An early phase II study of FK 037 for respiratory tract infections

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(Received May 11, 1994 · Accepted July 18, 1994)

An early phase II trial of FK 037, a parenteral cephalosporin, was conducted in patients with respiratory tract infections.

1) The efficacy, safety and usefulness of FK 037 were evaluated in 41 patients with respiratory tract infections who were intravenously infused with the drug at a dose of 0.5, 1.0 or 2.0 g, twice daily, for 3 to 14 days, as a rule.

2) Efficacy in 39 patients who were evaluable (26 with pneumonia, 8 with chronic respiratory tract infections, 3 with pyothorax or pleurisy, and 2 with acute bronchitis), was "excellent" in 15 and "good" in 19, an efficacy rate of 87.2%. The efficacy rates by dosage were 91.7% (11/12), 100% (19/19) and 66% (4/6) at 0.5 g b.i.d., 1.0 g b.i.d. and 2.0 g b.i.d., respectively.

3) All of 9 strains of *Streptococcus pneumoniae*, 7 strains of *Haemophilus influenzae* and 2 strains of *Pseudomonas aeruginosa* were eradicated by FK 037 dosing. Of 27 bacterial strains detected, 25 strains (92.6%) were eradicated.

4) No side effects were seen. Abnormal changes in laboratory tests were noted in 12 (30.0%) out of 40 patients who were evaluated for safety. These were mostly mild increases in hepatic enzyme levels, and there were no cases associated with clinical signs or serious cases.

5) The drug was rated "remarkably useful" in 10, of 38 evaluable patients, "useful" in 23, "slightly useful" in 2 and "not useful" in 3, a usefulness rate of 86.8%. These results suggest that FK 037 can be given with good results at clinical doses of 0.5 g b.i.d., 1.0 g b.i.d. and 2.0 g b.i.d.

Key words: FK 037, infections in internal medicine, respiratory tract infections, early phase II trial, clinical study.

FK 037 is a novel parenteral cephalosporin developed by Fujisawa Pharmaceutical Co., Ltd. As shown in Fig. 1, this drug possesses a hydroxyethylpyrazole group in the C-3 side chain and an aminothiazole and a methoxyimino group in the C-7 side chain of 7-aminocephalosporanic acid.

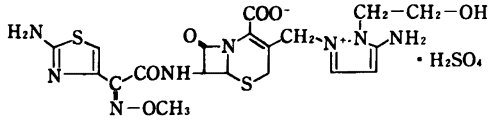


Fig. 1. Chemical structure of FK 037.

This drug is active against a wide range of both gram-positive and gram-negative bacteria, especially against *Staphylococcus* sp. and *Pseudomonas aeruginosa*, against which conventional parenteral cephalosporins of the 3rd generation were less active[1~3]. FK 037 is characterized by its moderate activity (the highest activity among β-lactam drugs) against methicillin-resistant *Staphylococcus aureus* (MRSA)[4] The *in vitro* and

in vivo antibacterial activity of FK 037 has been reported at the 31st Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)[5~13].

Various toxicological studies of FK 037 in animals showed no findings which might give rise to significant problems. The safety of the drug was ascertained in a phase I trial conducted in healthy male volunteers between June and November 1990[14].

We report here the results of an early phase II trial in patients with respiratory tract infection.

Subjects and methods

1. Subjects

Of patients aged 15-79 years who were suspected to have bacterial infection and who were hospitalized in one of the participating centers (15 hospitals) between July 1991 and June 1992, those who gave their informed consent were included in this study. Patients who met at least one of the following criteria were excluded from the study.

1) Patients with a history of allergy to cephalosporins or penicillins and those who are suspected to be allergic to FK 037.

2) Patients with impaired cardiac, liver or renal function and those with such a history.

3) Patients with a positive reaction on an intracutaneous test of FK 037.

4) Patients with severe or progressive underlying diseases or complications, sufficient to disturb the safety performance of the trial or judgment of efficacy.

5) Patients who are improving, or in whom the outcome remains unknown, with other antimicrobial agents.

6) Patients who require the concomitant use of loop diuretics such as furosemide.

7) Women who are pregnant or planning to get pregnant, and nursing women.

8) Patients who are judged ineligible by the investigator.

2. Administration Method

FK 037 was supplied in vials containing 0.5 or 1.0 g (potency) of the drug. FK 037 [0.5, 1.0 or 2.0 g (potency)] was dissolved in 100 ml of physiological saline solution. On confirmation of negative intracutaneous reaction test for the drug, the patients were intravenously infused with the drug for one hour twice daily (in the morning and evening). In principle, the period of treatment was set at 7 to 14 days (3 days in the shortest case). The dose of the first patient at each center was set at 0.5 g b.i.d. as far as possible, that of the next patient at 1.0 g b.i.d. and the next at 2.0 g b.i.d.

