Pharmacokinetics of FK027 (Cefixime) in Healthy Volunteers after Intravenous Injection

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The pharmacokinetics of FK027 was investigated in 6 healthy male volunteers after intravenous injection of 100 mg both without and with oral probenecid 1 g by a two-way crossover design. The serum concentrations of FK027 without probenecid declined biphasically. The distribution half-life ($t_{1/2\alpha}$) was 0.148±0.015 hr and the elimination half-life ($t_{1/2\beta}$) was 2.519±0.070 hr. The volume of distribution of the central compartment (Vc) was 4.032±0.379 L and the volume of distribution of the peripheral compartment (Vt) was 7.074±0.576 L. The total body clearance (Clbody) was 58.59±4.63 ml/min and the renal clearance (Clr) was 37.40±1.82 ml/min. The unchanged drug excreted in the 24-hr urine was 64.8±3.5%. When FK027 was given with probenecid, the serum concentrations and area under the concentration-time curve (AUC) increased significantly and $t_{1/2\beta}$ and the volume of distribution at steady state (Vdss) increased slightly, but Clbody and Clr decreased. These results indicate that FK027 is rapidly distributed to the tissues and thereafter gradually eliminated from the body, and it is excreted from the kidneys, mainly through glomerular filtration and to some extent through renal tubular secretion.

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Key words : FK027, cefixime, pharmacokinetic parameters, serum concentration, probenecid

Introduction

FK027 (Cefixime) is a new oral cephalosporin developed in the Central Research Laboratories of Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan. Its chemical nomenclature is (6 R, 7 R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(carboxymethoxyimino)-acetomido]-8-oxo-3-vinyl-5-thia-1-azabicyclo-[4, 2, 0]-octo-2-ene-2-carboxylic acid.

Unlike conventional oral cephalosporins and penicillins, FK027 is stable to various β-lactamases and has a broad spectrum of antibacterial activity against gram-positive and gram-negative organisms, especially gram-negative bacilli.

The time to reach maximum serum concentration of FK027 after oral dosing[1] was 3.8 to 4.0 hours, and the apparent elimination half-life was as long as 2.3-2.5 hours. The serum concentrations were prolonged. The excretion of the unchanged drug in the 24-hr urine was 21-28%. These oral studies suggest that FK027 is gradually absorbed after oral dosing and slowly excreted in the urine. However, the systemic bioavailability of FK027 which is very important for investigating the pharmacokinetics of the drug after oral dosing has not been elucidated.

In this study, we investigated the pharmacokinetics of FK027 in 6 healthy male volunteers after intravenous injection both without and with probenecid which is known to inhibit renal tubular secretion of antibiotics[2)3)4)], and discussed the systemic bioavailability after oral dosing.

Materials and Methods

Six healthy male volunteers between 29 and 49 years of age (mean : 40 years) and weighing 55-67 kg (mean : 59.7 kg) took part in this study. The six volunteers gave their written consent to participate in the study after the purpose and methods of the study and possible side effects of FK027 were fully explained.

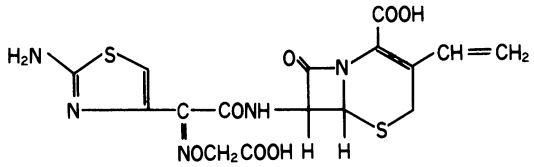

Fig. 1 Structure of FK027.

The protocol and consent form for this investigation had prior review and approval of the Ethical Committee, Fujisawa Pharmaceutical Company Ltd., Osaka, Japan.

All volunteers were deemed healthy on the basis of hematology, blood chemistry, urinalysis, and physical examination, and also were negative to the intradermal reaction test.

The volunteers were randomly assigned to 2 groups of 3. Each group was given FK027 intravenously both without and with probenecid by a two-way crossover design. A five-day washout period was provided between the 1 st and 2nd dosing periods. The volunteers fasted between 10 : 00 p. m. of the night before and 4 hours after intravenous injection.

