Urol Res (1983) 11:181–185

Urological Research

Long-Term Oral Treatment of Urinary Tract Infections with Single Daily Doses of a New Antibacterial Drug Combination (Kelfiprim)*

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Accepted: March 23, 1983

Summary. Of 30 patients with severe, complicated U.T.I. 27 have been given single daily doses of Kelfiprim (KP), a new sulfatrimethoprim combination, for 8 weeks. In 24 bacteriuria was lastingly controlled, one had a relapse, one had a reinfection, and in one, with bladder carcinoma, bacteriuria persisted. Three other patients received KP for shorter periods, as they presented gastric intolerance or skin hypersensitivity, but in two of them a lasting sterilization of the urine has been obtained. The usefulness of a single daily dose schedule is stressed.

Key words: Kelfiprim, Refractory U.T.I., Long-term antibiotic, Single daily doses, Sulfa-trimethoprim combination.

Introduction

Kelfiprim is a combination of trimethoprim (TMP) with sulfamethoxypyrazine (SMP) in a 5:4 ratio. Preliminary clinical studies [1, 3–10] showed the high efficacy and tolerability of single daily doses of 450 mg Kelfiprim (KP) in short-term (7–14 days) and mid-term (30 days) treatments of various infectious conditions. Since complicated forms of U.T.I., as e.g. after urinary tract surgery, often need longer periods of therapy, the choice of an active, low-toxicity and easily administered drug is indicated. In this study, the efficacy and acceptability of KP capsules (250 mg TMP + 200 mg SMP) given once daily p.o. for 2 months to surgical patients with UTI were investigated.

Patients and Methods

Thirty in-patients were included in this study. They suffered from U.T.I. requiring long-term antibacterial treatment (Table 1). Shortly before admission, some of them had undergone surgical intervention for genito-urinary problems (Table 2). Patients were admitted to the study on the basis of clinical status, and the presence in the urine of bacteria, sensitive to KP in vitro(1), in a concentration of at least 10^5 cells/ml(2). Informed consent was obtained from all patients who entered the study.

The initial control of the patients included a clinical examination with assessment of body weight, heart rate, blood pressure, and laboratory tests (haemoglobin, P.C.V., R.B.C., W.B.C., platelet count, E.S.R., blood sugar, B.U.N., creatinine, total bilirubin, S.G.O.T., S.G.P.T., alkaline phosphatase, and urinalysis).

All determinations were carried out in the morning, after a 10 to 12-h fasting period, before any antibacterial treatment was given. Immediately afterwards, each patient was given two KP capsules, then one KP capsule was given at 24-h intervals, for 2 months. Clinical and laboratory controls as indicated above, were repeated after the end of KP therapy. Clinical controls and urine cultures were also carried out after 2 and 4 weeks of treatment, as well as 2 weeks after the end of therapy. Appearance of unusual signs and symptoms was carefully monitored throughout the study.

Statistical analysis of the results was carried out by the paired data t-test, according to Bonferroni t statistics [2]. The McNemar test [11] was used in order to evaluate the significance of the frequency changes of normal and abnormal (higher or lower) values determined at times 0 (baseline) and at the endpoint control (8 weeks).

Results

1. Efficacy of KP Treatment

a) Bacteriological Criteria. Twenty-seven patients completed the 8-week course of KP treatment, while 3 patients discontinued it after 5 days to 4 weeks on account of appearance of unwanted symptoms.

At the beginning of the study 29 patients had infections with one organism, while one had urine infected with 2 different bacterial species (Tables 1 and 3).

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(1) Agar Diffusion method
(2) The bacterial count was 0.5×10^5 in three cases only in which, however, clinical considerations indicated the need for a prolonged antibacterial treatment

Table 1. Patients' characteristics at admission

Diagnosis	No. of cases	Age range (years)	Bacterial species found in the urine (no. of cases)					
			Staphylococcus epidermidis	Escherichia coli	Klebsiella spp.	Proteus vulgaris	Proteus mirabilis	Pseudomonas aeruginosa
a) *females*								
Recurrent cystitis	12	22–76	–	10	–	2	–	–
Severe acute cystitis	1	53	–	–	–	–	1	–
Recurrent cystitis with chronic pyelonephritis	1	62	–	1	–	–	–	–
b) *males*								
Acute prostatitis	2	29–40	1	2	–	–	–	–
Chronic or recurrent prostatitis	2	30–33	–	2	–	–	–	–
Acute cysto-prostatitis	1	65	–	1	–	–	–	–
Recurrent or refractory cysto-prostatitis	7	39–74	1	5	1	–	–	–
Chronic pyelonephritis	1	27	–	–	–	–	–	1
Refractory infection of the lower urinary tract	3	22–27	–	2	1	–	–	–

