PAPERS AND ORIGINALS

Double-blind Trial to Compare Ampicillin, Cephalexin, Co-trimoxazole, and Trimethoprim in Treatment of Urinary Infection

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Summary

In order to test their value in urinary infection a double-blind trial was carried out using ampicillin, cephalexin, trimethoprim-sulphamethoxazole (co-trimoxazole), and trimethoprim. Eighty-three courses of treatment were given to hospital patients, 149 to pregnant women, and 107 to patients with dysuria and frequency seen in domiciliary practice. Thus infections of varying severity in defined groups of patients caused by organisms with different antibiotic sensitivities were treated.

Analysis of the overall results (339 courses) was compared with those from the individual groups and considerable variation in response was found. In domiciliary infections and bacteriuria in pregnancy trimethoprim alone proved to be at least as effective as the other three compounds and caused fewer than half the number of side effects. In the hospital patients co-trimoxazole was superior to trimethoprim.

The overall results for ampicillin and cephalexin were similar although cephalexin proved to be inferior in treating symptomatic domiciliary infections.

Introduction

At present, for the treatment of urinary infection sulphonamide, trimethoprim-sulphamethoxazole (co-trimoxazole), ampicillin, and cephalexin are the most commonly used substances which produce effective blood and urine levels. Previous studies have shown that sulphonamide alone is likely to be suitable for domiciliary infections only. As trimethoprim itself is an active agent its role in the efficacy of co-trimoxazole and its contribution to the unwanted effects of this compound were worth defining. Cephalexin is a semisynthetic cephalosporin with a different nucleus from ampicillin but the same side chain. Ampicillin is more active against the common urinary pathogens than cephalexin is but this is balanced by the better serum and urine concentrations obtained with equal doses of the latter. This study was undertaken to define the relative value of the four substances in the treatment of urinary infection.

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Patients and Methods

The infections were studied in three defined groups of patients—96 patients with acute infections referred from general practice and characterized by dysuria and frequency, 129 patients with asymptomatic infections discovered by screening at the first antenatal examination in pregnancy, and 75 hospital patients who acquired infection after admission. Of the patients studied only 18 were male. The reason for studying these patients was that we had previously defined the success rate in these groups using a number of antibiotics (Brumfitt and Percival, 1967; Brumfitt, 1972).

A number of features of the patients receiving the four different drugs were compared, each group being considered separately. The features included age, social class, fever, urinary white cell count, infecting organisms and their sensitivities, specific serum antibody titre, and previous history of renal disease. Judged by comparison of these criteria the groups were found to be similar.

Ampicillin, cephalexin, trimethoprim, and co-trimoxazole were allocated on a double-blind random basis within each patient group regardless of the sensitivity pattern of the infecting organism. This allowed proper evaluation of unwanted effects but at the cost of occasional inclusion of an inappropriate treatment which previous knowledge of sensitivity would have avoided. Such an expedient, however, is common practice while awaiting laboratory results. A history of hypersensitivity to one of the compounds was the only reason for changing the allocation procedure. In this case randomization of the therapy was limited to the three remaining drugs.

In the event of failure the sensitivity of the organism was noted and provided the other three compounds were suitable a secondary treatment was allocated at random.

Unpublished preliminary work by us showed little difference

between the results of treatment with ampicillin given in the standard dose of 500 mg six-hourly and 1 g 12-hourly. The same observations were true for cephalexin. Therefore all drugs were administered at 12-hourly intervals. The dose for both ampicillin and cephalexin was 1 g each, for trimethoprim 200 mg, and for co-trimoxazole 2 tablets (trimethoprim 160 mg and sulphamethoxazole 800 mg). All treatments were given for seven days.

Diagnosis of Infection.—The criterion for infection was the isolation of the same bacterial species in counts of more than 10^5 organisms per ml from two consecutive specimens of urine.

Bacteriological Techniques.—Organisms were identified by standard methods and O-antisera were used to determine the serotypes of strains *Escherichia coli* and *Proteus mirabilis*. Sensitivity testing was carried out initially by the disc diffusion method and subsequently by estimation of the minimal inhibitory concentration (M.I.C.). The M.I.C. was determined by the plate dilution technique using nutrient agar for ampicillin and cephalexin and Oxoid DST agar plus 5% lysed horse blood for trimethoprim and sulphonamide (Darrell *et al.*, 1968).

Criterion of Cure.—Urine samples were collected at one week and four to six weeks after completing treatment. Absence of the original infecting organism at both follow-up times was taken to be a cure. Most failures were apparent after one week but a few patients free from infection at one week were found to be infected by the original organism at four to six weeks. The latter were also judged to have failed treatment. It is appreciated, however, that the same serotype can persist in the bowel, vaginal vestibule, or periurethral region. For this reason it is impossible to be sure that a further episode of infection by the same serotype is necessarily a failure of eradication, and this must be borne in mind when assessing the results. The isolation of an organism of a different genus, species, or serotype was not regarded as a treatment failure but as a reinfection.