The study was started from 9 : 00 a. m. For intravenous injection, FK027 110 mg and $NaHCO_3$ 33.4 mg contained in a vial were freshly reconstituted immediately before injection with 22 ml of 0.9% physiological saline. The pH was 6.31 and the osmotic pressure was 334 mOsm/kg. Twenty ml (100 mg potency as FK027) of the solution was given intravenously for 3 min at constant rate. The injection doses of FK027 per

body surface area ranged from 55.2 to 62.9 mg/m² (mean ± S.E. : 59.3±1.3 mg/m²). Probenecid was given in oral doses of 1 g (4 tablets×250 mg/tablet, Japan Merck-Banyu) with 200 ml of water one hour before injection of FK027. Blood pressure, pulse rate, and body temperature in the sitting position were measured, and physical interview, auscultation and percussion were made before and 0.5, 4, 8, and 24 hours after injection. ECG was recorded before and 30 minutes after injection. Blood chemistry and urinary tests were made before and 24 hours after injection. Blood was collected before and 1/12, 1/4, 1/2, 1, 2, 4, 6, 8, 12, and 24 hours after injection. Urine was collected before and 0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours after injection and the volume was determined at each collection time. The blood samples were centrifuged to obtain the serum, and serum and urine samples were stored at −20°C until assayed.

The serum and urinary concentrations of FK027 were determined by the bioassay method[5] with E. coli ATCC 39188 as the test organism. The sensitivity limit of the assay was 0.08 μg/ml for both serum and urine. The concentrations were also determined by the HPLC method[6] using automated column switching.

The HPLC was equipped with two solvent delivery pumps (Model 6000 A ; Waters Assoc.), an automatic liquid sampler (WISP 710 B ; Waters Assoc.) and a variable wave length UV detector (at 295 nm, UVIDEC 100-III ; Japan Spectroscopic).

The three columns used were an anion-exchange column (TSK-IEX 540 DEAE, 5 μm ; Toyo Soda) and two reversed-phase columns (TSK-LS 410 ODS, 5 μm ; Toyo Soda).

The mobile phases were 73% 0.03 M ammonium dihydrogen phosphate-phosphoric acid solution (pH 2.5) in methanol for analysis of serum and acetonitrile-water-1.8 M sulphuric acid (15 : 85 : 0.21) for analysis of urine.

The sensitivity limit of the analysis was 0.05 μg/ml for serum and 0.5 μg/ml for urine.

The pharmacokinetics of FK027 in the serum after intravenous injection was analyzed by the 2-compartment open model. The pharmacokinetic parameters were calculated with a non-linear regression analysis computer program NONLIN[7]. The serum concentrations, urinary excretion, and pharmacokinetic parameters of FK027 both without and with probenecid were statistically determined by analysis of variance. Each value was expressed in terms of mean ± S.E.

Results

The mean serum concentration-time curve and individual serum concentrations of FK027 in 6 healthy male volunteers after intraveous injec-

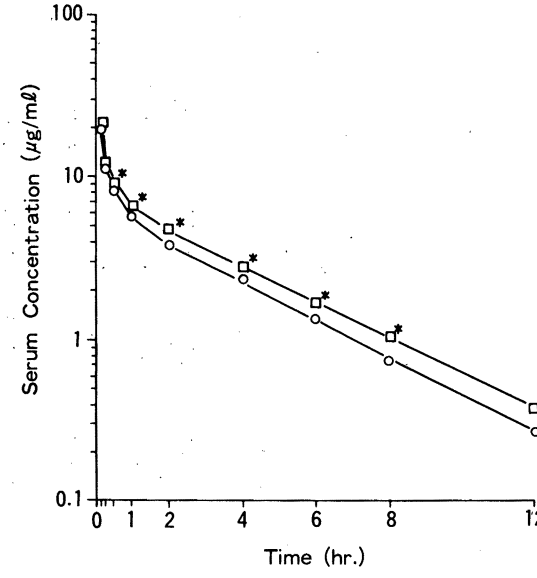

Fig. 2 Mean serum concentrations of unchanged drug after intravenous injection of FK027 without (○) and with (□) probenecid in 6 healthy volunteers.
*P<0.05 by analysis of variance

Tab. 1 Serum Concentrations of Unchanged Drug after Intravenous Injection of FK027 without and with Probenecid in Healthy Volunteers (dose : 100 mg)

