CLINICAL EVALUATION OF PIVAMPICILLIN IN THE FIELD OF UROLOGY

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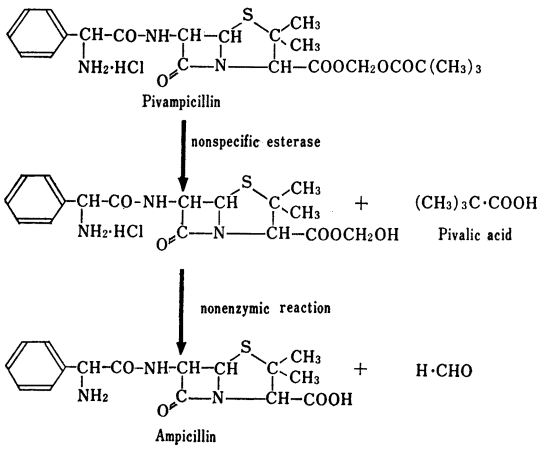
Pivampicillin is a new synthetic penicillin developed by Leo Pharmaceutical Products, Denmark (Fig. 1). Its antibacterial spectrum is similar to that of ampicillin, and its blood level is said to be 2~3 times higher than that of ampicillin after the oral administration. The present paper deals with the results of blood level and urinary concentration of the antibiotic in humans compared with those of ampicillin, as well as the clinical experiments in 46 cases of urinary tract infections.

Fig. 1 Structural formula of pivampicillin



Fundamental Studies

Concentrations of pivampicillin and ampicillin in body fluids were measured by cup plate method with *Bacillus subtilis* ATCC 6633 as the test organism, using heart infusion medium of nutrient agar Difco adjusted to pH 7.2. The judgement was made after 18-hour incubation, with phosphate buffer (pH 7.2) to make a standard curve.

Pivampicillin 125 mg (equivalent potency to ampicillin) and ampicillin 250 mg (potency) were aministered orally at an empty stomach to 5 healthy adults (males, 20~22 years), as well as pivampicillin 125 mg (equivalent potency to ampicillin) after meal respectively once, to compare the blood levels and excretion in urine by cross over method. The measurement was made 1 hour, 2 hours, 4 hours and 6 hours after the administration.

Pivampicillin 125 mg administered before meal was well absorbed, exhibiting a blood level higher than that of ampicillin 250 mg administered before meal. The highest levels of two antibiotics were observed 2 hours after the administration, the concentration being 1.38 and 1.14 mcg/ml respectively (Fig. 2 and 3).

When pivampicillin was administered after meal, the absorption was slightly delayed, the peak level being 60% of that administered before meal (Fig. 4).

As to the excretion in urine, the recovery portions of both drugs were mostly excreted during the first 6 hours after the administration, the amounts and rates being 60.99 mg, 48.7% (before meal), 51.0 mg, 40.8% (after meal) with pivampicillin and 62.0 mg, 24.8 % with ampicillin (before meal) (Table 1 and 2, Fig. 5, 6 and 7).

Clinical studies

Forty-six patients (28 cases of acute cystitis, 7 cases of pyelonephritis, 7 cases of gonorrhoea and 4 cases of prostatitis) were treated by pivampicillin at a daily dose of 500~2,000 mg for 3~30 days (Table 3).

Bacteria were eradicated in all but one patient (Table 4 and 5), though white blood corpuscles in urine or pus persisted after the treatment in 13 patients (Table 3).

Adequate dose for acute and simple urinary tract infections, such as acute cystits or gonorrhoea, would be 500 mg daily (Table 3, 4 and 6).

Fig. 2 Serum concentration of pivampicillin 125 mg orally (before meal)

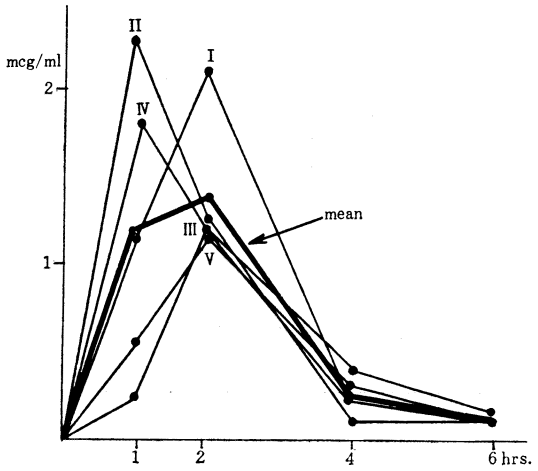


Fig. 3 Serum concentration of ABPC 250 mg orally (before meal)

