CHAPTER IV

RESULTS

1. Physiological Characteristics of the Subjects

Table 2 Physiological Characteristics of the Subjects

Subject no.	Sex	Age (yr)	Weight (kg)	Height (cm)	Surface area[a] (m^2)
01	M	23	57.8	166.0	1.64
02	M	30	61.0	164.0	1.66
03	F	34	51.0	148.5	1.43
04	M	25	61.5	169.0	1.70
05	F	26	40.0	147.0	1.28
06	M	30	62.0	170.0	1.71
07	M	41	58.0	166.5	1.64
08	M	37	55.0	167.0	1.61
09	F	22	41.0	151.0	1.32
10	F	31	35.0	150.0	1.23
11	F	35	44.5	153.0	1.37
12	F	25	68.4	165.5	1.75
13	F	22	42.0	146.0	1.30
14	M	45	46.0	164.0	1.47
Mean ± SD		30.4 ± 7.2	51.6 ± 10.2	159.1 ± 9.1	1.51 ± 0.18

M = Male ; F = Female

a Nomogram for Calculating the Body Surface Area of Adults (78)

2. The Assay of Ampicillin in Capsules

The actual content of ampicillin in capsules were determined microbiologically to assure any deviation from the labelled amount. The percentage amount of ampicillin obtained was in good agreement with the stated amount i.e., there were 102.90 and 110.97 percent of ampicillin in average in the 250- and 500 mg ampicillin capsules respectively.

3. Comparison of Pharmacokinetic Parameters of Ampicillin Obtained after Oral Administration of Ampicillin with Those Obtained after Oral Administration of Bacampicillin

Typical ampicillin serum concentrations versus time profiles following oral administration of bacampicillin 400 mg, ampicillin 250 mg and ampicillin 500 mg in 14 healthy subjects in fasting state were shown respectively in Table 3-5 and depicted in Figure 6-8. Each point in the figures represents the mean value of fourteen subjects, bars indicate the standard error of mean. Comparison between different treatments were illustrated graphically in Figure 9.

Table 6 showed the cumulative percentage urinary excretion of ampicillin at the end of 8 hours after the oral administration of ampicillin 250, 500 mg and bacampicillin 400 mg in fasting condition in 14 subjects. The mean cumulative amount excreted at each time interval were illustrated in Figure 10.

3.1 Non-compartmental Modeling Pharmacokinetic Parameters

From the raw data, some parameters e.g., individual peak

serum levels (C_p), individual time to reach the peak (t_p), the percentage urinary recovery and the area under the serum concentration-time curve (AUC_o^∞) calculated by the method of trapezoidal rule were obtained and compared statistically.

Table 7 showed the statistical comparison of the parameters obtained after oral administration of ampicillin 250 mg (Treatment C), ampicillin 500 mg (Treatment D) and bacampicillin 400 mg (Treatment A_1) in fasting condition in 14 subjects. They were all significantly different from each other according to the Student's t test and the ANOVA one-way classification test ($p < 0.01$). Treatment D yielded peak serum level which was higher than treatment C but lower than treatment A_1. No significant difference in peak time was found between treatment C and D while both of them were approximately two times longer than treatment A_1. The area under the serum concentration-time curves obtained after treatment A and D were not significantly different whereas treatment C showed significantly smaller AUC_o^∞ ($p < 0.05$) than the other two treatments. Additionally, treatment A_1 showed virtually two-folds higher in the percentage urinary recovery than treatment C and D. The degree of uniformity of individual data within the group of subjects were expressed as the coefficient of variation.

3.2 Compartmental Modeling Pharmacokinetic Parameters

In this study, the one-compartment open model with first order kinetic was proposed to fit the data. The goodness of fit was tested using the coefficient of variation between the experi-

mental data and the calculated values. The coefficient of variation obtained by assuming a one-compartmental model was not much different from that calculated by assuming a two compartmental model. Therefore, the simpler one-compartment open model was judged enough for explaning the data.

The relevant pharmacokinetic parameters calculated from serum data were summarized in Table 8. The peaks of ampicillin serum concentrations obtained after single oral doses of ampicillin 250 mg, ampicillin 500 mg and bacampicillin 400 mg were 1.58, 2.81 and 4.46 mcg/ml respectively. They were all significantly different from each other at $p < 0.05$. The time required to reach the peak was about one hour for ampicillin but only half an hour for bacampicillin. No significant difference was observed in the absorption rate constants after consuming ampicillin either 250 mg or 500 mg doses while administration of bacampicillin obviously resulted in higher absorption rate constant. There were small differences in elimination rate of drugs. The overall elimination rate constants were 0.71,0.63 and 0.72 $hr.^{-1}$ and the corresponding serum half-lives were 0.99, 1.15 and 0.97 hr. for the treatment C, D and A_1 respectively. The mean area under the serum concentration-time curves (AUC_o^∞) were considerably higher for treatment A_1 and D than for treatment C ($p < 0.01$). The mean apparent volume of distribution and the total body clearance were also calculated and presented in Table 8. They were not significantly different from each other ($p < 0.05$).

Table 9 presented the pharmacokinetic parameters calculated from urinary excretion data after oral administration of

ampicillin 250 and 500 mg and bacampicillin 400 mg. Whereas, the absorption rate constants and the urinary excretion rate constants could be calculated using the urinary excretion rate plot, the overall elimination rate constants and the biological half-lives could be obtained by both the urinary excretion rate plot and the sigma-minus plot. The statistical comparisons revealed no significant difference in these parameters obtained after oral administration of ampicillin 250 and 500 mg while the marked differences were existed between some parameters e.g., absorption rate constant and the urinary excretion rate constant obtained after the administration of ampicillin and bacampicillin.

