COMPARATIVE CLINICAL TRIAL OF TRIMETHOPRIM ALONE AND CO-TRIMOXAZOLE IN ACUTE UNCOMPLICATED URINARY TRACT INFECTION IN WOMEN

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Urinary infections in women are common in as much as 10-20% women experience a urinary infection in their life time (Kass *et al* 1964), because of such biological factors as colonization of introital mucose with *E. coli* from the rectal flora (Stamey 1980), sexual intercourse (Kunin and McCormack, 1968), pregnancy (Stamey 1980), secondarily infected congenital anomalies (Stamey 1980) and diabetes (Forland *et al* 1977). Treatment of acute uncomplicated urinary tract infection (UTI) with co-trimoxazole (TMP/SMX) is satisfactory, but for the avoidable risk of adverse reactions associated with its sulphonamide moiety. If trimethoprim (TMP) alone could be effective in acute uncomplicated UTI, then patients allergic to sulphonamides can be treated with TMP. In Finland (Kasanen *et al*, 1974; Mannistö, 1976), where the combination was not permitted, and elsewhere (Brumfitt and Pursell 1972 and Koch *et al* 1973), TMP alone gave excellent results. It is now thought that TMP is the dominant component of TMP/SMX (Greenwood and O'Grady 1976) and that, in urine, potentiation of TMP by sulphonamides is not necessary and indeed may be doubtful. By using TMP alone, the risk of emergence of pathogens resistant to TMP is not increased because, over half of the hospital Gram-negative bacilli are already resistant to sulphamethoxazole (SMX) (Hamilton-Miller 1979; Pearson *et al* 1979), in which case these organisms are subjected virtually to the TMP moiety alone. Further, concentration of TMP alone in urine exceeds, plasma levels by more, than 50 (Cartwright *et al* 1982; Brumfitt *et al* 1969 and Bach *et al* 1973), which are much higher than the minimum inhibitory concentration (MICs) of the sensitive urinary pathogens.

In view of the above reported efficacy of TMP alone in acute uncomplicated UTI, a trial of TMP alone in women suffering from acute uncomplicated UTI was planned and was designed to compare its efficacy and safety with TMP/SMX.

Material and Methods

Women, age between 12 and 60 years and presenting with clinical features of acute uncomplicated UTI, were admitted to the hospital and included in the trial, only if they had no past history suggestive of allergy to sulphonamides, or suffering from chronic UTI, obstructive uropathy, diabetes, gross renal and hepatic dysfunctions. Pregnant and lactating women and

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those already receiving any antibiotics for some other indications were excluded. Detailed pre-treatment clinical data of the patients admitted to the trial were recorded.

Bacteriological confirmation of acute uncomplicated UTI was made by microscopic examination and culture of freshly voided midstream urine collected aseptically. Significant bacteruria was confirmed by colony count $> 10^5$/ml. Bacterial pathogens, thus isolated, were identified and were subjected to antibiotic susceptibility testing. Standard culture media were used for antibiotic sensitivity testing by the standard disc diffusion method, using discs of chloramphenicol (30 mcg/disc), ampicillin (100 pcg/disc), nitrofurantion (100 mcg/disc) and nalidixic acid 30 mcg/disc), gentamicin (10 mcg/disc), kanamycin (30 mcg/disc), and tetracycline (30 mcg/disc). For sensitivity testing with TMP (1.25 mcg/disc) and TMP/SMX (25 mcg/disc), thymidine-free culture medium (Wellcotest agar) was used. Interpretation of sensitivity of pathogens to the antibacterials was by the standard method of measuring inhibitory zones in mm.

Patients, showing bacterial pathogens isolated from urine samples with a colony count $> 10^5$/ml and sensitive to TMP and TMP/SMX, were finally admitted to the trial. Forty-nine patients were, thus, included in the study and were allocated randomly into two groups:

GROUP A (Control): 25 patients receiving TMP/SMX 2 tablets twice daily for 7 days.

GROUP B (Test): 24 patients receiving TMP (100 mg) alone 1 tablet twice daily for 7 days.

Patients were followed up daily for clinical improvement. Routine urine analysis and culture were done on day-3, 7 and 21 to determine the rapidity of eradication of the causative pathogens. Criteria of assessment of drug therapy in the trial were:

1. *Clinical cure*: disappearance of all symptoms.

2. *Bacteriological cure*: eradication of causative pathogens by day-21 urine culture.

Adverse reactions to TMP or TMP/SMX were recorded, noting when drug withdrawal was necessary.

Results and Observations

Acute uncomplicated UTI was most commonly seen is age groups of 21 to 30 (17/49) and 31 to 40 years (15/49). Commonest symptoms was fever, followed by frequency of micturition and dysuria.

Bacterial isolates in 49 patients are shown in Table I. *E. coli* was the commonest pathogen (28/49 pitients), followed by klebsiella spp. (13/49) and proteus (6/49). All the pathogens were fully or moderately sensitive to TMP and TMP/SMX. Detiils of sensitivity pattern of the isolates are given in Table II. Six cases in Group A (TMP/SMX) and 7 cases in Group B (TMP) were lost for analysis due to inadequate follow-up.