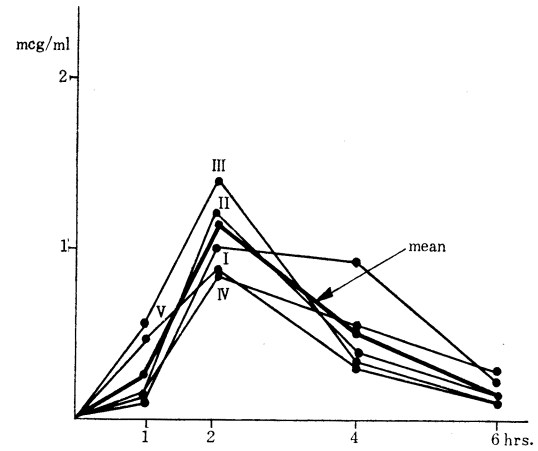


Fig. 4 Serum concentration of pivampicillin and ABPC

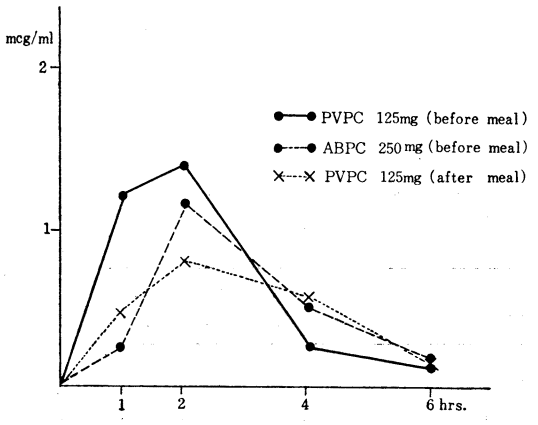


Table 1 Urinary excretion of pivampicillin 125mg orally (before meal)

	2	4	6	Total (%)
A	24.0mg (19.2%)	34.8mg (27.8%)	5.8mg (4.6%)	64.6mg (51.7%)
B	59.5mg (47.6%)	14.3mg (11.4%)	2.9mg (2.3%)	76.7mg (61.4%)
C	10.6mg (8.5%)	29.9mg (23.9%)	6.2mg (5.0%)	46.7mg (37.4%)
D	15.4mg (12.3%)	52.5mg (42.0%)	7.5mg (6.0%)	75.4mg (60.3%)
E	18.8mg (15.0%)	11.1mg (8.9%)	11.3mg (9.0%)	41.2mg (33.0%)
Mean	25.7mg (20.6%)	28.5mg (22.8%)	6.7mg (5.4%)	60.9mg (48.7%)

Fig. 5 Urinary excretion of pivampicillin of 125 mg orally (before meal)

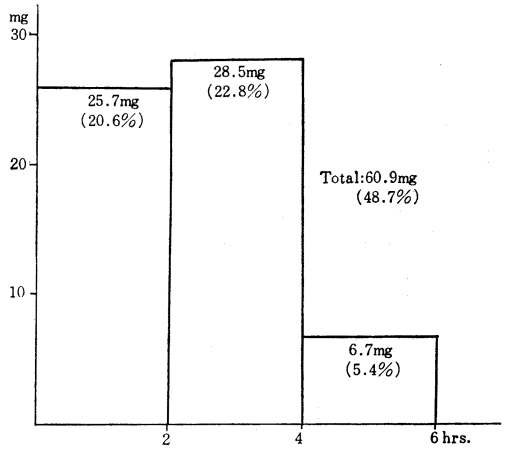


Table 2 Urinary excretion of ABPC 250mg orally (before meal)

	2	4	6	Total (%)
A	7.8mg (3.1%)	61.2mg (24.5%)	22.0mg (8.8%)	91.0mg (36.4%)
B	11.2mg (4.5%)	27.1mg (10.8%)	17.5mg (7.0%)	55.8mg (22.3%)
C	15.0mg (6.0%)	26.2mg (11.5%)	3.3mg (1.3%)	44.5mg (17.8%)
D	10.5mg (4.2%)	40.8mg (16.3%)	20.0mg (8.0%)	71.3mg (28.5%)
E	22.8mg (9.1%)	13.8mg (5.5%)	11.0mg (4.4%)	47.6mg (19.0%)
Mean	13.5mg (5.4%)	33.8mg (13.5%)	14.8mg (5.9%)	62.0mg (24.8%)

Table 3 Effect of pivampicillin on urinury tract infections (1)