Table 2. Patients' history

History			No. of cases
Surgery in the 2 years preceding the study	Trans-urethral resection of bladder		5
	Trans-urethral resection of prostate		5
	Urethra or meatus plastic surgery		3
	Pyeloplasty		1
	Penile amputation		1
	Hysterectomy		1
Pathological conditions preceding the study, and/or surgery more than 2 years before admission to the study	Still present at admission	Bladder carcinoma	5
		Prostate carcinoma	1
		Bilateral ureteral reflux	1
		Lumbar arthrosis	1
		Angina pectoris	1
		High blood pressure	3
		Multiple sclerosis	1
		Diabetes	1
		Obesity	1
	Not present at admission	Penile carcinoma	1
		Hysterectomy for fibroma	1
		Right pyeloureteral junction disease	1
		Urinary incontinence from stress	1
Adverse reactions to drugs		Skin rash after penicilin	1

The following organisms were isolated from the urines of the 30 patients before treatment (Tables 1 and 3): *Escherichia coli* 23 patients (74.1%), *Staphylococcus epidermidis, Klebsiella* spp., and *Proteus vulgaris*, 2 patients (6.5%) each, and *Proteus mirabilis* and *Pseudomonas aeruginosa*, 1 patient (3.2%) each.

Twenty-five (83.3%) out of 30 of these organisms were no longer present in the urine after 2 weeks of KP treatment (Table 3). Of the 5 (26.7%) strains still present in the urines at that control, 4 (13.3%) belonged to the species initially found, 2 of these (6.7%) having the same in vitro sensitivity pattern as before, whereas the remaining 2 had

Table 3. Urine bacteriology (no. of strains present)

Species	Before treatment	Time (weeks) since treatment was started			2 weeks after end of treatment
		2	4	8	
Staphylococcus epidermidis	2	0[a]	0[a]	0[a]	0[a]
Escherichia coli	23	5[b]	2[a,b]	3[a,b]	2[a]
Klebsiella spp.	2	0	0	0	0
Proteus vulgaris	2	0	0	0	0
Proteus mirabilis	1	0	0	0	0
Pseudomonas aeruginosa	1	0	0	0	0
Overall	31[c]	5	2	3	2
Percent sterilizations		83.3[a]	93.1[d]	89.3[d]	93.1[d]

[a] not ascertained in one case
[b] one reinfection
[c] there was one case with a double infection
[d] not ascertained in 2 cases

become partially resistant to KP. In one case the isolated strain differed from the species initially found (reinfection) and was sensitive in vitro to KP.

After 4 weeks of treatment 27 of the 29 strains checked (93%) had disappeared, one still persisted (same in vitro sensitivity pattern as before) and one other belonged to the same changed species (re-infection) as found at the preceding control. Urine bacteriological controls after 8 weeks (end) of treatment (28 strains checked) showed 25 cures (89.3%), the persistence of 2 previously present strains (of which one had caused a re-infection detected after the first 2 weeks of treatment), and the re-appearance of one of the strains temporarily inhibited after 2 weeks of therapy.

Two weeks after the end of therapy, 27 (93.1%) organisms had apparently been eradicated and only 2 *E. coli* strains were still found. One of these had been found constantly throughout the 8 week period of treatment. The other had re-appeared in the cultures after 8 weeks of KP therapy.

b) Clinical Criteria. The efficacy of KP treatment was clinically evaluated through monitoring of relevant signs and symptoms of U.T.I. such as pollakiuria, urgency, dysuria, haematuria, and leukocyturia. The evolution of these symptoms is recorded in Table 4. Since the end of the 2nd week of therapy on, the symptoms vanished or regressed in 71–100% of cases. Two weeks after the end of therapy, haematuria, leukocyturia, and pollakiuria were only persisting in 11%, 5% and 4% of cases, respectively.

The overall evaluation of the efficacy of KP therapy, according to the opinions of both physician and patients was "good" or "excellent" in 26 out of 29 evaluable cases (89.7%). Systolic blood pressure significantly decreased (from 133 to 126 mmHg on average) as early as 2 weeks after beginning KP treatment and remained about this level up to 2 weeks after the end of treatment.

A less pronounced average decrease, which reached statistical significance only at the 4th week after beginning treatment (from 83 to 78 mmHg), was shown by diastolic blood pressure.

2. Safety and Acceptability of KP Treatment

No significant untoward alterations from baseline levels of the monitored haemodynamic variables, blood morphology and blood chemistry or urine components were observed during KP treatment, at the end of it[3], and 2 weeks after its end[4].