	Volunteer No.	Dose (mg/m²)	serum level (μg/ml) 1/12hr	¼ hr	½ hr	1 hr	2 hr	4 hr	6 hr	8 hr	12hr	24hr
FK027 without probenecid	No.1	58.8	25.60	12.50	8.94	6.40	4.38	2.62	1.42	0.74	0.23	n.d.
	No.2	55.9	17.80	10.60	7.90	5.97	3.79	2.23	1.43	0.79	0.27	n.d.
	No.3	55.2	13.70	7.96	6.12	4.65	3.11	1.89	1.04	0.56	0.18	n.d.
	No.4	62.9	22.90	13.80	9.34	6.70	4.02	2.53	1.37	0.84	0.28	n.d.
	No.5	60.6	18.90	10.70	6.57	4.42	2.84	1.70	1.06	0.60	0.21	n.d.
	No.6	62.1	20.60	13.40	10.00	6.80	4.63	2.93	1.81	1.00	0.40	n.d.
	Mean	59.3	19.92	11.49	8.15	5.82	3.80	2.33	1.36	0.76	0.26	n.d.
	S.E.	1.3	1.69	0.89	0.64	0.43	0.29	0.18	0.12	0.07	0.03	n.d.
FK027 with probenecid	No.1	58.8	29.70	14.70	11.10	6.93	5.32	3.29	1.88	1.25	0.40	n.d.
	No.2	55.9	18.50	12.00	9.31	6.42	4.76	2.54	1.52	1.07	0.44	n.d.
	No.3	55.2	12.30	8.58	7.07	5.27	3.53	2.13	1.12	0.72	0.23	n.d.
	No.4	62.9	23.60	12.40	10.20	7.77	5.11	3.42	1.84	1.08	0.35	n.d.
	No.5	60.6	17.70	10.20	7.84	6.61	3.81	2.29	1.57	0.96	0.34	n.d.
	No.6	62.1	21.00	13.40	10.40	7.91	6.02	3.39	2.23	1.41	0.58	n.d.
	Mean	59.3	20.47	11.88	9.32*	6.82*	4.76*	2.84*	1.69*	1.08*	0.39*	n.d.
	S.E.	1.3	2.41	0.90	0.64	0.40	0.38	0.24	0.15	0.10	0.05	

* $P<0.05$ by analysis of variance

n.d. : not detected (<0.08 μg/ml)

tion both without and with probenecid are shown in Fig. 2 and Tab. 1. The serum concentrations of FK027 without probenecid rapidly decreased up to 2 hours after injection and thereafter gradually were eliminated. The serum concentrations of FK027 with probenecid were significantly higher 0.5 to 12 hours after injection than those of FK027 without probenecid. The decline in serum concentration of FK027 with time was expressed by the biexponential equation, $Ae^{-\alpha t}+Be^{-\beta t}$, corresponding to a two-compartment open model. The calculated pharmacokinetic parameters are summarized in Tab. 2. The distribution of FK027 to the tissues after injection without probenecid was rapid, with $t_{1/2}\alpha$ of 0.148 ± 0.015 hr. The serum concentrations were gradually eliminated, with $t_{1/2}\beta$ of 2.519 ± 0.070 hr. Clbody was 58.59 ± 4.63 ml/min and Clr was 37.40 ± 1.82 ml/min. AUC ($0-\infty$) was 29.31 ± 2.19 μg·hr/ml. FK027 was given with probenecid, with $t_{1/2}\alpha$ of 0.160 ± 0.023 hr and $t_{1/2}\beta$ of 2.730 ± 0.087 hr ($P<0.05$). Vdss decreased by about 7%, i.e. 10.313 ± 0.839 L ($P<0.05$). Clbody was 48.73 ± 4.33 ml/min and Clr was 31.65 ± 2.60 ml/min. These values were lower than those without probenecid ($P<0.05$). AUC ($0-\infty$) was 35.44 ± 2.83 μg·hr/ml, i.e. an increase of 21% ($P<0.05$).

The urinary excretion of FK027 without and with probenecid is shown in Tab. 3.