3. Criteria for Drug Withdrawal

Patients who met at least one of the following criteria were withdrawn from this study. The observations and examinations which are necessary at the end of study were performed in the event of withdrawal, and their results and the reason for withdrawal were recorded in the case report forms.

1) Patients who showed serious side effects or abnormal laboratory test findings with FK 037 treatment were thus judged impossible to be continued.

2) Patients who did not respond to the drug, and were thus judged as "poor". Improvement of each patient was judged on day 4 at the earliest after the start of treatment.

3) Patients who improved or recovered and thus did not require further treatment. Improvement or recovery was judged on the 8th day at the earliest after the start of treatment.

4) Violation of the inclusion criteria was proved after starting the administration.

5) Complication or other reasons made it impossible to continue the drug.

6) The patient or the legal guardian required discontinuation of the study.

7) Patients who were judged unsuitable for receiving further treatment by the investigator

4. Concomitant Drugs

The concomitant use of other antimicrobial agents was not allowed during treatment. The use of steroids, antiinflammatory agents and γ-globulin was avoided in principle. When use of these drugs was unavoidable, the name, dosage regimen, and duration of treatment were recorded in the case report forms.

5. Observations and Examinations

1) Clinical symptoms and signs

In principle, body temperature, symptoms, signs and objective findings peculiar to infectious diseases were checked every day.

2) Bacteriological tests

Clinical specimens (sputum) were obtained before treatment, on treatment days 4, 8 and 15, and the last day of treatment or the day of withdrawal. The isolation, identification and counting of microorganisms were done by methods applied at each center. The MICs of FK 037 and control drugs (cefpirome: CPR, flomoxef: FMOX, methicillin: DMPPC and others) were determined at Developmental Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. (in part at Department of Internal Medicine, Institute of Tropical Medicine, Nagasaki University) according to the standard method designated by the Japan Society of Chemotherapy[15].

3) Adverse reactions

Adverse reactions which developed after the start of treatment were examined for their type, severity, day of onset, counter therapy and clinical course, and their relation to this drug was assessed.

4) Laboratory tests

The following tests were done on days 1, 4, 8 and 15, and on the last day of treatment or the day of withdrawal.

(1) Blood analysis: red blood cell count, hemoglobin, hematocrit, white blood cell count (WBC), WBC differential %, platelets, prothrombin time, etc.

(2) Liver function tests: S-GOT, S-GPT, Al-Pase, LAP, γ-GTP, bilirubin (direct, total), etc.

(3) Renal function tests: BUN, S-creatinine, etc.

(4) Urinalysis: protein, glucose, urobilinogen, sediment, etc.

(5) Others: Coombs' test, CRP, erythrocyte sedimentation rate (ESR), etc.

6. Evaluation of Efficacy

1) Clinical efficacy

Clinical efficacy was assessed after deliberation by several doctors at each center, using subjective and objective findings, including clinical symptoms and signs, WBC, ESR, and CRP, as variables, and was classified into 4 grades: "excellent", "good", "fair" and "poor".

2) Bacteriological effect

Bacteriological effect was assessed by the investigator based on the change in the count of suspected causative organisms detected, and was classified into 4 grades: "eradicated", "decreased", "unchanged" and "replaced".

3) Safety

Safety was assessed by the investigator based on the side effects and abnormal changes in laboratory test values, and was classified into the following grades.

(1) "Safe" (no side effects or abnormal changes in laboratory test values)

(2) "Almost safe" (side effects or abnormal changes in laboratory test values were noted, but medication was continued with no additional treatment)

(3) "Problematic" (side effects or abnormal changes in laboratory test values were noted but medication was continued with reduced dosage and concomitant treatment)

(4) "Not safe" (side effects or abnormal changes in laboratory test values were noted, medication was withdrawn, or should have been stopped)

4) Usefulness

Usefulness was assessed by the investigator based on the clinical efficacy, bacteriological effect and safety, and was classified into 4 grades: "remarkably useful", "useful", "slightly useful" and "not useful".

7. Pharmacokinetics

Plasma and urinary concentrations and urinary excretion rate of FK 037 were determined as far as possible. The FK 037 concentration was determined by the disc method using *Bacillus subtilis* ATCC 6633 as the assay organism at Developmental Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. (in part at Department of Internal Medicine, Institute of Tropical Medicine, Nagasaki University). Samples were stored frozen at $-80°C$. Standard curves for plasma and urinary concentrations were obtained in human plasma or 1/15 M phosphate buffer, respectively.

