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LONG-TERM PROPHYLAXIS OF URINARY INFECTIONS IN WOMEN: COMPARATIVE TRIAL OF TRIMETHOPRIM, METHENAMINE HIPPURATE AND TOPICAL POVIDONE-IODINE

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ABSTRACT

We randomized 64 patients with a history of recurrent urinary tract infections among 3 regimens of long-term (1 year) prophylactic treatment: 20 were given 100 mg. trimethoprim at night, 25 received 1,000 mg. methenamine hippurate every 12 hours and 19 were asked to cleanse the perineum (especially the periurethral area) twice daily with povidone-iodine solution. The progress of patients in terms of urinary symptoms and/or bacteriuria, changes in periurethral flora, side effects, and hematological and biochemical profiles was followed at regular intervals. All treatments were effective in reducing the incidence of symptomatic attacks when compared to the 12 months immediately before therapy and there was little to choose between the individual regimens on this account. However, trimethoprim was tolerated better than were the other 2 treatment regimens. In the group given trimethoprim most of the breakthrough infections (71.4 per cent) that occurred were caused by trimethoprim-resistant organisms (usually Escherichia coli), while in the other 2 groups the incidence of trimethoprim-resistant organisms causing infection was low (2.7 per cent). Treatment with trimethoprim reduced significantly the periurethral colonization of Escherichia coli.

In many women who suffer recurrent urinary infections there is no obvious reason for recurrence. It has been suggested that these women have a deficiency in some defense mechanism, for example lack of cervicovaginal antibody[1] or a decreased serum bactericidal activity.[2] It has been known for many years that this type of patient benefits from long-term, low dose prophylaxis with an antibacterial agent.[3] However, by no means are all antibiotics suitable for use for up to 12 months continuously and of those tested only trimethoprim (with or without sulfamethoxazole), nitrofurantoin and methenamine salts have been used widely.[4-12] Trimethoprim alone has certain theoretical advantages over cotrimoxazole for long-term therapy[13] and initial reports on its use are encouraging.[4,12]

However, the use of an oral antimicrobial regimen to prevent bacterial growth in the bladder urine is only 1 approach to the problem of the management of patients with recurrent urinary infections. An alternative strategy would be to prevent bacteria entering the bladder from below in the first place. It has been suggested that pathogenic bacteria (usually Escherichia coli) always colonize the periurethral area immediately before ascending the urethra to initiate an infection.[14] This process might be halted by preventing colonization, for instance by application of an antiseptic to the urethral meatus and the surrounding area. There is some clinical evidence that this approach is successful in reducing the incidence of urinary infections.[15,16]

Therefore, we decided to compare the use of an antiseptic perineal wash (povidone-iodine solution) to trimethoprim or methenamine hippurate in a 3-way trial of clinical efficacy and patient acceptability in women suffering recurrent urinary infections.

MATERIALS AND METHODS

Patients. Patients were entered into the study if they had a history of ≧4 attacks of symptoms related to the urinary tract in the previous 12 months, most commonly frequency, dysuria and urgency. At least 1 of these episodes was documented bacteriologically as being caused by a urinary infection in all patients, the test often having been done in our laboratory. A requirement for entry was sterile urine at the time long-term prophylactic treatment was begun. Any existing infection was eradicated by a 7-day course of an appropriate antibiotic as described previously.[17-19] Long-term prophylaxis was started when a followup urine specimen obtained 5 weeks after the end of the short-term therapy had proved sterile.

In addition, a few patients were entered who had had repeated attacks of asymptomatic significant bacteriuria detected in our laboratory during the previous 12 months.

Any patient with a history of hypersensitivity or intolerance to nitrofurantoin, trimethoprim or iodine was excluded from the trial.

Of the 67 patients who satisfied our criteria only 3 failed to return to the clinic regularly after having been entered and, therefore, were unsuitable for assessment in this study, leaving 64 who could be assessed properly. Of these patients 20 received trimethoprim, 25 methenamine hippurate and 19 povidone-iodine. The 3 treatment groups were similar in terms of age, incidence of radiological abnormalities and recent history of symptomatic episodes (table 1).

