An early phase II study on FK 037 in urinary tract infections

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The clinical efficacy and safety of FK 037, a new parenteral cephem antibiotic, in patients with urinary tract infections (UTI) were preliminarily evaluated. The subjects consisted of inpatients, aged 15 to 79 years, with complicated UTI, underlying urinary tract diseases and no indwelling catheter. The drug was intravenously infused at doses of 0.5, 1.0 and 2.0 g (potency), twice daily (in the morning and evening), for 5 to 9 days. Clinical efficacy was evaluated using the criteria proposed by the Japanese UTI Committee. Of 32 patients who met the inclusion criteria, the overall clinical efficacy of FK 037 was "excellent" in 15 patients, "moderate" in 15 and "poor" in 2, an efficacy rate of 93.8%. Only 1 patient showed a clinical adverse reaction (rash), and only 1 patient showed a laboratory adverse reaction (mild increase in GPT). These results showed that FK 037 provided a good clinical effect, reflecting its activity against a wide range of gram-positive and gram-negative organisms, and that the drug might present no significant problems concerning safety. This drug, therefore, could be useful for the treatment of UTI.

Key words: FK 037, urinary tract infections, early phase II study

INTRODUCTION

FK 037 is a novel parenteral cephem antibiotic developed by Fujisawa Pharmaceutical Co., Ltd. Its chemical structure is illustrated in Fig. 1.

This drug is a broad-spectrum antibiotic that is active against both gram-positive and gram-negative bacteria, including *Staphylococcus* spp. and *Pseudomonas aeruginosa*, against which conventional parenteral cephem antibiotics of the third-generation are less active[1,2]. In addition,

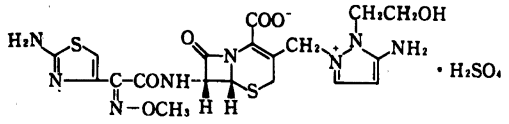

Fig. 1. Chemical structure of FK 037.

FK 037 is characterized by its moderate activity against methicillin-resistant *Staphylococcus aureus* (MRSA)[3]. FK 037 showed a preventive effect in various animal models of infection, reflecting its *in vitro* antibacterial activity[3,4]. The results described above were reported at the 31 st Interscience Conference on Antimicrobial Agents and Chemotherapy[5~13]. Various toxicological studies of the drug in animals showed no findings that might give rise to significant problems in clinical trial[14].

A phase I trial of FK 037 was conducted in healthy male adults between June and November 1990. The results showed that FK 037 follows linear pharmacokinetics with extensive elimination via the kidney after intravenous drip infusion, and has a half-life in blood of 2.3 hours and a recovery rate in urine of 95.0%[15]. The results of its pharmacokinetics and tolerance led to the suggestion that FK037 may be useful for the treatment of urinary tract infections (UTI). We have organized a multi-center study group and conducted an early phase II trial in complicated UTI. We report here the results of the trial.

SUBJECTS AND METHODS

1. Subjects

From patients with complicated UTI with underlying urinary tract diseases who visited one of 12 participating centers in Japan between July 1991 and June 1992, inpatients aged 15 to 79 years were included in this study. From the viewpoint of safety, older patients, who have a higher risk of impaired renal function, were excluded from this trial.

Since early phase II trials are aimed at preliminary evaluation of the safety, efficacy and pharmacokinetics of new drugs and should be performed with careful attention to each patient, we limited the number of subjects. In evaluating subjects, the disease profiles studied should be also restricted. Disease status is different between patients with and without an indwelling catheter. Patients with an indwelling catheter are regarded as inappropriate for evaluation of efficacy since the efficacy rate is usually lower and catheters can present problems of biofilm, high incidence of polymicrobial infection and replaced bacteriuria[16]. Thus, patients with an indwelling catheter were excluded from this study. All the patients included in this study gave informed consent to participate.