Results

1. Patients

Fig. 2 lists the breakdown of the patients and reasons for exclusion.

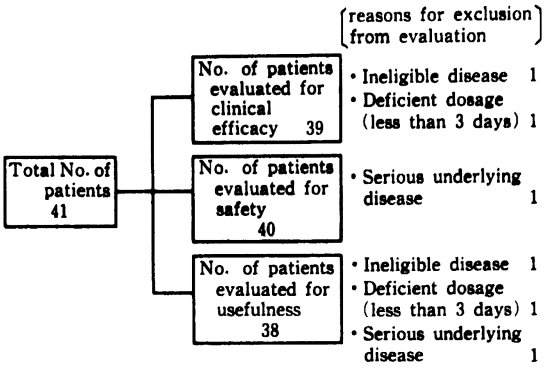


Fig. 2. Breakdown of patients.

Of 41 patients given FK 037, 39 were analyzed for efficacy, 40 for safety and 38 for usefulness. One patient was excluded from this study because of a positive intracutaneous test for the drug before treatment.

Two patients were excluded from the analyses of efficacy and usefulness because of ineligible disease (relapse of old pulmonary tuberculosis) and treatment period of less than 3 days, respectively. One patient was excluded from the analyses of safety and usefulness because of serious underlying disease (drug-induced liver dysfunction).

2. Background Factors

The background factors of 39 patients evaluated for efficacy are shown in Table 1.

Of these patients, 12, 19 and 6 received the

Table 1. General characteristics of patients

(Evaluated for efficacy)

Background factor		0.5 g×2	1.0 g×2	2.0 g×2	Changes*	Total
Sex	male	4	15	2	2	23
	female	8	4	4		16
Age (y)	35～<40		3			3
	40～<50	1	3	2		6
	50～<60		4	1	1	6
	60～<70	4	2	2	1	9
	70～<80	6	6	1		13
	80～ 82	1	1			2
Body weight (kg)	35～<40	2	1			3
	40～<50	3	6	4		13
	50～<60	4	8		1	13
	60～<70	2	1	1	1	5
	70～ 75		2			2
	unknown	1	1	1		3
Diagnosis	Pneumonia	9	11	6		26
	Chronic respiratory tract infections	3	5			8
	Pyothorax, pleurisy		1		2	3
	Acute bronchitis		2			2
Severity	mild	7	10	1		18
	moderate	5	9	5	2	21
Duration of treatment (days)	4～ 5			1	1	2
	6～ 7	1	3	2	1	7
	8～10	4	6	2		12
	11～15	7	10	1		18
Total		12	19	6	2	39

*0.5 g×2→1.0 g×2

drug at 0.5g b.i.d., 1.0g b.i.d. and 2.0g b.i.d., respectively, throughout the treatment period. Two patients received the drug at 0.5g b.i.d. and then 1.0g b.i.d.

There were 23 male and 16 female patients. Thirteen patients were in their seventies (33.3 %), followed by those in their sixties (9, 23.1 %). The most common body weight (kg) was 40～<50 (13, 33.3%), followed by 50～<60 (13, 33.3%).

The patients, diseases were pneumonia in 26, chronic respiratory tract infections in 8 (5 chronic bronchitis, 1 diffuse panbronchiolitis, 1 secondary infection of pulmonary emphysema, 1 secondary infection of pulmonary silicosis), pyothorax or pleurisy in 3 and acute bronchitis in 2. Cases were mild or moderate (similar in number); and severe cases were not enrolled in this study.

The duration of treatment was 4-5 days in 2 patients, 6-7 days in 7, 8-10 days in 12 and 11 -15 days in 18. The highest total dose of the drug was 56.0g.

3. Clinical Efficacy

1) Clinical efficacy by diagnosis

Table 2 shows the clinical efficacy of FK 037 by diagnosis. "Excellent" and "good" efficacy were noted in 11 and 12, respectively, of 26 patients with pneumonia, an efficacy rate of 88.5 %. "Excellent" and "good" efficacy were noted in 4 and 4 patients, respectively, out of 8 patients with chronic respiratory tract infections. "Good" efficacy was noted in 1 of 3 patients with pyothorax or pleurisy. Both of the patients with acute bronchitis were rated "good".

"Excellent" and "good" efficacy were seen in 15 and 19, respectively, out of a total of 39 patients evaluated. Thus, the overall efficacy rates of "excellent" and "good" or better response were 38.5 and 87.2%, respectively.

