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Kelfiprim, a New Sulpha-Trimethoprim Combination, Versus Cotrimoxazole, in the Treatment of Urinary Tract Infections: A Multicentre, Double-Blind Trial

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Summary. A new combination of trimethoprim with a sulphonamide, named Kelfiprim, differs from cotrimoxazole in that: a) the sulpha drug is sulphamethopyrazine instead of sulphamethoxazole; b) the trimethoprim to sulpha ratio is 5:4 instead of 1:5; c) the presence of a long-acting sulphonamide allows the administration of a daily dose of one capsule, following an initial loading dose of two capsules; d) a reduced amount of trimethoprim is given, as compared to cotrimoxazole, without any decrease of efficacy. Kelfiprim [KP] was compared to cotrimoxazole [Co] in a multicentre double blind trial. Sixty four patients suffering from acute and chronic infections of the upper and lower urinary tract entered the study. Urine sterilisation and clinical improvement without relapses showed no differences from the two treatment groups. Tolerance was excellent except in two patients, one treated with KP and the other treated with Co, who showed a transient exanthema.

Key words. Kelfiprim (KP), Trimethoprim (TMP), Sulphamethopyrazine (SMP), Sulphamethoxazole (SMX), Cotrimoxazole (Co), Urinary tract infections (U.T.I.).

Introduction

A new bacterial sulpha-trimethoprim combination, named Kelfiprim®, contains trimethoprim (TMP) and sulphamethopyrazine (SMP) in the ratio of 5:4. The two moieties have a different pharmacokinetic behaviour, as TMP has a half life in the range of 9–13 h, whereas SMP has a much longer half life, of 65–70 h [4].

Due to the peculiar pharmacokinetic properties of this combination [2], it is possible to administer a daily dose of one capsule (TMP 250 mg + SMP 200 mg), following an initial loading dose of two. Moreover, a reduced amount of TMP is given, as compared to cotrimoxazole, without any decreased efficacy.

Preliminary studies of this new combination have shown that it is a least as effective as co-trimoxazole in the treatment of infections of the lower respiratory tract and of the ear, nose and throat [2, 5, 9, 10].

A pilot study has demonstrated that this combination was effective in the treatment of urinary tract infections (U.T.I.) caused by sensitive bacterial strains [8].

The aim of the present investigation was to study the effects of Kelfiprim in urinary tract infections, in comparison to cotrimoxazole, a widely used trimethoprim/sulphonamide combination. It was designed as a multicentre double-blind trial.

The study was carried out in the urological departments of three Italian University Hospitals and concerned patients suffering from acute and chronic infections of the upper and lower urinary tract. Protocol monitoring and data elaboration were performed at the Medical Department, International Division, Farmitalia Carlo Erba, Milano, Italy.

Material and Methods

A total of 72 patients were admitted to the study.

According to the clinical diagnosis, the patients were stratified in two main groups: upper and lower urinary tract infections. A further stratification according to chronic or acute infections was performed and, finally, patients with lower U.T.I. were stratified according to sex (Fig. 1).

The patients were randomly allocated to two groups, receiving either Kelfiprim or cotrimoxazole. The duration of the treatment was 10 days.

Since the drugs under study differ in dosage and in schedule, it was necessary to obtain an identical form of administration for both compounds. Therefore, cotrimoxazole was supplied in capsules, rather than in tablets, each capsule containing 80 mg of trimetho-

