6315-S (FLOMOXEF), A NEWLY SYNTHESIZED OXACEPHEM, IN UROLOGY

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6315-S (flomoxef), a newly synthesized oxacephem, was evaluated in the urological field. The MICs of 6315-S against 18 reference strains and 188 clinical isolates from the urinary tract showed strong antibacterial activity against both Gram-positive and -negative bacteria except for *E. faecalis* and *P. aeruginosa*. Serum levels in patients with chronic renal failure were serially determined by bioassay. Serum levels of 6315-S after 0.5 g and 1 g injection were very high even on the second day. The elimination rate by hemodialysis was about 80%. We consider that a low dose such as 0.5 g administered every other day would be suitable in the treatment of these patients. In a continuous ambulatory peritoneal dialysis (CAPD)-patient, as much as 16% of 6315-S was detected in the dialysate in 24 h, suggesting that this drug would be useful against peritonitis occurring in such patients, by helping prevent the spread of infection due to persisting high serum levels. Seventeen patients with complicated urinary tract infections (UTI) were injected with 1g of 6315-S twice a day for 5 days. Of these, 14 cases were evaluable according to the criteria proposed by the Japanese UTI Committee. Overall clinical efficacy was 43%. In catheterized patients or cases of polymicrobial infection, the drug proved less effective. *E. faecalis* was eradicated, despite of *in vitro* study, but 6315-S was not effective against *P. aeruginosa* which agreed with basic studies. We observed no subjective or objective side-effects. These results suggest that 6315-S is useful and safe in urinary tract infections, with the exception of infections caused by *P. aeruginosa*.

6315-S (flomoxef : FMOX), an oxacephem newly synthesized at Shionogi Research Laboratories, Shionogi & Co., Ltd., Japan, is a derivative of latamoxef (LMOX). Various basic studies[1,2] have shown that it has strong antibacterial activity against both Gram-negative and -positive bacteria, whereas against the latter, LMOX—like other so-called third-generation cephems—is known to have only weak activity.

We report here our evaluation of 6315-S in

urinary tract infections (UTI) as a part of several cooperative studies performed in Japan.

I. MATERIALS AND METHODS

To determine the antibacterial activity of 6315-S, the minimum inhibitory concentration (MIC) of the drug was measured according to methods recommended by the Japanese Society of Chemotherapy. We examined 18 reference strains and 188 clinical isolates from the urinary tract. Of the 188 bacteria, species were : 89 of β-lactamase-producing *Escherichia coli* (*E. coli*), 29 of *Serratia marcescens* (*S. marcescens*), 25 of *Morganella morganii* (*M. morganii*), 7 of *Staphylococcus aureus* (*S. aureus*), 8 of *Staphylococcus epidermidis* (*S. epidermidis*), and 30 of *Enterococcus faecalis* (*E. faecalis*). Each bacterium was inoculated, at 100-fold dilution after overnight incubation in a broth. The MICs of 6315-S were compared with those of other cephems such as LMOX, cefazolin (CEZ), cefotiam (CTM), ceftizoxime (CZX), cefotaxime (CTX), cefmenoxime (CMX), cefbuperazone (CBPZ), cefotetan (CTT) and ceftriaxone (CTRX).

Bacterial regrowth with 1 MIC of 6315-S, or another cephem was also studied using a biophotometer (Bio-Log II).

In another study, serum concentrations of 6315-S were serially measured by bioassay, using *E. coli* 7437 strain as a test organism in 4 patients with chronic renal failure, who were being treated by hemodialysis (HD) 6 h/day, 3 times weekly. Just before the completion of regular HD, 0.5 g of 6315-S was injected in 20 ml of a 5% glucose solution. Blood samples were taken 5 min, 1 day and 2 days after injection. An additional 0.5 g was administered at the beginning of the next HD treatment, and serum samples taken again 5 min after HD, and on the two following days. In a cross-over, 1g of 6315-S was administered in the same manner 1 week later.

In another chronic renal failure patient on continuous ambulatory peritoneal dialysis (CAPD), 1g was injected i. v. every morning, and the discharged dialysate was sampled for 2 days. Concentration of the agent was assayed as were serum levels.

From May 1984 to May 1985, 6315-S was administered to 17 patients with chronic complicated UTI at our institutes. One gram of 6315-S in 20 ml of a 5% glucose solution was injected twice daily for 5 days. Urinalysis, bacterial studies and blood tests for cell counts, liver-function and electrolytes were performed before and after treatment. Subjective side-effects were also checked. Analysis of efficacy in UTI was conducted according to the criteria proposed by the Japanese UTI Committee[3].

II. RESULTS

A : Antibacterial activity of 6315-S *in vitro* : MICs of 6315-S and other cephems against 18 reference strains are presented in Table 1 and Fig. 1. As shown in Table 1, 6315-S showed strong activity against these bacteria except for *Pseudomonas* and *Acinetobacter*. In five β-lactamase-producing strains, it was found to work in the same manner as other cephems. Compared with LMOX, 6315-S was stronger against Gram-positive cocci, and the same or slightly weaker against Gram-negative rods.

The distribution of MICs and correlograms of 6315-S compared with other cephems against 89 clinical isolates of β-lactamase-producing *E. coli* are presented in Figs. 2 and 3. As shown in Fig. 2, MICs of 6315-S were less than 3.13 μg/ml. These values were better than those of LMOX and almost the same as those of CTX, CMX and CTRX.

Against *S. marcescens*, MICs of 6315-S were as widely distributed as those of LMOX and CTT. Antibacterial activity was shown to be weaker than that of CZX, CTX, CMX or CTRX (Figs. 4 and 5). Antibacterial activity of 6315-S was observed to be about average for third-generation cephems against *M. morganii*. Each strain was inhibited in growth by less than 3.13 μg/ml of 6315-S (Figs. 6 and 7).

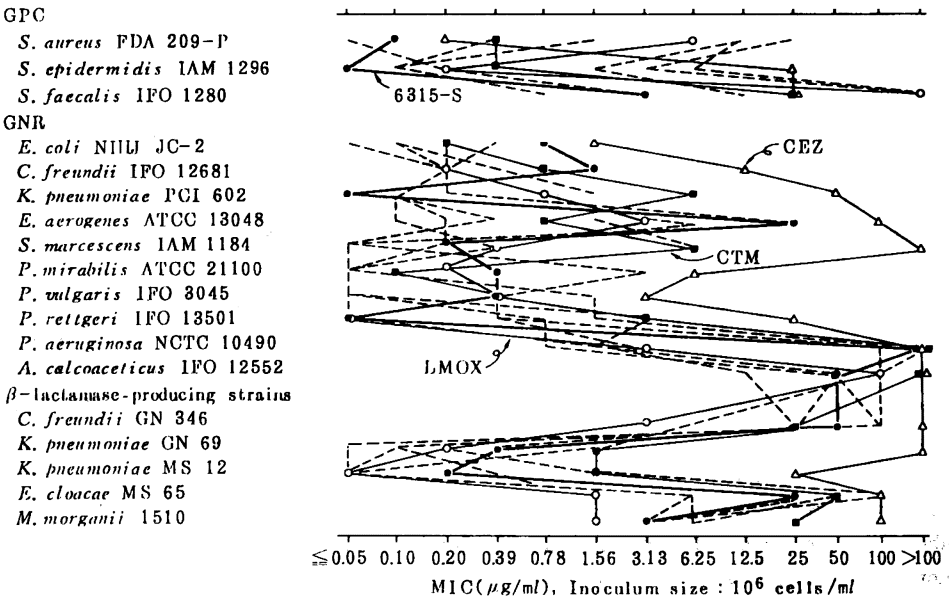
MICs were determined for 6315-S, LMOX, CEZ and CTM against Gram-positive cocci. 6315-S