2) Efficacy rate by daily dose

Table 3 shows efficacy rates by daily dose. The efficacy rates by dosage were 91.7%, 100% and 66% (4/6) at 0.5g b.i.d., 1.0g b.i.d. and 2.0g b.i.d., respectively.

3) Clinical efficacy by causative organisms

Table 4 shows clinical efficacy in patients in whom suspected causative organisms were detected. The efficacy rate was 87.0% in patients with single infections(84.6 and 90.0% in patients with gram-positive and gram-negative organisms,

Table 2. Clinical efficacy by diagnosis

Diagnosis	No. of patients	Excellent	Good	Fair	Poor	Efficacy rate (%)
Pneumonia	26	11	12	2	1	88.5
Chronic respiratory tract infections	8	4	4			
Pyothorax, pleurisy	3		1	1	1	
Acute bronchitis	2		2			
Total	39	15	19	3	2	87.2

Efficacy rate (%) = (excellent+good/No. of patients)

Table 3. Efficacy rate by daily dose

Disease	0.5 g×2	1.0 g×2	2.0 g×2	Changes
Pneumonia	8/9	11/11 (100)	4/6	
Chronic respiratory tract infections	3/3	5/5		
Pyothorax, pleurisy		1/1		0/2
Acute bronchitis		2/2		
Total	11/12 (91.7)	19/19 (100)	4/6	0/2

( ): Efficacy rate (%)

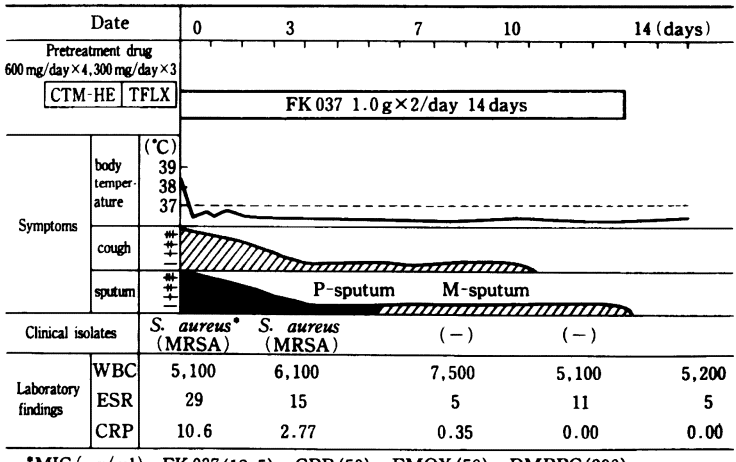
respectively).

Both patients with polymicrobial infections were rated "good".

As for the organisms detected in 5 or more patients, the efficacy against *Streptococcus pneumoniae* and *Haemophilus influenzae* was "excellent" or "good". One of 3 patients with *S. aureus* (MRSA) was rated "excellent". This patient had pneumonia and a fatty liver, and MRSA was detected in the sputum sample before treatment (Fig. 3). As shown in Fig. 3, the symptoms and findings of pneumonia seen with the course of treatment finally disappeared. The patient was thus judged as "excellent". Both patients

Table 4. Clinical efficacy by causative organisms

Causative organisms		No. of patients	Excellent	Good	Fair	Poor	Efficacy rate (%)
G (+)	*S. aureus* (MSSA)	1		1			
	S. aureus (MRSA)	3	1		2		
	S. pneumoniae	8	5	3			
	Streptococcus sp.	1		1			
	Subtotal	13	6	5	2	0	84.6
G (−)	*M. catarrhalis*	1			1		
	E. coli	1	1				
	K. pneumoniae	1		1			
	P. aeruginosa	2	2				
	H. influenzae	5	2	3			
	Subtotal	10	5	4	1	0	90.0
Total		23	11	9	3	0	87.0
H. influenzae + *S. pneumoniae*		1		1			
H. influenzae + *B. catarrhalis*		1		1			
Total		25	11	11	3	0	88.0



*MIC (μg/ml): FK 037 (12.5), CPR (50), FMOX (50), DMPPC (200)
CTM-HE: cefotiam hexetil, TFLX: tosufloxacin, CPR: cefpirome, FMOX: flomoxef, DMPPC: methicillin

Fig. 3. Clinical course (59 y.o., male, pneumonia).

with chronic bronchitis who had *P. aeruginosa* also showed "excellent" results and their organisms were eradicated.

The overall efficacy rate in 25 patients in whom organisms were detected was 88.0%.

4) Evaluation in patients with poor response

The efficacy of the drug was judged as "fair" or "poor" in 5 patients; 3 had pneumonia and 2 had pyothorax or pleurisy (Table 5).