The urinary excretion of FK027 without probenecid was 30.5 ± 1.4% in the first 2 hours and 64.8 ± 3.5% up to 24 hours after injection and that with probenecid was 28.4 ± 1.7% in the first 2 hours and 65.5 ± 3.8% up to 24 hours. There were no statistically significant differences between the two groups in the 0−2, 2−4, 4−6, 6−8,

Tab. 2 Pharmacokinetic Parameters after Intravenous Injection of FK027 without and with Probenecid in Healthy Volunteers (dose : 100 mg)

	Volunteer No.	A (μg/ml)	B (μg/ml)	α (hr^{-1})	β (hr^{-1})	Kel (hr^{-1})	$t_{\frac{1}{2}\alpha}$ (hr)	$t_{\frac{1}{2}\beta}$ (hr)
FK027 without probenecid	No.1	30.33	8.56	7.095	0.303	1.194	0.098	2.291
	No.2	15.17	6.93	4.562	0.271	0.764	0.152	2.560
	No.3	12.71	5.99	6.127	0.293	0.831	0.113	2.364
	No.4	20.43	7.39	3.907	0.274	0.863	0.177	2.533
	No.5	19.64	5.14	4.556	0.267	1.051	0.152	2.598
	No.6	16.42	7.86	3.538	0.250	0.674	0.196	2.768
	Mean	19.12	6.98	4.964	0.276	0.896	0.148	2.519
	S.E.	2.53	0.51	0.559	0.008	0.078	0.015	0.070
FK027 with probenecid	No.1	31.90	9.18	5.864	0.259	1.004	0.118	2.677
	No.2	13.58	6.78	2.887	0.233	0.601	0.240	2.981
	No.3	7.54	6.27	3.328	0.276	0.552	0.208	2.512
	No.4	26.14	9.96	7.879	0.279	0.926	0.088	2.483
	No.5	14.86	6.83	4.613	0.250	0.710	0.150	2.772
	No.6	16.49	9.32	4.524	0.235	0.595	0.153	2.953
	Mean	18.42	8.06*	4.849	0.255*	0.731	0.160	2.730*
	S.E.	3.65	0.65	0.742	0.008	0.078	0.023	0.087

* $P<0.05$ by analysis of variance

A and B = coefficients

α and β = rate constants

Kel = elimination rate constant

$t_{\frac{1}{2}\alpha}$ = distribution half-life

$t_{\frac{1}{2}\beta}$ = elimination half-life

Tab. 2 Continued

	Volunteer No.	Vc (liters)	Vt (liters)	Vdss (liters)	Clbody (ml/min)	Clr (ml/min)	AUC $_{0-\infty}$ (μg·hr/ml)
FK027 without probenecid	No.1	2.571	6.299	8.870	51.14	31.06	32.59
	No.2	4.525	6.868	11.393	57.65	40.93	28.91
	No.3	5.348	8.485	13.833	74.11	41.91	22.49
	No.4	3.595	6.033	9.628	51.71	39.14	32.23
	No.5	4.035	9.119	13.154	70.66	38.62	23.59
	No.6	4.119	5.637	9.756	46.25	32.72	36.04
	Mean	4.032	7.074	11.106	58.59	37.40	29.31
	S.E.	0.379	0.576	0.831	4.63	1.82	2.19
FK027 with probenecid	No.1	2.434	5.807	8.241	40.75	29.55	40.90
	No.2	4.912	6.167	11.079	49.22	38.37	33.86
	No.3	7.242	6.051	13.293	66.66	40.98	25.00
	No.4	2.770	5.661	8.431	42.73	26.74	39.00
	No.5	4.611	7.181	11.792	54.59	28.07	30.53
	No.6	3.874	5.168	9.042	38.43	26.18	43.37
	Mean	4.307	6.006	10.313*	48.73*	31.65*	35.44*
	S.E.	0.710	0.275	0.839	4.33	2.60	2.83

* $P<0.05$ by analysis of variance

Vc = volume of distribution of central compartment

Vt = volume of distribution of peripheral compartment

Vdss = volume of distribution at steady state

Clbody = total body clearance

Clr = renal clearance

$AUC_{0-\infty}$ = area under the serum concentration-time curve from 0 to infinite hour

Tab. 3 Urinary Excretion Rates of Unchanged Drug after Intravenous Injection of FK027 without and with Probenecid in Healthy Volunteers (dose : 100 mg)

