METHENAMINE HIPPURATE ('HIPREX') IN THE TREATMENT OF CHRONIC URINARY TRACT INFECTIONS: A TRIAL IN A GERIATRIC HOSPITAL

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Methenamine Hippurate ('Hiprex')† in the Treatment of Chronic Urinary Tract Infections: A Trial in a Geriatric Hospital

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Fifty-two patients, all of whom were more than 66 years-old and who were hospitalized for periods in excess of two years were treated for chronic urinary tract infection. All patients received a course of antibiotic treatment for seven to ten days and were then put onto treatment with methenamine hippurate 1 g twice daily for six months.

Of the original fifty-two patients, twelve did not complete the six month course. During the six month period with 'Hiprex' there were far fewer re-infections than in the previous six months during which time they had received intermittent antibiotic therapy and other long-term treatment. There were no adverse reactions and bacterial resistance did not occur.

Introduction

More than 25% of women aged 65 and above suffer from chronic urinary tract infection. The treatment of this condition is complicated by concurrent conditions typical of this age group such as diabetes, cardiovascular disorders and psychiatric disturbances.

Infections of the urinary tract, which are not controlled may result in renal damage, and so it is mandatory that such infections be rigorously treated. In the geriatric patient, urinary tract infection not only lowers the patient's general condition, but may also cause incontinence. The treatment of urinary tract infection by antibiotic and chemotherapeutic agents presents difficulties because they cause resistant bacterial strains when used for long periods of time.

†Methenamine hippurate was supplied by 3M Riker Laboratories, United Kingdom and is known as 'Hiprex' in Europe and as 'Urex' in the United States of America

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Improved treatment has increased the average age of hospitalized geriatric patients by some five years, but, at the same time, problems have increased. When urinary infection occurs we aim to give symptomatic relief to our patients using minimum medication appropriate to each individual case.

In 1973 methenamine hippurate ('Hiprex') was made available to us for trial by 3M Riker Laboratories. Two Swedish studies had shown 'Hiprex' to be effective, and it had been used in England, Australia and the United States of America since 1968.

'Hiprex' is available as tablets containing 1 g of methenamine hippurate to be taken twice daily. It is excreted unchanged in the urine via the kidneys, and dissociates into hippuric acid and methenamine. In the acid urine, the methenamine moiety breaks down yielding formaldehyde which has a bactericidal action. The hippuric acid helps to lower urinary pH which optimally should be 5·5 or below. The pH of the urine may be lowered by administering ascorbic acid 2–4 g daily.

Patients

Fifty-two female patients, all of whom had been in hospital for periods ranging from 2–18 years, were admitted to the study. Their age range was 65–96 years (mean 84·7 years). As will be explained later, a six-month period of treatment was completed in only forty of these patients, details of whom are given in Table 1.

Although all of the patients investigated had urinary tract infection, they were hospitalized for other conditions such as degenerative cardiovascular disease, senile dementia, diabetes and musculo-skeletal disorders.

A history of recurrent urinary tract infection was obtained from the patients selected for the trial and also established by a number of laboratory tests. All fifty-two of them had had pyuria during the previous two years with more than 10^5 bacteria per ml (Kass 1956). Urine cultures and sensitivities were determined on average four to five times a year.

Twenty-two patients had chronic *E coli* infections, but when the general condition of the patient deteriorated *Proteus mirabilis* became the infecting organism and *E coli* disappeared, or the infection became mixed. *Proteus vulgaris*, *Pseudomonas* and *Klebsiella* occurred in some patients and these were the most difficult to treat. Table 2 shows the organisms treated and the number of occasions on which they were cultured.

After determining the sensitivity of organisms present, a seven to fourteen day course of an appropriate antibiotic was given, followed by long-term treatment.

Serum creatinine levels were not significantly raised at the beginning of treatment and the possibility of impaired renal function in this type of patient was taken into account in giving the initial short-term treatment. The antibiotics used during a six-month period were ampicillin, nalidixic acid, erythromycin, fenoxymethyl-penicillin potassium, methacycline chloride, doxicycline, chloramphenicol, tetracycline, kefalexine and gentamycin sulphate. In the long-term treatment period the following agents had been used: sulphamethoxyidiatsine, 500 mg, sulphamethorin 100 mg/sulphafurazol 400 mg, nitrofurantoin 50 mg, trimethoprim 80 mg/sulphamethoxazole 400 mg and trimethoprim 100 mg.

All fifty-two patients who participated in the trial had received short courses of treatment with these agents on several occasions during the six months before the trial began, in addition to long-term prophylactic therapy. The organism responsible for the last infection before entry to the trial is shown in Table 3.