Table 1 Antibacterial activities of cephems against reference strains

MIC : μg/ml, inoculum size : 10^6 cells/ml

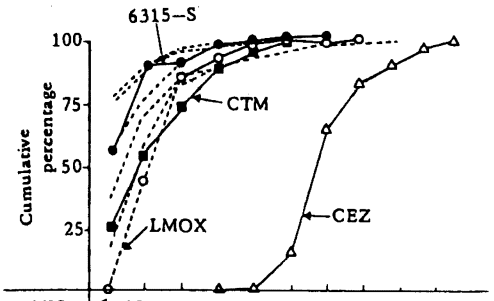
Strains	6315-S	LMOX	CEZ	CTM	CZX	CTX	CMX	CBPZ	CTT	CTRX
GPC										
S. aureus FDA 209-P	0.10	6.25	0.20	0.39	1.56	0.39	≦0.05	25	12.5	12.5
S. epidermidis IAM 1296	≦0.05	0.20	25	0.39	0.10	0.10	0.20	3.13	6.25	1.56
S. faecalis IFO 12580	3.13	>100	25	25	3.13	0.78	3.13	>100	>100	12.5
GNR										
E. coli NIHJ JC-2	0.78	0.20	1.56	0.20	≦0.05	0.10	0.20	0.39	0.39	0.10
C. freundii IFO 12681	1.56	0.20	12.5	0.78	0.20	0.20	0.20	0.20	0.20	0.39
K. pneumoniae PCI 602	≦0.05	0.78	50	6.25	0.10	0.10	0.10	0.20	0.20	1.56
E. aerogenes ATCC 13048	25	3.13	100	0.78	0.39	0.10	0.20	6.25	25	1.56
S. marcescens IAM 1184	0.20	0.39	>100	6.25	≦0.05	0.39	0.20	0.39	≦0.05	6.25
P. mirabilis ATCC 21100	0.39	0.20	6.25	0.10	≦0.05	≦0.05	≦0.05	≦0.05	3.13	0.10
P. vulgaris IFO 3045	0.39	0.39	3.13	0.39	≦0.05	≦0.05	≦0.05	1.56	0.39	0.39
P. rettgeri IFO 13501	≦0.05	≦0.05	25	3.13	≦0.05	0.78	3.13	1.56	0.39	0.39
P. aeruginosa NCTC 10490	>100	3.13	>100	>100	1.56	0.78	1.56	100	>100	3.13
A. calcoaceticus IFO 12552	50	100	>100	>100	12.5	50	50	100	100	50
β-lactamase-producing strains										
C. freundii GN 346	50	3.13	>100	25	25	25	12.5	6.25	100	100
K. pneumoniae GN 69	0.39	0.20	>100	1.56	0.10	≦0.05	≦0.05	1.56	0.20	0.10
K. pneumoniae MS 12	0.20	≦0.05	25	1.56	≦0.05	≦0.05	≦0.05	≦0.05	1.56	0.39
E. cloacae MS 65	25	1.56	100	50	6.25	6.25	3.13	12.5	100	50
M. morganii 1510	3.13	1.56	100	25	6.25	3.13	1.56	6.25	3.13	3.13

Fig. 1 Antibacterial activities of cephems against reference strains



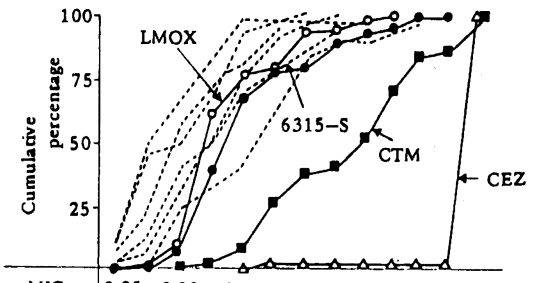
* Broken lines include so-called 3rd-generation cephems such as CZX, CTX, CMX, CBPZ, CTT and CTRX.

Fig. 2 Distribution of MICs of cephems against clinical isolates of β-lactamase-producing *E. coli* (89 strains)



MIC (μg/ml)	≦0.05	0.10	0.20	0.39	0.78	1.56	3.13	6.25	12.5	25	50
6315-S	52	29	1	5	1		1				
LMOX	1	37	39	6	3	2		1			
CEZ					1	17	42	14	9	4	2
CTM	2	27	25	22	8	3	2				
CZX	68	13	3	3		1	1				
CTX	66	13	5	2	2		1				
CMX	32	31	13	6	2	3	2				
CBPZ	5	32	33	11	3		4	1			
CTT	14	41	20	3	7	1		2	1		
CTRX	52	19	8	8	1		1				

Fig. 4 Distribution of MICs of cephems against clinical isolates of *S. marcescens* (29 strains)



