B.P. or co-trimoxazole. The

therapy and a randomization code were kindly prepared by Roche Products Ltd according to a double-blind technique designed to ensure that at any particular end-point in the trial approximately equal numbers of patients would exist in either the sulphadimidine treated group or the co-trimoxazole treated group. Each bottle was labelled 'four tablets at once and then two tablets four times daily until finished'. Each tablet of sulphadimidine contained 500 mgm of the drug. Each tablet of co-trimoxazole contained trimethoprim 40 mgm and sulphamethoxazole 200 mgm; these half strength co-trimoxazole tablets were prepared, and given four times daily instead of twice daily as normally recommended in order to have matching tablets during the study.

The procedure for females with organism counts of 10^4 per ml. or below was identical with the exception that for this group therapy with co-trimoxazole was compared with a placebo.

5 Follow-up

Appointments were arranged for further urine specimens two days, nine days, six weeks and three months after therapy had finished. Particular care was taken to ensure that the instructions given to the patient about therapy were carefully followed and any patient who digressed from her instructions was removed from the study.

Assessment of the response to each drug in the infected group was based on the rate of improvement of symptoms, the elimination of significant bacteriuria, quantitative and qualitative changes in the urinary pathogens isolated before and after treatment and any toxic effects observed. For the females with organism counts of 10^4 per ml or less the development of significant bacteriuria during three months was compared in the co-trimoxazole treated group and the placebo treated group.

Results

1.0 Infected females

Seventy infected females provided a urine specimen for the isolation of pathogens *in vitro*; 69 of these were involved in the drug trial as one was excluded because of a history of sulphonamide allergy. Three other patients were withdrawn because they stopped therapy prematurely; two were taking co-trimoxazole and one sulphadimidine. It was found on breaking the code at the end of the study that 32 of the remaining 66 had been taking sulphadimidine and 34 had been taking co-trimoxazole.

1.1 *In vitro* studies

Of the 70 specimens examined *in vitro*, 24 were from females experiencing their first attack of symptoms and the remaining 46 were from females who had a past history of urinary tract infection on one or more (usually more) occasions.

Another group of organisms examined was isolated from 29 patients who developed significant bacteriuria within the three month follow-up period; that is from patients who had recently taken a seven day course of sulphadimidine or co-trimoxazole.

It was found that 90 per cent of the 70 initial infections examined were caused by *Escherichia coli*. The remaining 10 per cent were caused by *Proteus species.*, *Staph. albus*, *Strep. faecalis*, and *Pseudomonas pyocyaneus*. Of all pathogens isolated 38 per cent were resistant to sulphadimidine and 4 per cent to co-trimoxazole (Figure 1). Tetracycline and ampicillin resistances were common.

Resistance to sulphadimidine varied according to the group studied. Although 38 per cent of organisms isolated initially from all cases demonstrated *in vitro* resistance to sulphadimidine, this figure fell to 25 per cent in organisms isolated from females experiencing their first attacks of symptoms and increased to 46 per cent in females who had experienced two or more (usually more) attacks in the past.

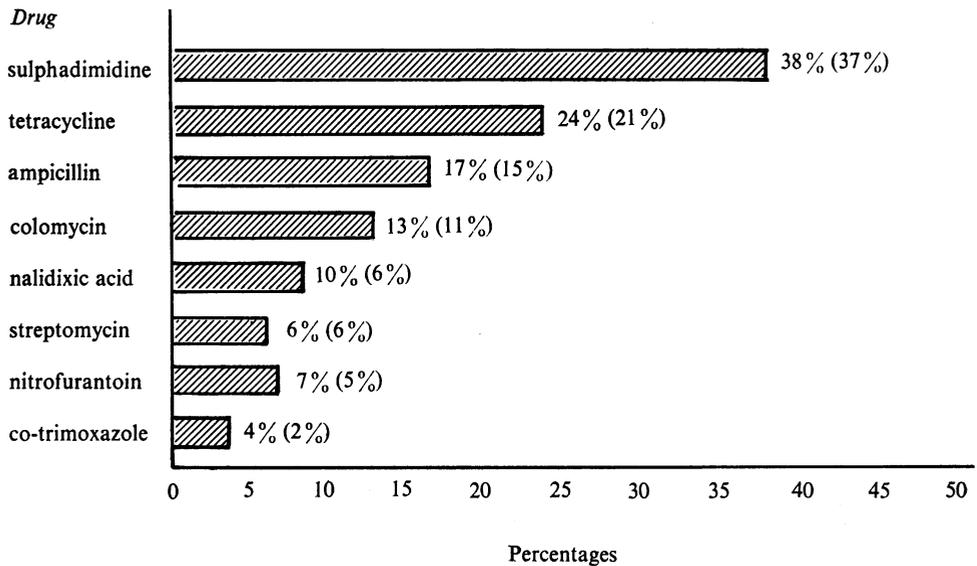


FIGURE 1

Resistance of all urinary pathogens isolated from 70 females with acute symptomatic urinary infection. (Figure in brackets applies to *Esch. coli*)

