Urological Research 1, 152-156 (1973)

Short-Term Treatment of Patients with Chronic and Recurrent Urinary Tract Infections with Co-Trimoxazole

H. J. de Voogt and H. Mattie

Departments of Urology and Infections Diseases and the Clinical Pharmacology Group from the Academic Hospital of Leiden University

Received: July 30, 1973

Summary. A study is presented in which patients with recurrent urinary tract infections with and without anatomical defects or obstructive diseases are treated with a short-term, high-dosage followed by a short-term, low-dosage regimen of co-trimoxazole.

Key words: Urinary tract infections, co-trimoxazole, anatomical defects

Introduction

Many detailed studies (1-10) have been published on the action and efficiency of the combination of trimethoprim and sulfonamide, known today as co-trimoxazole, and available under different trade names in different countries. However, to our knowledge, only three of these studies (3, 7, 8) have dealt with the effect on chronic and recurrent infections in patients with anatomical defects or obstructive diseases of the urinary tract, that cannot be treated by surgical correction.

Although the number of such patients in urological out-patient clinics, is never very high, they represent the most difficult part of the urologist's practice. They usually harbour strains of bacteria that have gradually become resistant to nearly all the antibacterial drugs available. The labour of keeping them free from clinically manifest infections may be hampered by many unexpected difficulties.

Regarding co-trimoxazole Cattell (3) and Lykkegaard Nielsen et al. (7) mention long-term, low-dosage therapy in their patients.

Nanra (8), on the other hand, only gives short-term, low-dosage therapy. In our study we compared the effect of short-term, high-dosage as well as short-term, low-dosage treatment with that of short-term treatments with ampicillin, nitrofurantoin and/or sulfonamides.

Materials and Methods

A total of 26 patients was treated by co-trimoxazole. They were separated in two groups. The first group consisted of 14 patients with chronic or recurrent infections and anatomical defects or obstructive diseases of the urinary tract.

Table 1 shows their diagnoses, determined radiologically or otherwise. There were 5 men and 9 women, and their mean age was 63 years (ranging from 54 to 79 years).

The second group consisted of 12 women with a mean age of 54 years (ranging from 10-80 years). They all had recurrent lower urinary tract infections but no urinary tract abnormalities other than distal urethral stenosis, which was treated by dilatation. However, 5 of them had diabetes as a possible complicating factor.

Most of the patients in the first group had already been treated for a considerable period of time with either long- or short-term medications. Conditions for admission to our trial were that they had undergone at least one short-term course of ampicillin (2 grams daily for 10 days) and one of either nitrofurantoin (400 mg. daily for 10 days) or sulfonamide (4 grams daily for 10 days). No antibacterial therapy was given for at least two weeks before the co-trimoxazole was started. A significant bacteriuria (more than 10^5 bacteria per ml. midstream urine) had to be established.

The patients in the second group were treated from the onset of the infection. When a significant bacteriuria was diagnosed first a course of ampicillin was given. When a relapse or reinfection occurred a second course with nitrofurantoin or sulfonamide, according to the sensitivity tests, was administered. When a second relapse occurred, treatment with co-trimoxazole was started.

For both groups the first course of co-trimoxazole consisted of 2 tablets (containing 80 mg

TMP and 400 mg SMX each) 3 times a day for one week.

All patients were seen at two-week intervals and their urine cultured. When a relapse or reinfection occurred, the second course of co-trimoxazole consisted of 2 tablets twice a day for 2 weeks. All patients were followed up until the completion of this investigation. If after the second course of co-trimoxazole a reinfection occurred, therapy was continued with other drugs.

Before commencing antibacterial treatment, all strains of bacteria were identified and their sensitivity tested by the disc method. Sensitivity for SMX, TMP and co-trimoxazole was tested on the same plate for each micro-organism. The medium consisted of DST agar (oxoid) with 5% haemolysed horse blood. Filter paper discs 6 mm in diameter were loaded with 25 ug SMX and 1.25 ug TMP, respectively. Twelve millimeters was regarded as critical diameter of the growth inhibition zone. Only when a strain was not sensitive to SMX nor to TMP, but sensitive to co-trimoxazole, were patients treated with the combination. In this way we could avoid the use of co-trimoxazole in cases where treatment with either of the two components would have been sufficient.

Blood analyses were done on all patients, including Hb, WBC-count, platelet-count and serum creatinine. In 10 randomly selected patients more intensive laboratory studies were done, including various kidney- and liver-function tests.

