Comparison of trimethoprim-sulfamethoxazole with sulfamethoxazole in urinary tract infections of children

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Summary: The effect of trimethoprim-sulfamethoxazole was compared with that of sulfamethoxazole alone in 26 children with urinary tract infection, randomly assigned according to a double-blind procedure to two equally sized groups. TMP-SMX was found to be superior in rendering the urine culture negative for the 3 months after the start of treatment. Also, over the 12-month follow-up period there were fewer recurrences in the patients who received TMP-SMX but here the difference between the two groups did not reach statistical significance.

Résumé: *La comparaison du triméthoprime-sulfaméthoxazole avec le sulfaméthoxazole dans des infections des voies urinaires chez l'enfant*

Nous avons comparé l'effet de l'association triméthoprime-sulfaméthoxazole (TMP-SMX) avec celui du sulfaméthoxazole seul chez 26 enfants souffrant d'infections urinaires. L'assignation de ces malades a été faite au hasard en deux groups d'importance égale, suivant la méthode du double anonymat. Le TMP-SMX s'est révélé supérieur en négativant la culture urinaire pendant les 3 mois qui ont suivi le début du traitement. Un autre point est qu'au cours de la période de postobservation de 12 mois, les récidives ont été moins nombreuses chez les malades recevant le TMP-SMX, mais il faut admettre que la différence entre les deux groupes n'avait guère de signification sur le plan statistique.

The recurrence of urinary tract infection (UTI) is common although the exact incidence is not known. In the series of McCabe and Jackson two thirds of adults with UTI had a recurrence of infection within 3 years.[1] Forbes, Drummond and Nogrady reported a recurrence rate of 24% in children with UTI within 16 months.[2] Kunin, Deutscher and Paquin demonstrated that in 60% of affected children UTI recurred within 1 year and in 75% recurred within 2 years.[3]

In view of the high rate of recurrence of UTI with the use of antimicrobial therapy, the combination trimethoprim-sulfamethoxazole (TMP-SMX) was compared with sulfamethoxazole (SMX) alone in a prospective double-blind trial to compare the effectiveness in reducing the number of recurrences. This is the first controlled study among pediatric subjects using these agents in short-term therapy with long-term follow up.

Methods and material

Letters were sent to a group of family physicians and pediatricians informing them of the study protocol and enlisting their cooperation. These physicians notified one of us whenever they had under their care a patient with UTI confirmed by a colony count higher than 100 000 organisms per ml. Twenty-six such patients were included in our study.

All colony counts and hematologic and radiologic investigations were performed in a standardized manner in one of three hospital laboratories that are linked together in a district laboratory program in Hamilton.

Patient characteristics

The ages of the patients ranged from 4 months to 18 years, with a mean age of 6¼ years. In the group of 26 children 23 were girls (88%) and 3 were boys (12%) (Table I).

First and repeat infections

The distribution of first and repeat infections on initial diagnosis is shown in Table II. Based on the history, 18 (69%) of the 26 children had first infections. There were eight repeat infections in children who had been previously treated with other antibiotics. There was no significant difference in the number of children with first infections between the two treatment groups.

Table I — Age (in years) and sex distribution of treatment groups

		SMX group	TMP-SMX group	Both groups
Girls	Number	12 (92%)	11 (85%)	23 (88%)
	Age, mean	6	7	6
	Age, range	⅓ - 12	1 - 18	⅓ - 18
Boys	Number	1 (8%)	2 (15%)	3 (12%)
	Age, mean	5	6	6
	Age, range		3 - 10	3 - 10

Table II—First and repeat infections at initial diagnosis

	SMX group (%)	TMP-SMX group (%)	Total (%)
First	10 (77)	8 (62)	18 (69)
Repeat	3 (23)	5 (38)	8 (31)
Total	13	13	26

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Symptoms

Twenty-four patients (92%) had symptomatic urinary tract infections, borne out by colony counts higher than 100 000/ml. The other two cases were discovered on routine urinalysis and confirmed by subsequent culture and colony count. The two treatment groups each contained one asymptomatic patient.

The frequency of initial clinical manifestations was comparable in the two treatment groups. Fever, increased frequency of micturition, dysuria, secondary enuresis and hematuria were the most common manifestations.

Radiologic findings

Intravenous pyelography was carried out in all the patients; eight had also voiding cystourethrograms. The radiologic findings in the two treatment groups are compared in Table III. Mild vesicoureteral reflux and dilatation of the ureters and minor calyces were the abnormalities reported. One patient with recurrent UTI who was in the TMP-SMX group had a neurogenic bladder associated with paraplegia.

Bacteriologic findings

Escherichia coli was cultured from the initial urine specimen in 22 (85%) of the 26 cases; in two cases the organism isolated was *Proteus mirabilis* and in one case each it was *Pseudomonas* and *Klebsiella* species. The infrequent organisms, which are commonly associated with resistance to antimicrobials, were all cultured from the TMP-SMX-treated group (Table IV).