2. Doses and Administration

The purpose of this study was to roughly estimate the correlation between the dose and safety of FK 037 in clinical practice. The dose of the drug was set at 0.5, 1.0 and 2.0 g (potency) based on the pharmacokinetic and tolerance data obtained from the phase I trials, the results of preclinical studies, including studies of its antibacterial activity against various bacteria which can cause UTI, and the dosages and administration method of conventional cephem antibiotics. To proceed with the study carefully, in principle the dose in the first patient in each center was set at 0.5 g, and if there was no problem, the dose in the second patient was set at 1.0 g and then 2.0 g in the third patient. FK 037 was dissolved in 100 ml of physiological saline solution and intravenously infused for 1 hour twice a day (in the morning and evening). The period of treatment was set at 5 to 7 days as a rule. FK 037 was supplied as vials containing 0.5 or 1.0 g (potency) of the drug.

3. Identification of Urinary Isolates and Determination of MIC

Bacteria were isolated from urine specimens by the dip slide method (using Uricult®). After 24 hours of incubation, bacteria were counted at each center. Immediately after counting, the dip slides with bacterial specimens were sent to Developmental Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., for identification and MIC determination. The MIC of FK 037 was determined according to the standard agar

dilution method designated by the Japan Society of Chemotherapy[17]. The MIC of methicillin (DMPPC) was also determined for *Stapylococcus* spp.

4. Evaluation of Clinical Efficacy

Urinalysis and urine culture were performed before and after treatment. The overall clinical efficacy and bacteriological response were evaluated according to the Criteria for Evaluation of Clinical Efficacy of Antimicrobial Agents on UTI (the third edition) proposed by the Japanese UTI Committee (the UTI criteria)[18]. Apart from evaluation according to the criteria, clinical efficacy was assessed by each attending physician and classified into one of 4 grades, "excellent", "good", "fair", and "poor", at his or her discretion. Patients who violated the inclusion criteria defined in advance were excluded from the evaluation of clinical efficacy as incomplete cases.

5. Evaluation of Safety

All patients including those excluded from the evaluation of clinical efficacy, were analyzed for safety. If accompanying symptoms and signs or abnormal laboratory findings were noted, their causal relation to the drug was classified by the attending physician according to the UTI criteria into one of 5 grades: "definite", "probable", "possible", "unlikely"and "definitely not". Patients with events classified as "definite", "probable" and "possible", were defined as those with clinical or laboratory adverse reactions.

6. Evaluation of Clinical Value

Clinical value was evaluated by the attending physician on the basis of clinical efficacy and safety. The method of evaluation of clinical value was as follows: a mark was made on a visual analogue scale of 10-cm in length ranging from "very satisfactory" at one end to "very unsatisfactory" at the other.

7. Pharmacokinetics

The peak plasma (or blood) concentration, urinary concentration and recovery rate in urine of FK 037 were determined in some patients immediately after the completion of intravenous drip infusion, in principle, at the initial and final dosings. Plasma and urine were collected and sent to Developmental Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., to determine drug concentration by the disc method using *Bacillus subtilis* ATCC 6633 as the assay organism. Standard curves for blood and urinary concentrations were obtained in human plasma, serum or 1/15 M phosphate-buffered solution (pH 7.0).

RESULTS

1. Number of Evaluable Patients

Of 40 patients given FK 037, 32 were available for evaluation of clinical efficacy. Eight patients were excluded from the analysis of clinical efficacy: 2 had bacterial counts of less than 10^4 cfu/ml before treatment, 2 had ineligible disease (prostatitis and acute uncomplicated cystitis), 2 violated the age requirement of less than 80 years, and 2 had an indwelling catheter. Safety was evaluated in all of the patients treated with FK 037. Clinical value was assessed in all of the 32 patients who were evaluated for clinical efficacy according to the UTI criteria.