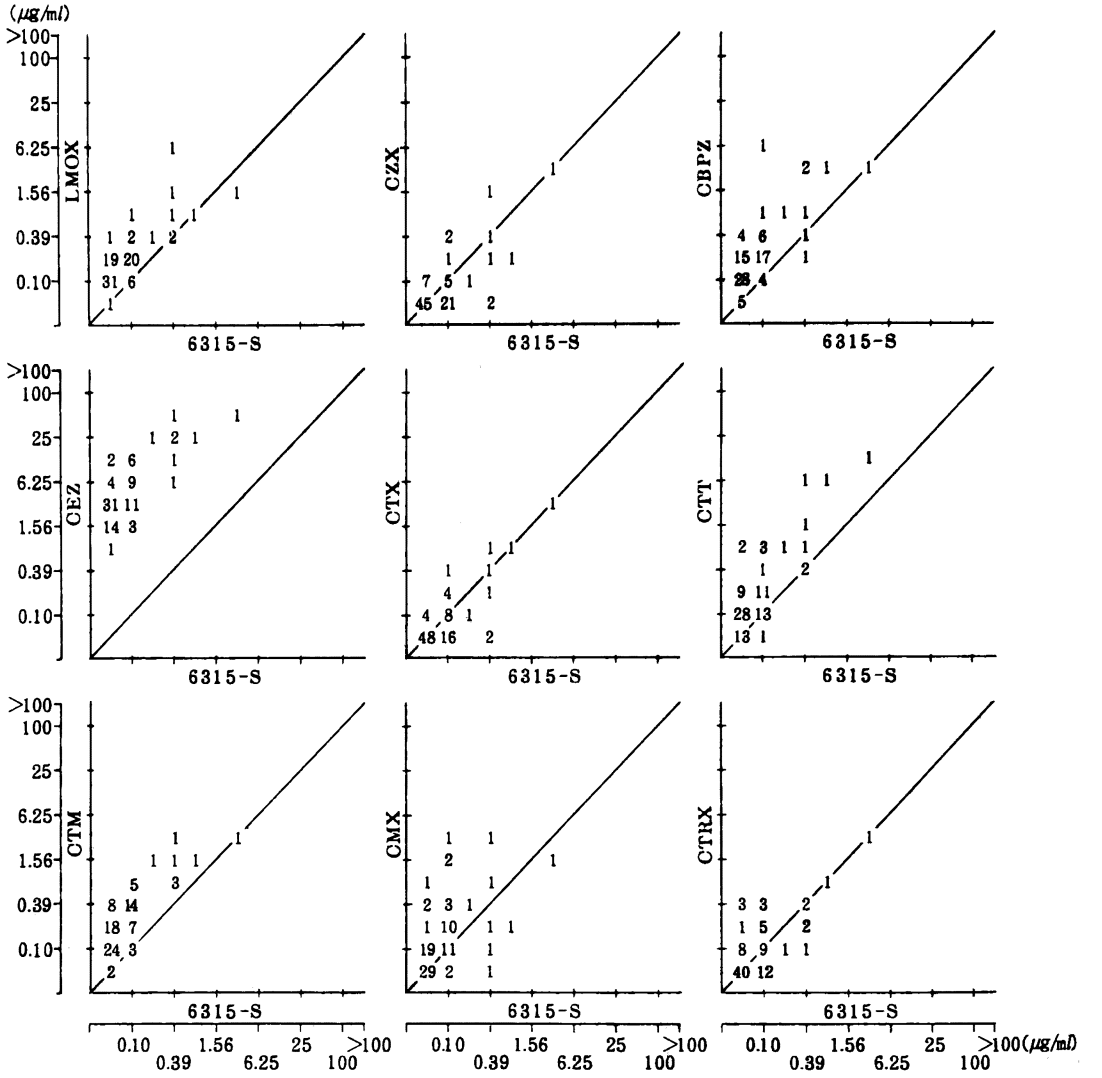
MIC (μg/ml)	0.05	0.10	0.20	0.39	0.78	1.56	3.13	6.25	12.5	25	50	100	>100
6315-S	1		2	8	8	4		3	1	1		1	
LMOX		1	2	15	4	1	4		1	1			
CEZ						1							28
CTM	1				1	7	2	1	3	4	5	1	4
CZX	3	11	5	5	4		1						
CTX	3	10	1	5	8	1		1					
CMX	2	4	10	4	3	4	2						
CBPZ	1	3	7	3	6	3	2	2	2				
CTT			7	2	3	5	7	2			1	1	1
CTRX	1	1	7	10	3	4	2		1				

was very effective against *S. aureus* and *S. epidermidis*, and much more so than LMOX (Figs. 8, 9, 10 and 11). It was, however, not effective *in vitro* against *E. faecalis*. More than 50 % of the strains showed MICs of 100 μg/ml for this drug (Figs. 12 and 13).

Bacterial regrowth curves were studied in concentrations of 1 MIC of 6315-S, LMOX, CEZ, CTM, and CTRX. In drug-free controls, *E. coli* NIHJ JC-2 (10^3 cells/ml) started to grow visibly at about 5 h and reached 10^9cells/ml levels at 10 h. With 1 MIC of 6315-S (0.78 μg/ml), the strain was inhibited in regrowth for about 10 h, the longest time among the drugs examined. Each drug acted bacteriocidally on *S. aureus* 209P at 1 MIC (Fig. 14). Against *S. epidermidis* IAM 1296, 1 MIC of 6315-S showed weak inhibitory action, slightly better than LMOX or CTRX, but weaker than CEZ. 6315-S showed a 10-hour inhibition compared with the control against *E. faecalis* IFO 12580, whereas, LMOX, CEZ and CTM were all bacteriocidal at this concentration (Fig. 15).

B : Pharmacokinetic studies in patients with chronic renal failure : In 4 patients with chronic renal failure being treated by HD, the time of injection was changed (pre-and post-HD) and serum concentrations of 6315-S were serially determined for 4 days (Fig. 16). In case B, urine volume was less than 500 ml/day, and in the other cases it was zero. In a cross-over, 0.5 g and 1g of the drug were administered to 3 patients (cases A, B and C). After 0.5 g injection, at the end of HD, peak serum levels of 6315-S were 83μg/ml on average, then gradually decreased and reached 9.3 μg/ml at 42 h, just before the next HD. When an additional 0.5 g was injected at the beginning of HD, serum levels reached 97 μg/ml 5 min later, then 87% of the drug was dialyzed. Seven days after the first injection, when no antibacterial activity in serum was confirmed, 1g was injected

Fig. 3 MIC correlograms between 6315-S and other cephems against β-lactamase-producing *E. coli*

