

PAPERS AND ORIGINALS

Long-term low-dose co-trimoxazole in prophylaxis of childhood urinary tract infection: Clinical aspects

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Summary

Long-term low-dosage prophylaxis may be used in children with recurrent urinary tract infection to prevent reinfection of the urinary tract while the underlying cause of infection persists. Co-trimoxazole in a dose of 2 mg trimethoprim combined with 10 mg sulphamethoxazole per kg body weight daily has proved very effective: only six out of 130 children receiving this treatment during a total period of 2637 months developed a reinfection. Co-trimoxazole was acceptable, compliance was good, and there were no important adverse effects. Supportive measures during prophylaxis are important. Sixty-five children were followed up after completion of their co-trimoxazole prophylaxis. Twenty-seven developed reinfections with fresh organisms, over two-thirds occurring within three months of discontinuing prophylaxis. Each one of these reinfections was sensitive to trimethoprim. The rectal flora were similarly sensitive.

Introduction

In children it is usually easy to eradicate the infecting organism in urinary tract infections provided there is no urinary outflow obstruction. But because such infection generally indicates impaired bladder defences reinfection is likely to occur if the sometimes obscure underlying cause of bladder susceptibility persists. Bergström¹ found that urinary infection recurred within

a year in half the children treated. The control of these further infections constitutes the main therapeutic problem, and both intermittent short courses of treatment for each infection²⁻³ and prolonged low-dosage prophylaxis⁴⁻⁶ have been used. We report here our clinical experience of using co-trimoxazole in low doses for periods of six months to six years in 130 children.

Patients and methods

Seventeen boys and 113 girls whose ages ranged from 1-12 years (mean 6.2 years) were seen in a hospital outpatient department because of urinary infection. We regarded a child as having significant bacteriuria if two consecutive samples yielded a pure growth of at least 10^5 organisms/ml fresh urine. There was a history of repeated infection in 114 children, but 16 (three boys and 13 girls) presented with their first known infection. Children with neurological defects, lower urinary tract obstruction, raised serum creatinine levels ($>100 \mu\text{mol/l}$ ($>1.13 \text{ mg/100 ml}$)), or hypertension ($>140/90 \text{ mm Hg}$) were excluded from the study.

At the time of starting prophylaxis the urine was uninfected in every child. Immediately before entering the study 69 children had received a short course of full-dosage antibacterial treatment (co-trimoxazole in 47 children) for an acute infection. Eighteen children had been receiving low-dose prophylaxis with another drug, and a change to co-trimoxazole was made because of an adverse reaction or a "break-through" infection. Forty-three children had had no antibacterial treatment during the preceding three weeks but started prophylactic co-trimoxazole because of their history or radiological findings.

METHODS

The initial study consisted of clinical history and examination, urine microscopy and culture, rectal swab culture, and blood count including platelets. An intravenous urogram (IVU) and micturating cystourethrogram (MCU) were carried out using standard techniques, the latter after at least two weeks' freedom from urinary tract infection.

Clean specimens of urine were collected after local cleansing and drying. Specimens were chilled immediately to 4°C and examined and plated within one hour using a surface viable counting technique on cysteine lactose electrolyte-deficient medium (CLED). Doubtful results were checked by culture of urine obtained by bladder puncture. This was necessary on only three occasions.

Organisms were identified by standard bacteriological techniques

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and strains of *Escherichia coli* by their O (somatic) antigen. Stokes's method of sensitivity testing was used.

Rectal swabs were collected into Stuart's transport medium. Only those showing faecal staining were accepted by the laboratory. They were plated on to two plates of MacConkey's agar and incubated overnight, and 10 colonies of coliforms were picked off, tested for sensitivity to antimicrobial agents, and identified.

Urine samples were tested for their antibiotic content by placing urine in wells cut into plates of lysed horse blood agar which had been flooded with a control strain of *Esch coli* sensitive to antibiotics and incubated overnight. Large zones of inhibition of the surface growth of *Esch coli* could then be seen around the wells into which the antibiotic-containing urine samples had been placed.