2. Background Characteristics

Table 1 shows the background characteristics of 32 patients who were evaluable for clinical efficacy. There were 25 (78.1%) men and 7 (21.9%) women. In the distribution by age, patients aged 60 or older numbered 23 (71.9%). Of these patients, 13, 9 and 8 received the drug at 0.5 g b.i.d., 1.0 g b.i.d., and 2.0 g b.i.d., respectively, throughout the study. Two patients received the drug at 2.0 g b.i.d. and then 1.0 g b.i.d. The period of treatment most commonly used was 5 days (30 patients, 93.8%). The patients were diagnosed as follows: complicated pyelonephritis in 10 (31.3%), and complicated cystitis in 22 (68.8%). When patients were classified according to the UTI criteria, Group 4 (15 patients, 46.9%) was predominant. Monomicrobial infection (23, 71.9%) was more frequent than polymicrobial infection (9, 28.1%). Table 2 shows organisms isolated before treatment. *Escherichia coli* was the most common organism isolated (9 strains, 21.4%), followed by *Enterococcus faecalis* (5 strains, 11.9%). The MIC distribu-

Table 1. Background characteristics of the patients

Characteristics			No. of patients (%)
Sex		male	25 (78.1)
		female	7 (21.9)
Age (years)		32~39	2 (6.3)
		40~59	7 (21.9)
		60~79	23 (71.9)
Treatment duration (days)		5	30 (93.8)
		8	1 (3.1)
		9	1 (3.1)
Daily dose		0.5 g×2	13 (40.6)
		1.0 g×2	9 (28.1)
		2.0 g×2	8 (25.0)
		Change (2.0 g×2→1.0 g×2)	2 (6.3)
Diagnosis		pyelonephritis	10 (31.3)
		cystitis	22 (68.8)
Type of infection	monomicrobial infection	group 2 (post-prostatectomy)	1 (3.1)
		group 3 (upper UTI)	7 (21.9)
		group 4 (lower UTI)	15 (46.9)
		sub-total	23 (71.9)
	polymicrobial infection	group 6 (no indwelling catheter)	9 (28.1)

Table 2. Organisms isolated before treatment

Isolated organisms		No. of strains (%)
GPC[a]	*S. aureus*	2 (4.8)
	S. aureus (MRSA)	1 (2.4)
	S. epidermidis	2 (4.8)
	S. haemolyticus	1 (2.4)
	S. capitis	1 (2.4)
	S. cohnii	1 (2.4)
	E. faecalis	5 (11.9)
	E. faecium	1 (2.4)
	Enterococcus sp.	1 (2.4)
	sub-total	15 (35.7)
GNR[b]	*E. coli*	9 (21.4)
	C. freundii	2 (4.8)
	K. oxytoca	2 (4.8)
	K. pneumoniae	3 (7.1)
	E. aerogenes	2 (4.8)
	E. cloacae	1 (2.4)
	S. marcescens	2 (4.8)
	P. mirabilis	1 (2.4)
	P. rettgeri	1 (2.4)
	P. aeruginosa	4 (9.5)
	sub-total	27 (64.3)
Total		42

[a]GPC: Gram-positive cocci
[b]GNR: Gram-negative rods

tion is shown in Table 3. The drug inhibited the growth of 90% of the strains isolated from the evaluable patients at a concentration of 100 μg/ml.

3. Clinical Efficacy

1) Overall Clinical Efficacy

Evaluation of clinical efficacy of FK 037 according to the UTI criteria was "excellent", "moderate" and "poor" in 15, 15 and 2, respectively, of 32 evaluable patients, an efficacy rate of 93.8%. The efficacy rate by the type of i fection was 1/1 in Group 2, 6/7 in Group 3, 15/15 (100%) in Group 4 and 8/9 in Group 6 (Table 4). The efficacy rate by dosage was 12/13 (92.3%), 8/9 and 8/8 at dosages of 0.5 g b.i.d., 1.0 g b.i.d. and 2.0 g b.i.d., respectively, indicating that the efficacy rate was high for each of the dosages used (Table 5).