Table 3 : Serum concentrations of ampicillin (mcg/ml) after oral administration of Bacampicillin 400 mg; fasting condition (Treatment A_1) in 14 subjects.

Subject no. / Time (hr.)	01	02	03	04	05	06	07	08	09	10	11	12	13	14	Mean	SEM
0.25	3.19	1.46	0.61	-	1.24	0.79	3.06	0.70	1.57	2.20	0.65	2.00	1.33	1.50	1.56	0.23
0.5	6.64	4.49	2.67	3.45	2.34	2.86	6.52	4.70	4.72	5.73	-	4.36	5.49	4.31	4.48	0.37
0.75	5.64	6.10	2.31	4.68	4.62	2.58	6.15	7.11	5.79	6.85	4.78	4.99	7.04	7.07	5.41	0.41
1.0	3.80	7.11	2.04	4.49	4.85	4.17	3.46	5.51	7.20	5.84	5.78	3.65	6.97	5.51	5.03	0.41
1.5	1.93	3.17	2.30	2.27	5.02	2.86	1.87	3.09	3.83	2.47	6.86	2.65	5.27	3.19	3.34	0.39
2.0	1.09	1.64	1.25	1.49	2.95	1.33	1.44	1.76	1.52	1.94	2.90	1.57	3.62	2.08	1.90	0.20
3.0	0.44	0.40	0.51	0.97	0.84	0.53	0.17	0.70	0.66	0.96	1.09	0.71	1.01	1.01	0.79	0.07
6.0	0.08	0.04	0.04	0.11	0.06	0.07	0.15	0.26	0.12	0.14	0.13	0.10	0.11	0.19	0.11	0.02
8.0	0.02	0.02	0.01	0.05	0.03	0.02	0.04	0.02	0.05	0.06	0.06	0.02	0.03	0.08	0.04	0.0054

Table 4 : Serum concentrations of ampicillin (mcg/ml) after oral administration of Ampicillin 250 mg; fasting condition (Treatment C) in 14 subjects.

Subject no. / Time (hr.)	01	02	03	04	05	06	07	08	09	10	11	12	13	14	Mean	SEM
0.5	0.46	1.15	0.87	0.24	1.85	1.29	1.01	0.61	0.44	0.24	0.39	0.57	1.47	0.01	0.76	0.14
1.0	1.86	3.54	2.12	1.60	3.37	1.41	0.97	1.18	0.73	0.43	1.99	1.90	1.76	0.38	1.66	0.25
1.5	1.45	2.94	2.51	1.83	3.48	1.54	0.76	1.28	1.15	0.28	2.39	2.54	1.65	0.48	1.74	0.25
2.0	1.25	1.66	2.94	1.42	2.56	1.84	0.80	1.10	1.46	0.23	2.08	2.59	0.99	1.61	1.61	0.20
2.5	0.63	0.50	2.31	1.58	1.54	1.35	0.78	0.70	0.99	0.45	2.35	2.09	0.88	-	1.24	0.18
3.0	0.46	0.34	1.66	1.44	0.96	1.03	1.00	0.59	0.97	0.77	1.90	1.03	0.57	1.83	1.04	0.13
4.0	0.18	0.18	0.89	0.63	0.44	0.52	0.52	0.29	0.38	0.47	0.68	0.44	0.25	1.80	0.55	0.11
6.0	0.03	0.06	0.20	0.17	0.10	0.15	0.11	0.10	0.12	0.17	0.26	0.10	0.06	0.35	0.14	0.02
8.0	≪	0.01	0.05	0.06	0.03	0.03	0.02	0.02	0.02	0.02	0.11	0.03	0.03	0.08	0.04	0.0073

Table 5 : Serum concentrations of ampicillin (mcg/ml) after oral administration of Ampicillin 500 mg; fasting condition (Treatment D) in 14 subjects.

Subject no. / Time (hr.)	01	02	03	04	05	06	07	08	09	10	11	12	13	14	Mean	SEM
0.5	0.57	1.16	1.56	0.81	2.76	2.18	1.86	0.80	0.93	1.52	1.04	0.29	0.68	0.33	1.22	0.20
1.0	2.76	5.91	2.03	2.12	6.38	1.92	2.24	4.47	5.20	4.46	3.40	1.78	-	0.30	3.31	0.49
1.5	2.80	4.57	1.61	1.74	6.93	2.12	1.74	2.80	5.04	4.48	4.59	2.91	3.08	0.21	3.19	0.47
2.0	2.25	2.98	3.11	1.59	5.41	2.48	1.72	1.64	4.09	4.05	6.70	2.43	3.88	0.22	3.04	0.45
2.5	2.12	1.41	3.43	1.69	3.10	3.09	1.49	1.10	3.44	4.83	-	2.88	3.32	-	2.66	0.29
3.0	1.48	0.82	2.85	1.80	2.07	2.81	1.39	0.81	3.28	3.97	3.97	2.29	2.94	0.49	2.21	0.30
4.0	0.67	0.35	1.26	1.21	0.88	1.25	1.01	0.52	1.77	2.53	1.52	1.59	1.73	0.21	1.18	0.17
6.0	0.10	0.07	0.33	0.37	0.16	0.24	0.31	0.12	0.40	0.48	0.80	0.48	0.08	0.13	0.29	0.06
8.0	0.03	0.02	0.07	0.09	0.05	0.06	0.13	0.03	0.16	0.19	0.36	0.12	0.08	0.04	0.10	0.024