Results

The bacteriological results of co-trimoxazole therapy are given in Table 2. All strains cultured at the beginning of the trial were eradicated, but reinfection occurred in 8 cases, 5 of which were with co-trimoxazole-resistant bacteria. Two of these were Pseudomonas-strains which were already co-trimoxazole-resistant before the therapy was started.

Table 1. Diagnoses of 14 patients with anatomical defects and recurrent urinary tract infections

Renal calculi	3
Pyelonephritis (papillitis necroticans)	2
Single kidney with stone or pyelonephritis	2
Duplication of urinary path-ways and pyelonephritis	1
Neurogenic bladder with retention of urine	2
Besnier-Boeck with coral stones	1
Urethro-perineal fistula and recurrent epididymitis	1
Patient with several operations for uretero-vaginal fistula	1
Radionecrosis of bladder with recurrent cystitis	1

Tables 3 and 4 show the periods, during which the urine cultures remained negative after treatment with co-trimoxazole, for both groups of patients. As can be seen the results in the second group are much better than those in the first.

Finally, comparison of the results of standard antibiotic treatment with those of co-trimoxazole, in terms of infection-free periods is displayed in Figs. 1 and 2. The different drug regimens were

Table 2. Bacteriologic results Cotrimoxazole-therapy

Bacteria cultured at beginning Cotrimoxazole-trial	Number of patients	Eradicated	Reinfected	Cotrim-oxazole-resistent
Esch. Coli	15	15	2	1
Proteus vulgaris	1	1	1	1
Proteus mirabilis	4	4	4	-
Klebsiella	2	2	1	1
Klebsiella + Coli	1	1	-	-
Pseudomonas	2	-	-	2
Enterococ.	1	1	-	-
Total	26	24	8	5

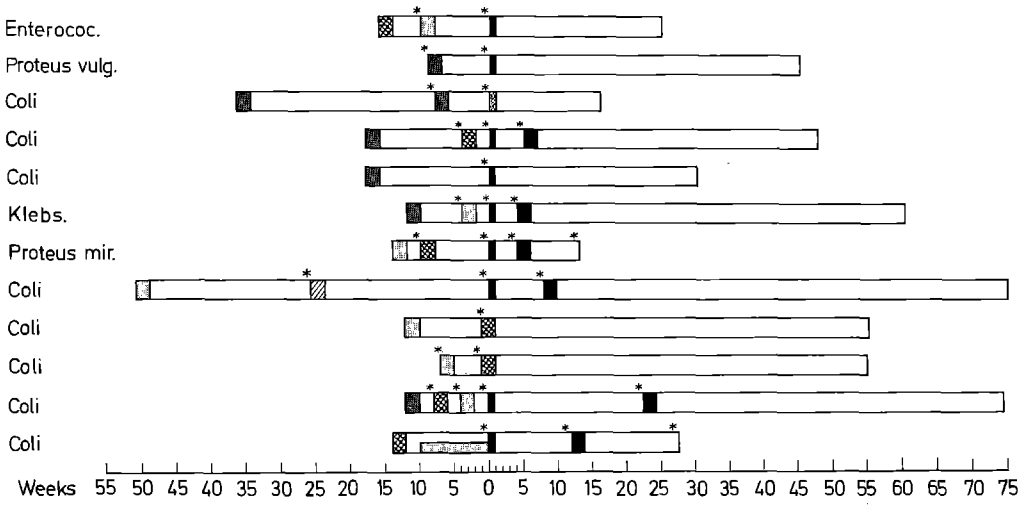
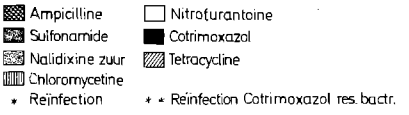


Fig. 1. Infection-free periods after treatment of 12 patients with recurrent urinary tract infections but no anatomical defects.