	Volunteer No.	Urinary excretion (% of dose) 0-2 hr	2-4 hr	4-6 hr	6-8 hr	8-12 hr	12-24 hr	0-24 hr
FK027 without probenecid	No.1	31.3	13.6	9.0	3.8	0.6	2.4	60.7
	No.2	33.6	13.8	10.0	5.0	5.7	2.8	70.9
	No.3	27.2	11.5	7.4	4.2	4.2	2.0	56.5
	No.4	34.5	13.5	12.3	6.4	6.2	2.7	75.6
	No.5	25.6	9.5	8.0	4.5	4.5	2.5	54.6
	No.6	31.0	13.6	9.6	6.1	6.0	4.3	70.6
	Mean	30.5	12.6	9.4	5.0	4.5	2.8	64.8
	S.E.	1.4	0.7	0.7	0.4	0.9	0.3	3.5
FK027 with probenecid	No.1	30.2	16.1	9.7	6.6	5.7	4.1	72.4
	No.2	34.5	15.5	11.4	6.5	5.9	3.9	77.7
	No.3	28.5	11.4	8.9	4.9	4.9	2.8	61.4
	No.4	26.8	11.7	9.7	5.4	5.9	3.0	62.5
	No.5	21.7	9.9	7.8	4.5	5.0	2.4	51.3
	No.6	28.7	13.6	10.2	4.5	6.7	4.2	67.9
	Mean	28.4	13.0	9.6	5.4	5.7	3.4*	65.5
	S.E.	1.7	1.0	0.5	0.4	0.3	0.3	3.8

* $P<0.05$ by analysis of variance

8−12 or 0−24 hr urinary excretion except the 12−24 hr excretion.

The above values were determined by bioassay and HPLC method, with good correlation between the values obtained by both methods. Serum ($n=108$) : $y=1.128x-0.156$, $r=0.989$, $P<0.01$; urine ($n=72$) : $y=1.114x-1.025$, $r=0.981$, $P<0.01$, where x is the value obtained by HPLC and y is the value obtained by bioassay.

FK027 was well tolerated by volunteers and all physical examination and laboratory test values obtained during and after the study were within the normal range. There were no particular complaints on verbal interview, abnormal findings on auscultation or percussion or subjective symptoms.

Discussion

The serum concentrations of FK027 without probenecid were well fitted to the 2-compartment open model. $t_{1/2}\alpha$ of FK027 was as short as 0.148 hr, and FK027 was rapidly distributed from the central compartment to the peripheral compartment. The elimination of FK027 from the serum was far slower than that of other oral cephalosporins (cephalexin, 0.9 hr[8]; cephradine, 0.8 hr[9]; cefaclor[9], 0.6 hr ; and cefamandole, 1.1 hr[10]) with $t_{1/2}\beta$ of 2.519 hr. Clbody was 58.59 ml/min, i.e. lower than that of the reference antibiotics. These findings suggest that FK027 is rapidly distributed to the target organs and exerts a potent antibacterial activity against gram-positive and gram-negative organisms, especially gram-negative bacilli. Clr, an index for excretion of an antibiotic from the kidneys, was 37.40 ml/min, i.e. about 64% of the Clbody value and shows that FK027 is excreted mainly from the kidneys.

The 2-hr urinary excretion was 30.5% and the 24-hr urinary excretion was 64.8%.

To investigate the effect of probenecid on the urinary excretion of FK027 in detail, the pharmacokinetics of FK027 with probenecid was studied. Probenecid is known to competitively inhibit the renal tubular secretion of antibiotics, and to enhance the serum concentrations of antibiotics[11]. There have been many reports on the effect of probenecid on the antibacterial activity of such antibiotics as ceftizoxime[2], cefmenoxime[3]and cefatrizine[4]. These studies indicate that probenecid increases $t_{1/2}\beta$, serum concentrations and AUC but decreases Clbody, Clr and urinary excretion. In the present study, (1) $t_{1/2}\beta$ and (2) serum concentrations and AUC were higher and (3) Clbody and Clr and (4) Vdss were lower after injection with probenecid than after injection without probenecid, which shows that the renal tubular secretion of FK027 was inhibited by probenecid. However, the differences between these values were small, and there were scarcely any differences between the two groups in total urinary excretion. These results suggest either that FK027 is excreted mainly by glomerular filtration and to some extent by renal tubular secretion, or that probenecid only slightly affects the renal tubular secretion of FK027.

The reason for the decrease of Vdss values in the presence of probenecid is not known. Gibaldi et al.[12][13]pointed out that probenecid not only inhibits the renal tubular secretion of β-lactam antibiotics but also decreases the volume of distribution. In other words, antibiotics and probenecid compete at the binding site in the kidneys, liver, and other tissues and enhance the serum concentrations, resulting in decreased volume of distribution.