KP treatment was discontinued in 3 patients (10%), on account of the appearance of untoward clinical symptoms. One of these patients presented, after 5 days of KP treatment, with severe skin erythema and itching. Treatment was withdrawn and the skin symptomatology disappeared 7 days later. This patient had been treated for 3 months (until 15 days before beginning KP therapy) with trimethoprim + sulfamethoxazole (160 + 800 mg b.i.d., orally). In another patient a generalized skin erythema appeared after 11 days of KP treatment. KP was immediately withdrawn and four days later the erythematous eruption had completely disappeared. The third patient was admitted for a recurrent cystoprostatitis with *E. coli*, 3 days after a 3-week course of ampicillin had been discontinued for inefficacy. After the 4th week of KP therapy the patient complained of moderate nausea after each KP dose. Eleven days later KP therapy

3 Haemodynamic variables only
4 One patient presented with hyperglycaemia and glycosuria at the end of treatment, but his baseline blood sugar levels, too, had been higher than normal

Table 4. Urinary symptomatology during and after Kelfiprim (KP) therapy (No. of cases/total controlled)

Before KP treatment (baseline)	Evolution	Weeks of KP treatment			2 weeks after end of KP treatment
		2	4	8	
a) *Pollakiuria*	Disappearance or regression	23/26	24/26	24/25	25/26
intense = 2	No change or worsening	3/26	2/26	1/25	1/26
moderate = 19	Appearance during trial	0	0	1	0
slight = 7					
b) *Urgency*	Disappearance or regression	12/12	12/12	11/11	12/12
intense = 2	No change or worsening	0/12	0/12	0/11	0/12
moderate = 9	Appearance during trial	2	2	2	2
slight = 3					
c) *Dysuria*	Disappearance or regression	5/7	6/7	7/7	8/8
intense = 0	No change or worsening	2/7	1/7	0/7	0/8
moderate = 3					
slight = 6					
d) *Haematuria*	Disappearance or regression	9/10	10/11	9/10	8/9
intense = 0	No change or worsening	1/10	1/11	1/10	1/9
moderate = 4					
slight = 8					
e) *Leukocyturia*	Disappearance or regression	19/23	20/23	21/22	21/22
intense = 0	No change or worsening	4/23	3/23	1/22	1/22
moderate = 14					
slight = 11					

was discontinued, and the symptom did not recur, while his infection was lastingly cured.

Discussion

The 8-week treatment of 30 patients with single daily KP administrations has resulted in a high rate of clinical and bacteriological recovery from severe or complicated urinary tract infection.

In 26 patients sterilization of the urine, obtained in the first 2–4 weeks, still lasted the 2nd week after the end of treatment. Two of these patients had received KP for only 2 and 4 weeks respectively.

Among the 4 "failures", one patient was treated for 5 days only, and therefore should probably not be considered for the evaluation of treatment efficacy. Another patient had a bladder carcinoma, and his general condition could largely account for the failure of therapy. In a third patient who had undergone a pyeloplasty 6 months before being admitted to the present study, a strain of *Pseudomonas aeruginosa* sensitive in vitro to KP and to its components was isolated from the urine. After 2 weeks of KP treatment this strain had disappeared, but a re-infection with a strain of *E. coli* occured. KP therapy, continued for 6 more weeks, failed to eradicate the new infection.

Four other patients, of those who responded well to KP treatment, had been treated in the preceding 3 months with other antibacterial drugs which failed to cure their urinary tract infections: cotrimoxazole (960 mg orally b.i.d. for 23 days), nitrofurantoin (orally for 30 days, dose unknown), cephalexin (3 g daily for 10 days) and ampicillin (for 3 weeks, dose unknown). In the present study with Kelfiprim, the limitation of the number of daily administrations to a single capsule was particularly appreciated by both doctor and patient.

These results should encourage the use of KP as an antibacterial drug in complicated, refractory or recurrent urinary tract infections necessitating longer periods of therapy. However, more studies appear necessary in order to extend the indications and duration of long-term KP antibacterial treatments.

Conclusions

1. Kelfiprim (KP) given to patients with severe, complicated, refractory or recurrent urinary tract infections in single daily doses of 450 mg (one capsule) over an 8-week period proved active against up to 93% of the pathogenic bacterial strains which infected their urines (sterilization of 27 out of 29 strains).

2. The sterility of the urines after KP therapy was still persisting 2 weeks after the end of treatment.

3. In some cases, it was possible to obtain a lasting bacteriological cure in U.T.I. patients who did not respond to other antibacterial treatments (trimethoprim + sulfamethoxazole, cephalexin, nitrofurantoin, ampicillin).

4. Unwanted effects were observed in 3 patients (one with gastrointestinal intolerance and two other with skin hypersensitivity) whose symptoms promptly disappeared after treatment withdrawal.

5. The high compliance of the patients with a long-term KP treatment was favoured by the limitation of the number of daily administration to a single oral capsule.

Acknowledgment. The authors are most grateful for the help received in the preparation of this paper from Dr. Sara Gallico and Mrs. H. Leeks.

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