[1] *Editors Note:* This drug is not marketed outside Italy

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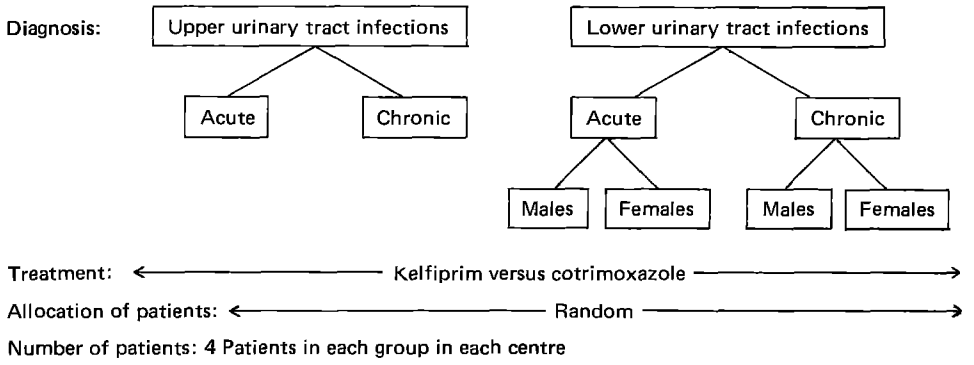

Fig. 1. Kelfiprim (KP) versus cotrimoxazole (Co) in U.T.I. multicentre double blind trial: Trial design

Table 1. Kelfiprim versus cotrimoxazole in U.T.I. multicentre double blind trial. Evaluation criteria: efficacy

Days	Excellent	Good	Poor	Nil
3 or 4	Disappearance of symptoms urine sterilisation reduction in leukocyturia	Disappearance of symptoms urine sterilisation reduction in leukocyturia	No change	No improvement (both bacteriologically and clinically)
10 (End of the treatment)	idem	idem	Mild clinical improvement urine sterilisation or bacterial count $\leqslant$ 50.000	As above
20 (10 days after the end of treatment)	idem	positive urine culture	positive urine culture	Other treatment necessary

Tolerance:		
	Excellent:	No unwanted signs or symptoms
	Good:	Mild side effects not calling for withdrawal of treatment
	Bad:	Severe side effects calling for withdrawal of treatment

prim and 400 mg of sulphamethoxazole, to be administered at the dose of four capsules daily. The patients treated with Kelfiprim also received four capsules daily. However, only two of the capsules given on the first days, and one of those given on the following days, contained the active compounds, whereas the remaining capsules contained corn starch as inert placebo.

The admission criteria were: clinical diagnosis confirmed by two positive urine cultures with a bacterial count higher than 10^5; in vitro sensitivity of bacterial population to both Kelfiprim and cotrimoxazole.

Patients were excluded when one or more of the following conditions were present: allergy to trimethoprim and/or to sulphonamides, hepatic insufficiency, renal insufficiency (plasma creatinine > 3 mg/dl), leucopenia (leucocytes < 3,000/mm^3), pregnancy and nursing, genito-urinary tuberculosis, difficulties in attending follow-up visits.

A complete history, with special reference to symptoms due to U.T.I. was taken, a full examination was made, urinalysis, urine culture and sensitivity tests, full blood count, determination of blood glucose, alkaline phosphatase, G.O. and G.P. transaminases, creatinine and urea were performed before, during and after the treatment, and 10 days after its termination. Cultures of clean-catch midstream urine specimens, colony counts and identification of the isolated bacteria were performed according to standard bacteriological techniques. For sensitivity testing, the Bauer-Kirby method was adopted, using Müller-Hinton agar plates and Oxoid discs containing the most commonly employed antibiotics and chemotherapeutic agents in standard dosage. Discs for testing sensitivity to Co contained 1.25 mcg of TMP and 23.75 mcg of SMX, whereas discs for KP sensitivity testing contained 3 mcg of TMP and 30 mcg of SMP.

The criteria for the evaluation of both efficacy and tolerance are shown in Table 1. As far as efficacy is concerned, "excellent" refers to prolonged urinary sterilisation and symptomatic improvement, whereas "good" indicates initial sterilisation and subjective response, followed by a relapse or reinfection at 10 days after discontinuation of the treatment.

Results

Of 72 patients entered, eight went off study and 64 were evaluable, 34 receiving Kelfiprim and 30 received cotrimoxazole.

The following bacteria were isolated in the 64 evaluable patients: *Escherichia coli* 43 (67.2%), *Klebsiella* 3 (4.7%), *Proteus mirabilis* 8 (12.5%), *Proteus spp. indole-positive* 5 (7.8%), *Citrobacter freundii* 2 (3.1%), *Enterobacter spp.* 2 (3.1%), *Streptococcus faecalis* 1 (1.6%).