Table 6 shows the relationship between the effects on pyuria and bacteriuria, which were taken as parameters for evaluating overall clinical efficacy. Pyuria was cleared in 16 patients (50.0%), and bacteriuria was eliminated in 28

Table 3. Sensitivity distribution of clinical isolates

	FK 037 MIC (μg/ml) (10^6 CFU/ml)																ND[a]	Total
	≤0.025	0.05	0.1	0.2	0.39	0.78	1.56	3.13	6.25	12.5	25	50	100	200	400	>400		
No. of strains	1	12	2	2	2	2	2	5	1	2	2	2	2		2		3	41

[a]ND: not done

Table 4. Overall clinical efficacy related to type of infection

Group		No. of patients	Excellent	Moderate	Poor	Efficacy rate[a]
Monomicrobial infection	group 2 (post-prostatectomy)	1		1		
	group 3 (upper UTI)	7	3	3	1	
	group 4 (lower UTI)	15	8	7		100%
	sub-total	23	11	11	1	95.7%
Polymicrobial infection	group 6 (no indwelling catheter)	9	4	4	1	
Total		32	15	15	2	93.8%

[a]Excellent+moderate/no. of patients

Table 5. Overall clinical efficacy according to daily dose

Daily dose	No. of patients	Excellent	Moderate	Poor	Efficacy rate[a]
0.5 g×2	13	6	6	1	92.3%
1.0 g×2	9	4	4	1	
2.0 g×2	8	5	3		
Change[b]	2		2		
Total	32	15	15	2	93.8%

[a]Excellent+moderate/no. of patients
[b]2.0 g×2→1.0 g×2

patients (87.5%).

2) Clinical Efficacy as Assessed by Attending Physician

Table 7 shows clinical efficacy as assessed by the attending physician: it was "excellent" in 17, "good" in 12, "fair" in 1 and "poor" in 2 of 32 evaluable patients. The efficacy rate was 90.6%, almost the same as that evaluated by the UTI criteria. The efficacy rates by diagnosis were 9/10 (90.0%) and 20/22 (90.9%) in patients with complicated pyelonephritis and complicated cystitis, respectively.

3) Bacteriological Response

Of 42 bacterial isolates, 41 (97.6%) were eradicated with FK 037, and only 1 strain of *P. aeruginosa* (MIC: 25 μg/ml) persisted, indicating that a high eradication rate was obtained with FK 037 (Table 8). Bacteria occurring newly in the urine after treatment were 4 strains in 4 of the 32 patients evaluated for clinical efficacy: two strains of *Enterococcus faecium*, one strain of *P. aeruginosa* and one strain of *Candida albicans* (Table 9). The MICs for the *P. aeruginosa* strain and two *E. faecium* strains were 50, 400 and >400 μg/ml, respectively.

4. Safety

Table 6. Effects on pyuria and bacteriuria

Pyuria / Bacteriuria	Cleared	Decreased	Unchanged	Effect on bacteriuria
Eliminated	15	3	10	28 (87.5%)
Decreased				
Replaced	1	1	1	3 (9.4%)
Unchanged			1	1 (3.1%)
Effect on pyuria	16 (50.0%)	4 (12.5%)	12 (37.5%)	patient 32 total
Excellent	15 (46.9%)	Overall efficacy rate[a] 30/32 (93.8%)		
Moderate	15 (46.9%)			
Poor	2 (6.3%)			

[a]Excellent+moderate/no. of patients

Table 7. Clinical efficacy as assessed by attending physician

Diagnosis	No. of patients	Excellent	Good	Fair	Poor	Efficacy rate[a]
Pyelonephritis	10	4	5	1		90.0%
Cystitis	22	13	7		2	90.9%
Total	32	17	12	1	2	90.6%

[a]Excellent+moderate/no. of patients

Of the 40 patients evaluated for safety, only 1 (2.5%, male, 70 years of age, complicated cystitis), who was given FK 037 0.5 g b. i. d., showed an adverse reaction considered to be attributable to administration of the drug, with the causal relation to the drug evaluated as "possible". The reaction was a mild rash which developed just after intravenous drip infusion of the drug. Since it was mild and disappeared after the intravenous drip infusion, treatment was continued with careful attention, and completed without resulting in any other side effects.