Clinical methods. Patients were seen at the outpatient urinary infection clinic. On the first visit a detailed history was obtained. Patients were examined and specimens of blood were obtained for hematological and biochemical analyses. Particular attention was paid to obtaining a properly collected midstream urine specimen. At the first visit to the clinic test results were assessed and further tests were done as indicated, including excretory urography as well as voiding cystourethography. If long-term prophylactic treatment seemed suitable the procedures involved and the reasons for treatment were explained carefully, and the necessity for the patient to cooperate was stressed. Before treatment was started the periurethral flora was analyzed by a technique described previously.[20] Each patient was given a dipslide with a container suitable for mailing, a prepaid envelope addressed to the department of medical microbiology, a simple questionnaire on symptoms and instructions for the use of the dipslide. Patients were asked to inoculate the dipslide and send it immediately if they experienced any symptoms between visits to the clinic.

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Patients receiving long-term prophylaxis were asked to return to the clinic monthly for 6 months, and at 9 and 12 months after starting therapy. At these followup visits they were asked about any symptoms or adverse effects that had occurred since the previous visit. A midstream urine specimen was collected, a periurethral swab was obtained and the flora was examined. Blood samples were obtained as before for hematological and biochemical investigations. The importance of continuing cooperation was stressed to the patient at each visit.

Any infections, confirmed in the laboratory, that occurred during the course of prophylactic therapy were treated with a 7-day course of an appropriate oral antibacterial agent, and the patient was followed 1 and 5 weeks after the end of the course. The patient was asked to stop the prophylactic regimen as soon as an infection was confirmed. Therapy was not restarted until the first followup confirmed sterile urine.

Patients who experienced any problems during the course of prophylaxis were encouraged to attend the treatment room in the department of medical microbiology, where a history and examination were done, appropriate specimens were obtained and the necessary treatment was given.

All episodes of infection and symptoms were recorded on specially designed forms, as were details of any adverse reactions.

Patients were asked to return 3 and 6 months after completion of the prescribed 12-month course of prophylaxis. Urine was examined, and the standard hematological and biochemical tests were done. If there were no problems at this stage the patients were discharged from the clinic but were invited to return if they experienced recurrent urinary symptoms.

Treatment. Patients were randomized to 1 of 3 treatment regimens: 1) 1,000 mg. methenamine hippurate every 12 hours, 2) 100 mg. trimethoprim at night and 3) frequent application of povidone-iodine solution to the perineal region. Detailed instructions were given. Thus, patients were supplied every month with a kit comprising a stock solution of 10 per cent povidone-iodine (1 per cent free iodine) and a flexible dispenser bottle. Each treatment involved diluting 15 ml. of the concentrate to 240 ml. with warm water in the dispenser bottle, which then was squeezed. The jet was directed over all parts of the perineal region while the patient was seated on the toilet or on the edge of the bath with the legs separated and the labia spread. This procedure was to be followed at least twice every day.

We do not have an untreated group since it would be considered unethical in Great Britain to withhold prophylactic treatment deliberately for patients such as those attending our clinic.

RESULTS

Duration of treatment. The over-all mean duration of treatment was 237 ± 154 days (standard deviation) for trimethoprim, 254 ± 140 days for methenamine hippurate and 193 ± 141 days for povidone-iodine. There appeared to be a tendency for a certain number of patients to stop treatment within 100 days. In contrast, those who continued treatment after this time usually did so for the entire course of the treatment. Of our patients 15 stopped treatment prematurely: pain on voiding occurred in 3 in the methenamine hippurate group, 1 became pregnant and was advised to stop taking trimethoprim, 1 was lost to followup and the remaining 10 failed to attend clinic appointments despite being sent several reminders by mail. This latter group was recorded as being noncompliant.

Clinical efficacy of prophylactic regimens. All 3 treatments reduced the incidence of symptomatic attacks 2 or 3-fold, compared to the interval before prophylaxis started (tables 1 and 2).

A detailed breakdown of the clinical efficacy is given in table 2, in which the treatment intervals for all patients have been cumulated. None of the 3 regimens was outstandingly better than the others. Methenamine hippurate seemed slightly less effective in maintaining patients free of symptomatic attacks but was as good as trimethoprim at keeping the patients abacteriuric. In terms of the interval between bacteriuric attacks, methenamine hippurate was marginally the best of the 3 treatments, trimethoprim was second and povidone-iodine was third. However, none of the differences was significant.

An alternative method of analysis is based on the experience of individual patients (table 2). There are no significant differences between the proportion of patients remaining either asymptomatic or abacteriuric in the 3 treatment groups (chi-square test). As noted, it was not possible to assess all patients in each group in terms of whether the attack rate had decreased while on therapy. This usually was because not all patients could give an accurate estimate of the attack rate during the previous 12 months.