Results

The result of the random allocation to treatment is shown in Table I. Altogether 339 courses of treatment were given, of which 300 were primary and 39 secondary. The overall results are shown in Table II. The cure rate was 83% with co-trimoxazole, 83% with trimethoprim, 73% with ampicillin, and 69% with cephalexin. Further analysis, however, showed that the effectiveness of the antimicrobial substances varied within the three groups, and therefore it was essential to study the defined groups independently.

TABLE I—*Allocation of Treatment to Each Group of Patients*

	Ampicillin	Cephalexin	Co-trimoxazole	Trimethoprim	Total
Pregnancy ..	40	37	33	39	149
General practice	27	26	31	23	107
Hospital ..	21	21	19	22	83
Total ..	88	84	83	84	339

TABLE II—*Results of the 339 Courses of Treatment*

	Success	Failure	Total
Ampicillin	64 (73%)	24	88
Cephalexin	58 (69%)	26	84
Co-trimoxazole ..	69 (83%)	14	83
Trimethoprim ..	70 (83%)	14	84
Total..	261	78	339

PREGNANCY

The results of the 149 courses of treatment given during pregnancy are shown in Table III. The highest cure rates were found with co-trimoxazole (85%) and trimethoprim (82%). In previously published studies (Williams *et al.*, 1968, 1969; Leigh *et al.*, 1970) when conventional doses of ampicillin, cephalexin, and co-trimoxazole were given the cure rates were similar to those in the present investigation (ampicillin 69%, cephalexin 77%, and co-trimoxazole 83%). The finding of a relatively lower cure rate with ampicillin (Table III) could not be explained by resistant organisms. The reversal of results with ampicillin (65%) and cephalexin (78%) when compared with the overall results is noteworthy (Table II). Of the 129 women in the study 20 who failed the primary course of treatment received secondary treatment. Although the number of patients given secondary treatment is small it is nevertheless apparent that the cure rate was diminished in those patients who had already failed one course of therapy. These results agree with previous findings (Brumfitt *et al.*, 1966; Norden and Kass, 1968).

It is interesting to note that the patients who failed primary treatment did better when re-treated with co-trimoxazole or trimethoprim alone than with ampicillin (Table III). This finding is again in agreement with previous observations (Williams *et al.*, 1968, 1969).

TABLE III—*Results of Treating 129 Women with Bacteriuria in Pregnancy*

	Primary		Secondary		Overall Success (%)
	Success	Failure	Success	Failure	
Ampicillin	24 (73%)	9	2	5	65
Cephalexin	25 (81%)	6	4	2	78
Co-trimoxazole ..	25 (83%)	5	3	—	85
Trimethoprim ..	29 (83%)	6	3	1	82
Total	103	26	12	8	

χ^2 = 1·4. Not significant (for primary treatment).

GENERAL PRACTICE PATIENTS

Ninety-six primary and 11 secondary courses of treatment were given to patients referred from general practice. The overall cure rates obtained were trimethoprim 96%, co-trimoxazole 81%, ampicillin 89%, and cephalexin 62% (Table IV). The results for cephalexin were significantly lower (P <0·02) than for the other antimicrobial agents. Of the 10 patients who failed to respond to cephalexin eight were infected with *E. coli*, of which only two were resistant. In the same way the small number of patients who failed treatment with the other three compounds could not be accounted for by resistant organisms.

TABLE IV—*Results of 107 Courses of Treatment in 96 Domiciliary Patients with Symptomatic Infections*

	Primary		Secondary		Overall Success (%)
	Success	Failure	Success	Failure	
Ampicillin	23 (88%)	3	1	—	89
Cephalexin	16 (62%)	10	—	—	62
Co-trimoxazole ..	20 (91%)	2	5	4	81
Trimethoprim ..	22 (100%)	—	—	1	96
Total	81	15	6	5	

For cephalexin compared with the other antimicrobials χ^2 = 10·8 (P <0·02).