Twenty-nine out of 66 females who had received a complete course of therapy with either sulphadimidine or co-trimoxazole developed significant bacteriuria on a three month follow-up and organisms isolated were resistant to sulphadimidine in 19 (65 per cent) of cases. This difference in resistance to sulphadimidine between females experiencing their first attack of urinary symptoms and 29 females recently taking sulphadimidine or co-trimoxazole is statistically significant at the five per cent level.

Multiple resistances

When the number of drugs to which each organism had resistance was studied (Figure 2) an interesting phenomenon was observed. Bacteria isolated from infections discovered within three months of a course of co-trimoxazole or sulphadimidine were apparently modified by the drug previously received in that the number of organisms with resistance to two or more drugs increased three-fold from 24 per cent before therapy to 73 per cent after.

	Number *multisensitive	Number resistant to a single drug	Number resistant to two or more drugs
Before treatment 66 infections before treatment	31 (47%)	19 (29%)	16 (24%)
After treatment 29 failures of therapy or recurrences after therapy	3 (10%)	5 (17%)	21 (73%)

FIGURE 2

The effect of antimicrobial therapy on drug resistance in a urinary pathogen.

*Multisensitivity is defined as a pathogen sensitive to the eight commonly used anti-bacterial drugs tested in the *in vitro* studies.

This increase was largely due to a post-therapy increase in the number of pathogens with two resistances (five times) and pathogens with four resistances (eight times). The resistance combination sulphadimidine-ampicillin was often seen after therapy but no particular pattern was seen in the organisms with four resistances. There was no appreciable difference in the two treatment groups as far as the development of resistance to sulphadimidine was concerned; the development of resistance to co-trimoxazole was not observed.

This undesirable effect of antibacterial therapy for urinary infection may persist for some time. When resistance patterns are studied in organisms isolated from females with first attacks of urinary symptoms and compared with organisms isolated from females experiencing their second and subsequent attacks the proportion of organisms with resistance to two or more drugs is larger in the latter group (32 per cent) than it is in the former (16 per cent) (Figure 3).

	<i>Number multisensitive</i>	<i>Number resistant to a single drug</i>	<i>Number resistant to two or more drugs</i>
24 organisms from first attacks	12 (50%)	8 (34%)	4 (16%)
46 organisms from second or subsequent attacks	21 (45%)	11 (23%)	14 (32%)

FIGURE 3

Resistance patterns in organisms isolated from 24 females experiencing their first attack of urinary symptoms and 46 females experiencing their second or subsequent attack of urinary symptoms.

1.2 Time taken for symptoms to respond to treatment

Whether sulphadimidine or co-trimoxazole was given made no difference to the rate of disappearance of symptoms as 74 per cent of the patients given co-trimoxazole and 82 per cent of the patients given sulphadimidine were cured of their symptoms within four days (Figure 4).

<i>Number of days until recovery</i>	<i>Number responding out of 34 females given co-trimoxazole</i>		<i>Number responding out of 32 females given sulphadimidine</i>	
		%		%
1	0	0	1	3
2	8	24	5	16
3	11	32	13	41
4	6	18	7	22
5	2	6	2	6
6	2	6	2	6
7	2	6	1	3
over 7	3	8	1	3

FIGURE 4

Time taken for symptoms to respond to therapy with co-trimoxazole and sulphadimidine.

Fifty-one infected females took four days or less to recover from their symptoms. In only four of these (eight per cent) was infection still present at the first post-treatment urine examination. In 16 others (32 per cent) infection, though initially cleared, was discovered during the three month follow-up period.

Fifteen females took five or more days to recover from their symptoms. In four of these (27 per cent) infection was still present at the first post-treatment urine examination. In five others (33 per cent) infection though initially clearing, was discovered subsequently during the three month follow-up period.

It would appear that females who have symptoms persisting four days or less while on therapy are three times more likely to respond to therapy with a bacteriological cure but this difference just failed to reach statistical significance at the five per cent level.