Of the 40 patients, only 1 (2.5%, male, 63 years of age, complicated cystitis), who was given 0.5 g b. i. d., showed a laboratory adverse reaction which was suspected to be related to administration of the drug. It was an increase in GPT (22→48), and the causal relation to the drug was classified as "possible". The follow-up data obtained 13 months later showed a GPT value of 14, within the normal range. There were no abnormal changes in GOT, Al-P or other laboratory test values. The attending physician assessed that this abnormal event was of no clinical significance.

5. Clinical Value

Table 10 shows clinical value as evaluated by

Table 8. Bacteriological response to treatment

Isolate		No. of strains	Eradicated (%)	Persisted[a]
GPC[b]	*S. aureus*	2	2	
	S. aureus (MRSA)	1	1	
	S. epidermidis	2	2	
	S. haemolyticus	1	1	
	S. capitis	1	1	
	S. cohnii	1	1	
	E. faecalis	5	5	
	E. faecium	1	1	
	Enterococcus sp.	1	1	
	sub-total	15	15 (100)	0
GNR[c]	*E. coli*	9	9	
	C. freundii	2	2	
	K. oxytoca	2	2	
	K. pneumoniae	3	3	
	E. aerogenes	2	2	
	E. cloacae	1	1	
	S. marcescens	2	2	
	P. mirabilis	1	1	
	P. rettgeri	1	1	
	P. aeruginosa	4	3	1
	sub-total	27	26 (96.3)	1
Total		42	41 (97.6)	1

[a]Regardless of bacterial count
[b]GPC: Gram-positive cocci
[c]GNR: Gram-negative rods

Table 9. Strains[a] appearing after treatment

Isolate	No. of strains
E. faecium	2
P. aeruginosa	1
C. albicans	1
Total	4
No. of patients in whom strains appeared / Total no. of patients	4/32 (12.5%)

[a]Regardless of bacterial count

Table 10. Clinical value

Score (mm)	100~80	79~60	59~40	39~20	19~0	Total	Median
No. of patients	24 (75.0)	7 (96.9)			1 (100)	32	87.5

(Cumulative percentage %)

the attending physician on the basis of clinical efficacy and safety. Except for the patient who had a low score because of an adverse reaction, all patients had scores of 60 or higher.

6. Pharmacokinetics

The FK 037 concentration in plasma (or blood) was monitored in 3 patients studied in this trial. Measurements were done at the end of infusion (1 hour after the start of infusion), when the drug concentration is assumed to peak, on the initial dosing, and treatment day 4 or the final dosing (treatment day 5). The results are given in Table 11. One patient (patient no. 1), who was given 0.5 g b.i.d., had blood concentrations of 20.4 μg/ml after both the initial and final dosings. Another patient (patient no. 2), given 1.0 g b.i.d., had plasma concentrations of 65.3 μg/ml and 91.0 μg/ml after the initial dosing and after dosing on treatment day 4, respectively. The other patient (patient no. 3), who was given 1.0 g b.i.d., had 92.7 μg/ml and 62.9 μg/

Table 11. Plasma and urinary concentration of FK 037

Patient no.	Sex Age (years) Body weight (kg)	Daily dose	Plasma[a]		Urine			Urinary recovery rate
			day	conc.[b] (μg/ml)	day	time	conc.[b] (μg/ml)	
1	♂ 59 57.0	0.5 g×2	0	20.4[c]	2	0~2	1,240	102.5%
						2~4	810	
			5	20.4[c]		4~6	710	
						6~12	479	
2	♂ 62 44.5	1.0 g×2	0	65.3				
			4	91.0				
3	♂ 60 60.0	1.0 g×2	0	92.7				
			5	62.9				

[a]Concentration just after intravenous drip infusion
[b]Conc.: concentration
[c]Blood concentration

ml, after the initial and final dosings, respectively. Drug concentration in urine was monitored in patient no. 1 on treatment day 2, and was 1,240 μg/ml at 0-2 hours after the start of infusion. The urinary recovery rate within 12 hours after the start of infusion was as high as 100%.