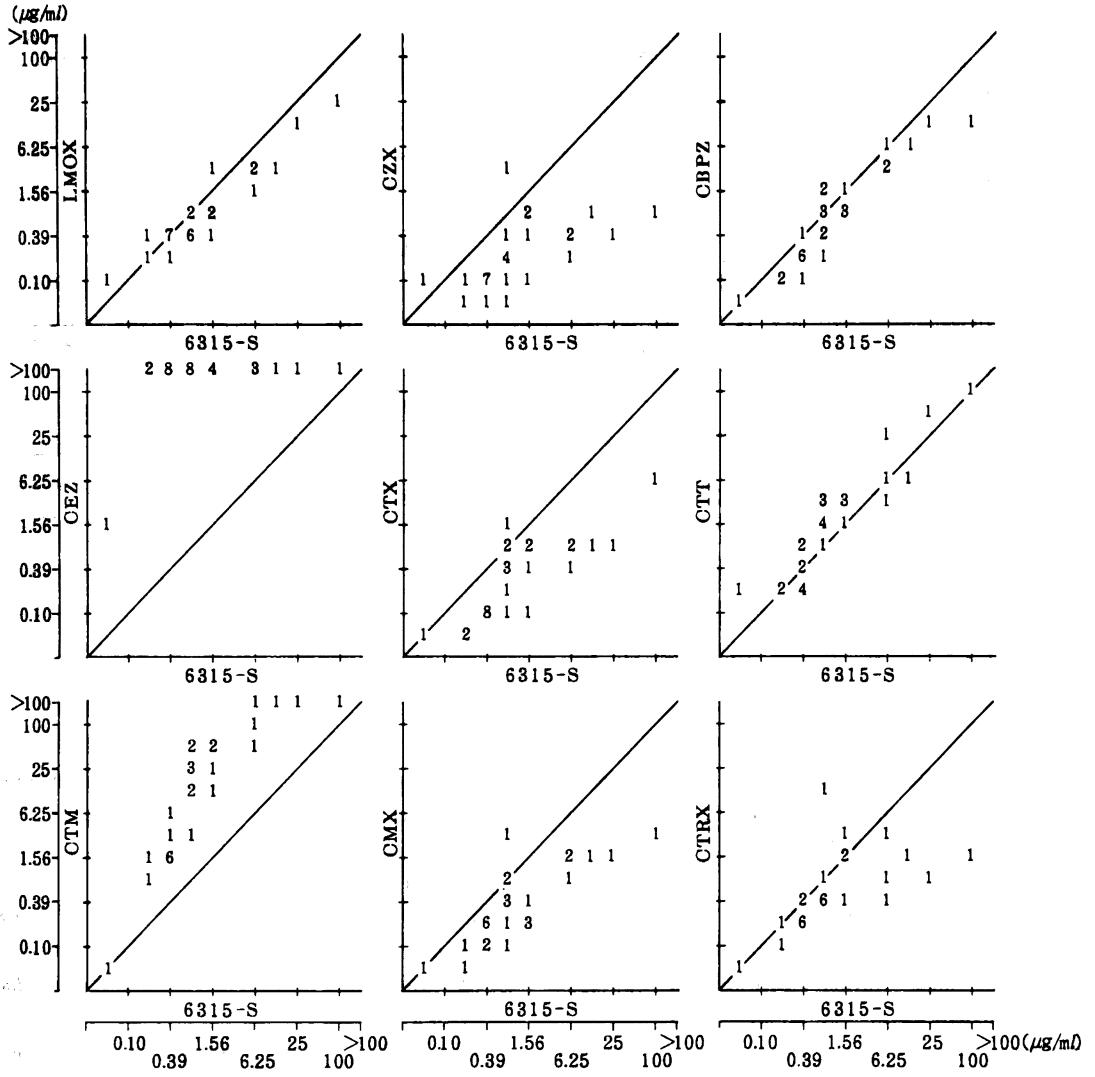


in the same manner. Peak serum levels were determined as 116 and 140 μg/ml, respectively, 5 min after the first and second injection (Fig. 16). A serum concentration of 15 μg/ml, about twice the amount after 0.5 g, was still observable two days after injection. The elimination rate by HD with this dosage was 80%.

In another patient undergoing CAPD, 6315-S levels in the dialysate were measured after a dose of 1g i. v. daily. On the first day, values ranged from 7.2 – 26 μg/ml and 16% of the 6315-S injected was eliminated. About 56% was recovered in 2 days. On both days, maximum concentrations were observed 2 – 10 h after administration (Table 2).

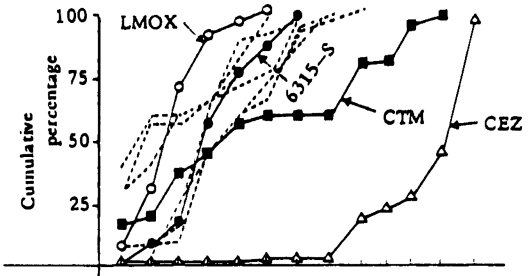
C : Clinical application of 6315-S against chronic complicated urinary tract infections : A total of 17 patients took part in this clinical trial.

Fig. 5 MIC correlograms between 6315-S and other cephems against *S. marcescens*



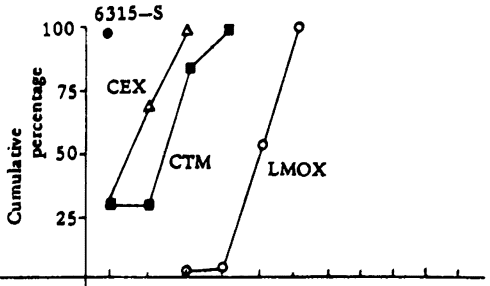
Of these, 14 cases were evaluable according to the criteria proposed by the Japanese UTI Committee. Case summaries are presented in Table 3. Overall clinical efficacy was : excellent 2, moderate 4 and poor 8 ; the overall efficacy rate being 43 % (6/14) (Table 4). By type of infection, groups 1 - 4 (monomicrobial infection) showed good effect ; the overall efficacy rate being 67%. But in polymicrobial infections (groups 5 and 6) no effect was observed (Table 5). Bacteriologically, 12 of 19 strains cultured before treatment were eradicated. Of these strains, all cocci, 5 of *E. coli*, and *K. pneumoniae* disappeared, but other Gram-negative rods persisted (Table 6). Five new strains appeared after treatment (Table 7). As shown in Table 3, no subjective side-effects were observed in any of the 17 patients. Laboratory tests showed deterioration in 9 cases, but this was

Fig. 6 Distribution of MICs of cephems against clinical isolates of *M. morganii* (25 strains)



MIC (μg/ml)	0.05	0.10	0.20	0.39	0.78	1.56	3.13	6.25	12.5	25	50	100	>100
6315-S	1	1	3	9	5	2	4						
LMOX	2	6	10	5	1	1							
CEZ	1								4	1	1	5	13
CTM	4	1	4	3	2	1			5		4	1	
CZX	7	3	5	1	2	1	4	1	1				
CTX	10	5		1	4	5							
CMX	2		2	12	6	1	2						
CBPZ	1	1	1	9	4	3	3	3					
CTT	1		5	6	3	2	7	1					
CTRX	7	7		2	3		6						

Fig. 8 Distribution of MICs of cephems against clinical isolates of *S. aureus* (7 strains)



MIC (μg/ml)	≦0.20	0.39	0.78	1.56	3.13	6.25	12.5	25	50	100	>100
6315-S	7										
LMOX				1	3	3					
CEZ	2	3	2								
CTM	2		4	1							

thought to be due to the patients' basic diseases. No bleeding tendency was established by thrombotest or normotest (Table 8).