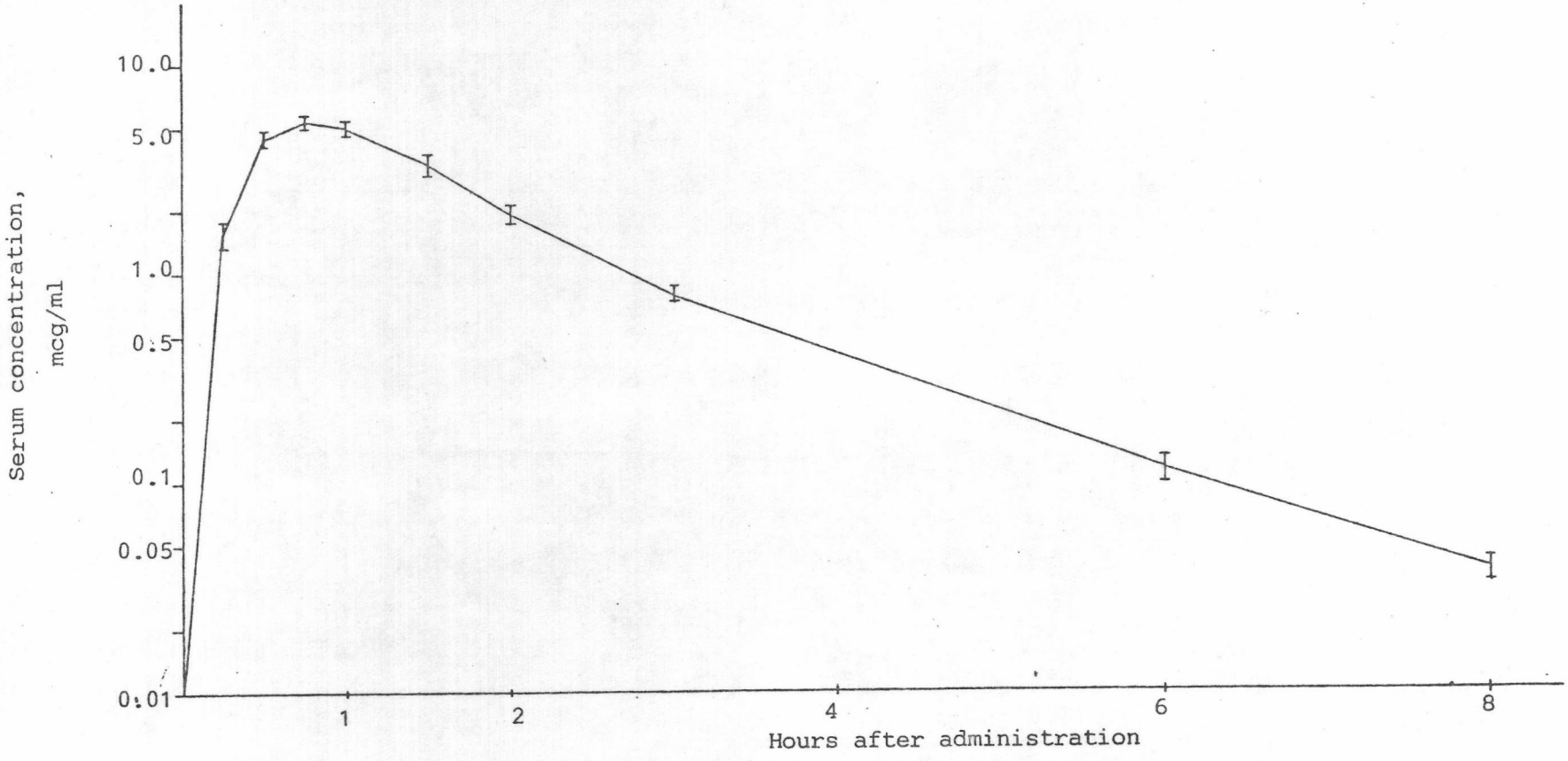

Figure 6 Mean serum levels of ampicillin following oral administration of bacampicillin 400 mg; fasting condition in 14 subjects. The bars represent the standard errors of mean (SEM).