DISCUSSION

1. Clinical Efficacy

The efficacy of antibacterial agents against complicated UTI can be evaluated objectively using the UTI criteria by observing the course of pyuria and bacteriuria. The main purpose of this early phase II trial was to evaluate preliminarily the safety, efficacy and pharmacokinetics of FK 037 in patients. A rough estimate of the clinical dosage of the drug in an early phase II trial can lead to finding the optimal dosage of the drug in the next phase[19]. Since we believe that objective criteria should be used to estimate the clinically recommended dosage, we will discuss it mainly based on the results obtained according to the UTI criteria, which were not influenced by the attending physician's subjectivity.

The overall clinical efficacy rate in this study was 93.8% [92.3%, 88.9% (8/9) and 100% (8/8) in patients given 0.5 g b. i. d., 1.0 g b. i. d. and 2.0 g b. i. d., respectively]. "Poor" response was noted in only 2 patients who were given 0.5 g b. i. d. and 1.0 g b. i. d., respectively, of all the patients treated with FK 037. The efficacy rates obtained at these three dosages of FK 037 were equal to or higher than those (76.3—96.2%)[20~25] in patients without indwelling catheter who were treated with other currently available parenteral cephem antibiotics. This suggests that FK 037 at 0.5 g b. i. d. may be sufficiently effective in clinical practice. Phase I trials suggest that the peak urinary concentration of FK 037 after 60-min intravenous drip infusion of 0.25 g could be as high as about 1,000 μg/ml. Considering the urinary concentration and its antibacterial activity against the major causative organisms of complicated UTI, FK 037, at 0.25 g b. i. d., could provide sufficient clinical effect.

The bacteriological response of FK 037 was shown to be so good that the drug failed to eradicate only 1 strain of *P. aeruginosa* (MIC: 25 μg/ml). The MICs of FK 037 for bacterial strains isolated from urine before treatment ranged from $\leqq$0.025 to 400 μg/ml. The drug inhibited the growth of 80% of the strains at a concentration of 25 μg/ml. Of 3 isolates of *S. aureus*, the MICs of DMPPC for these strains were >400, 6.25 and 1.56 μg/ml, respectively, including 1 MRSA (MIC of DMPPC: $\geqq$12.5 μg/

ml). The MICs of FK 037 for these strains were 12.5, 3.13 and 0.78 μg/ml, respectively, and they were completely eradicated with FK 037. This suggests that FK 037 could be useful for the treatment of MRSA infections, although more cases should be investigated. Although all the strains of *Enterococcus* spp. were eradicated, the MIC of FK 037 for *Enterococcus* spp. was 25 μg/ml in 1 strain, 100 μg/ml in 2 strains and 400 μg/ml in 2 strains, indicating that the antibacterial activity of FK 037 was not sufficient against *Enterococcus* spp.

Two strains of *E. faecium*, one of *P. aeruginosa* and one of *C. albicans* appeared newly in the urine after treatment, and the MIC of FK 037 could be determined in the two strains of *E. faecium* (>400 and 400 μg/ml) and 1 strain of *P. aeruginosa* (50 μg/ml). These MIC values were high.

Of 2 patients who showed "poor" response, one with diabetes, who was given 0.5 g b.i.d., had been operated on for benign prostatic hyperplasia within 1 month before FK 037 treatment and had polymicrobial infection. *P. aeruginosa* (MIC: 25 μg/ml) and *Enterococcus* sp. (MIC not determined) were isolated with a bacterial count of 10^7 before treatment. Although *Enterococcus* sp. was eradicated with FK 037, *P. aeruginosa* remained at a bacterial count of 10^8. Pyuria (3+) of this patient remained unchanged on treatment, and thus was assessed as "poor". Subsequently, the patient was treated with tosufloxacin (450 mg/day), but the response was also poor.