RADIOLOGICAL FINDINGS

Sixty-one children had no significant radiological abnormality (see table I). Fifty-seven had vesicoureteric reflux of varied severity, 44 of them with unscarred kidneys and 13 with established renal scarring (coarse irregular scarring, with associated calyceal deformity). The remaining 12 included five girls with duplex systems, one with a horseshoe kidney, and one with a large-capacity unobstructed bladder. The remaining three boys and two girls had undergone surgical treatment for stones, obstruction, or vesicoureteric reflux and had residual changes.

TABLE I—Results of treatment with low-dosage prophylactic co-trimoxazole in 130 children: number of infections occurring during treatment

Radiological findings	No of children	Child-months of treatment	No of infections
Normal	61	713	0
Abnormal; no obstruction or reflux	12	304	0
Reflux; no renal scarring	44	1173	3
Reflux with renal scarring	13	447	3
Total	130	2637	6

TREATMENT

A prophylactic dose of 2 mg trimethoprim (TMP) and 10 mg sulphamethoxazole (SMX) per kg per day was given either as a suspension (paediatric suspension containing 200 mg SMX, 40 mg TMP in 5 ml) or in tablet form (100 mg SMX, 20 mg TMP in one paediatric tablet) according to the child's preference. Dosage was adjusted to the nearest 50 mg SMX. About a quarter of the children started with the suspension, suitably diluted if necessary for young children. When the dose could be easily divided it was given twice daily; otherwise it was given in one nightly dose (to cover the longest interval without voiding).⁸

The duration of treatment and follow-up were determined by the radiological findings and previous history. Children with normal radiological appearances received a prophylactic dose for 6-12 months and those with an abnormality but no reflux received treatment for 12-24 months. Follow-up after stopping treatment was continued for at least one year. In children with vesicoureteric reflux prophylaxis was continued until one year after reflux had disappeared if the kidneys were unscarred and until renal growth was complete if renal scarring was present. Follow-up was continued for at least two years after stopping prophylaxis and indefinitely in those with scarred kidneys.

When an infection developed during the course of prophylactic treatment 10 days' full-dosage treatment with an appropriate anti-

bacterial drug was substituted for prophylaxis, which was then resumed. When an infection developed during follow-up, after prophylactic treatment had been stopped, a 10-day course of full-dosage treatment was given followed by further prophylaxis, the duration of which depended on the radiological findings and history.

Our encouragement of the children to drink liberally and to void regularly, frequently, and completely, with double micturition at bedtime if reflux was present was essential to the treatment. Constipation was corrected, potential local irritants such as antiseptics or detergents in the bath water were discouraged, and threadworms were treated.

FOLLOW-UP STUDY

Children were seen after two, four, and eight weeks and then every three months throughout treatment and at the same intervals after prophylaxis was stopped and also if symptoms returned. Urine samples and rectal swabs were collected at each attendance without interruption of treatment. Haematological studies were repeated every six months during treatment, and standard two-film IVUs and limited MCUs were repeated after two years in children with reflux, or if infection had recurred. Plasma urea and creatinine estimations were made yearly in children with renal scarring.

Results

RECURRENCE OF INFECTION DURING PROPHYLACTIC TREATMENT

No further infections occurred during 1017 months of prophylactic treatment with co-trimoxazole in the 73 children with no obstruction or reflux (mean 13.9 months per child; table I).

Among 57 children with vesicoureteric reflux six girls developed a single infection each during 1620 months' treatment (or about one further infection in 22 years). Three of them had renal scarring and three had normal kidneys. Although four of these children had pyuria, only two had symptoms and these were minor. None had fever. Table II shows that the infecting organism differed in each child from that causing the preceding infection, indicating that these were reinfections. These reinfections occurred nine to 25 months after starting treatment in children with reflux alone and after 26 to 62 months in three with renal scarring. Their timing was unrelated to age, preceding treatment, or the length of treatment. Four of these reinfections were caused by *Streptococcus faecalis*, one by *Klebsiella oxytoca*, and only one by *Esch coli*.

All were resistant to both sulphonamide and TMP, but were fully sensitive to another antibacterial drug so that their elimination did not present any problem (table II). The nature and sensitivity pattern of the corresponding rectal organisms are reported in part II.