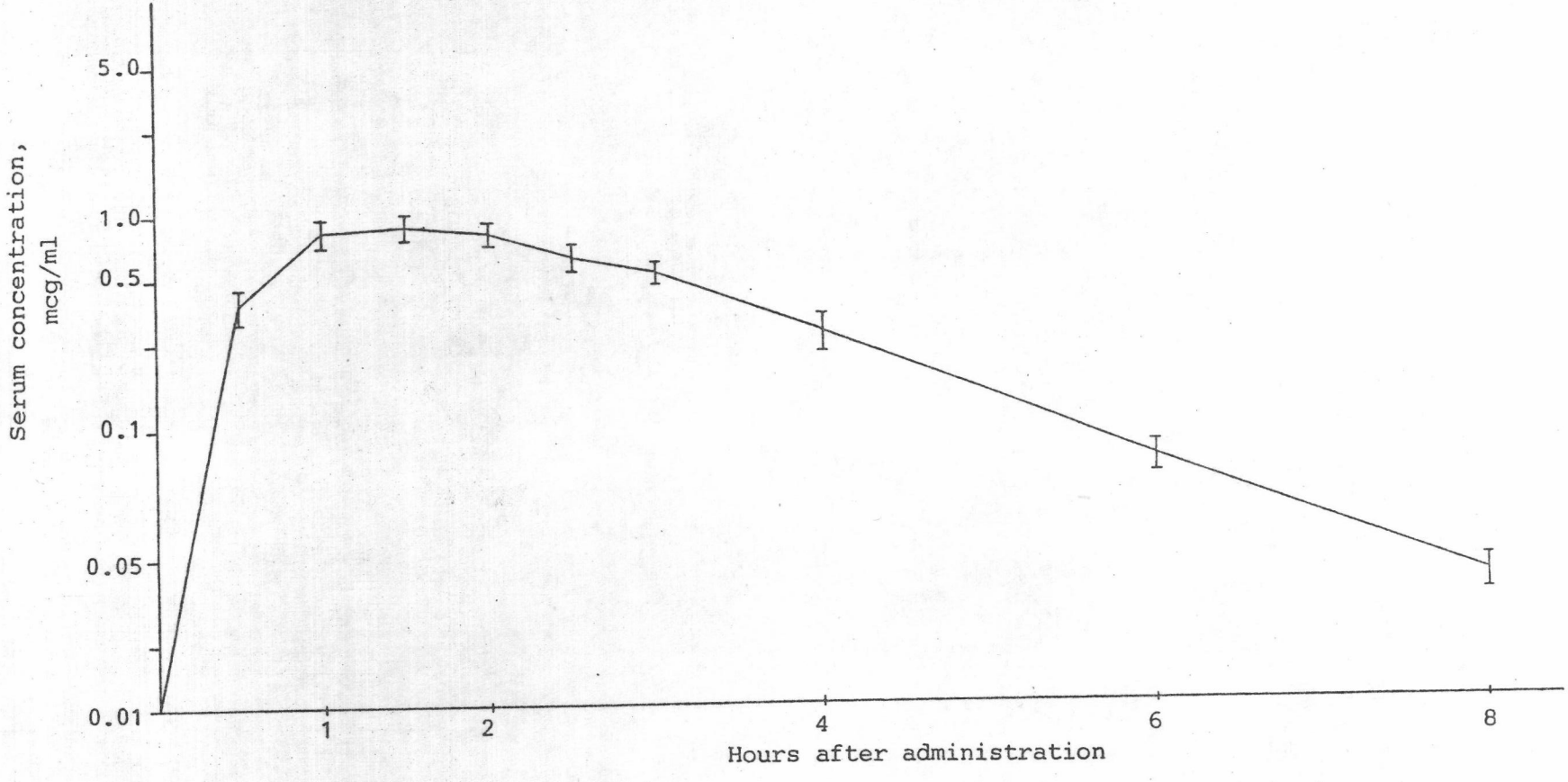

Figure 7 Mean ampicillin serum concentrations (± SEM) after oral administration of ampicillin 250 mg; fasting condition in 14 subjects

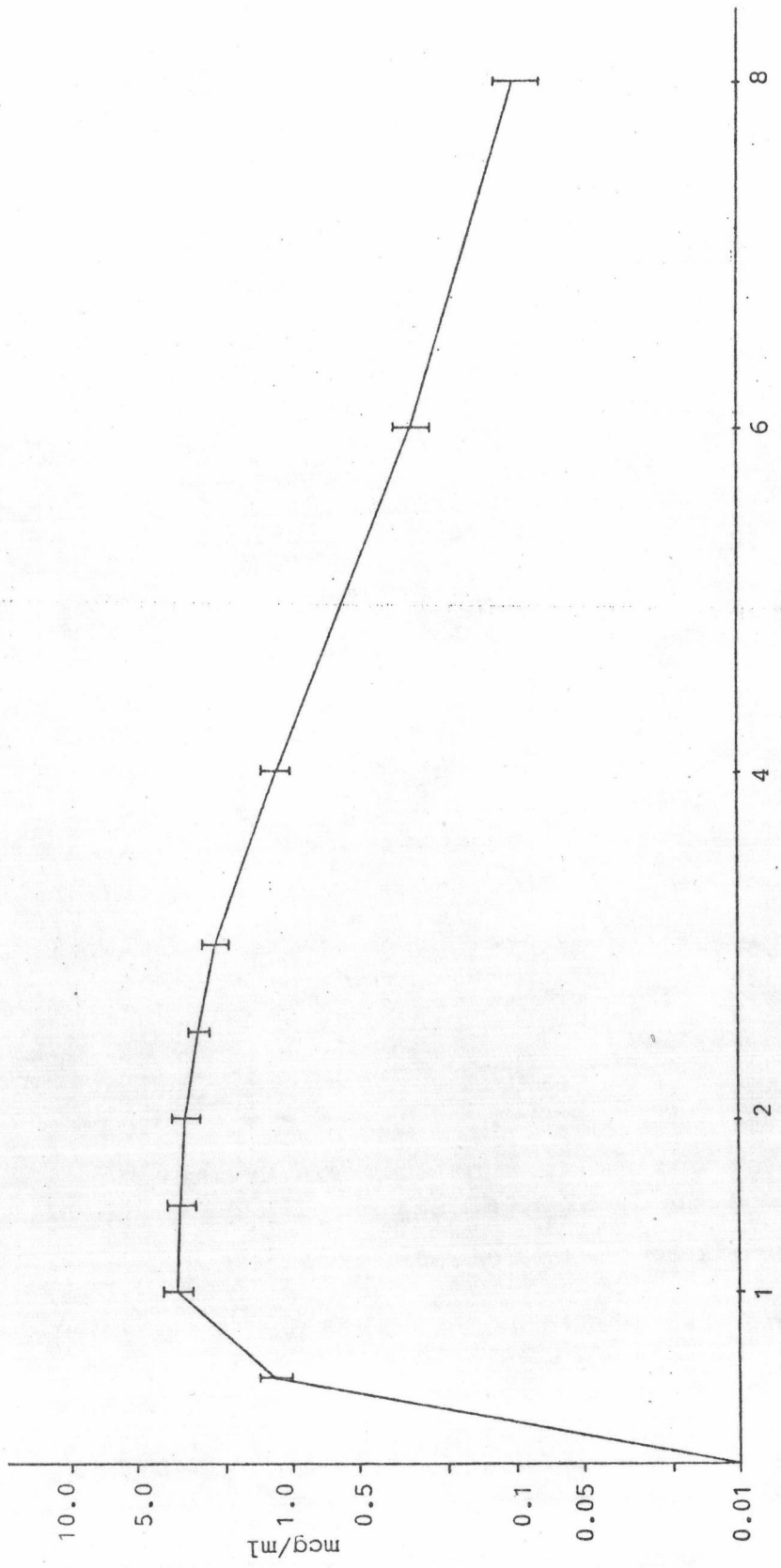

Figure 8 Mean ampicillin serum concentrations (± SEM) after oral administration of ampicillin 500 mg; **fasting** condition in 14 subjects.