Treatment

All patients were treated for 4 weeks with either SMX alone or TMP-SMX. The medications were prepared in liquid form and were identical in colour, taste and consistence. In the control group SMX was used in a dosage of 500 mg thrice daily for patients weighing less than 25 kg (mean weight, 13.3 kg) and 1 g thrice daily for patients weighing more than 25 kg. TMP-SMX was given with the constituents in a ratio of 1:5 (40 mg TMP to 200 mg SMX per teaspoonful) in a dose of 1 tsp thrice daily for children weighing less than 25 kg and 2 tsp thrice daily for children over 25 kg.

The children were allocated to treatment with one or the other medication in a random double-blind manner. Sealed envelopes containing the name of the medication were numbered so that five of each 10-number series were TMP-SMX and five were SMX alone. Each series of 10 numbers was specified as to use for the first infections or repeat infections. The number groupings were also designated as to weight of the patient. Thus, a child with a first infection and weighing less than 25 kg would have an envelope drawn from that series of 10 numbers, half representing TMP-SMX and half SMX alone.

None of the patients or physicians knew which medication had been used until follow-up was completed and the code broken. All children were private patients and were treated and followed up as outpatients.

Two weeks after starting medication all patients had a repeat colony count, leukocyte count, hemoglobin estimation and blood smear. These measurements were repeated 5 weeks after starting medication (1 week after its discontinuance). Intravenous pyelography was also performed about this time in all patients who had not had such a study done within the previous year. A smaller number of patients also had voiding cystograms done at this time.

Follow-up colony counts were subsequently repeated at 3, 6, 9 and 12 months after the onset of treatment (Table V). A recurrence was defined as a positive colony count in a patient whose urine had previously been rendered sterile. If symptoms and pyuria were present, however, a colony count between 10 000 and 100 000 was accepted as sufficient evidence of recurrence. Treatment failure was defined as a positive colony count 2 weeks after medication was started.

No significant hematologic or other side effects were noted in either of the two groups of children who completed the study.

Treatment failure and recurrence

Fifteen of the 26 children (58%) had a recurrence or failure of treatment of UTI during the 12-month follow-up. In the group treated with SMX alone, 9 out of 13 (69%) had a

Table III—Radiologic findings

	SMX group	TMP-SMX group	Total
Intravenous pyelogram			
Normal	11	11	22
Abnormal	2	2	4
Voiding cystourethrogram			
Normal	1	3	4
Abnormal	3	5	8

Table IV—Organisms isolated on initial urine culture (100 000 colonies / ml)

	SMX group	TMP-SMX group	Total
Escherichia coli	13	9	22
Klebsiella sp.	0	1	1
Pseudomonas sp.	0	1	1
Proteus mirabilis	0	2	2
Total	13	13	26

Table V—Duration of follow-up

	SMX group	TMP-SMX group	Total
12 months	11	11	22
9 months	1	1	2
6 months	1	1	2
Total	13	13	26

Table VI—Time of positive urine cultures over 12-month follow-up

	SMX group	TMP-SMX group	Total
2 weeks	3	0	3
5 weeks	3	0	3
3 months	3	2	5
6 months	3	4	7
9 months	0	1	1
12 months	3	2	5
Total	15	9	24

Differences before 3 months are significant (P = 0.005)

recurrence or did not respond within 2 weeks. In the TMP-SMX group the infection recurred in 6 out of 13 (46%); there were no treatment failures in this group.

Although the advantage appeared to be in favour of TMP-SMX with regard to subsequent recurrences, the difference in the recurrence rate between the two treatment groups was not significant. However, when the positive urine cultures obtained over the 12-month follow-up period were analysed with respect to the interval after the start of treatment, a significant difference was found between the two treatment groups (Table VI). There were no positive cultures before 3 months in the TMP-SMX-treated group, whereas there were six positive cultures during the same period in the SMX group. This difference is significant and suggests that the combination of TMP-SMX is superior to SMX alone in ensuring a sterile urine up to 3 months after the onset of treatment.

Discussion

Many controlled studies employing TMP-SMX in adults have been performed.[4-9] In general their reports suggest that TMP-SMX is more effective than other antimicrobials in eradicating organisms from the genitourinary tract.

Studies of children given TMP-SMX for UTI have either been uncontrolled,[10,11] uncontrolled in patients with meningomyelocele,[12] controlled but not double-blind in patients with meningomyelocele,[13] controlled with double-blind long-term administration,[14] or controlled, double-blind with short-term administration and short-term follow-up.[15] In general these studies have found TMP-SMX to be an effective and safe urinary antimicrobial for use in children.

We report the first controlled, double-blind study in children with UTI employing TMP-SMX in a manner that most closely approximates usual clinical practice, namely short-term administration with long-term follow-up.

The randomization procedure succeeded in separating the two groups equitably except that there were more of what are generally believed to be resistant organisms in the TMP-SMX group. This chance occurrence favoured the SMX results. Nevertheless, the results for the first 3 months were significantly superior in the TMP-SMX group. At the end of 12 months there were fewer recurrences in the TMP-SMX group but the difference was not significant.

Our experience supports previous work showing no difference in side effects whether patients are treated with TMP-SMX or with SMX alone.

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