1.3 Failure to eradicate the original infection

Thirty-four infected females given co-trimoxazole eradicated their infection as judged by the first post-treatment urine examination when none had significant bacteriuria. Of 32 infected females given sulphadimidine eight (25 per cent) still had significant bacteriuria after therapy. This difference is statistically significant at the five per cent level.

Four patients had sulphadimidine resistant organisms to start with, two patients had organisms with sulphadimidine resistance when tested after therapy and the other two patients had *Staph. albus* infections at the first post-treatment urine examination. These were left untreated and both patients developed *Escherichia coli* infections within three months.

1.4 Infections discovered on follow-up

Of 34 females treated with co-trimoxazole (and cured) ten (29 per cent) developed infections during the three month follow-up period compared with 11 (46 per cent) of 24 females treated (and cured) with sulphadimidine. These figures, however, did not quite reach conventional levels of statistical significance.

The 21 females who developed these subsequent infections (asymptomatic in 11) were treated with a change of therapy according to *in vitro* sensitivity studies but seven (33 per cent) developed infections yet again.

1.5 IVP examination

IVP examination of females with infection discovered on follow-up revealed no anatomical abnormalities.

2.0 Non-infected females

Forty-five females with organism counts in their urines of 10^4 per ml or below were placed in the trial between co-trimoxazole and a placebo. One was withdrawn because she stopped therapy prematurely. Of the 44 left, 24 had been given co-trimoxazole and 20 had been given the placebo.

Six (25 per cent) of the 24 females given co-trimoxazole developed significant bacteriuria on follow-up compared with seven (35 per cent) of 20 females given the placebo. These observations do not differ significantly.

Figure 5 illustrates the timing of the development of significant bacteriuria. It appears that the placebo treated group developed significant bacteriuria earlier than the co-trimoxazole treated group. It is of interest that four out of six organisms isolated from the co-trimoxazole treated group were resistant to two or more antibacterial agents compared with two out of seven organisms isolated from the placebo treated group (Figure 6). Of the 13 patients developing significant bacteriuria six had asymptomatic infections.

<i>Number of days after treatment had ended</i>	<i>Co-trimoxazole treated</i>	<i>Placebo treated</i>
2	0	3
9	0	1
6 weeks	3	2
3 months	3	1
Total	6	7

FIGURE 5

Timing of the eventual development of significant bacteriuria on follow-up in co-trimoxazole and placebo treated patients with symptoms and no infection.

	<i>Number multisensitive</i>	<i>Number with a single resistance</i>	<i>Number resistant to two or more drugs</i>
Bacteriuria developed in 7 patients treated with a placebo	3	2	2
Bacteriuria developed in 6 patients treated with co-trimoxazole	1	1	4

FIGURE 6

Development of significant bacteriuria and the resistance pattern of the organisms in 24 initially uninfected females treated with co-trimoxazole and 20 initially uninfected females treated with a placebo.

When the effect of drug and placebo on symptoms is considered 76 per cent of 24 patients given co-trimoxazole were clear of their symptoms within four days compared with 60 per cent of 20 females given the placebo. Twenty-five per cent of females given the placebo still had symptoms after seven days therapy which cleared during the following week. Only two out of this group of five patients developed significant bacteriuria on follow-up, however.

3.0 Side-effects

Only four patients stopped therapy because of side-effects. Two were taking co-trimoxazole and complained of a sore mouth in one case and general malaise in the other. The patient on sulphadimidine complained of a violent frontal headache. The remaining patient had been taking the placebo and complained of general malaise.

Two patients taking co-trimoxazole complained of a sore tongue, one complained of a black furred tongue, one developed an allergic skin rash and one complained of vomiting. One patient on sulphadimidine complained of a sore tongue, one developed an allergic skin rash and two complained of vomiting. During the course of the study a careful watch was kept on the pre- and post-therapeutic blood counts in case of any changes which might be the result of drug therapy but none were seen. Toxic effects then were generally trivial and similar in both co-trimoxazole and sulphadimidine.

Discussion

Recent literature on the *in vitro* sensitivity of urinary pathogens to sulphonamides can be confusing as there is some dispute in the reported figures, particularly from general practice.