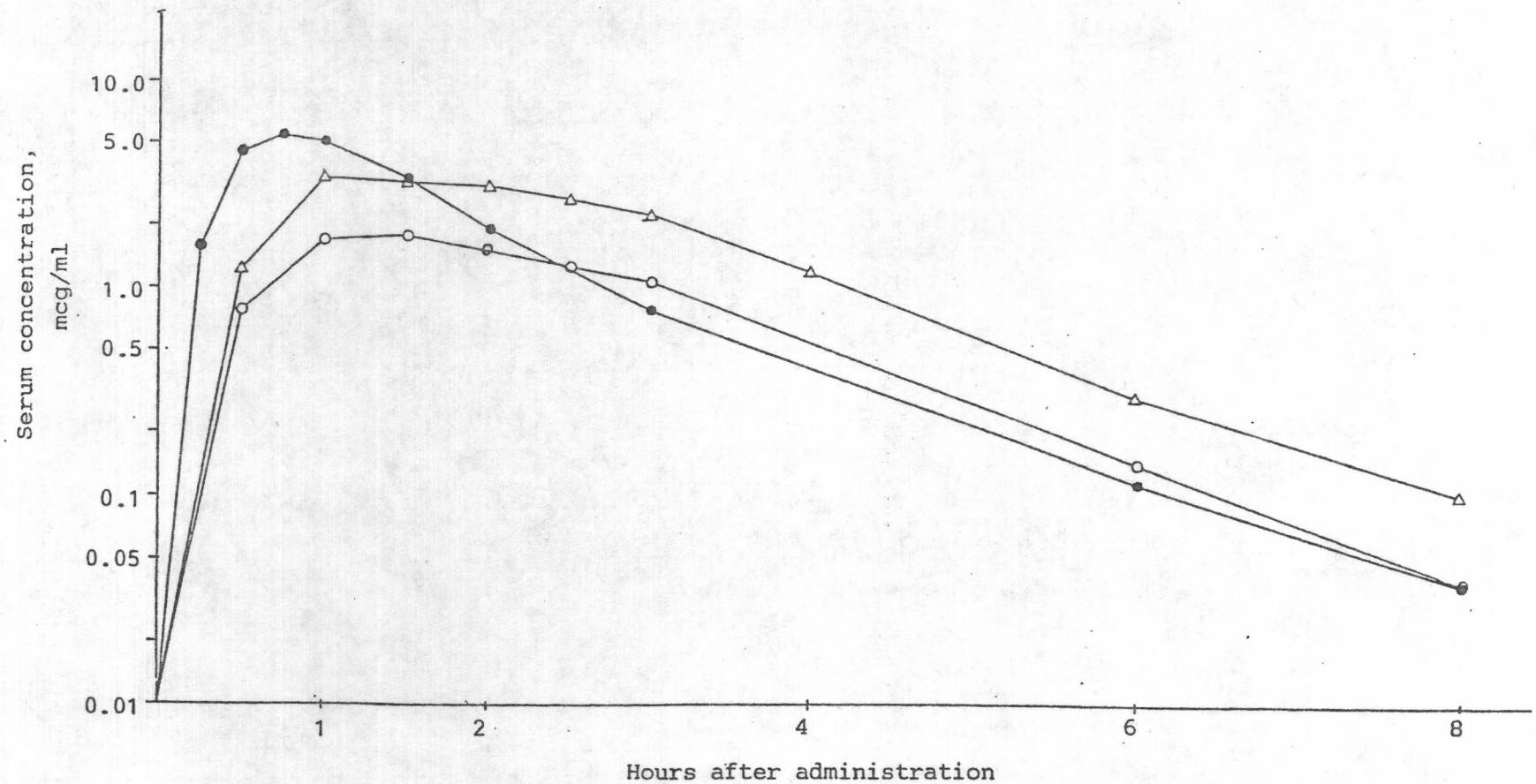

Figure 9 Mean ampicillin serum concentrations after oral administration of bacampicillin 400 mg ●——●, ampicillin 250 mg ○——○ and ampicillin 500 mg △——△ ; fasting condition in 14 subjects.

Table 6 : Cumulative urinary excretion of ampicillin at the end of 8 hours after single oral administration of Ampicillin 250 mg, Ampicillin 500 mg and Bacampicillin 400 mg; fasting condition in 14 subjects expressed as the percentage of dose.

Treatment / Subject no.	Cumulative urinary excretion 0-8 hours (% of dose)		
	Ampicillin 250 mg	Ampicillin 500 mg	Bacampicillin 400 mg
01	21.79	59.02	49.32
02	34.79	33.43	51.37
03	60.74	25.86	89.17
04	44.75	29.16	77.13
05	68.05	32.68	88.70
06	19.02	17.92	34.33
07	30.77	30.12	52.73
08	19.20	16.26	65.54
09	26.55	49.82	61.53
10	23.93	27.18	44.33
11	30.81	36.77	75.80
12	27.24	31.61	56.81
13	27.82	18.83	69.40
14	26.76	25.31	57.88
Mean	33.02	31.00	62.43
SEM	3.98	3.14	4.33
CV	0.45	0.38	0.26