Patient compliance—Co-trimoxazole both in suspension and in tablet form was acceptable and well-tolerated. Evidence of antibacterial activity was present in urine samples from 50 of the 54 children tested. In only one of the four defaulters was the result unexpected.

Side effects and haematology—Very few side effects were encountered on this prophylactic dose. Three children were said to be sleepy or tired, two of them improving after changing to prophylactic nitrofurantoin. Two children developed a generalised maculopapular rash, which disappeared when co-trimoxazole was discontinued, but no formal sensitivity testing was done. Two hundred and one measurements of haemoglobin and white blood cells were made during treatment in 94 children. All were normal. One girl developed a leucopenia of 2.2×10^9 white blood cells/l ($2200/\text{mm}^3$) (neutrophils

TABLE II—Details of six urinary infections that occurred during prophylactic treatment with low-dosage co-trimoxazole of 57 children with vesicoureteric reflux

Case No	Preceding infection				Time in months after starting treatment	Organism	Details of recurrence				
	Organism	Sensitivity		Organism			Sensitivity				
		Trimethoprim	Sulphonamide				Trimethoprim	Sulphonamide	Nitrofurantoin	Ampicillin	Nalidixic acid
1	<i>Esch coli</i> NG	S	S	9	<i>Str faecalis</i>	R	R	S	S		
2	<i>Esch coli</i> 075	S	S	19	<i>Str faecalis</i>	R	R	S	S		
3	<i>Esch coli</i> 04	S	R	25	<i>Str faecalis</i>	R	R	S	S		
4*	<i>Esch coli</i> 075	S	S	26	<i>Str faecalis</i>	R	R	S	S		
5*	<i>Esch coli</i>	S	Not done	26	<i>Kleb oxytoca</i>	R	R	S	R	S	
6*	<i>Pr morgani</i>	S	S	62	<i>Esch coli</i> NG	R	R	S	R	S	

*Renal scarring present. NG = Non-groupable. S = Sensitive. R = Resistant on in-vitro testing.

43%) during treatment of a concurrent respiratory illness with a higher dose of 5 mg TMP and 25 mg SMX/kg/day. The count rose spontaneously to $5.2 \times 10^9/l$ ($5200/mm^3$) within one week of resuming the prophylactic dose. Sixty-seven platelet counts were performed in 58 children during co-trimoxazole prophylaxis of at least three months' duration. All the counts were greater than $180 \times 10^9/l$ ($180\,000/mm^3$); 91% were between 200×10^9 and $400 \times 10^9/l$ ($200\,000$ and $400\,000/mm^3$).

Reflux, renal growth, and function—During the period of prophylaxis reflux decreased or stopped in 34 of the 45 children reviewed and persisted unchanged in 11. Renal growth was assessed in 37 children and was unimpaired except in two with severely scarred kidneys that grew slowly. Renal growth was normal in all six with reinfections. There was no extension of scarring. Renal function was normal initially in all children included in this study, and there was no rise during the study in plasma urea or creatinine concentration in children with renal scarring.

RECURRENCE OF URINARY INFECTION AFTER STOPPING PROPHYLACTIC TREATMENT

Of the 130 children treated 65 (8 boys and 57 girls) were followed up after prophylaxis was completed. Follow-up was maintained either until a further infection developed or for at least 12 and up to 42 months—a total of 681 months. The average follow-up time off treatment was 17 months.

A further infection developed in 27 (42%) of these children (table III). Comparison of the serotype of the organism causing the preceding infection with that of fresh infection was possible in 19 of the 27 children with recurrences, and in each of these the infection was shown to be a reinfection. Twenty-four of these 27 were due to *Esch coli*, one to *Str faecalis*, and two to *Proteus spp*; all 27 of the infecting organisms were sensitive to TMP. The corresponding bowel flora were similarly sensitive so that treatment with co-trimoxazole could be resumed.

Nineteen (70%) of the reinfections occurred within three months of stopping treatment, 21 (78%) within six months, and all but one within one year (table IV). Follow-up extended beyond one year for varying periods up to 42 months in 27 children.