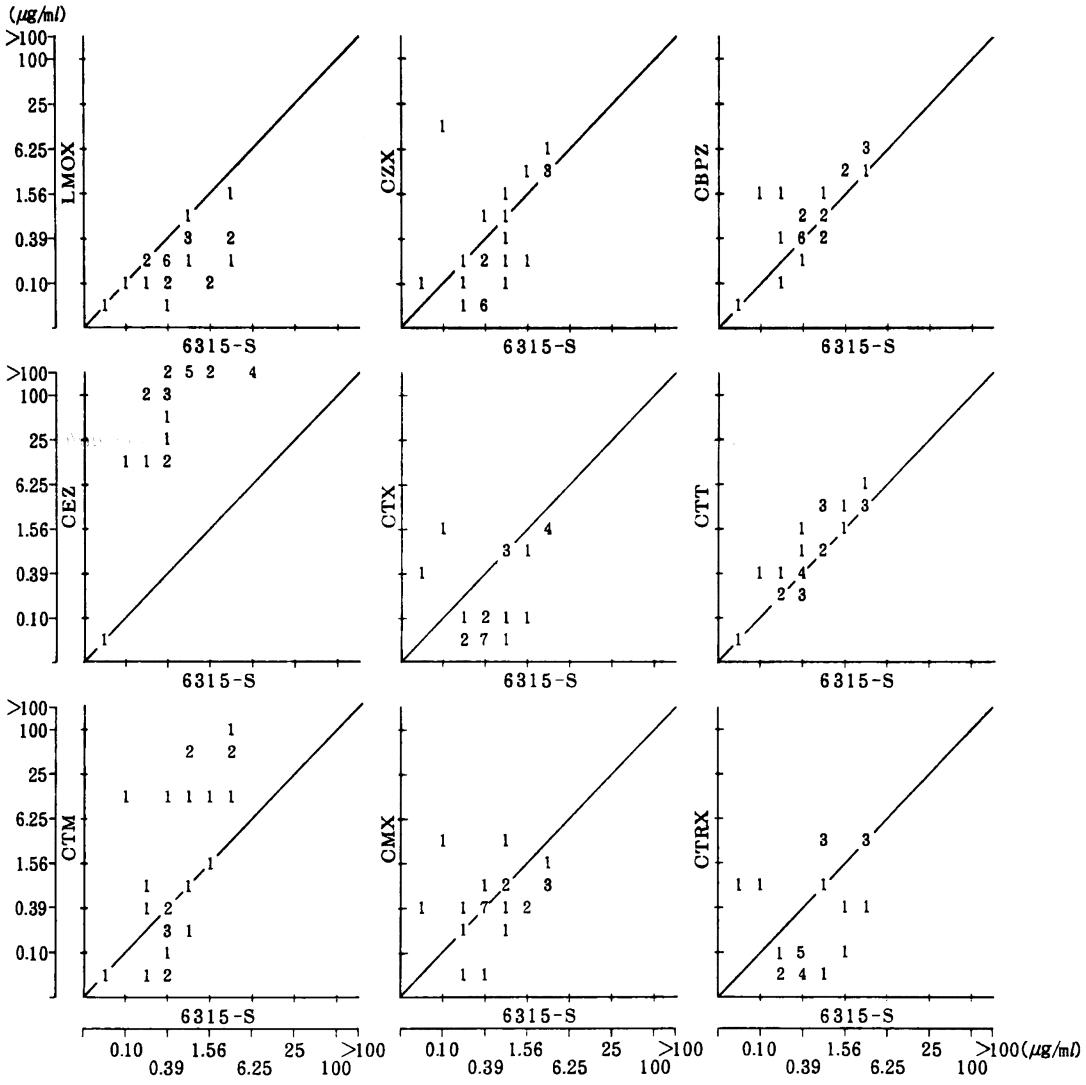
Ⅲ. DISCUSSION

6315-S, a derivative of latamoxef (LMOX), seems to have antibacterial activity against Gram-positive cocci, and potency against Gram-negative rods equal to that of other so-called third-generation cephems[1,2] Its pharmacokinetics have been studied by YASUNAGA *et al.*[4]. According to these studies, 6315-S may be of use against UTI as well as in other fields. In this report, a part of a cooperative study, we present our findings on 6315-S for the evaluation of its usefulness in the urological field.

In vitro studies on its antibacterial activity demonstrated that 6315-S was potent against both Gram-positive and -negative bacteria, except for *E. faecalis* and *Pseudomonas* spp. These effects were stronger than those of LMOX against Gram-positive cocci and average for third-generation cephems against Gram-negative rods. These phenomena were also confirmed in a biophotometric study. Supposing due to the low value of 1 MIC, 6315-S could not act bacteriocidally against *S. epidermidis* and *E. faecalis*, whereas CEZ did.

Serum levels in patients with chronic renal failure showed interesting results. In the study of YASUNAGA *et al.*[4], peak serum levels after 0.5 g and 1 g i.v. injection were 39 and 102 μg/ml, respectively, and at 6 h after injection serum levels of 6315-S were traced at both doses. More than 80 % of the drug was secreted in the urine. In our study, if the daily urine volume was 0, serum levels were higher than 10 μg/ml even two days after 0.5 g injection, the same value as at 1 h in normal controls. With 1 g injection, serum levels on the second day were equivalent to the 2-h value

Fig. 7 MIC correlograms between 6315-S and other cephems against *M. morganii*



in healthy volunteers. The drug was confirmed as being easily dialyzed, and the protein-binding rate was therefore thought to be very low. Indeed, Shionogi Research Laboratories, have reported this as being 35%[1]. These results support our findings that in HD patients, 0.5 g of 6315-S every other day is a sufficient dose from the viewpoint of serum levels.

On the other hand, the drug moved easily into the ascitic fluid in a CAPD patient, even in the absence of infection. This drug may therefore be a good choice for patients with the peritonitis often experienced in such cases. Moreover, the high serum levels would help prevent spread of the disease.

The results of our clinical trial were not completely satisfactory. Only 43% clinical efficacy was observed in 14 evaluable cases. This was

Fig. 9 MIC correlograms between 6315-S and other cephems against *S. aureus*

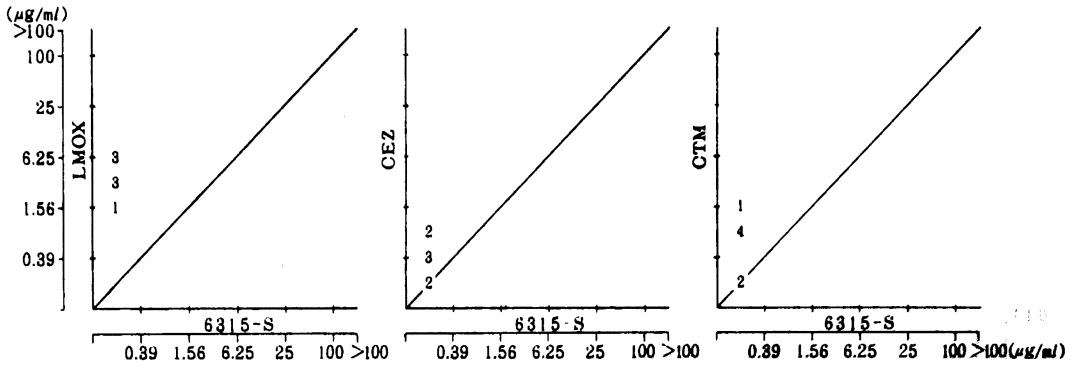


Fig.11 MIC correlograms between 6315-S and other cephems against *S. epidermidis*