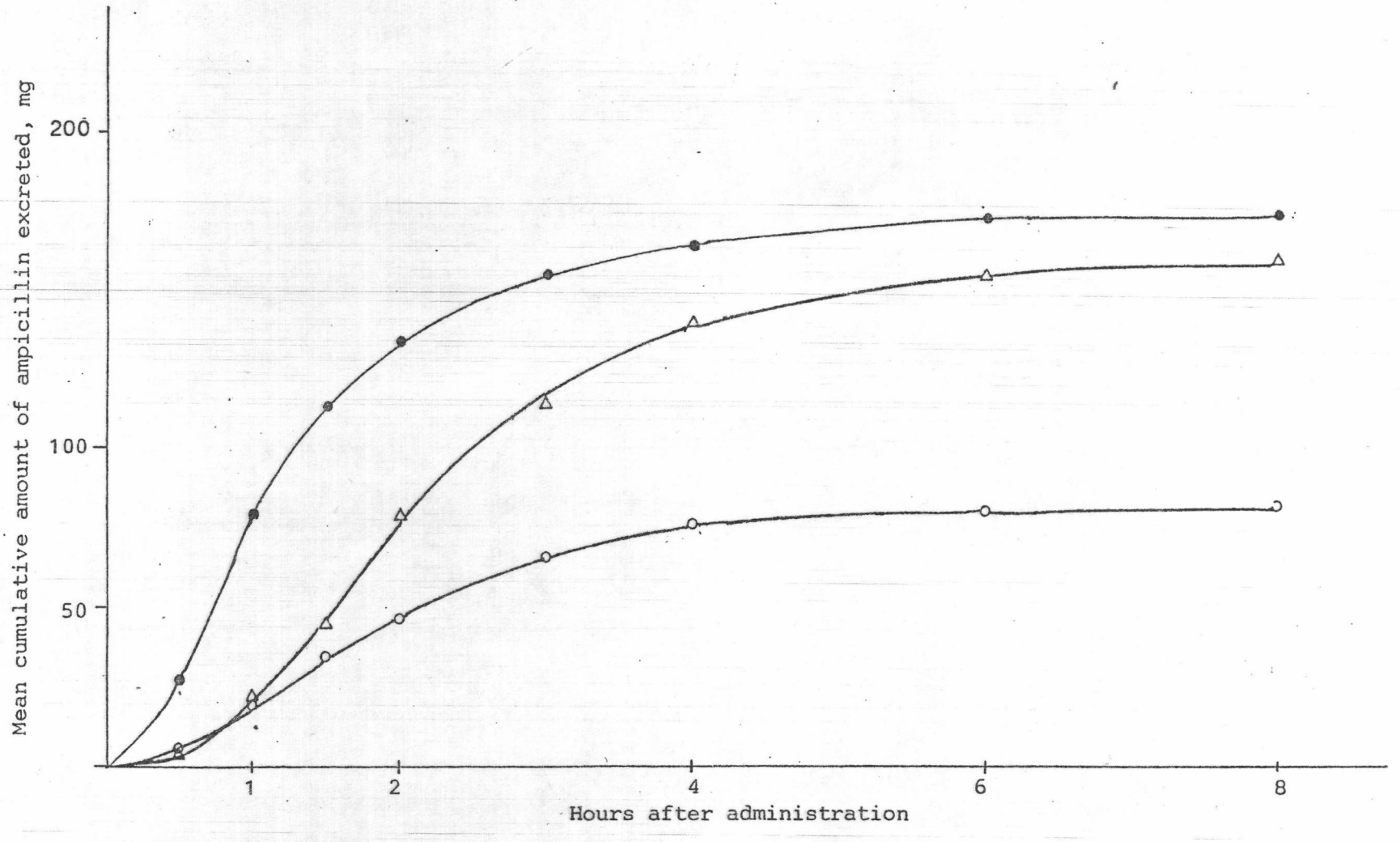

Figure 10 Cumulative urinary excretion of ampicillin following oral administration of bacampicillin 400 mg ●——● , ampicillin 250 mg o——o and ampicillin 500 mg △——△ in 14 subjects.

Table 7 : Non-modeling pharmacokinetic parameters after oral administration of Ampicillin 250 mg, Ampicillin 500 mg and Bacampicillin 400 mg, fasting condition in 14 subjects.

Drug	C_p (mcg/ml)			t_p (hr)			AUC_o^∞ (hr. mcg/ml)			% urinary recovery 0-8 hr.		
	Mean	SEM	CV	Mean	SEM	CV	Mean	SEM	CV	Mean	SEM	CV
Ampicillin 250 mg(C)	2.04	0.23	0.42	1.68	0.19	0.43	5.51	0.51	0.34	33.02	3.98	0.45
Ampicillin 500 mg(D)	3.93	0.49	0.47	1.71	0.70	0.41	10.97	1.24	0.42	31.00	3.14	0.38
Bacampicillin 400 mg(A_1)	5.98	0.38	0.24	0.82	0.07	0.32	9.93	0.74	0.28	62.43	4.33	0.26
F-test[a]	$F_{2,40} = 105.17$			$F_{2,40} = 9.90$			$F_{2,40} = 11.63$			$F_{2,40} = 196.32$		
Paired t-test[b]	$A_1 > C, D$ $D > C$			$C, D > A_1$ NS between C, D			$D, A_1 > C$ NS between D, A_1			$A_1 > C, D$ NS between C, D		

C_p mean individual peak serum levels
t_p mean individual time to peak
SEM standard error of mean
CV coefficient of variation
a Significant at $p < 0.01$
b Significant at $p < 0.05$
NS No significant difference at $p > 0.05$

Table 8 Serum pharmacokinetic data of ampicillin (Mean ± SEM) after oral administration of ampicillin 250, 500 mg and bacampicillin 400 mg in fasting state in 14 subjects