HOSPITAL PATIENTS

Seventy-five hospital patients were treated, and of these eight were given a second course of treatment. There was a higher cure rate with co-trimoxazole (84%) than with trimethoprim alone (73%) (Table V), but relatively few patients were involved and the difference was not significant. All seven of the ampicillin failures were *E. coli* infections, but only two were resistant. By contrast, four of the six failing to respond to trimethoprim alone (two *Pr. mirabilis* and two *Klebsiella spp.*) were highly

TABLE V—*Results of 83 Courses of Treatment in 75 Hospital Patients*

	Primary		Secondary		Overall Success (%)
	Success	Failure	Success	Failure	
Ampicillin	14 (74%)	5	—	2	67
Cephalexin	11 (61%)	7	2	1	62
Co-trimoxazole ..	16 (89%)	2	—	1	84
Trimethoprim ..	14 (70%)	6	2	—	73
Total	55	20	4	4	

resistant. Such infections are much more common in hospital than in domiciliary practice and may account for the superiority of the co-trimoxazole for the treatment of hospital-acquired infections. Of the six patients with sulphonamide-resistant organisms given co-trimoxazole five were cured. In all these patients, however, the organism was sensitive to trimethoprim ($\leq$ 1 µg per ml).

E. COLI INFECTIONS

E. coli accounted for the majority of infections and thus justified independent assessment. Nevertheless, Table VI shows that although *E. coli* was the most common cause of infection in

TABLE VI—*Results of Treatment of E. Coli Infections in the Three Groups of Patients*

	Pregnancy		General Practice		Hospital	
% Infected with *E. Coli:*	84·6		84·1		67·5	
	Success	Failure	Success	Failure	Success	Failure
Ampicillin ..	22 (65%)	12	19 (91%)	2	8 (53%)	7
Cephalexin ..	24 (77%)	7	14 (64%)	8	10 (67%)	5
Co-trimoxazole	26 (87%)	5	22 (82%)	5	10 (91%)	1
Trimethoprim	27 (87%)	4	19 (95%)	1	13 (88%)	2
Total ..	99	28	74	16	41	15

hospital a significantly smaller proportion was due to this organism than in the other two groups. Many more of the hospital strains of the *E. coli* were resistant to one or a number of chemotherapeutic agents although no difference in sensitivity to trimethoprim was found between the hospital and domiciliary strains.

UNWANTED EFFECTS

Altogether 64 (19%) of the 339 courses of chemotherapy caused side effects, but the percentage varied from group to group. Unwanted effects resulted from 35 (24%) of the 149 courses given to pregnant women, 23 (22%) of the 107 courses in general practice, but only 6 (7%) of the 83 courses given to hospital inpatients.

The smaller number in hospital patients may have been due to their failure to associate more minor complaints with the antimicrobial therapy. For example, diarrhoea is obviously a greater handicap in an asymptomatic ambulant domiciliary patient than in a hospital patient. The number of pregnant women known not to have completed their course of treatment because of side effects was significantly greater than the number of patients who failed to complete treatment in the other groups ($P < 0.05$). Ten pregnant women failed to complete their treatment compared with only two non-pregnant domiciliary patients and two hospital patients.

Since the study was double-blind it is possible to compare the unwanted effects of the four varieties of treatment. The nature of many of the side effects (Table VII) agree with those that have previously been shown to be characteristic of the particular antimicrobial agent. Nevertheless, two points deserve comment. Firstly, the total side effects caused by ampicillin, cephalexin,

TABLE VII—*Unwanted Effects resulting from 339 Courses of Treatment*

	Ampicillin	Cephalexin	Co-trimoxazole	Trimethoprim	Total
No. treated ..	88	84	83	84	339
No. with side effects:	19 (22%)	21 (25%)	17 (21%)	7 (8%)	64 (19%)
Vaginal discharge ..	4	8	3	—	15
Rash	6	4	2	3	15
Nausea	2	2	8	2	14
Diarrhoea	4	1	1	—	6
Vomiting	—	—	2	2	4
Sore mouth	1	1	1	—	3
Headache	—	—	1	1	2
Dizziness	—	—	3	—	3
Proctitis	—	2	—	—	2
Miscellaneous ..	2	5	3	2	12

and co-trimoxazole were similar and occurred twice as often as when trimethoprim was given alone, and only one patient in the whole study, who received trimethoprim, failed to complete the course of treatment. Secondly, certain effects of co-trimoxazole, which have been attributed previously to the effect of trimethoprim on the central nervous system (A. S. E. Fowle, personal communication), in fact occurred much more often with co-trimoxazole than with trimethoprim alone, and this was especially true of nausea (Table VII). Trimethoprim given alone was shown to be much better tolerated.

HYPERSENSITIVITY

All patients were questioned about hypersensitivity. No pregnant woman gave a history of hypersensitivity, but this symptom occurred in five hospital and five general-practice patients. Of these 10 patients nine gave a history of sensitivity to penicillin and one to sulphonamide. As already mentioned, these patients were treated with alternative compounds and retained within the study.

In spite of exclusion of ampicillin because of penicillin hypersensitivity six patients developed rashes after the use of ampicillin. A further four without a history of penicillin hypersensitivity developed a rash after treatment with cephalexin. An unexpected finding was that three patients developed rashes after treatment with trimethoprim alone.