Case	Age & sex	Diagnosis	Before treatment				Dose	After treatment			Result
			Symptom	Leukocyte	Bacteria	Culture		Leukocyte	Bacteria	Symptom	
1	28 ♀	Acute cystitis	Pain on urination, pollakisuria	+++	Rod	*E. coli*	0.5g×7days	−	−	−	Excellent
2	21 ♀	〃	Pain on urination, hematuria	+++	Rod	*E. coli*	0.5g×7days	−	−	−	Excellent
3	25 ♀	〃	Pain on urination, pollakisuria	3~4	Rod	*E. coli*	0.75g×10days	−	−	−	Excellent
4	28 ♀	〃	〃	++	Rod	*E. coli*	0.75g×7days	−	−	−	Excellent
5	50 ♀	〃	〃	+++	Rod	*E. coli*	0.75g×10days	−	−	−	Excellent
6	75 ♀	〃	〃	4~5	Rod	*E. coli*	0.75g×14days	−	−	−	Excellent
7	25 ♀	〃	〃	++	Rod	*E. coli*	1.0g×7days	7	−	Pain on urination, pollakisuria	Good
8	61 ♀	〃	〃	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
9	60 ♀	〃	〃	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
10	42 ♀	〃	Pain on urination, hematuria	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
11	60 ♀	〃	〃	8	Rod	*E. coli*	1.0g×7days	−	−	−	Execellent
12	25 ♀	〃	Pain on urination, pollakisuria	7	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
13	25 ♀	〃	Pain on urination, hematuria	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
14	54 ♀	〃	Pain on urination pollakisuria	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
15	31 ♀	〃	Pain on urination, hematuria	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
16	27 ♀	〃	〃	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent

Table 3 Effect of pivampicillin on urinary tract infections (2)

Case	Age & sex	Diagnosis	Before treatment				Dose	After treatment			Result
			Symptom	Leukocyte	Bacteria	Culture		Leukocyte	Bacteria	Symptom	
17	29 ♀	Acute cystitis	Pain on urination, hemturia	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
18	27 ♀	〃	Pain on urination, pollakisuria	+++	Rod	*E. coli*	1.0g×7days	−	−	−	Excellent
19	23 ♀	〃	〃	30	Rod	*E. coli*	2.0g×7days	−	−	−	Excellent
20	45 ♀	〃	〃	+++	Rod	*E. coli*	0.5g×5days	−	−	−	Excellent
21	29 ♀	〃	Pollakisuria, feeling of residual urine	+++	Coccus	*Staphylo-coccus*	0.5g×7days	−	−	−	Excellent
22	24 ♀	〃	Pain on urination, pollakisuria	+	Coccus	*Staphylo-coccus*	0.75g×7days	−	−	−	Excellent
23	29 ♀	〃	Pollakisuria, feeling of residual urine	+++	Coccus	*Staphylo-coccus*	1.0g×7days	0~3	−	−	Excellent
24	22 ♀	〃	Pain on urination, pollakisuria	+++	Coccus	*Staphylo-coccus*	1.0g×7days	−	−	−	Excellent
25	33 ♀	〃	〃	++	Coccus	*Strept. hemolyticus*	0.75g×7days	−	−	−	Excellent
26	48 ♂	〃	Pain on urination, feeling of redidual urine	+	Rod	*Coryne-bacterium*	0.75g×7days	−	−	−	Excellent
27	72 ♀	〃	Feeling of residual urine	2~3	Coccus	*Entero-coccus*	0.75g×7days	−	−	−	Excellent
28	24 ♀	〃	Pollakisuria, feeling of residual urine	+++	Rod *Diplococcus*	Unknown	0.5g×7days	−	−	−	Excellent
29	28 ♂	Gonorrheal urethritis	Pain on urination pus	+++	*Gonococcus*	−	0.5g×4days	5	−	−	Good
30	30 ♂	〃	〃	+++	*Gonococcus*	−	0.5g×3days	5	−	−	Good
31	21 ♂	〃	〃	+++	*Gonococcus*	−	0.5g×9days	10	−	−	Good
32	24 ♂	〃	〃	+++	*Gonococcus*	−	0.5g× 7 days	5	−	−	Good

Table 3 Effect of pivampicillin on urinary tract infections (3)

Case	Age & sex	Diagnosis	Before treatment				Dose	After teratment			Result
			Symptom	Leukocyte	Bacteria	Culture		Leukocyte	Bacteria	Symptom	
33	34 ♂	Gonorrheal urethritis	Pain on urination pus	++	*Gonococcus*	*Gonococcus*	0.75g×10days	−	−	−	Excellent
34	20 ♂	〃	〃	+++	*Gonococcus*	*Gonococcus*	1.0g×7days	5	−	−	Good
35	28 ♂	〃	〃	+++	*Gonococcus*	−	1.0g×7days	−	−	−	Excellent
36	42 ♀	Pyelonephritis	Fever, CVA pain	+	Rod	*E. coli*	0.75g×14days	7~8	−	−	Good
37	37 ♀	〃	Fever	++	Rod	*E. coli*	1.0g×10days	−	−	−	Excellent
38	69 ♂	〃	Fever, CVA pain	+++	Rod	*Proteus mirabilis*	0.75g×30days	6~7	−	−	Good
39	32 ♀	〃	Fever	+	Rod	*E. coli*	0.75g×20days	6~7	−	−	Good
40	26 ♀	〃	Fever CVA pain	+++	Rod	*Proteus mirabilis*	0.75g×20days	4~5	−	−	Good
41	24 ♀	〃	Fever	+++	Rod	*E. coli*	0.75g×7days	+	−	−	Good
42	34 ♀	〃	〃	+	Rod	*Proteus mirabilis*	0.75g×10days	−	−	−	Excellent
43	19 ♂	Prostatitis	Pain on urination, pollakisuria	++	Rod	*Proteus mirabilis*	0.75g×24days	5~6	−	−	Good
44	38 ♂	〃	Pollakisuria, Fever	++	Rod	*E. coli*	0.75g×7days	−	−	−	Excellent
45	68 ♂	〃	Pollakisuria, feeling of residual urine	4~5	Coccus	*Strept. hemolyt.*	0.75g×24days	−	−	−	Excellent
46	33 ♂	〃	Feeling of residual urine	+	Rod	*E. coli*	0.75g×14days	5~6	*E. coli*	−	Ineffective