Determination	Ampicillin 250 mg (C)	Ampicillin 500 mg (D)	Bacampicillin 400 mg (A_1)	Paired t- test[a]
Peak serum concentrations (mcg/ml)	1.58 ± 0.28	2.81 ± 0.45	4.46 ± 0.34	C < D C < A_1
Time to reach the peak (hr)	1.05 ± 0.06	1.19 ± 0.07	0.60 ± 0.02	C < D A_1 < C
Theoretical drug concentration at t_o extrapolated from the elimination phase (mcg/ml)	8.42 ± 1.07	13.88 ± 2.11	8.94 ± 0.75	C < D NS between C, A_1
Absorption rate constant, Ka (hr^{-1})	1.37 ± 0.15	1.17 ± 0.08	3.40 ± 0.28	NS between C, D C < A_1
Overall elimination rate constant, Ke (hr^{-1})	0.71 ± 0.02	0.63 ± 0.04	0.72 ± 0.02	C > D NS between C, A_1
Serum half-life, $t_{\frac{1}{2}}$ (hr)	0.99 ± 0.03	1.15 ± 0.07	0.97 ± 0.03	C < D NS between C, A_1
Area under the serum concentration-time curve from the time zero to infinity, AUC_o^∞ (hr. mcg/ml)	5.51 ± 0.51	10.97 ± 1.24	9.93 ± 0.74	C < D C < A_1
Apparent volume of distribution, Vd (lit.)	37.94 ± 2.41	35.24 ± 3.58	35.73 ± 3.96	NS
Total body clearance, Cl_T (lit/hr)	27.38 ± 1.96	24.84 ± 2.61	22.82 ± 1.95	NS

Table 9 Pharmacokinetic parameters calculated from urinary excretion data (mean ± SEM) after oral administration of ampicillin 250 and 500 mg and bacampicillin 400 mg; fasting state in 14 subjects

Parameters	Ampicillin 250 mg, C	Ampicillin 500 mg, C	Bacampicillin 400 mg, A_1	Paired-t test[a]
Absorption rate constant, Ka (hr^{-1})	1.44 ± 0.15	1.19 ± 0.08	2.35 ± 0.24	$C < A_1$ NS between C, D
Overall elimination rate constant, Ke (hr^{-1})	0.68 ± 0.05 (0.88 ± 0.06)	0.63 ± 0.06 (0.79 ± 0.06)	0.79 ± 0.03 (0.96 ± 0.04)	$C < A_1$ NS between C, D
Urinary excretion rate constant, ke (hr^{-1})	0.46 ± 0.08	0.38 ± 0.03	1.07 ± 0.12	$C < A_1$ NS between C, D
Biological half-life, $t_{1/2}$ (hr)	1.10 ± 0.08 (0.84 ± 0.06)	1.23 ± 0.11 (0.94 ± 0.06)	0.90 ± 0.03 (0.74 ± 0.03)	$C > A_1$ NS between C, D

Note : The numbers outside parentheses calculated from urinary excretion rate plot while the numbers in parentheses obtained from the sigma-minus method

a significant level at $p < 0.05$

NS not significantly different ($p > 0.05$)

4. The Dose-Drug Concentration Response

The ampicillin serum concentrations obtained after single oral administration of ampicillin 250, 500mg in fasting condition in 7 subjects were shown in Table 4-5 and illustrated graphically in Figure 7-8. In figure 11, the ampicillin serum concentration profiles of the two treatments were shown in the same graph for comparison. The serum concentrations of ampicillin obtained after oral administration of bacampicillin 800 mg (Treatment B) infasting condition in 7 subjects were presented in Table 10 and depicted in Figure 12. Figure 13 showed the comparison of ampicillin concentration profile obtained from treatment B with that obtained after oral administration of bacampicillin 400 mg in 7 subjects. The cumulative percentage urinary recoveries of ampicillin at the end of 8 hours after oral administration of ampicillin 250 mg and 500 mg were shown in Table 6 and the means cumulative amount excreted at each time interval were depicted in Figure 10. Those obtained after oral administration of bacampicillin 400 mg and 800 mg were presented in Table 11 and illustrated in Figure 14.

4.1 Non-compartmental Modeling Pharmacokinetic Parameters

The non-modeling pharmacokinetic parameters obtained after single oral administration of two progressive doses 400- and 800 mg of bacampicillin in fasting condition in 7 subjects were presented in Table 12. The Student's t test revealed no significant difference in peak time and the percentage urinary recovery of the two doses, whereas significant differences were

noted for the individual peak serum levels and the AUC_o^∞ ($p < 0.05$)

The dose-bioavailability response of the two progressive doses of ampicillin and bacampicillin were summarized in Table 13. For both ampicillin and bacampicillin, the extent of absorption considered by C_p and AUC_o^∞ increased approximately in proportional to the increase in doses, while the time to reach the peak appreciably unchanged. The total amounts of ampicillin excreted in urine after the administration of ampicillin 250 and 500 mg were virtually a linear function of the dose whereas there seemed to be some diminution of ampicillin excretion after the administration of bacampicillin 400 and 800 mg.

4.2 Compartmental Modeling Pharmacokinetic Parameters

Table 14 presented the pharmacokinetic parameters calculated from the serum data after the administration of two different doses of bacampicillin. No significant difference was observed for the time to reach the peak, the absorption rate constant, the overall elimination rate constant, the serum half-life, the apparent volume of distribution and the total body clearance. However, there were markedly increased in the peak serum concentration and the AUC_o^∞ ($p < 0.05$). Likewise, after two progressive doses 250- and 500 mg of ampicillin were given, their pharmacokinetic parameters were determined and compared statistically. The results were shown in Table 8. The absorption rate constants, the apparent volumes of distribution and the total body clearances were not significantly different, however, the slightly longer half-life obtained after the admi-

nistration of ampicillin 500 mg was noted.