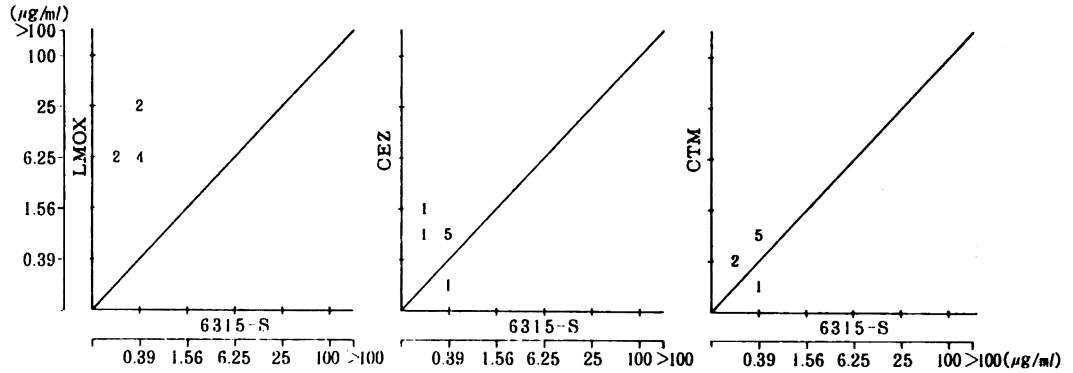
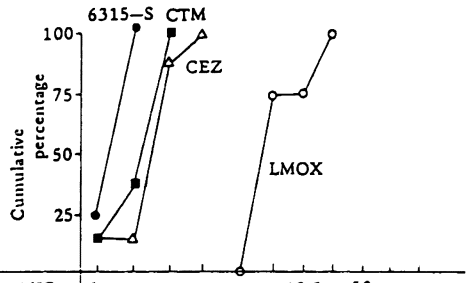
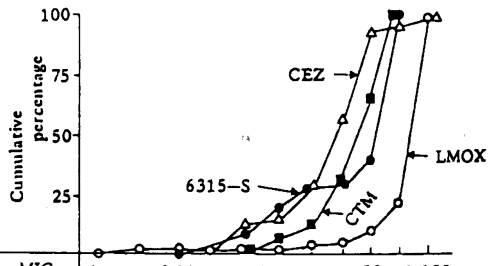


Fig.10 Distribution of MICs of cephems against clinical isolates of *S. epidermidis* (8 strains)



MIC (μg/ml)	≦0.20	0.39	0.78	1.56	3.13	6.25	12.5	25	50	100	>100
6315-S	2	6									
LMOX						6		2			
CEZ	1			6	1						
CTM	1		2		5						

Fig.12 Distribution of MICs of cephems against clinical isolates of *E. faecalis* (30 strains)



MIC (μg/ml)	≦0.20	0.39	0.78	1.56	3.13	6.25	12.5	25	50	100	>100
6315-S			1	2	3	3			3	18	
LMOX	1							1	3	4	23
CEZ					4	1	4	8	11	1	1
CTM			1			1	2	5	11	10	

Fig.13 MIC correlograms between 6315-S and other cephems against *E. faecalis*

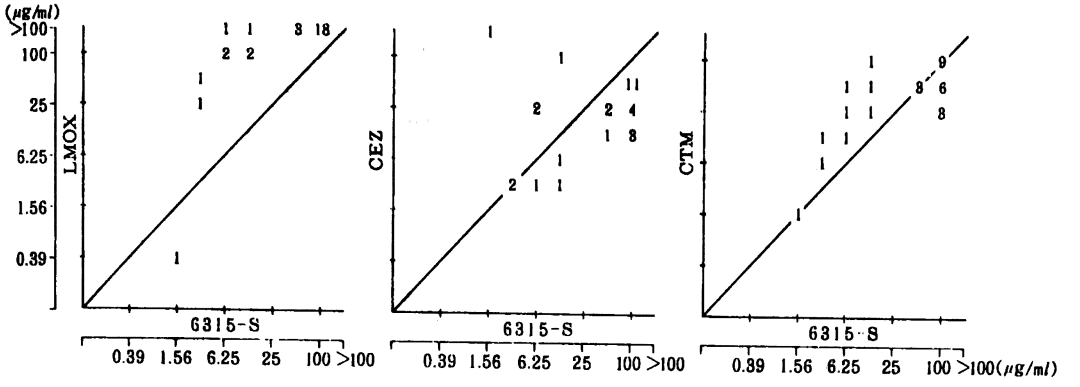


Fig.14 Growth inhibition of cephems including 6315-S at a concentration of 1 MIC against *E. coli* and *S. aureus*

	MIC(μg/ml)				
	6315-S	LMOX	CEZ	CTM	CTRX
E. coli NIHJ JC-2	0.78	0.20	1.56	0.20	0.10
S. aureus 209-P	0.10	6.25	0.20	0.39	12.5

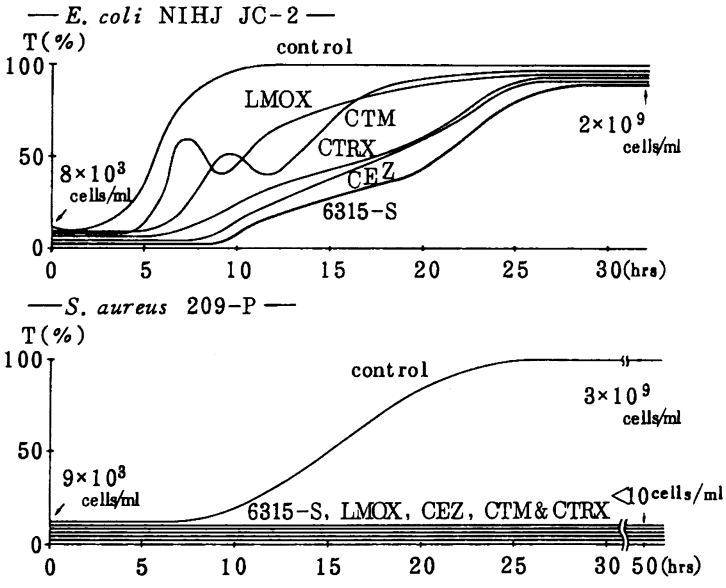
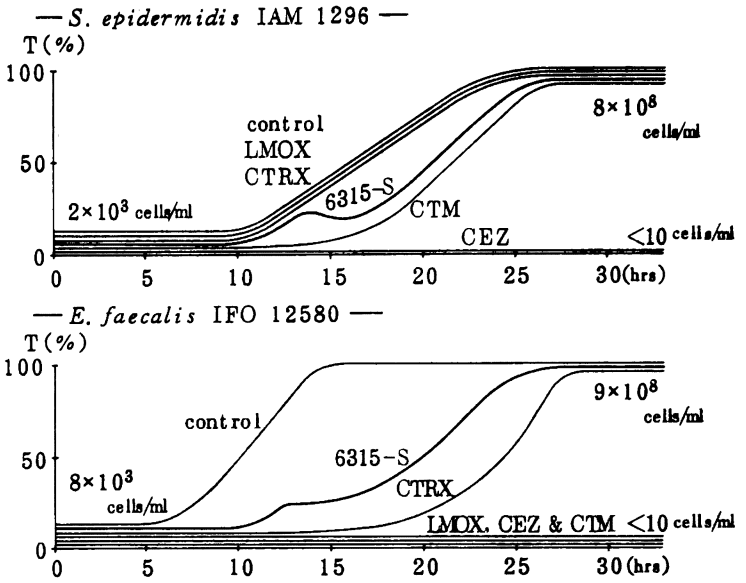


Fig.15 Growth inhibition of cephems including 6315-S at a concentration of 1 MIC against *S. epidermidis* and *E. faecalis*

	MIC (μg/ml)				
	6315-S	LMOX	CEZ	CTM	CTRX
S. epidermidis IAM 1296	≦0.05	0.20	25	0.89	1.56
E. faecalis IFO 12580	3.13	100<	25	25	12.5



mainly due to ineffectiveness in catheterized patients or in cases of polymicrobial infection, in which situations *P. aeruginosa* or *E. faecalis* are frequently isolated. In spite of an *in vitro* study, all three strains of *E. faecalis* could be eradicated. But the drug was ineffective against *P. aeruginosa* ; of five isolated strains four persisted. No subjective or objective side-effects, including bleeding tendency or antabuse like action, were experienced.