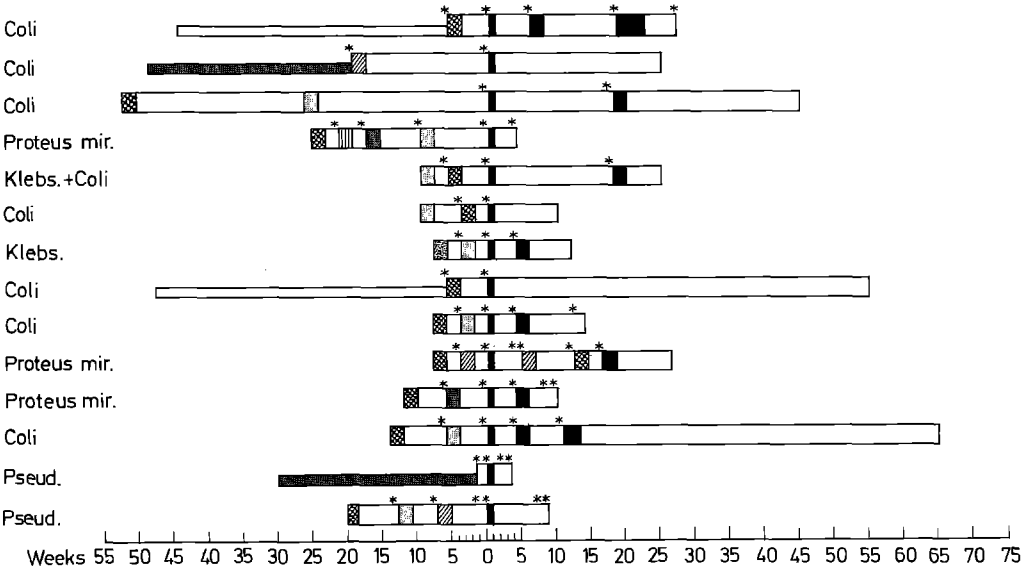
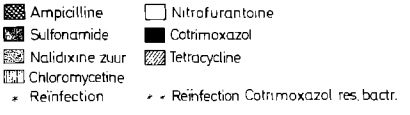


Fig. 2. Infection-free periods after treatment of 14 patients with chronic / recurrent urinary tract infections and anatomical defects or obstruction.



compared to one another for the free intervals between infections or between the last infection and the end of the trial. Statistical analysis of this comparison was assessed by Wilcoxon's test. In the second group there appeared to be no difference between standard antibiotic treatment and the first course of co-trimoxazole. ($P > 0.10$).

But after the second course of co-trimoxazole the infection free intervals were significantly longer ($P = 0.05$).

In the first group (patients with anatomical defects or obstructive diseases) there was also no difference between the standard antibiotic treatment and the first course of co-trimoxazole, and after the second course of co-trimoxazole the infection free intervals were not significantly longer ($P = 0.10$).

Table 3. Results Cotrimoxazole-therapy in weeks of bacterial free urine in 14 patients with anatomical defects or obstructive uropathy

Negative after 1 course of Cotrimoxazole for 10 weeks or longer	3
Negative after 2 courses of Cotrimoxazole for 10 weeks or longer	3
Negative after 2 courses of Cotrimoxazole for 4-10 weeks	2
Negative after 2 courses of Cotrimoxazole vor 2 weeks	2
No results from Cotrimoxazole	4

Table 4. Results Cotrimoxazle-therapy in terms of weeks of bacterial-free urine in 12 patients with lower urinary tract infections

Negative without Cotrimoxazole-therapy	3
Negative after 1 course of Cotrimoxazole-therapy for 10 weeks or longer	3
Negative after 2 courses of Cotrimoxazole-therapy for 10 weeks or longer	5
No results	1

Discussion

One of the difficulties with the kind of patients, we described in our study, is, that a single or double blind trial, using placebos, is not feasible. First the number of these patients is usually small and secondly, the use of placebos is not justifiable, because of the risks involved. Therefore we decided to use the patient as his own control, comparing the length of periods in which no significant bacteriuria was found after a given treatment. This has also the advantage of comparing different drug regimens.

In our series the rate of bacteriological cure was high, as all original strains of bacteria were eradicated, except 2 Pseudomonas strains that were co-trimoxazole-resistant from the beginning.

The fact that reinfection with other strains occurred in 8 cases, 5 of which were co-trimoxazole-resistant, should be regarded as a warning-sign. Cattell et al. pointed out, that in these cases of reinfection, the new bacteria probably were already present from the beginning but were merely suppressed by the co-trimoxazole therapy. However he does not mention co-trimoxazole-resistance. Lykkegaard et al. and Nanra mention the appearance of resistant strains of Streptococcus faecalis after termination of their treatment; in our series no Streptococcus faecalis were found, but resistant strains of E. Coli and Citrobacter did occur, which is of more importance, meaning an extra hazard for those high-risk patients. This also raises some doubt about co-trimoxazole inhibiting the acquisition of resistance as was suggested by Darrell (5) et al.