Two patients (Nos. 1 and 4) had MRSA as causative organisms. The MRSA isolated in patient No. 1 (MIC of FK 037 not determined) remained "unchanged" on treatment. The MRSA isolated in patient No. 4 (MIC of FK 037: 12.5 μg/ml), in whom the dosage was changed from 0.5 g b.i.d. to 1.0 g b.i.d., was eradicated with the drug. The clinical efficacy of FK 037 was "fair" in both of the patients. Patient No. 1 improved after administration of teicoplanin, and one patient (No. 4) improved after drainage by thoracotomy.

One patient (No. 2) had moderate pneumonia attributed to an unknown organism and diabetes as an underlying disease, and did not respond to treatment with FK 037 2.0 g b.i.d. for 3 days. The drug was discountinued and that efficacy was judged as "poor". Subsequently, the patient received clarithromycin (CAM), ceftazidime (CAZ) and antituberculous drugs, but response was again poor. A patient (No. 3) with moderate pneumonia had old pulmonary tuberculosis, prostatic cancer and drug-induced liver dysfunction as underlying diseases or complications. Sputum was cleared by treatment with FK 037 0.5 g b.i.d. for 7 days, and the causative organism (*Moraxella catarrhalis*) was considered eradicated. However, because of a persistent slight fever, the efficacy of FK 037 was judged as "fair". Subsequently, imipenem/cilastatin (IMP/CS) and clindamycin (CLDM) were given with slight and moderate responses, respectively.

A patient (No. 5) with pleurisy had diabetes as an underlying disease, and received FK 037 0.5 g b.i.d. for 3 days and then 1.0 g b.i.d. for 1.5 days. Although cough, sputum and chest pain disappeared, fever persisted and chest X-ray findings remained unchanged. The efficacy of FK 037 was thus judged as "poor". Subsequently, the patient received combination therapy with CLDM and cefmenoxime (CMX), but the response was poor. The fever finally remitted with minocycline.

5) Bacteriological effect

Table 6 gives the bacteriological effect of FK 037 by suspected causative organisms.

Fourteen strains of gram-positive organisms were detected, 92.9% of which were eradicated. Similarly, 13 strains of gram-negative organisms were detected, 92.3% of which were eradicated.

Table 5. Clinical results ("fair" or "poor" response cases)

No.	Age Sex	Diagnosis	Severity	Underlying disease complication	Pretreatment chemotherapy	FK 037 Treatment		Causative organisms	Bacteriological effect	Clinical efficacy
						daily dose	duration			
1	75 F	pneumonia	moderate	heart failure	CPDX-PR	2.0 g×2	7	*S. aureus* (MRSA)	unchanged	fair
2	63 F	pneumonia	moderate	diabetes mellitus	OFLX	2.0 g×2	4	unknown	unknown	poor
3	78 M	pneumonia	moderate	old pulmonary tuberculosis prostatic cancer drug induced liver dysfunction	(−)	0.5 g×2	8	*M. catarrhalis*	eradicated	fair
4	53 M	pyothorax (pleurisy)	moderate	(−)	(−)	0.5 g×2 1.0 g×2	3 4	*S. aureus* (MRSA)	eradicated	fair
5	68 M	pleurisy	moderate	diabetes mellitus	(−)	0.5 g×2 1.0 g×2	3 2	unknown	unknown	poor

CPDX-PR: cefpodoxime proxetil, OFLX: ofloxacin

Table 6. Bacteriological effect by causative organisms

Causative organisms	No. of strains	Eradicated	Decreased	Unchanged	Eradication rate (%)
S. aureus (MSSA)	1	1			
S. aureus (MRSA)	3	2		1	
S. pneumoniae	9	9			
Streptococcus sp.	1	1			
Subtotal	14	13	0	1	92.9
M. catarrhalis	2	2			
E. coli	1	1			
K. pneumoniae	1			1	
P. aeruginosa	2	2			
H. influenzae	7	7			
Subtotal	13	12	0	1	92.3
Total	27	25	0	2	92.6

Eradication rate (%): (eradicated/No. of strains)

All of 9 strains of *S. pneumoniae* and 7 strains of *H. influenzae*, the major causative organisms in respiratory tract infection, were eradicated. Of a total of 27 strains detected, 25 were eradicated, an overall eradication rate of 92.6%. Causative organisms unresponsive to the drug were one strain each of *S. aureus* and *Klebsiella pneumoniae*.

6) Distribution of MICs for causative organisms

The MICs of FK 037 (10^6cfu/ml) were determined for 14 bacterial strains isolated from patients. Table 7 shows the distribution of the MICs.