Fig. 6 Urinary excretion of ABPC 250 mg orally (before meal)

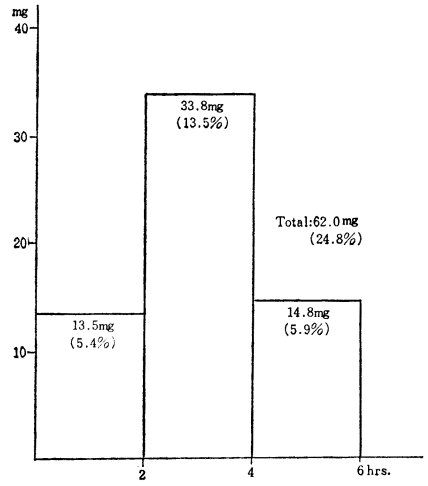


Fig. 7 Urinary excretion of pivampicillin of 125 mg orally (after meal)

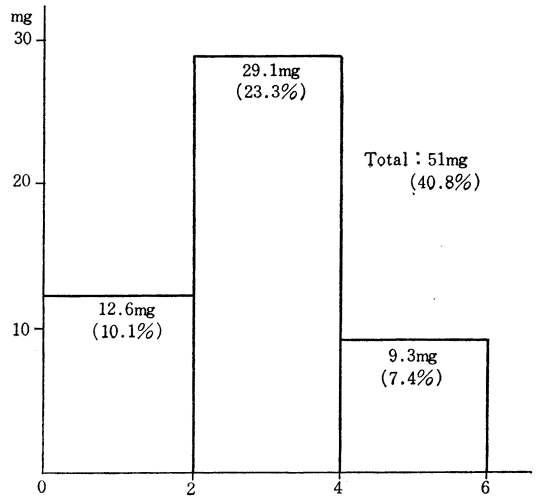


Table 4 Evaluation of pivampicillin in urinary tract infection

Diagnosis	No. of cases	Excellent	Good	Ineffective	Rate of bacterial eradication
Acute cystitis (500 mg (5), 750 mg (8), 1, 000 mg (14), 2, 000 mg/day (1 case))					
E. coli	20	19	1	0	100.0
Staphylococcus	4	4	0	0	
Strept. hemolyticus	1	1	0	0	
Corynebacterium	1	1	0	0	
Enterococcus	1	1	0	0	
Unknown	1	1	0	0	
Total	28	27	1	0	100.0
Gonorrhea (500 mg (4), 750 mg (1), 1, 000 mg/bay (2 cases))					
Neisseria gonorrhoeae	7	2	5	0	100.0
Prostatitis (750 mg/day)					
E. coli	2	1	0	1	50.0
Proteus mirabilis	1	0	1	0	
Strept. hemolyticus	1	1	0	0	
Total	4	2	1	1	75.5
Pyelonephritis (750 mg/day)					
E. coli	4	1	3	0	
Proteus mirabilis	3	1	2	0	
Total	7	2	5	0	100.0
Grand Total	46	33	12	1	
Rate of effectiveness		71.7	26.1	2.2	97.8

Clinical laboratory tests revealed various values as follows. Erythrocyte count and hemoglobin values remained normal, while leucocytes decreased rather after the administration, and this may prove an alleviation of the infection. As to the renal functions, BUN and creatinine were tested, and the values remained in normal ones, though there observed some variations.

As to the side effects with pivampicillin, rash (3 cases, 6.5%) and gastrointestinal disorder (6 cases, 13.0%) were noticed, though the effects were all slight and only transient (Table 7, Fig. 8~15).