Relation to x-ray findings and general health—Thirty (57%) of the 53 children with no reflux or outflow obstruction remained free from infection (table III) during 12 to 34 months' observation (an average of 17 months' observation per child). In general these were healthy children from stable homes. The other 23 (43%), however, developed a

reinfection within one year, relating in many cases to adverse social factors or intercurrent illness resulting in a lapse in improved voiding habits. Eight of the nine children whose prophylaxis was discontinued a year after reflux had stopped spontaneously remained free from infection for at least 12 and up to 42 months; one girl was found to have significant bacteriuria on routine urine culture two years after stopping treatment. Three girls who stopped their prophylactic treatment through misunderstanding while reflux persisted all developed a reinfection within two months. Prophylaxis was not stopped during this study in any children with renal scarring.

Age, sex, and symptoms—The risk of developing further infections was unrelated to age but was greater in girls than boys (26 out of 57 girls compared with one out of eight boys). Among the 27 children with reinfections, significant pyuria was found in 10, seven of whom had minimal symptoms and only one of whom, with normal x-ray appearances, was febrile and unwell.

Duration of prophylactic treatment and previous history—No conclusion could be drawn about the effect of the length of treatment on the likelihood of reinfection after stopping treatment since the duration was determined by the previous history, children with a greater tendency to recurrence receiving longer courses. Duration did not affect the rapidity of reinfection after stopping; 70% of reinfections occurred within three months, irrespective of the length of course. No relation was found between the risk of further infections and either the treatment preceding prophylaxis or the initial infecting organism.

Discussion

These results indicate that co-trimoxazole is very successful in preventing further urinary tract infections during its continued administration in low dosage. Others have had similar experience with adults,^{8, 9} and children.¹⁰⁻¹²

Co-trimoxazole in a dose of 2 mg TMP and 10 mg SMX/kg/day was taken readily and well tolerated for up to six years, antibacterial activity being found in 93% of children tested at random. (This contrasts with Daschner and Marget's¹³ finding that only 71% took their prescribed treatment at all and only 32% exactly as prescribed.) This dose produced no important side effects or haematological complications and a similar lack of toxicity was reported by Forbes and Drummond¹¹ and Zoethout,¹⁰ the latter using 4 mg TMP and 20 mg SMX/kg/day. Böse,¹⁴ however, recorded a temporary depression of the platelet count in some patients using a higher dose, though this effect disappeared within four days of stopping treatment.

Over a period of administration lasting up to six years we have found no deterioration of renal function in children with renal scarring, and renal growth has continued as expected.

Twice-weekly administration of co-trimoxazole has been used successfully,^{9, 15} but in our experience a nightly dose is more easily remembered by parents.

Recurrences during prophylactic treatment were virtually eliminated and even in children with vesicoureteric reflux the recurrence rate was only one in 22 patient years. The infections that did occur were reinfections, as would be expected, but although the urinary organisms were resistant to sulphonamide and TMP the infection responded rapidly to another antibacterial drug.

Successful prophylaxis allows time for the possible recovery of normal bladder function and for reflux to stop; during this time renal growth will proceed normally.¹⁶ If the bladder defences are still impaired when antibacterial treatment is stopped further infections are likely to develop. In contrast to reinfections occurring during prophylactic treatment, all of the reinfections after stopping treatment were sensitive to TMP and two-thirds to sulphonamide; their treatment posed no problem.

Among the 33 children developing reinfections either during or after stopping treatment, only one had fever or significant symptoms. Four others had mild dysuria or an increase in enuresis. All of the children included in this study originally had symptoms even if these were unrelated to the urinary tract. This raises the possibility that the strains of the infecting organism may have been changed in some way during co-trimoxazole prophylaxis, since Lindberg *et al*¹⁷ have found differences in the

TABLE III—Urinary infections occurring during follow-up of 65 children after stopping prophylactic co-trimoxazole

Radiological findings	Children with infection	Children with no infection	Total followed
Normal	21	26	47
Abnormal; no obstruction or reflux	2	4	6
No renal scarring:			
Reflux persisting	3*	0	3
Reflux stopped one year or more	1	8	9
Reflux with renal scarring	0	0	0
Total	27	38	65

*Three children who stopped treatment in error.