However, our present study showed that probenecid had little effect on the volume of distribution of FK027, since Vdss only slightly decreased and Vc and Vt showed no decrease. After all,

FK027 was rapidly distributed to the tissues and eliminated gradually from the body, possibly through glomerular filtration as the main route, and to some extent through renal tubular secretion.

In the previous study[1], we reported the pharmacokinetics of the drug after oral dosing. Therefore, an attempt at the comparison of oral and intravenous bioavailabillity was made as follows:

The time to reach the maximum serum concentration (T_{max}) after oral dosing with 50-200 mg ranged from 3.8 to 4.0 hours, with an apparent half-life ($t_{1/2}$) of 2.3-2.5 hours, i.e. nearly equal to $t_{1/2\beta}$ of 2.5 hours after intravenous injection in our present study. The maximum serum concentration (C_{max}) and AUC after oral dosing were dose-dependent[1].

There were no statistically significant differences between dosing on an empty stomach and dosing after breakfast in any parameters (C_{max}, T_{max}, $t_{1/2}$ and $AUC_{0-\infty}$). The coefficient of variation for the absorption and excretion ranged from 31 to 38%, providing evidence of the stable absorption and excretion. Since there were no differences between fasting and non fasting conditions in any pharmacokinetic parameters, we used the AUC values and urinary excretion after oral dosing under fasting conditions to compare oral and intravenous bioavailabilities.

The systemic bioavailability of FK027 was calculated by the following formulas from the AUCs and urinary excretion after oral and intravenous dosings:

$$\frac{AUC(po)\times body\ weight(po)\times dose(iv)}{AUC(iv)\times body\ weight(iv)\times dose(po)}\times 100(\%)\ \text{and}$$

$$\frac{\%\ of\ dose\ excreted(po)\ in\ urine}{\%\ of\ dose\ excreted(iv)\ in\ urine}\times 100(\%)$$

The systemic bioavailabilty values calculated from the AUC and urinary excretion were 26-37% and 33-43%, respectively; i.e. the AUC values were sligtly lower than those from the urinary excretion.

There are some references related to the above pharmacokinetic findings.

Gugler et al.[14] stated that the systemic bioavailability values of phenytoin from AUSs are also lower than those from the urinary excretion, since a capacity-limited process exists in the metabolims of the drug.

Nagwekar et al.[15] reported that the Michaelis-Menten kinetics is related to the renal tubular secretion of p-methyl mandelic acid in rats.

Chremos et al.[16] showed that the postabsorptive decline of blood bethanidine concentrations with time was noticeably slower than the corresponding decline in the urinary excretion rate. This discrepancy was attributed to the continual decrease in renal clearance of bethanidine.

Moreover, Lanman et al.[17] and Axelson et al.[18] stated that tetracycline and riboflavin were actively transferred to the bile.

In the case of FK027, the drug was excreted unchanged and the 24-hr biliary excretion in rats and patients were as high as 22%[19] and 4-10%[5], respectively.

The discrepancy in systemic bioavailability is probably related, at least in part, to the non-linear elimination of FK027. However, whether the non-linear aspect of the excretion of the drug can be attributed to the renal or non-renal elimination process, especially the biliary excretion process, is not known.

As pointed out by Wagner et al.[20], AUC values are known to differ according to collection time of blood samples and calculation method. Therefore, the systemic bioavailability values of FK027 from the urinary excretion would be more accurate than those from the AUCs.

The oral urinary excretion of other cephalos-

porins such as cefaclor, cefadroxil and cephalexin was 50-90%[21], whereas that of FK027 was 21-28%, lower than other cephalosporins. The reasons for this low urinary excretion of FK027 are unknown, and further studies are needed to elucidate the rational reasons.

However, FK027 has a broad spectrum of antibacterial activity and its minimal inhibition concentrations are lower than those of currently available cephalosporins.

Moreover, FK027 is gradually absorbed and slowly eliminated with a longer half-life than other oral antibiotics, and its serum concentration and urinary excretion profiles are commensurately prolonged.

Therefore, FK027 is expected to provide sufficient clinical effects in spite of its low urinary excretion.

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