Table 5 Evaluation of pivampicillin for bacteria in urinary tract infection

Bacteria	No. of cases	Eradicated	Eradicated but findings or symptoms remained	Ineffective	Rate of bacterial eradication
E. coli	26	25	0	1	96.2
Neisseria gono.	7	6	1	0	100.0
Proteus mirabilis	4	1	3	0	100.0
Staphylococcus	4	4	0	0	100.0
Streptococcus	2	2	0	0	
Corynebacterium	1	1	0	0	
Enterococcus	1	1	0	0	
Unknown	1	1	0	0	
Total	46	41	4	1	
Rate of bacterial eradication		89.1	8.7	2.2	97.8

Table 6 Evaluation for dosage a day

Dosage (mg/day)	No. of cases	Excellent	Good	Ineffective	Rate of effectiveness
500	9	5	4	0	100.0
750	19	12	6	1	94.7
1,000	17	16	1	0	93.5
2,000	1	1	0	0	
Total	46	34	11	1	97.1

Table 7 Side effects

Dosage (mg/day)	500	750	1,000	2,000	Total	
G-I disorder	0	3	3	0	6	13.0 %
Rash	0	0	3	0	3	6.5 %
S-GPT ↑	0	2	1	0	3*	7.9**%
S-GOT ↑	0	2	1	0	3*	7.9**%
Total cases of side effects	0	7	8	0	15	32.6 %
Total cases of PVPC administrated patient	9	19	17	1	46	

* Rise of both S-GPT and S-GOT was seen in 2 cases.
** S-GPT and S-GOT were measured in 38 cases.