In our study, contrary to that of Nanra, the site of infection was not localized, but to our opinion, this was of no importance as the main problem in our patients was the fact that their anatomical defects or obstructive diseases could not be corrected surgically. In Nanra's series 42% did not have radiological abnormalities and therefore should be compared with our second group.

It then appears that a combined short-term, high-dosage and short-term, low-dosage regimen is better than a short-term, low-dosage alone.

As to the long-term, low-dosage regimens, Lykkegaard does not present results in terms of infection-free periods after the treatment was discontinued; which makes comparison impossible. Cattell, on the other hand, makes it clear that in 21 of his patients the long-term low-dosage therapy was merely prophylactic or suppressive, and failed to eradicate the primary causative bacteria. Both authors favour their own regimen because of the lack of side-effects and the possibility to keep their patients free of clinically manifest infections for long periods of time.

In our series 2 patients remained infection free for 6 months and 2 patients for more than a full year after our combination of a short-term, high-dosage and short-term, low-dosage therapy, while in 10 of 12 patients the causative agent was eradicated. Eradication can be of paramount importance in patients with calculous disease, when Proteus and E. Coli, notorious as stoneformers, are pres-

ent. For these reasons, if the use of co-trimoxazole is indicated by sensitivity-testing after other antibiotic treatments failed, we feel encouraged to favour a combination of short-term, high-dosage and short-term, lowdosage regimen in these cases.

In patients with recurrent infections but no abnormalities of the urinary tract the combined short-term treatment with co-trimoxazole deserves a definite place when eradication with other antibiotics failed.

Although in our study, as in those of Lykkegaard and Cattell, serious side effects were not encountered, we remain of the opinion that during treatment with co-trimoxazole repeated determinations of haemoglobin, WBC and platelet count are necessary.

Acknowledgement. The firm of Wellcome-Netherlands kindly provided us with Eusaprim-tablets for the present study.

References

1. Brumfitt, W., Reeves, D.S.: Trimethoprim in the treatment of urinary tract infections. J. infect. Dis. 120, 61 (1969)
2. Brumfitt, W., Faiers, M.C., Pursell, R.E., Reeves, D.S., Turnbull, A.R.: Bacteriological, pharmacological and clinical studies with trimethoprim-sulphonamide combinations - with particular reference to the treatment of urinary infections. Postgrad. med. J. (Suppl.) 45, 56 (1969)
3. Cattell, W.R., Chamberlain, D.E., Fry, J.K., McSherry, M.A., Broughton, C., O'Grady, F.: Long-term control of bacteriuria with TMP/SMX. Brit. med. J. 1971 I, 377
4. Cox, C.E., Montgomery, W.G.: Combined TMP/SMX therapy of urinary infections. Clinical studies. Postgrad. med. J. (Suppl.) 45, 65 (1969)
5. Darrell, J.H., Garrod, L.D., Waterworth, P.M.: Trimethoprim laboratory and clinical studies. J. clin. Path. 21, 202 (1968)
6. Grimelberg, R.N., Kolbe, R.: Trimethoprim in the treatment of urinary infections in hospitals. Brit. med. J. 1969 I, 545
7. Lykkegaard Nielsen M., Laursen, H., Christensen, P.: Control of bacteriuria with TMP/SMX in patients with urinary tract obstruction and chronic infection. Scand. J. Urol. Nephrol. 6, 239 (1972)
8. Nanra, R.S.: The use of TMP/SMX in the management of chronic and recurrent upper and lower urinary tract infection. In: Renal Infection and Renal scarring, p. 223 Melbourne: Mercedes Publ. Serv. 1970
9. O'Grady, F., Chamberlain, D.A., Stark, J.E., Cattell, W.R., Sardeson, J.M., Fry, I.K., Spiro, F.I., Waters, A.H.: Long-term, low-dosage TMP/SMX in the control of chronic bacteriuria Postgrad. med. J. (Suppl.) 45, 61 (1969)
10. Reeves, D.S., Faiers, M.C., Pursell, R.F., Brumfitt, W.: TMP/SMX: comparative study in urinary infection in hospital. Brit. med. J. 1969 I, 541

H. J. de Voogt, M.D.
Department of Urology
University Hospital
Leiden
The Netherlands