MINIMAL INHIBITORY CONCENTRATIONS

These were carried out on all organisms but are not presented in detail. As expected, most domiciliary organisms (in pregnant and general-practice patients) were sensitive to less than 10 µg ampicillin, 15 µg cephalexin, 50 µg sulphonamide, and 1 µg/ml trimethoprim. Thus failure to respond to treatment with these agents could not be attributed to bacterial resistance. As shown previously (Reeves *et al.*, 1969), however, although the success or failure of treatment with trimethoprim-containing drugs in hospital patients was clearly related to the sensitivity of the organism to the compound used, other factors related to the patient's illness also influence the result of treatment. In contrast a lack of correlation with antibiotic sensitivity was especially true of ampicillin, where only two of the seven failures were due to a resistant organism.

Discussion

The overall results from patients with urinary infection in general practice, bacteriuria in pregnancy, and hospital patients show that co-trimoxazole and trimethoprim give a similar and highly acceptable cure rate of about 83%. Ampicillin cured 73% and cephalexin 69%. These differences did not result from an undue proportion of resistant organisms in any one group.

Further information, however, can be obtained by examining the results found in each of the three defined groups. In the hospital patients the relatively small numbers suggested that

co-trimoxazole was superior to trimethoprim, ampicillin, and cephalexin, although the difference did not reach the conventional level for statistical significance. In pregnancy the results with co-trimoxazole (85% cure) were similar to those reported in a previous study involving 86 patients who were also given co-trimoxazole (Williams *et al.*, 1969), but trimethoprim gave equally good results. Ampicillin (65% cure) and cephalexin (78% cure) were less satisfactory. In general practice highly satisfactory cure rates were obtained with trimethoprim (96%), ampicillin (89%), and co-trimoxazole (81%), but cephalexin cured only 62% of the patients treated. The different results in the domiciliary patients could not be explained by the sensitivities of the organisms to the drugs in the trial. Possible reasons for the apparent inferiority of cephalexin were discussed elsewhere (Leigh *et al.*, 1970).

Co-trimoxazole and trimethoprim appeared to give better results in patients who had already failed primary treatment. These findings with co-trimoxazole are in agreement with those of Williams *et al.* (1969). Furthermore, O'Grady *et al.* (1969) reported favourable results using co-trimoxazole in reducing dosage in patients with chronic relapsing urinary infection. Trimethoprim alone was remarkable in causing fewer than half the side effects that resulted from administration of the other three compounds, and only one patient receiving trimethoprim failed to complete the course of treatment. It was unfortunate that at the time of the study 80-mg tablets of trimethoprim were not available, but although the 100-mg tablet may have slightly improved the cure rate this must be balanced against the small number of side effects that might have resulted from giving a smaller dose of trimethoprim.

There was no evidence that trimethoprim caused resistance of the organism responsible for the urinary infection, and so far we have not found resistant organisms in the faeces after therapy or increased resistance of the same organism after treatment. Darrell *et al.* (1968) reported that sulphonamide combined with trimethoprim delayed the emergence of resistant organisms although the present study showed no change in the sensitivity of the organisms isolated in hospital compared with those reported in the same hospital (Reeves *et al.*, 1969) when co-trimoxazole was first introduced. Nevertheless, co-trimoxazole is an effective drug for the treatment of the wide variety of urinary infections (Garrod and O'Grady, 1971) and it would therefore be unwise to recommend the substitution of trimethoprim alone until more studies have been carried out under careful supervision.

Lacey *et al.* (1972) studied 725 "coliform bacilli" isolated from inpatients and outpatients during 1971 and found 18 (2·5%) to be resistant to varying levels of trimethoprim. Eight of the resistant organisms were *E. coli* and at least five came from patients previously treated with co-trimoxazole. These workers suggest that resistance to co-trimoxazole may be increasing. Our preliminary findings, however, based on treating patients with recurrent urinary infections for periods of up to one year with a dose of 100 mg trimethoprim daily, have not led to the appearance of trimethoprim-resistant organisms in the faeces (Brumfitt *et al.* 1969).

Regarding ampicillin and cephalexin our overall results show that ampicillin cured 64 (73%) of 88 patients and cephalexin 58 (69%) of 84 patients (Table II). As mentioned above, side effects were similar in both groups. In hospital patients ampicillin was also more successful, curing 14 (67%) of 21 patients, whereas cephalexin cured 13 (62%) of 21 patients. Domiciliary patients responded poorly to treatment with cephalexin.

The results in hospital patients were similar to those found in the small study of Davies *et al.* (1971), who found no difference between ampicillin and cephalexin in the treatment of 41 hospital patients but considered cephalexin to be slightly better tolerated. Judged by their criteria our overall findings indicate that ampicillin is slightly superior, although the number of unwanted effects is similar.

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