Fig. 8 Influence of pivampicillin 18 cases
RBC

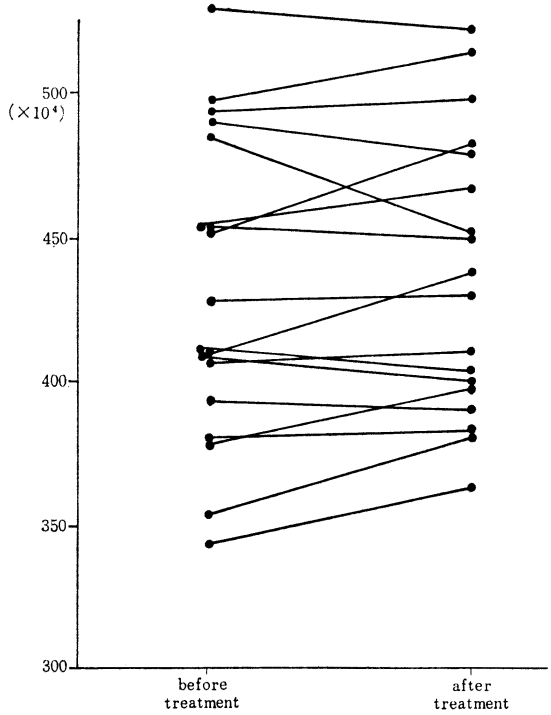


Fig. 9 Influence of pivampicillin 18 cases
WBC

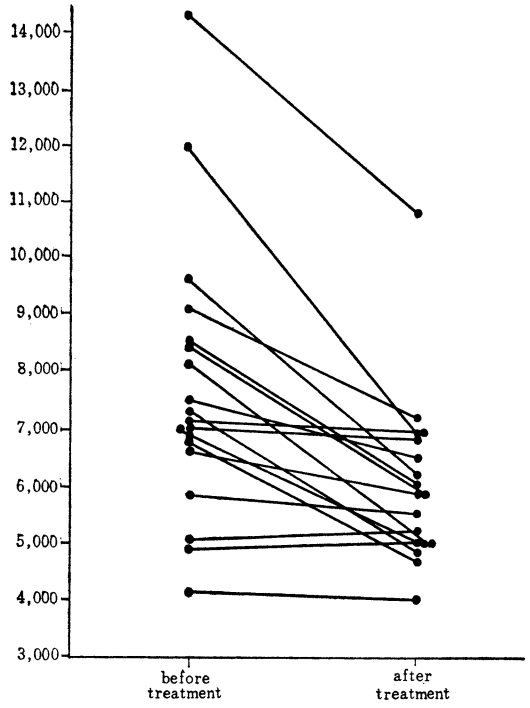


Fig. 10 Influence of pivampicillin 18 cases
Hb

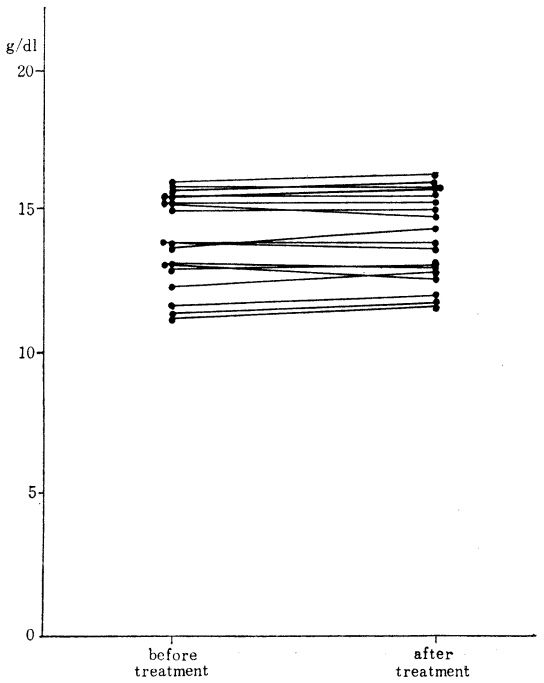


Fig. 11 Influence of pivampicillin 19 cases
BUN

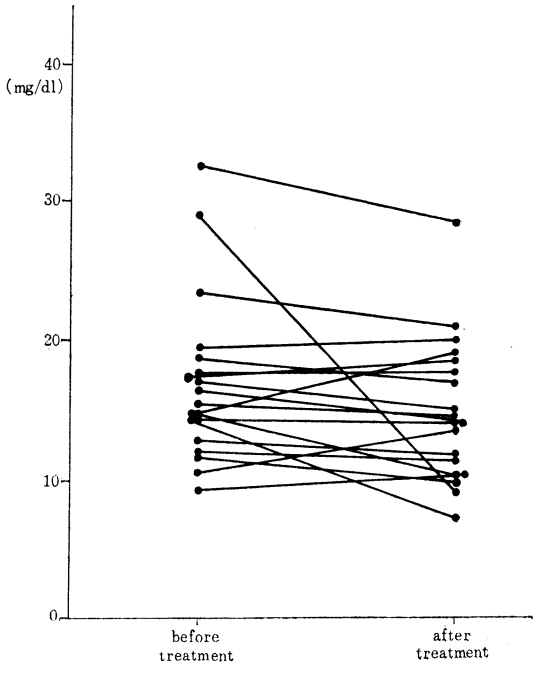


Fig. 12 Influence of pivampicillin (35 cases)
Creatinine

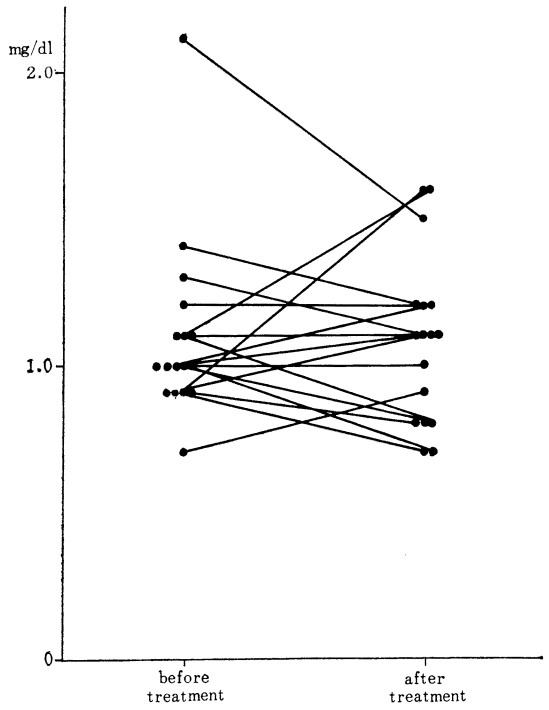


Fig. 13 Influence of pivampicillin (35 cases)
LDH

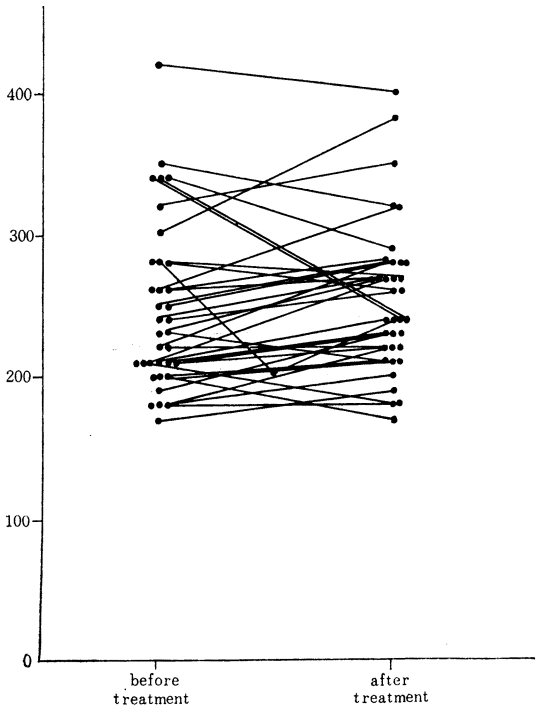


Fig. 14 Influence of pivampicillin (38 cases)
S-GOT

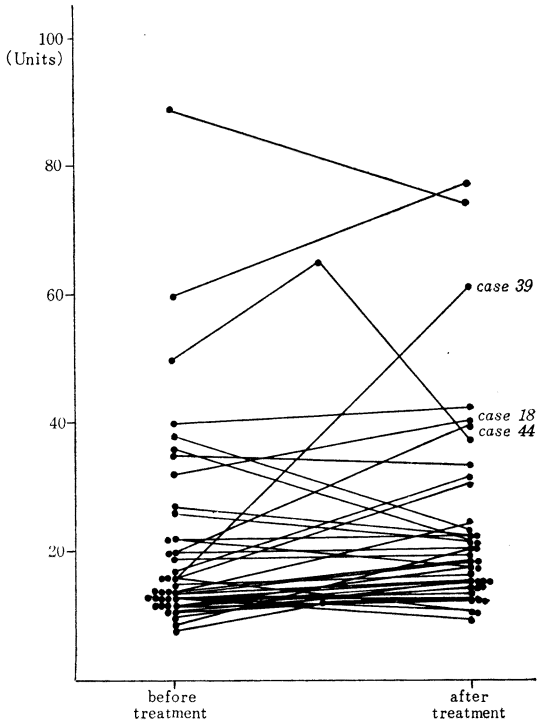


Fig. 15 Influence of pivampicillin (38 cases)
S-GPT

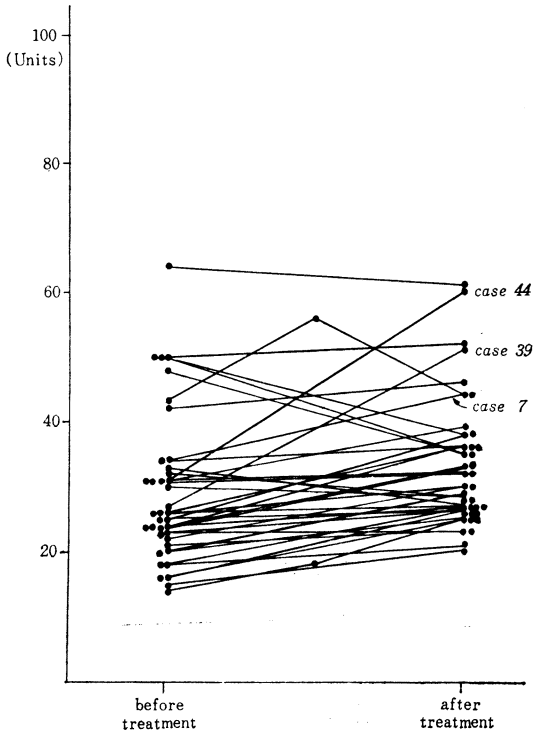


Table 8 Laboratory findings (1)

No.	Age Sex	Diagnosis	Dosage g/day × days	Hepatic function								Renal function						Hematological findings						Side effect	Test day
				Al-P		TTT		GOT		GPT		Creatinine		BUN		LDH		RBC (×10⁴)		WBC		Hb (g/dl)			
				Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After		
1	28♀	Acute cystitis	0.5×7																					–	