Breakthrough infections. The organisms that caused breakthrough infections are listed in table 3. The majority (73 per cent) were E. coli and 19 per cent of the total were gram-positive species. This pattern of infecting organisms is similar to that observed by us in other studies.[17-19]

A striking finding was made with respect to the sensitivity patterns of the infecting organisms causing breakthrough in-

TABLE 1. *Comparability of treatment groups*

	Trimethoprim	Methenamine Hippurate	Povidone-Iodine Wash
No. pts. assessable	20	25	19
Mean age (standard deviation)	39.9 (20.5)	38.2 (18)	31.7 (14.3)
Pts. with previous bacterial infections confirmed in our laboratory (%)	50	32	58
Abnormal radiology (%)	3/20* (15)	3/24† (12)	1/18‡ (6)
Mean No. symptomatic attacks during previous 12 mos. (standard deviation)	6.4 (4)	4.9 (1.8)	5.2 (2)
Mean days between symptoms	57	74	70

* Chronic pyelonephritis in 1 patient, extrarenal dilatation in 1 and residual urine >100 ml. in 1.
† Calculus in 1 patient, chronic pyelonephritis in 1 and clubbed calices in 1.
‡ Residual urine >100 ml.

TABLE 2. *Effectiveness of different treatments in preventing urinary infection*

	Trimethoprim	Methenamine Hippurate	Povidone-Iodine Wash
	Cumulated data		
No. pts.	20	25	19
Total pt. days on treatment	3,574	6,350	3,470
No. symptomatic episodes while on treatment	22	35	23
Av. interval between symptomatic episodes (days)	162	181	151
No. bacteriuric episodes	15	24	17
Mean interval between bacteriuric episodes (days)	238	258	208
	Individual data		
No. pts.	20	25	19
No. remaining asymptomatic (%)	9 (45)	7 (28)	10 (53)
No. remaining abacteriuric (%)	12 (60)	15 (60)	9 (47)
Effect on incidence of attacks:*			
Less frequent (%)	10 (50)	13 (52)	8 (42)
No change	3	6	6
More frequent	1	0	1

* Not all patients could be assessed in the analysis.

effective is harder to explain. Povidone-iodine was applied externally only and there can be no question of the urine in the bladder becoming antibacterial as a result of its use. The original rationale behind the use of a bactericidal perineal wash was that it might reduce the incidence of periurethral colonization by uropathogenic strains. This idea is based on the theory of Stamey and Sexton that infection always is preceded by colonization with the infecting organism.[14] In theory, by killing the colonizing strains it would be possible to avoid infection. However, povidone-iodine was ineffective at reducing the perineal colonization of E. coli (table 6). The observation that the incidence of recurrent urinary infections can be reduced despite an unchanged perineal colonization rate of E. coli substantiates the results of our earlier study,[21] which suggests that the role of the flora might not be as important after all as had been suggested by Stamey and Sexton.[14]

Landes[15] and Meyhoff[16] and their associates found povidone-iodine ointment applied to the urethral meatus twice daily to be an effective prophylactic measure, and Jameson also recommended its use.[28] All 3 reports suggested that the effect of the antiseptic on the perineal flora does not explain its clinical efficacy. We were not surprised that methenamine hippurate did not alter the periurethral flora. However, this finding agrees with that of Colleen and associates.[29] Trimethoprim is said to be excreted in the vaginal secretions[30] and, therefore, some change in periurethral flora was not unexpected. The carriage of E. coli was decreased significantly in patients taking trimethoprim (table 6). However, it must be remembered that it is not necessary to change the periurethral flora to reduce the incidence of urinary infections.

The fact that trimethoprim-resistant organisms were responsible for breakthrough infections in patients receiving trimethoprim is cause for concern. In view of the increasing incidence of trimethoprim-resistant strains (especially those with R-factors) in patients seen by us,[31] we have now adopted the policy of monitoring monthly rectal swabs from patients on long-term trimethoprim prophylaxis for the presence of trimethoprim-resistant coliforms. Should trimethoprim resistance continue to increase it is only a matter of time before this useful antibiotic will be of little value. However, our most recent study indicates a leveling off of trimethoprim resistance in organisms isolated from patients in and outside the hospital.[32] Since many antibiotics (for example β-lactam agents) rapidly select for resistance in the bowel, we regard them as being unsuitable for long-term prophylaxis. The possibility of using agents related to nalidixic acid, such as cinoxacin[33] or norfloxacin,[34] presently is being investigated.

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