The MICs of FK 037 were 1.56 μg/ml for *S. aureus* (MSSA), 12.5 μg/ml for MRSA, ≦0.025 and 0.2 μg/ml for *S. pneumoniae*, ≦0.025 μg/ml for *Escherichia coli*, 0.05 μg/ml for *K. pneumoniae*, 3.13 and 12.5 μg/ml for *P. aeruginosa*, and 0.05 and 0.1 μg/ml for *H. influenzae*.

7) Pharmacokinetics

The time course changes in plasma concentration and the one-point plasma concentration of FK 037 were measured in 3 and 1 patients, respectively. Urinary concentration, urinary recovery rate and concentration in sputum were determined in 2 of the 4 patients (Fig. 4).

The dose of the drug was 1.0 g for cases A and B, and 0.5 g for cases C and D. Plasma drug concentration reached the maximum (C_{max}) just after the completion of infusion (57.3, 49.6, 26.7 and 35.0 μg/ml, respectively). The half-life ($T_{1/2}$) in the β-phase ranged from 1.6 to 2.4 hours, and the 8-h urinary excretion accounted for 64.4-79.6% of the drug administered. C_{max}

Table 7. Distribution of FK 037 MICs for causative organisms

Causative organisms (No. of strains)	≦0.025	0.05	0.1	0.2	0.39	0.78	1.56	3.13	6.25	12.5 (μg/ml)
S. aureus (MSSA) (1)							1			
S. aureus (MRSA) (1)										1
S. pneumoniae (6)	5			1						
E. coli (1)	1									
K. pneumoniae (1)		1								
P. aeruginosa (2)								1		1
H. influenzae (2)		1	1							

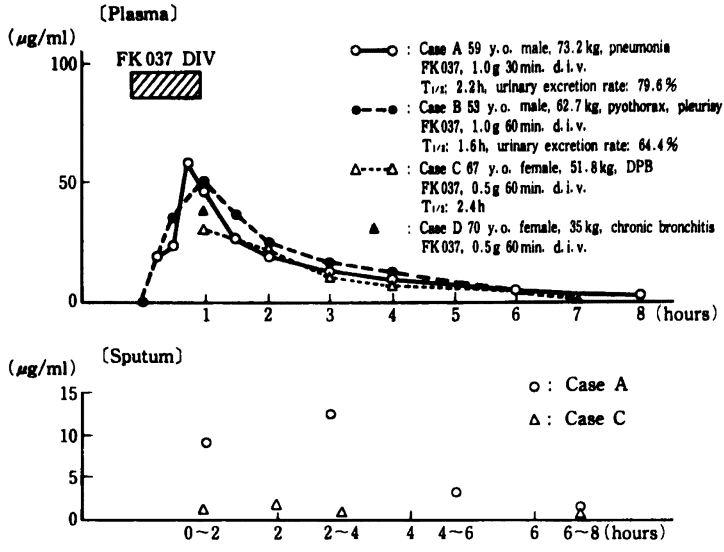


Fig. 4. Plasma and sputum levels of FK 037 —bioassay method—.

Table 8. Side effects and abnormal changes in laboratory tests

Side effects: none

Abnormal changes in laboratory tests

Item	0.5 g×2	1.0 g×2	2.0 g×2	Changes	Total
WBC↓	1/11	1/21	1/6		3/40 (7.5)
Eosino.↑		1/20			1/39 (2.6)
Neutro.↓	1/11				1/39 (2.6)
GOT↑		1/21	1/6	1/2	3/40 (7.5)
GPT↑	1/11	1/21		1/2	3/40 (7.5)
Al-P↑			1/6	1/2	2/40 (5.0)
LAP↑			1/6	1/1	2/28 (7.1)
γ-GTP↓		1/19		1/2	2/38 (5.3)
Serum K↑		1/ 1			1/ 1

( ): incidence of abnormal changes (%)

in sputum was 12.5 and 1.9 μg/ml in patients given 1.0 g and 0.5 g, respectively.

4. Safety

1) Side effects

No side effects were observed (upper column of Table 8).

2) Abnormal changes in laboratory test values

Abnormal changes in laboratory test values whose causal relationship to the drug was suspected are listed in the lower column of Table 8.

Abnormal changes were noted in 12 (30.0%) of the 40 patients: 3 (7.5%) events of leukopenia; 1 (2.6%), eosinophilia; 1 (2.6%), neutropenia; 3 (7.5%), increase in GOT; 3 (7.5%), increase in GPT; 2 (5.0%), increase in Al-P; 2 (7.1%), increase in LAP; 2 (5.3%), increase in γ-GTP and 1, increase in serum potassium. None of the abnormal laboratory findings was serious or associated with clinical symptoms.