2	21♀	〃	0.5×7			1.2	1.4	16	25	11	14					230	210							–	7
3	25♀	〃	0.75×10					25	26	12	12			12.0	11.2	170	190	457	450	5,000	5,200	13.9	13.9	–	10
4	28♀	〃	0.75×7	4.5	4.0			33	27	20	20	1.0	0.8	14.9	10.0	180	200	497	515	8,200	5,000	15.5	15.8	G.I.disorder(7th day)	7
5	50♀	〃	0.75×10					31	32	22	17	2.1	1.5	29.0	9.0	260	320	410	439	7,000	6,900	13.8	14.4	–	10
6	75♀	〃	0.75×14	5.3	4.8			42	46	26	21	1.0	1.2	19.5	20.0	340	240	410	404	6,800	4,700	12.4	12.8	–	14
7	25♀	〃	1.0×7	9.3	9.0	2.3	2.2	34	44	35	33													–	4
8	61♀	〃	1.0×7																					–	7
9	60♀	〃	1.0×7	7.1	7.5	1.3	1.8	24	27	16	10					420	400							–	6
10	42♀	〃	1.0×7																					–	
11	60♀	〃	1.0×7	5.3	5.9	2.0	2.2	20	25	13	12					300	380							–	
12	25♀	〃	1.0×7	5.3	6.0	1.8	1.6	16	26	10	15					210	230							–	
13	25♀	〃	1.0×7			1.9	3.1 (2.8)	14	18 (25)	8	12 (14)					280	200 (240)							Rash (3rd day)	4 (7)
14	54♀	〃	1.0×7	7.5	6.7	1.4	2.3	26	30	12	14					350	320							Rash (6th day)	15
15	31♀	〃	1.0×7	4.3	4.7	1.8	1.2	23	26	15	16					340	210							Rash (7th day) G.I. disorder(3rd day)	7
16	27♀	〃	1.0×7	3.7	4.0	2.0	1.5	15	20	12	15					240	270							–	7

Table 8 Laboratory findings (2)