TABLE I
Pre-treatment Urinary Pathogens in Two Groups (49 Cases)

	Group A (TMP/SMX)	Group B (TMP)	Total
E. coli	13	15	28
Klebsiella	8	5	13
Staph. pyogenes	3	3	6
Alk. faecalis	1	—	1
Paracolon	—	1	1
	25	24	49

TABLE II

Sensitivity of Urinary Pathogens to Antibacterials Isolated in 49 Cases

Isolates (49)	ANTIBIOTIC SENSITIVITY PATTERN : NUMBER OF STRAINS SENSITIVE TO								
	TMP	TMP/SMK	Nitro-furantoin (NFT)	Ampicillin (AMPI)	Chloramphenicol (Chloram)	Nalidixic Acid (NDA)	Kanamycin	Gentamicin GENTA)	Tetracycline
E. coli (28)	28	28	14	12	7	14	3	6	3
Klebsiella (13)	13	13	4	8	7	6	—	—	—
Staph. pyogenes (6)	4	6	4	4	4	2	—	—	—
Alk. faecalis (1)	1	1	—	—	—	—	—	—	—
Paracolon (1)	1	1	—	1	1	—	—	—	—

NOTE All isolates of *E. coli* sensitive to TMP and SMX; 50% sensitive to NFT & NDA; 41% to AMPI, 25% GENTA & CHLORAM.

All isolates of klebsiella sensitive to TMP and TMP/SMX; 50% sensitive to NDA & CHLORAM; 61% to AMPI & 33% to NFT

All isolate of *Staph. pyogenes* sensitive to TMP and TMP/SMX; 66% sensitive to NFT, AMP & CHLORAM: 33% to NDA; the uncommon isolates—all sensitive to TMP & TMP/SMX.

Adverse Reactions

Two cases of skin allergy in the Group A (TMP/SMX) were seen, one on day-3 and the other on day-4 and were withdrawn from the study. TMP was well tolerated by all the patients.

Thus, out of a total of 49 cases in the study, only 34 could be finally evaluated—17 in Group A (TMP/SMX) and 17 in Group B (TMP).

Clinical and bacteriological responses as per pre-determined criteria of cure, are tabulated in Tables III and IV respectively. 14/17 cases in Group B improved clinically by day-3 as against 10-17 cases in Group A. Similarly, bacteriological cure was seen in 15/17 cases on day-3 in Group B as against 12/17 in Group A. Comparatively, therefore, there was only a marginal superiority of TMP alone over TMP/SMX in achieving clinical and bacteriological cure.

Discussions

TMP alone has been proved in various studies (Brumfitt and Pursell, 1972; Mannistö, 1976 and Andrewes *et al* 1971) to be at least as effective as TMP/SMX and other antibacterial drugs in the treatment of acute uncomplicated UTI. However, in quest of a suitable dosage regimen, a wide range of dosages of TMP, i.e., 50 mg. b.i.d. (Asscher *et al* 1981), 100 mg. b.i.d. (Stamm *et al* 1979; Asscher *et al* 1981), 200 mg. b.i.d. (Asscher *et al* 1981), 240 mg. b.i.d. (Kasanen *et al* 1974) and 300 mg once daily (Andrewes *et al* 1981, Cartwright *et al* 1982), has been tried and found satisfactory. However, Kasanen *et al* (1974) did not find, in his studies, 100 mg. b.i.d. as satisfactory. As many workers in the field found TMP 100 mg. b.i.d. satisfactory, we used this dosage schedule for our study.

Predominance of *E. coli* as the urinary pathogen causing acute uncomplicated UTI is widely recognised. (Brumfitt and Pursell, 1972; Stamm *et al* 1979; Asscher *et al* 1981; Koch *et al* 1973; Andrewes

TABLE III

Clinical Response: Relief of Presenting Symptoms in 34 Cases Finally Assessed

Drugs	Assessment on day							
	1	2	3	4	5	6	7	21
TMP/SMX (17 cases GROUP—A)	1	5	4	2	1	1	3	—
TMP alone (17 cases GROUP—B)	3	7	4	—	—	1	2	—

TABLE IV

Bacteriological Response: Eradciation of Primary Pathogen in 34 Cases Finally Assessed

DRUGS	Assessment on day		
	3	7	21
TMP/SMX (GROUP A, 17 cases)	12	4	1
TMP alone (GROUP B, 17 cases)	15	2	—

et al 1981; Cartwright *et al* 1982). In our studies we noted *E. coli* in 28/49 cases as the commonest causative pathogen, followed by klebsiella and proteus. It was interesting to note that studies in general practice (Andrewes *et al* 1981; Cartwright *et al* 1982; Asscher *et al* 1981) found *E. coli* as the predominant offending pathogen in UTI, while those in hospital practice (Brumfitt and Pursell, 1972 and Koch *et al* 1973) found klebsiella and proteus, in addition to *E. coli*. Results of our antibiotic sensitivity studies with the bacterial isolates showed that *E. coli*, klebsiella spp. and proteus were sensitive to TMP and TMP/SMX. This closely corroborates with the findings of Brumfitt and Pursell (1972), Asscher *et al* (1981), Andrewes *et al* (1981), Cartwright *et al* (1982). Although Cartwright *et al* (1982) had reported a strain of *E. coli* resistant to TMP and TMP/SMX, we found none so in our series.