The distribution was similar in the two treatment groups. The overall results are presented in Table 2.

A prompt and complete eradication of the infection was obtained in about 75% of the cases in both treatment groups. Temporary sterilisation of urine was obtained in another

Table 2. Kelfiprim versus cotrimoxazole in U.T.I. multicentric double blind trial. Overall results (84 evaluable patients)

Group	No. of pts.	Kelifiprim				No. of pts..	Cotrimoxazole			
		Excellent	Good	Poor	Nil		Excellent	Good	Poor	Nil
Acute upper U.T.I.	4	4	–	–	–	3	3	–	–	–
Chronic upper U.T.I.	9	6	3	–	–	9	5	3	–	1
Acute lower U.T.I., male pts.	3	1	1	–	1	2	2	–	–	–
Acute lower U.T.I., female pts.	5	5	–	–	–	4	4	–	–	–
Chronic lower U.T.I., male pts.	8	6	1	–	1	8	6	–	–	2
Chronic lower U.T.I., female pts.	5	3	–	1	1	4	3	–	–	1
Total (%)	34	25 (74%)	5 (15%)	1 (2%)	3 (9%)	30	23 (77%)	3 (10%)	–	4 (13%)

Table 3. Kelfiprim versus cotrimoxazole in U.T.I. multicentric double blind trial: clinical tolerance

Drug	No. od pts.	Excellent	Good	Bad
Kelfiprim	34	30 (88%)	3 (9%) Heartburn	1 (3%) Purpura, oedema, fever
Cotrimoxazole	30	27 (90%)	2 (7%) Vomiting, gastralgia, headache	1 (3%) Rash and itching

15% of cases. Negative results were obtained in only 10% of cases. Of the seven patients (three in the KP and four in the Co group) who had a negative response, super-infection with a resistant bacterial strain was observed in six cases (Pseudomonas in four, Esch. coli in one, Citrobacter in one). In the remaining case a sensitive strain of Esch. coli, which was present at the beginning of the treatment, was also isolated during and after the course of therapy. This was, however, a patient with diabetes mellitus suffering from bladder cancer with extensive necrotic areas.

It is noteworthy that all the 13 cases of acute or chronic pyelonephritis treated with Kelfiprim responded to the treatment with 10 excellent and three good results, even in patients with severe underlying pathology, such as ureteral obstruction and staghorn calculi. Similarly, of 12 patients with acute or chronic upper urinary tract infections treated with cotrimoxazole, the results were excellent in eight, good in three and negative only in one case.

Thirteen out of 14 cases of acute lower U.T.I. treated with either Kelfiprim or cotrimoxazole responded to the therapy, 12 with a excellent and one with a good result, whereas of the 25 cases of chronic lower U.T.I. included in both treatment group, the results were negative in five and poor in one patients. Three of the latter patients had indwelling urethral catheters.

Kelfiprim Versus Cotrimoxazole in Urinary Tract Infections

No significant difference was observed between the two treatment groups. The patients' sex did not appear to have any influence upon the results.

The tolerance was excellent in about 90% of the patients. It was good, with only minor side-effects, in 10% of the patients in both groups (Table 3).

Discussion

The numbers are too small to allow any valid comparison between the various subgroups. However, both treatments were highly effective in both acute and chronic infections of the upper and the lower urinary tract due to in vitro sensitive strains.

The very high efficacy observed in acute chronic pyelonephritis is likely to be due to the high concentrations of both sulpha-trimethoprim combinations attained in the renal parenchyma.

Similar results were obtained in a parallel double-blind trial carried out in various nephrological centres [3]. Preliminary results from on-going studies also seem to indicate effectiveness in gonococcal urethritis [1] and in chronic prostatitis [6].

In conclusion, this double blind trial has shown no major differences between Kelfiprim and cotrimoxazole in the treatment of urinary tract infections due to in vitro sensitive bacteria. The simplified dosage schedule of Kelfiprim may be of value and improve the patient's compliance, especially when long-term treatments are needed.

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