3) Safety

Safety was evaluated based on the side effects

Table 9. Safety

Daily dose	No. of patients	Safe	Almost safe	Problematic	Not safe
0.5 g×2	11	8 (72.7)	2 (90.9)	1	
1.0 g×2	21	17 (81.0)	3 (95.2)	1	
2.0 g×2	6	4	2		
Changes	2	1	1		
Total	40	30 (75.0)	8 (95.0)	2	0

( ): Cumulative%

Table 10. Usefulness

Daily dose	No. of patients	Remarkably useful	Useful	Slightly useful	Not useful
0.5 g×2	11	3 (27.3)	8 (100)		
1.0 g×2	19	4 (21.1)	14 (94.7)	1	
2.0 g×2	6	3	1		2
Changes	2			1	1
Total	38	10 (26.3)	23 (86.8)	2	3

( ): Cumulative%

and abnormal changes in laboratory test values, as shown in Table 9.

"Safe", "almost safe" and "problematic" were seen in 30, 8 and 2, respectively, of the 40 evaluable patients. Thus, the rates of "safe" and "almost safe" or better were 75.0 and 95.0%, respectively.

5. Usefulness

Table 10 shows usefulness as assessed on the basis of clinical efficacy, bacteriological effect and safety.

"Remarkably useful", "useful", "slightly useful" and "not useful" were seen in 10, 23, 2 and 3, respectively, of the 38 patients analyzed, for a "useful" or better rate of 86.8%.

Discussion

FK 037 is highly active against a wide range of both gram-positive and gram-negative organisms and is resistant to β-lactamases. This drug is a new parenteral cephalosporin with a pyrazole group in the 3-C side chain of 7-aminocephalosporanic acid and an aminothiazole and a methoxyimino group[16], both of which are widely used in conventional cephalosporins, in the 7-C side chain. When compared with ceftizoxime (CZX)[17], which has the same 7-C side chain as FK 037, with respect to antimicrobial activity against the major causative organisms of respiratory tract infections, FK 037 is apparently more active against *S. aureus* and *P. aeruginosa*. The MIC_{90} of FK 037 for *S. pneumoniae*, *M. catarrhalis*, *K. pneumoniae*, and *H. influenzae* were 0.1, 1.56, 0.1 and 0.2 μg/ml, respectively, being as active as those of CZX[1].

FK 037 has moderate activity (the most potent among β-lactam drugs) against MRSA ($MIC_{50/90}$ 12.5/25 μg/ml)[4,7], which has recently become a social problem. It is interesting to know how this finding is reflected in clinical studies.

A phase I trial of FK 037 has been conducted, following preclinical studies including various toxicity studies and pharmacokinetic studies[18] in animals. On the basis of the results of these studies, we performed an early phase II trial to evaluate the efficacy and safety of FK 037 in patients with respiratory tract infections.

The doses of FK 037 given were 0.5, 1.0, and 2.0 g, in accordance with those used in the phase I trial. The drug was given at twice daily doses based on its plasma half-life of about 2.3 hours[14] and the dosages of conventional

cephalosporins.

Early phase II trials are designed to preliminarily evaluate the safety and efficacy of new drugs at doses used in clinical practice, where they are given to patients for the first time. In principle, therefore, the dose of the first patient at each center was set at the lowest dose of FK 037 (0.5 g b.i.d.), as far as possible, and the next patient at 1.0 g b.i.d. and then 2.0 g b.i.d.

For comparison of pharmacokinetics with normal adults and for use as reference for evaluation of safety and efficacy, concentrations in plasma, urine and sputum, and the urinary excretion rate of the drug were determined as far as possible.

Plasma maximum concentrations (C_{max}) of FK 037 in 2 patients intravenously infused with 1.0 g of FK 037 were 49.6 and 57.3 μg/ml, respectively, and those in 2 other patients given 0.5 g were 26.7 and 35.0 μg/ml, respectively. These values are similar to those obtained in normal adults (average 60.0 and 32.0 μg/ml after administration of 1.0 and 0.5 g, respectively)[14]. The peak drug concentration in sputum from a patient intravenously given 1.0 g was 12.5 μg/ml (about 25% of the plasma C_{max}), slightly higher than that of conventional cephalosporins. This finding may reflect the fact that our patient had pneumonia with severe inflammatory findings. The peak drug concentration in sputum from a patients intravenously given 0.5 g was 1.9 μg/ml (about 7% of plasma C_{max}).