Bacteriological cure rate in our series was 100%, all 34 patients responding. This is, however, at variance with the findings of Brumfitt and Pursell (1972), who noted bacteriological cure in only 83% of the hospital patients. But our results corroborate with those of Koch *et al* (1973).

On the rapidity of eradication of bacteria, TMP and TMP/SMX were equally rapidly effective and the significance of the marginal difference cannot be validated in this small series.

TMP was better tolerated than TMP/SMX, with which we observed skin rashes in 2 cases. TMP/SMX was discontinued and these 2 cases withdrawn from the study. Skin rashes with TMP/SMX have commonly been reported (Coch *et al* 1973, Andrewes *et al* 1981, Asscher *et al* 1981). Although skin rash with TMP alone has also been reported earlier (Brumfitt and Pursell, 1972; Cartwright *et al* 1982), we had found none in our series. A comparative study of the patterns of adverse reactions reported earlier (Brumfitt and Pursell, 1982; Koch *et al* 1973; Cartwright *et al* 1982; Andrewes *et al* 1981; Asscher *et al* 1981) leaves no doubt that TMP is much better tolerated than TMP/SMX, which has been observed in this series too.

Summary and Conclusion

In a randomised open comparative clinical trial in 34 women suffering from acute uncomplicated UTI, TMP alone 100 mg. b.i.d. was found to be as effective as TMP/SMX 2 tablets twice daily, both the drugs having been given for 7 days. All 34 patients had bacteriological cure. TMP and TMP/SMX were otherwise well tolerated.

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References

1. Andrews, D. A., Chuter, P. J., Dawson, M. J., Eden, B. W., Moore, A. A., Freestone, D. S. and Morris, C. A.: Gen. Pract., 31: 274, 1981.
2. Asscher, A. W., Brumfitt, W., Charlton, C. A. C., Davey-Smith, C., Davis. J. G., Harvard Davis, R. Graham, A. A., Gurney, J. D., Hamilton-Miller, J. Mann, P. G., and Smith, R. D.: J. Antimicrob, Chemother. 7: 179, 1981.

3. Bach, M. C., Gold, O. and Finland, M.: J. Infect. Dis., 128: Suppl., S584.
4. Brumfitt, W., Faiers, M. C., Pursell, R. E., Reeves, D. S. and Turnbull, A. E.: Bacteriological, Pharmacological and clinical studies with Trimethoprim-Sulphonamide combinations—with particular reference to the treatment of Urinary Infections, Postgrad. Med. J., 45: Suppl., 56, 1969.
5. Brumfitt, W. and Pursell, R.: Brit. Med. J. 2: 673, 1972.
6. Cartwright, K. A., Stanbridge, T. N. and Cooper, J.: Pract., 226: 152, 1982.
7. Forland, M., Thomas, V. and Shelokov A.: J. Am. Med. Assc., 238: 1924, 1977.
8 Greenwood, D. and O'Grady, F.: J. Clin. Path., 29: 162, 1976.
9. Hamilton-Miller, J. M. T.: J. Antimicrob. Chemother. 5: (Suppl. B), 61, 1979.
10. Kasanen. A., Taivanen, P., Sourander, L., Kaarsalo, E. and Aantaa, S.: Scand. J. Infect. Dis. 6: 91, 1974.
11. Kass, E. H., Savage, W. D. and Santamarine, B. A. G.: Thee significance of bacteria in preventive medicine. In E. H. Kass (Ed.), Progress in Pyelonephritis, Philadelphia, F. A. Davis & Co., 1964, p. 3.
12. Koch, U. J., Schumann, K. P., Kochler, R. and Kewitz, H.: Chemotherapy, 19: 314, 1973.
13. Kunin, C. M. and McCormack, R. C.: N. Engl. J. Med., 278: 635, 1968.
14. Mannistö: P. T.: Curr. Ther. Res., 20: 645, 1976.
15. Pearson, N. J., Towner, K. J., McSherry, A. M., Cattell, W. R. and O'Grady, F.: Lancet, 2: 1205, 1979.
16. Stamey, T. A.: Pathogenesis and Treatment of Urinary Tract Infections, Wi liams and Wilkins, Baltimore/London, 1980, p. 141.
17. Stamey, T. A.: Pathogenesis and Treatment of Urinary Tract Infections, Williams and Wilkins, Baltimore/London, 1980, p. 162.
18. Stamey, T. A.: Pathogenesis and Treatment of Urinary Tract Infections, Williams and Wilkins, Baltimore/London, 1980, p. 181.
19. Stamm, W. E., Counts, G. W., Wagner, K. F., Martin, D., Tu Turck, M. and Holmes, K. K.: 11th Int. Congr. Chemother. and 19th Intersoi. Congress Antimicrob. Agents and Chemother., 1-5 Oct., Boston, Abstract 60.