Table 1

Details of patients

Ages	*Number of patients (within parenthesis number of treatment interruptions)*
65–69	2
70–74	2
75–79	7 (3)
80–84	9 (3)
85–89	10 (5)
90–	10 (1)

Table 2

Organisms found in the urine during a six month period		
E coli	125 times	10^5 bact/ml
Proteus mirabilis	23 times	10^5 bact/ml
Proteus vulgaris	2 times	10^5 bact/ml
Klebsiella	6 times	10^5 bact/ml
Pseudomonas	5 times	10^5 bact/ml
Enterococcus	6 times	10^5 bact/ml
Staphylococcus	3 times	10^5 bact/ml
Streptococcus β-haemolyticus A-positive	1 time	10^5 bact/ml
Streptococcus β-haemolyticus A-negative	2 times	10^5 bact/ml

Method

Of the fifty-two patients studied nine were fully ambulant, thirty-one had restricted movement and twelve were confined to bed. Sixteen patients experienced occasional incontinence, twenty-one were completely incontinent and the remaining fifteen were

Table 3

Organism(s) causing the last infection

	Number of cases
E coli	34
Proteus mirabilis	7
Proteus vulgaris	1
E coli + *P. mirabilis*	7
P. mirabilis + *klebsiella*	1
Pseudomonas + *Streptococcus β-haemolyticus* (*A negative*)	1
Pseudomonas + *P. mirabilis* + *Enterococcus*	1

Table 4

Subdivision of patients according to degree of incontinence and immobility

	Degree of incontinence			*Degree of immobility*		
Group	*N*	*P*	*T*	*N*	*P*	*T*
I	15			7	8	
II		16		1	15	
III			21	1	8	12

N = Normal, P = Partial, T = Total

normal in this respect. According to these criteria the patients were divided into three groups (Table 4).

Before patients were put onto long-term treatment with 'Hiprex', it was ascertained that their urine was not infected. The normal value for pus cells was defined as 4–12 per field of vision under the lower power microscope. If a higher count was reported, in spite of negative bacterial culture, the cause was investigated.

The first post-treatment culture was made two weeks after patients had started treatment with 'Hiprex'. If the urine was clear and the pH was 5 or less, treatment was continued and laboratory investigations were made at monthly intervals. When the pH of the urine was found to be greater than 5, 2–4 g of ascorbic acid were given daily but this was seldom necessary because the pH remained between 4 and 5 if no infection occurred.

Results

Forty of the fifty-two patients completed a six months course of 'Hiprex' but the other twelve were lost to the trial for the following reasons: two died of cerebrovascular accident, one developed a bladder tumour, and the remainder refused to take the medication on account of tablet size or taste, or because they had no symptoms. Seventeen cases of re-infection occurred in the forty patients completing six months treatment. This was far fewer than in the preceding six months period. These episodes of infection were treated with an appropriate antibiotic (Table 5) and the patient returned to the trial. A suitable antibiotic was selected after bacterial sensitivity had been determined.

Ambulant patients were allowed to go home for two to three weeks during the summer whereas patients who were non-ambulant, and who were completely incontinent were not. There were more cases of re-infection in the former group than the latter group. This was attributed to the lack of supervision over administration of medicine whilst patients were at home.

Side-effects

There were no changes in liver function, kidney function or haematology during the trial. The only side-effects recorded were soreness of the mouth in two patients and abdominal pain in one.

Table 5

Rate of re-infection of patients in two six-month periods, with and without treatment with hexamine hippurate

	Re-infections for patient	
Group	*'Hiprex' period*	*Previous six months*
I	0·45	2·82
II	0·58	4·33
III	0·29	5·24

Discussion

Andelman (1968) reported encouraging results with 'Hiprex' in geriatric patients. Also, in bacteriuria of pregnancy an 81% success was shown. In this latter study particular attention was drawn to the safety of 'Hiprex'. Almgård, Ericsson & von Garrelts (1972) demonstrated the use of 'Hiprex' as a prophylactic agent prior to instrumentation of the bladder. In this study more than 1,000 investigations were carried out in over 800 patients who took 1 g 'Hiprex' twice daily before instrumentation and afterwards. There were no complaints of side-effects and infection of the urinary tract did not occur.

Almgård & Lundberg (1973) carried out work on patients with neurogenic bladder disturbances. They demonstrated that long-term treatment with 'Hiprex' led to eradication of infection in three cases and in the rest of their patients 'Hiprex' maintained sterile urine after an initial treatment with an antibiotic agent.

The results of the present study confirm the findings of other investigators. All fifty-two patients participating in the study had received several courses of treatment for acute attacks for several years and during the six months preceding the study two to four active courses of treatment as well as continuous long-term treatment. However, resistant bacterial strains developed and it was necessary to change the treatment each time this occurred. The results of continuous 'Hiprex' therapy were particularly striking in the institutional patients of Group III who received their treatment regularly under supervision. Only five episodes of re-infection occurred in four patients out of a total of twenty-one in this group; a very good result.

'Hiprex' has been shown to be a useful treatment for urinary tract infection in the geriatric patient who is a difficult therapeutic problem.

After the trial was completed most patients were kept on 'Hiprex'. At present there are thirty patients on treatment, sixteen of whom have successfully taken the drug continuously for twelve months. However, some patients have found the large 1 g tablet difficult to swallow. A liquid preparation might be worthwhile developing for these patients.

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