TABLE IV—Timing of further infections in 65 children followed for one year after stopping prophylaxis and in 27 of the 39 children who remained free from infection for one year, followed up for varying periods up to three and a half years

Time off treatment (months)	Children followed without infection	Children with recurrence	
0-3	65	19	} 40% of 65 children followed for one year
4-6	46	2	
7-9	44	3	
10-12	41	2	
13-15	27	0	
16-18	21	0	} 10% of 10 children followed for two years
19-21	13	0	
22-24	10	1	
25-42	5	0	

coliform strains causing symptomatic and asymptomatic bacteriuria.

Co-trimoxazole is a safe and effective antibacterial drug in conditions for which long-term low-dosage prophylaxis may be indicated. These include the management of the child who is repeatedly ill or off school because of recurrent symptomatic urinary infection or whose kidneys are potentially at risk of infective damage because of incompetence of the vesicoureteric valve or the child who has renal scarring. There is a very low incidence of "breakthrough" infections during treatment and the induction of resistant organisms has not proved to be a problem.

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Long-term low-dose co-trimoxazole in prophylaxis of childhood urinary tract infection: Bacteriological aspects

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Summary

The bacteriological consequences of giving long-term low-dose co-trimoxazole to children to prevent reinfection of the urinary tract were studied. Only six "breakthrough" infections occurred during 2637 child-months of prophylaxis. The children complied well with treatment. During prophylaxis the number of rectal coliform bacilli recovered was greatly and rapidly reduced, but at least 70% of the surviving coliform organisms remained sensitive to the two components of co-trimoxazole. Changes in sensitivity pattern were evident within a month of starting treatment and the proportion of rectal organisms resistant to sulphonamide or trimethoprim did not increase with time.

After stopping co-trimoxazole prophylaxis the number of rectal organisms recoverable returned rapidly to normal, as did their sensitivities to trimethoprim and sulphonamide. Further episodes of urinary tract infection developing after prophylaxis was stopped were caused by organisms sensitive to a wide range of antimicrobial agents, including trimethoprim.

Introduction

Reinfection of the urinary tract after eradication of the initial infecting organism is common in childhood. Since the rectal

flora is the source from which new organisms causing urinary tract infection are derived, a good prophylactic drug should not generate a resistant rectal flora and should also be active against a high proportion of potential urinary pathogens, thereby maintaining a sterile urine.

Nitrofurantoin is an effective prophylactic drug,^{1,2} and we have shown that it does not generate a resistant bowel flora, whereas sulphonamide and ampicillin are less satisfactory.²

We have shown (see part I) that continued low-dose co-trimoxazole is also very effective in preventing reinfection during treatment. This paper reports the bacteriological effects on the urine and bowel flora of long-term low-dose co-trimoxazole, which is a mixture in fixed proportions of trimethoprim (TMP) and sulphamethoxazole (SMX).

Patients and methods

One hundred and thirty children aged 1-12 were studied. They each received at least six months' prophylactic treatment with co-trimoxazole in a dose of 2 mg TMP and 10 mg SMX/kg/day.

Urine samples and rectal swabs were collected immediately before starting prophylaxis, at two, four, and eight weeks and then every three months during treatment and at the same intervals after stopping treatment. The methods of sample collection and the duration of treatment and follow-up have already been described (see Part I).

All rectal swabs were plated on to two plates of MacConkey's agar to give separate colonies, and the plates were then incubated overnight. With this method rectal swabs generally yield many coliforms, but early in this study it was noted that the growth of coliforms was often scanty or absent. This was attributed to faulty sampling until it became apparent that this was an effect of co-trimoxazole treatment. Whenever possible 10 colonies of coliform organisms were picked off, purified, tested for sensitivity to antimicrobial agents and identified. When several colonial types were present they were sampled in proportion to their frequency.

Results

COMPLIANCE

During prophylactic treatment with low-dose co-trimoxazole

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