No	Age Sex	Diagnosis	Dosage g/day ×days	Hepatic function								Renal function						Hematological findings						Side effect	Test day
				Al-P		TTT		GOT		GPT		Creatinine		BUN		LDH		RBC (×10⁴)		WBC		Hb (g/dl)			
				Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After		
17	29♀	Acute cystitis	1.0×7	6.2	5.0	1.2	1.5	21	23	14	18					240	260							−	9
18	27♀	〃	1.0×7	8.9	8.9	2.5	2.5	50	38	32	40					280	220							−	9
19	23♀	〃	2.0×7	5.5	6.1	1.5	1.5	64	61	89	74													−	
20	45♀	〃	0.5×5	5.0	3.7	2.9	1.2	26	27	9	20					220	220							−	7
21	29♀	〃	0.5×7	4.2	4.4	0.9	1.0	30	28	14	15					230	270							−	7
22	24♀	〃	0.75×7	4.2	4.0			32	28	22	22	0.9	0.8	11.8	9.8	180	220	450	467	7,300	4,800	15.0	15.1	−	
23	29♀	〃	1.0×7	4.1	4.5	2.4	2.5	22	30	14	18					320	350							G.I.disorder (4th day)	7
24	22♀	〃	1.0×7	4.0	4.7	1.8	2.0	18	21	11	12					280	270							G.I.disorder (3rd day)	7
25	33♀	〃	0.75×7					48	35	38	23	1.0	0.7	9.1	10.6	200	210	409	399	8,000	4,000	13.1	12.6	−	7
26	48♂	〃	0.75×7					24	33	17	31	1.1	1.6	17.2	18.4	210	270							−	7
27	72♀	〃	0.75×7					34	36	27	22	1.1	1.0	16.1	14.0	260	280	379	380	5,800	5,500	13.0	13.1	−	7
28	24♀	〃	0.5×7																					−	
29	28♂	Gonorrheal urethritis	0.5×4																					−	
30	30♂	〃	0.5×3	3.5	3.4	3.5	2.5	50	35	40	42					340	290							−	7
31	21♂	〃	0.5×9																					−	
32	24♂	〃	0.5×7																					−	

Table 8 Laboratory findings (3)

No.	Age Sex	Diagnosis	Dosage g/day ×days	Hepatic function								Renal function						Hematological findings						Side effect	Test day
				Al-P		TTT		GOT		GPT		Creatinine		BUN		LDH		RBC (×10⁴)		WBC		Hb (g/dl)			
				Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After		
33	34♂	Gonorrheal urethritis	0.75×10	7.0	6.8			31	39	36	21	1.2	1.2	12.8	11.9	280	260	489	499	14,300	10,800	15.7	16.0	–	10
34	20♂	〃	1.0×7																					–	
35	28♂	〃	1.0×7	4.2	5.1	1.1	1.3	24	36	16	30					250	280							–	7
36	42♀	Pyelonephritis	0.75×14					31	32	13	13	1.4	1.2	19.3	17.0	260	270	457	450	9,200	7,300	15.3	15.3	–	14
37	37♀	〃	1.0×10	4.4	3.6			23	23	13	10	0.9	1.1	14.4	7.1	210	220							–	10
38	69♂	〃	0.75×30					20	29	13	9			32.5	28.6	200	210	354	370	7,500	6,500	11.6	12.0	–	7
39	32♀	〃	0.75×20	7.5	5.5			27	51	16	61	0.9	1.6	15.1	14.8			344	363	8,500	5,800	11.2	11.7	–	7
40	26♀	〃	0.75×20					26	36	12	17	0.7	0.9	14.2	14.0	180	180	406	410	9,600	6,200	13.9	13.7	–	20
41	24♀	〃	0.75×7	6.9	6.5			18	27	13	15					200	170	378	398	8,400	6,000	11.4	11.8	G.I.disorder (12th day)	7
42	34♀	〃	0.75×10					25	38	14	24	0.9	0.7	23.5	21.0	190	230	392	390	6,600	5,800	13.2	13.0	G.I.disorder (1st day)	10
43	19♂	Prostatitis	0.75×24					43	56 (44)	50	65 (37)	1.3	1.1	10.2	13.5	250	280 (230)	536	533	7,000	5,000	16.0	16.2	–	14 (21)
44	38♂	〃	0.75×7					31	60	20	39	1.0	1.0	17.0	15.0	210	180	452	482	12,000	6,900	15.3	14.9	–	7
45	68♂	〃	0.75×24	5.3	6.9			24	33	19	19	1.2	1.2	17.5	17.7	210	230	482	452	7,100	6,900	15.9	15.9	–	14
46	33♂	〃	0.75×14					50	52	60	77			14.8	19.0	210	240	490	480	4,900	5,000	15.5	15.5	–	14

GOT, GPT, Al-ph. and TTT were investigated with regard to the hepatic functions (Table 8). In 3 cases, following abnormal values were observed, that is, No. 39, No. 44 and No. 46 (Table 9), and they demonstrated the increase of both GOT and GPT. Degree of the increase is not so high, however, and the conclusion would not able to draw yet whether pivampicillin affects or not, as the cases were not purchased after the administration had finished.

Table 9 Cases with the increased values of hepatic functions tests

No.	GOT		GPT		Al-ph	
	before	after	before	after	before	after
39	27	51	16	61	7.5	5.5
44	31	60	20	39	-	-
46	50	52	60	77	-	-

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