These results suggest 6315-S may be very useful in UTIs due to both Gram-positive and -negative bacteria, and have a high degree of safety. We would, however, caution against its use if *P. aeruginosa* is isolated.

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References

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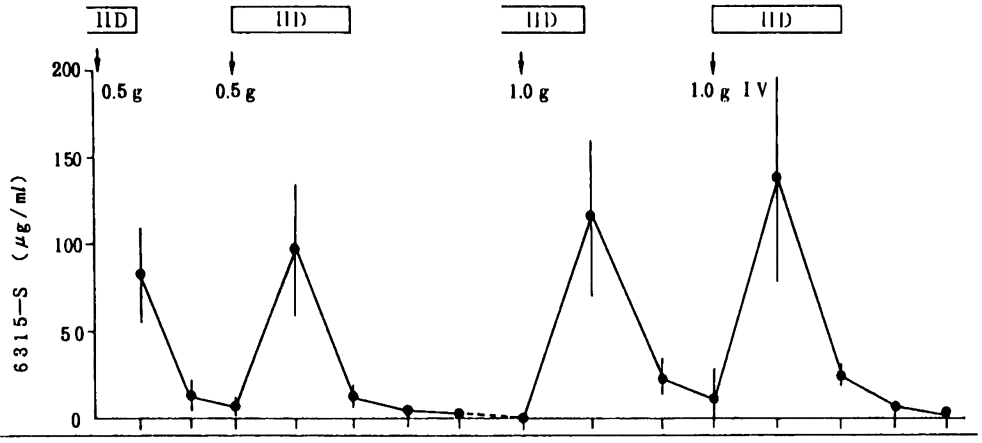
Fig.16 Serum 6315-S levels in patients with chronic renal failure



Case	0	1/12	24	42	42 1/12	48	72	90	168	168 1/12	192	216	216 1/12	222	230	254
A	0	86	22	15	104	16	8.6	3.2	0	170	36	32	210	32	7.8	6.2
B	0	54	4.7	2.0	58	7.6	2.3	0.64	0	100	15	3.7	120	22	4.5	1.6
C	0	110	13	11	130	11	5.6	2.4	0	130	22	15	150	22	7.2	4.0
D									0	62	12	10	80			
mean	0	83	13	9.3	97	12	5.5	2.1	0	116	21	15	140	25	6.5	3.9

Table 2 Secretion to dialysate of daily injected 6315-S in a patient on continuous ambulatory peritoneal dialysis (CAPD)

No.	Day-Time	Time after 1st injection	CAPD-dialysate Concentration (μg/ml)	Volume (ml)	Total dose (mg)	Remarks
1	0 -10:00	-20m	0	2,100	0	
2	-10:20	0				1g IV
3	-12:38	2h 18m	19	2,480	47	
4	-20:22	10h 02m	26	2,100	55	
5	1 - 0:21	14h 01m	7.2	2,450	18	
6	- 8:27	22h 07m	18	2,250	41	
7	-10:30	24h 10m				1g IV
8	-12:27	26h 07m	29	2,500	73	
9	-20:25	34h 05m	130	2,020	260	
10	2 - 0:22	38h 02m	15	2,610	39	
11	-10:10	47h 50m	7.6	2,100	16	

Urine volume per day of the patient is 0 ml

Table 3－1 Clinical summary of complicated UTI cases treated with 6315－S

Case No.	Age	Sex	Diagnosis* / Underlying condition	Catheter (route)	UTI group	Treatment: Dose (g×/day)	Route	Duration (day)	Symptoms**	Pyuria**	Bacteriuria**: Species	Count	MIC	Evaluation***: UTI	Dr.	Side-effects
1	59	M	C. C. C. / Renal Tumor	(+) (urethra)	G-1	1.0×2	I.V.	5	－／－	7－8／10－15	*K. pneumoniae*／*P. aeruginosa* *E. faecalis*	10^7／10^7		Poor	Poor	－
2	75	F	C. C. C. / Neurogenic bladder	(+) (urethra)	G-1	1.0×2	I.V.	5	－／－	＋／＋	*P. aeruginosa*／*S. marcescens*	10^5／10^7	400<／400<	Poor	Poor	－
3	64	M	C. C. C. Postprostatectomy UTI / B. P. H.	(+) (urethra)	G-1	1.0×2	I.V.	5	－／－	＋／20－30	*S. aureus*／No growth	10^5／	400<	Moderate	Excellent	－
4	73	M	C. C. C. Postprostatectomy UTI / Prostate cancer B. P. H.	(－)	G-2	1.0×2	I.V.	5	－／－	＋＋／＋＋＋	*P. aeruginosa*／*P. aeruginosa*	10^7／10^7		Poor	Fair	－
5	76	M	C. C. C. Postprostatectomy UTI / B. P. H.	(－)	G-2	1.0×2	I.V.	5	－／－	＋＋／5－10	*E. faecalis*／No growth	10^4／		Moderate	Excellent	－
6	72	F	C. C. P. / Lt.－renal pelvic tumor	(－)	G-3	1.0×2	I.V.	5	＋／－	20－30／0－1	*E. coli*／No growth	10^7／	≧0.20	Excellent	Excellent	－
7	36	F	C. C. P. / Rt.－renal stone	(－)	G-3	1.0×2	I.V.	5	＋／－	5－10／7－10	*E. coli*／No growth	10^5／		Moderate	Excellent	－

* C. C. C. : Chronic complicated cystitis
C. C. P. : Chronic complicated pyelonephritis
B. P. H. : Benign prostatic hypertrophy