Robertson (1971) reporting urines sent to him from general practice gave figures of 17.8 per cent pathogens resistant in 1964, 27.9 per cent in 1965, 42.7 per cent in 1966, 62.3 per cent in 1967, 42.7 per cent resistant in 1968, and 29.1 per cent resistant in 1969. Other figures include Sleet (1969) 80 per cent resistant, Milne *et al.* (1969) 45 per cent of *Escherichia coli* infections resistant and McAllister *et al.* (1971) reporting a six-centre study on *Escherichia coli* infections in hospital outpatients 30 per cent resistant.

Other workers, however, have produced less pessimistic figures. Mond *et al.* (1965) stated that only one out of 35 *Escherichia coli* infections was resistant to sulphonamides. Brumfitt *et al.* (1971) found that only four out of 37 women seen in general practice had *Escherichia coli* infections resistant to sulphonamides. Gillespie *et al.* (1971) reporting a 12 year study found sulphonamide resistance in 18 per cent of coliform infections in urine samples received from general practice during 1969 and 1970. They emphasise the difficulties inherent in *in vitro* sensitivity testing, particularly to sulphonamides, which the Association of Clinical Pathologists pointed out in 1965. Mistakes can easily be made because of over-heavy inoculation of plates and the inexperience of technicians who read them. The medium must also be free from sulphonamide inhibitors.

We fully accept the importance of these factors and having previously made these errors ourselves (Brooks, 1968) were particularly careful to avoid them in reporting our figure of 38 per cent on this occasion. This figure is high compared with those recently given by Brumfitt *et al.* and Gillespie *et al.*

It is possible that differing previous experience of a sulphonamide could be responsible as we have demonstrated that therapy with sulphadimidine or co-trimoxazole can not only result in a sulphonamide-resistant urinary infection on follow-up but can also result in infection with a pathogen possessing resistance to two or more drugs. This development of a pathogen with multiple resistance could be mediated through the selection of faecal organisms carrying transfer factors for multiple resistance (Watanabe, 1963), and subsequent infection of the urine. Datta *et al.* (1971) were unable to demonstrate this, however, in faecal *Escherichia coli* using therapeutic doses of sulphadimidine.

Grüneberg and Kolbe (1969) suggested that co-trimoxazole should replace a sulphonamide in domiciliary as well as hospital practice although Brumfitt and Reeves (1969) pointed out that the superiority of co-trimoxazole in this context over a sulphonamide alone remained to be demonstrated; this study has demonstrated a significant superiority on bacteriological assessment two days after therapy had ended.

Assessment was made immediately after the completion of therapy rather than at three months as Brumfitt and Reeves (1969) stressed the value of serotyping *Escherichia coli* infections so that relapses of the original infection (in which therapy can fairly be implicated) can be differentiated from recurrences or reinfection with a different organism (when therapy cannot fairly be blamed). Unfortunately, we did not have access to suitable antisera at the start of the study and, therefore, no firm conclusion can be drawn about the infections discovered on subsequent follow-up when the above factors are more likely to be significant.

Milne *et al.* (1969) suggested that IVP examination of patients in whom infection was discovered on follow-up would reveal anatomical abnormalities but none were discovered in our study.

As therapy with sulphadimidine or co-trimoxazole for acute dysuria and frequency appears to modify organisms isolated from subsequent infection it might justifiably be held that antibacterial therapy should be avoided when significant bacteriuria is not isolated, particularly as it has also been demonstrated that co-trimoxazole is little better than a placebo in preventing subsequent significant bacteriuria. On the other hand therapy with an antibacterial agent did appear to help the symptoms and it may also help to delay subsequent infection.

In our present state of knowledge of the pathogenesis of bacterial urethritis these questions are difficult to resolve and no doubt the individual physician will use his clinical judgement of the severity of the illness instead of relying too much on the actual organism count in the urine in making a decision about antibacterial therapy.

Summary

A double-blind controlled trial centred on domiciliary practice and involving 66 adult females with acute symptomatic urinary infection has demonstrated the superiority of co-trimoxazole over sulphadimidine in the management of these infections.

Thirty eight per cent of pathogens were resistant to sulphadimidine *in vitro* and four per cent to co-trimoxazole. All patients receiving co-trimoxazole had the infecting organism eradicated at the first post-treatment urine examination as distinct from 75 per cent of those treated with sulphadimidine. Other factors considered in the evaluation of the two drugs, i.e. time taken to respond to treatment, infection on subsequent follow-up, and toxicity revealed no significant difference between them.

The results of a double-blind trial between co-trimoxazole and a placebo are discussed in females with symptoms and insignificant bacteriuria. Implications for management are considered.

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ADDENDUM

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