The other patient, who was given 1.0 g b.i.d., had a past history of cerebral thrombosis and had bilateral renal calculi and diabetes. The patient was given an oral antibiotic in another hospital before treatment, but did not respond adequately. The causative organism was *E. faecalis* (MIC: 100 μg/ml, bacterial count 10^6), which was replaced during treatment by *E. faecium* (MIC: 400 μg/ml, bacterial count 10^4). Pyuria remained unchanged (++ to +), and thus was assessed as "poor". After treatment with FK 037, the renal calculi were removed by extracorporeal shock wave lithotripsy, and sultamicillin (1,125 mg/day) was given. However, this case was intractable and pyuria was not cleared.

Although both of the patients who showed "poor" response had diabetes and could be considered intractable, in the former case, the bacteriological effect of FK 037 suggests that this drug is not sufficiently effective against *P. aeruginosa* at a dose of 0.5 g b.i.d. In the latter case, in spite of eradication of *E. faecalis*, *E. faecium* appeared and pyuria was not changed after treatment. This case could also be considered intractable because of diabetes and bilateral renal calculi.

2. Safety

Of all the patients given FK 037, only 1 patient showed a clinical adverse reaction (rash). The rash developed just after the initial dosing. The rash was mild and the treatment was continued. A laboratory adverse reaction was noted in only 1 patient (increase in GPT). However, it was considered to be almost at the upper limit of the normal range, and the drug did not appear to present any problems concerning safety.

3. Pharmacokinetics

The peak blood concentrations of FK 037 after drip intravenous infusion determined in this study were similar to those in the phase I trial[15] (31.9 and 60.0 μg/ml at doses of 0.5 and 1.0 g, respectively). The urinary concentration and recovery rate of the drug determined in this study were favorable and also similar to those in the phase I trial (urinary concentration at 0—2 hours after single dosing of 0.5 g was 1,350 μg/ml and 24—hour recovery rate was 94.8%). Patients included in this study had normal renal function and their age (range 59 to 62 years) was higher than that of healthy adults included in the phase I trial (range 30—49 years, average 40.8 years in the 0.5 g group; range 27—49 years, average 37.7 years in the 1.0 g group). However, the pharmacokinetics of FK 037 were similar in these patients and healthy adults, suggesting that the pharmacokine-

tics of the drug do not vary with the age range studied.

In conclusion, FK 037, as given at three different dosages in this trial, was shown to provide a high efficacy rate and favorable bacteriological response without any significant problems of safety. Plasma (or blood) and urinary concentrations of the drug in patients were similar to those in healthy adults as determined in the phase I trial, with a high urinary recovery rate. Therefore, FK 037 could be useful in the treatment of UTI, and it is worthwhile to proceed to late phase II dose-finding trials.

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FK 037の泌尿器科領域感染症に対する前期第II相試験成績

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新しい注射用セフェム剤FK 037の泌尿器科領域感染症に対する臨床効果と安全性を予備的に検討した。対象は尿路に基礎疾患を有するカテーテル非留置の複雑性尿路感染症で，15歳以上80歳未満の入院患者とした。用法・用量は1回0.5g（力価），1.0g（力価）または2.0g（力価）を朝・夕の1日2回，5～9日間点滴静注し，UTI薬効評価基準に従い臨床効果を判定した。UTI薬効評価基準に合致した32例における臨床効果は著効15例，有効15例，無効2例で有効率は93.8%であった。副作用は1例に発疹がみられ，臨床検査値の異常変動は1例に軽度のGPT上昇が認められたのみであった。以上の成績から，本剤はグラム陽性菌からグラム陰性菌まで幅広い抗菌スペクトルを有しており，これを反映して臨床試験においても優れた効果を示し，安全性も特に問題がないことから，泌尿器科領域感染症に対して有用性が期待される薬剤であると考えられる。

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