** Before treatment / After treatment

*** UTI : Criteria proposed by the UTI Committee
Dr. . Dr's evaluation

Table 3 — 2 Clinical summary of complicated UTI cases treated with 6315-S

Case No.	Age	Sex	Diagnosis* / Underlying condition	Catheter (route)	UTI group	Treatment: Dose (g×/day)	Route	Duration (day)	Symptoms**	Pyuria**	Bacteriuria**: Species	Count	MIC	Evaluation***: UTI	Dr.	Side-effects
8	65	F	C.C.C. / Bladder tumor	(-)	G-4	1.0×2	I.V.	5	- / -	## / 15-20	α-hemolytic streptococcus / No growth	10^6 /	400< /	Moderate	Good	-
9	61	F	C.C.C. / Neurogenic bladder	(-)	G-4	1.0×2	I.V.	5	- / -	17-20 / 1-3	*E. coli* / No growth	10^7 /	400< /	Excellent	Excellent	-
10	91	F	C.C.P. / Urinary diversion Bladder tumor	(+) (ureter)	G-5	1.0×2	I.V.	5	# / +	# / 5-6	*E. coli* *P. aeruginosa* / *P. aeruginosa* *E. faecium*	10^7 / 10^7	0.39 400< / 400< 400<	Poor	Fair	-
11	63	M	C.C.P. / Urinary diversion	(+) (condnit)	G-5	1.0×2	I.V.	5	+ / ±	20-25 / #	*P. aeruginosa* *E. faecalis* / *P. aeruginosa*	10^7 / 10^7	/	Poor	Good	-
12	88	M	C.C.C. Postprostatectomy UTI / B.P.H.	(+) (urethra)	G-5	1.0×2	I.V.	5	- / -	25 / 25-30	*E. coli* *P. aeruginosa* / *P. aeruginosa*	10^7 / 10^7	400< 400< / 400<	Poor	Poor	-
13	83	F	C.C.C. / Neurogenic bladder	(+) (urethra)	G-5	1.0×2	I.V.	5	- / -	5-7 / 2-3	*E. cloacae* *E. faecalis* / *E. cloacae*	10^7 / 10^7	≤0.20 0.78 / 400<	Poor	Fair	-
14	84	M	C.C.C. Postprostatectomy UTI / B.P.H. Bladder stone	(-)	G-6	1.0×2	I.V.	5	+ / +	+ / 3-4	*S. marcescens* NF-GNR**** / *P. aeruginosa* *S. marcescens* NF-GNR****	10^7 / 10^7	400< 400< / 50 400< 400<	Poor	Poor	-
15	65	M	C.C.C. / B.P.H.	(-)		1.0×2	I.V.	5	+ / +	15-20 / #	No growth / No growth	/	/	Not evaluable	Unknown	-
16	77	M	C.C.P. / Neurogenic bladder	(+) (urethra)		1.0×2	I.V.	5	+ / +	# / #	Fungi / No growth	/	/	Not evaluable	Poor	-
17	76	F	C.C.C. / Neurogenic bladder	(-)		1.0×2	I.V.	5	- / ±	/	Not tested / *P. aeruginosa*	/ 10^7	/	Not evaluable	Unknown	

* C.C.C.: Chronic complicated cystitis; C.C.P.: Chronic complicated pyelonephritis; B.P.H.: Benign prostatic hypertrophy

** Before treatment / After treatment

*** UTI: Criteria proposed by the UTI Committee; Dr.: Dr's evaluation

**** NF-GNR: Glucose non-fermentative Gram-negative rods except for *P. aeruginosa*

Table 4 Overall clinical efficacy of 6315-S in complicated UTI (1 g×2/day, 5-day treatment)

Pyuria / Bacteriuria	Cleared	Decreased	Unchanged	Effect on bacteriuria
Eliminated	2	2	2	6 (43%)
Decreased				0
Replaced			2	2 (14%)
Unchanged	1	1	4	6 (43%)
Effect on pyuria	3 (21%)	3 (21%)	8 (57%)	Patient total 14

Excellent	2	Overall effectiveness rate 6/14 (43%)
Moderate	4	
Poor(including Failure)	8	

Table 5 Overall clinical efficacy of 6315-S classified by type of infection

Group		No. of patients	(Percent of total)	Excellent	Moderate	Poor	Overall effectiveness rate
Monomicrobial infection	1 st group (Catheter indwelt)	3	(21)		1	2	33%
	2 nd group (Post prostatectomy)	2	(14)		1	1	50%
	3 rd group (Upper UTI)	2	(14)	1	1		100%
	4 th group (Lower UTI)	2	(14)	1	1		100%
	Sub total	9	(64)	2	4	3	67%
Polymicrobial infection	5 th group (Catheter indwelt)	4	(29)			4	0%
	6 th group (No Catheter indwelt)	1	(7)			1	0%
	Sub total	5	(36)	0	0	5	0%
Total		14	(100)	2	4	8	43%

Table 6 Bacteriological response to 6315-S in complicated UTI

Isolates	No. of strains	Eradicated (%)	Persisted
S. aureus	1	1 (100)	
E. faecalis	3	3 (100)	
α-hemolytic Streptococcus	1	1 (100)	
E. coli	5	5 (100)	
K. pneumoniae	1	1 (100)	
E. cloacae	1	0	1
S. marcescens	1	0	1
P. aeruginosa	5	1 (20)	4
NF-GNR	1	0	1
Total	19	12 (63)	7

Table 7 Strains appearing after 6315-S treatment in complicated UTI

Isolates	No. of strains	(%)
E. faecium	1	(20)
E. faecalis	1	(20)
S. marcescens	1	(20)
P. aeruginosa	2	(40)
Total	5	(100)

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Table 8 Changes in laboratory test results

Item	Total No. of patients evaluated	Doctor's evaluation								
		Aggravated (Relation to the drug)							Unchanged	Improved
		Definite	Probable	Possible	Subtotal	Probably not	Definitely not	Subtotal		
RBC	17				0		1	1	16	
Hb	17				0		2	2	15	
Ht	17				0		2	2	15	
WBC	17				0	2		2	15	
Thrombocytes	15				0			0	15	
S-GOT	17				0	1	1	2	15	
S-GPT	17				0	1	1	2	15	
Al-P	17				0			0	17	
T-Bil	14				0			0	14	
BUN	16				0	1		1	15	
S-Cr	17				0		1	1	16	
Na	17				0		1	1	16	
K	17				0			0	17	
Cl	17				0			0	17	
Thrombo test	2				0			0	2	
Normo test	2				0			0	2	
No. of patients with aggravated laboratory test results		0				9				

泌尿器科領域における新合成オキサセフェム系抗生剤 6315-S (Flomoxef) の検討

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新しく合成されたオキサセフェム系抗生物質 6315-S (Flomoxef) の尿路感染症に対する有用性を評価するために，本剤の抗菌力，腎不全患者における体内動態，臨床応用の検討を行なった。6315-S は，標準株，臨床分離株（合計 206 株）に対する MIC の検討では，*P. aeruginosa*, *E. faecalis* を除き，グラム陽性・陰性菌を問わず優れた成績であった。腎不全患者の血中 6315-S 濃度は，投与後 2 日目でも，健常人の 2 時間値と同様の値を維持していた。6 時間の血液透析にて 80%の本剤が透析されることも判明した。このことは，こうした病態の患者での投与量および投与間隔に一考を要するものと思われた。14 名の慢性複雑性尿路感染症に対して 6315-S 1 g/回× 2 回/日，5 日間の静注を行なって薬効評価を行なった。総合臨床効果は 43%と低かったが，これはカテーテル留置例および複数菌感染症に無効のためであった。抗菌力検討の結果と異なり，*in vivo* では，*E. faecalis* は全て除菌できたが，*P. aeruginosa* の 80%は残存した。自・他覚的副作用は認めなかった。

以上より，*P. aeruginosa* を原因菌としない尿路感染症には，本剤は安全に使用しうるものと考えられた。また，球菌，桿菌を問わない点は，注目されるべきだと思われた。