There were no side effects that would suggest any causal relationship to the drug in 40 patients evaluated for safety. There were 12 patients who showed abnormal changes in laboratory test values. However, none of the abnormal laboratory findings was serious or associated with clinical symptoms. All of these abnormalities were seen in patients with pneumonia or pyothorax. The incidence of abnormal laboratory findings seemed to be almost the same as that in phase III comparison studies of conventional cephalosporins[19~21] in patients with pneumonia. No dose dependency was noted in the incidence of abnormal laboratory findings. There were no findings that might give rise to problems concerning safety or obstruct proceeding to late phase II trials.

An efficacy rate of 87.2% was obtained in 39 evaluable patients. The efficacy rate for pneumonia was 88.5%. All patients with chronic respiratory tract infections showed "good" or better response. The efficacy rate by dosage was 91.7 and 100% at 0.5 g b.i.d. and 1.0 g b.i.d., respectively, indicating that a favorable effect was provided by both of the dosages studied. The rate of "good" or better was somewhat low (4/6) in patients given the highest dosage (2.0 g b.i.d.). This may be due to the small number of patients analyzed and inclusion of relatively severe cases. The 2.0 g b.i.d. dosage should be investigated using more patients.

FK 037 showed good or better efficacy for respiratory tract infections with *S. pneumoniae* or *H. influenzae*, the major causative organisms. Similar results were obtained in the evaluation of bacteriological effect. Also, in both patients with chronic bronchitis caused by *P. aeruginosa*, FK 037 showed excellent clinical results and bacteriological response.

Of 3 patients with MRSA infection, 1 was rated "excellent", and of 3 MRSA strains, 2 were eradicated. One strain was eradicated with the drug at 1.0 g b.i.d., the other was not eradicated with 0.5 g b.i.d. but was then eradicated with 1.0 g b.i.d. These results, although not sufficient, indicate that the drug is effective to some extent against MRSA.

The peak plasma concentration and half-life of FK 037 after 1-hour infusion of 1.0 g were estimated to be 60.0 μg/ml and 2.3 hours, respectively[14]. The drug concentration could remain over the MIC_{90} for MRSA (25 μg/ml) for about 2 hours. Thus, a recommended single dose of FK 037 for the treatment of MRSA should be at least 1.0 g. MICs of FK 037 were determined in a total of 14 bacterial strains in this study. The MICs for *S. aureus* (MSSA), *S. pneumoniae*, *E. coli*, *K. pneumoniae* and *H. influenzae* were

0.2 μg/ml or less, and that for MRSA and *P. aeruginosa* were 12.5 μg/ml or less. These results were as good as those in previous basic studies.

The efficacy rate of the drug was low in patients with pyothorax or pleurisy, including a patient with pleural effusion. Efficacy data on these diseases should be further accumulated.

The results of this study showed that FK 037, given at doses of 0.5 g b.i.d. and 1.0 g b.i.d., presented no problems concerning safety and could be effective for the treatment of respiratory tract infections. Further studies should, therefore, be made on the drug using the three clinical daily doses studied in this trial.

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FK 037 の内科領域感染症における前期第二相試験

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注射用セフェム剤FK 037の呼吸器感染症患者を対象とした前期第二相試験を実施した。

1) 呼吸器感染症41例にFK 037 1回0.5g, 1.0gあるいは2.0gを1日2回原則として3～14日間点滴静注し，有効性，安全性，有用性を検討した。

2) 有効性評価可能例39例（肺炎26例，慢性気道感染症8例，膿胸・胸膜炎3例，急性気管支炎2例）における臨床効果は著効15例，有効19例で有効率87.2%であった。1回投与量別有効率は0.5g×2/日，1.0g×2/日，および2.0g×2/日でそれぞれ91.7% (11/12), 100% (19/19), 4/6であった。

3) *Streptococcus pneumoniae* 9株，*Haemophilus influenzae* 7株，*Pseudomonas aeruginosa* 2株はすべて消失，検出菌27株中25株 (92.6%) が消失した。

4) 副作用は認められなかった。臨床検査値異常変動は，安全性評価可能例40例中12例 (30.0%) にみられ，主として肝機能酵素値の軽度上昇であり，臨床症状を伴うものあるいは重篤な症例は認められなかった。

5) 有用性評価可能例38例における有用性はきわめて有用10例，有用23例，やや有用2例，有用でない3例であり，有用率は86.8%であった。

以上の成績から，FK 037は0.5g×2/日，1.0g×2/日，および2.0g×2/日を臨床投与量として今後さらに検討し得る薬剤であると考えられた。

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