The pharmacokinetic parameters calculated from urinary excretion data after the administration of ampicillin 250 and 500 mg were shown in Table 9 while those obtained after oral administration of bacampicillin 400 and 800 mg were presented in Table 15. Statistical significant differences were not found between the parameters obtained after the administration of bacampicillin 400 and 800 mg.

The findings described above could suggest that the pharmacokinetics of ampicillin following ampicillin and bacampicillin ingestion were not dose-dependent.

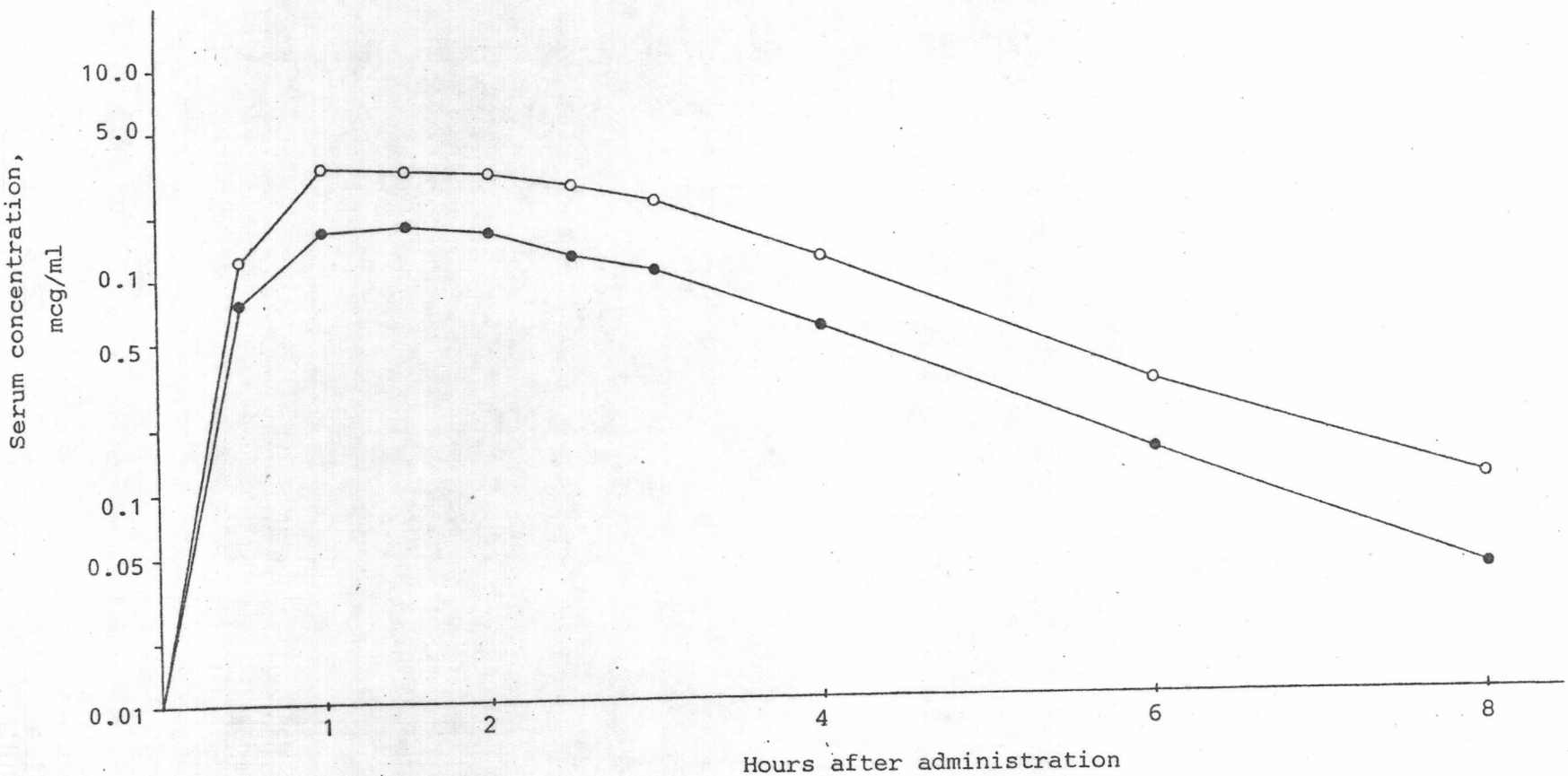

Figure 11 Mean ampicillin concentration profiles following oral administration of ampicillin 250 mg ●—● and ampicillin 500 mg o—o ; fasting state in 14 subjects.

Table 10 : Serum concentrations of ampicillin (mcg/ml) after oral administration of Bacampicillin 800 mg; fasting condition (Treatment B) in 7 subjects

Subject no. / Time (hr.)	01	03	04	07	08	11	12	Mean	SEM
0.25	4.60	0.94	2.07	4.23	1.47	1.43	1.66	2.34	0.55
0.5	11.82	6.10	7.30	6.05	9.63	10.89	5.15	8.14	0.99
0.75	13.92	7.20	10.88	6.42	15.80	12.25	7.40	10.55	1.38
1.0	11.21	8.18	11.83	6.55	12.66	11.25	5.66	9.62	1.05
1.5	7.21	10.36	8.90	6.72	8.34	12.76	4.53	8.40	1.00
2.0	3.78	9.50	5.55	3.53	5.20	7.82	2.86	5.46	0.92
3.0	1.21	3.74	2.09	2.08	2.67	3.21	1.11	2.30	0.37
6.0	0.14	0.40	0.13	0.21	0.20	0.37	0.15	0.23	0.04
8.0	0.07	0.06	0.06	0.07	0.15	0.11	0.05	0.08	0.01

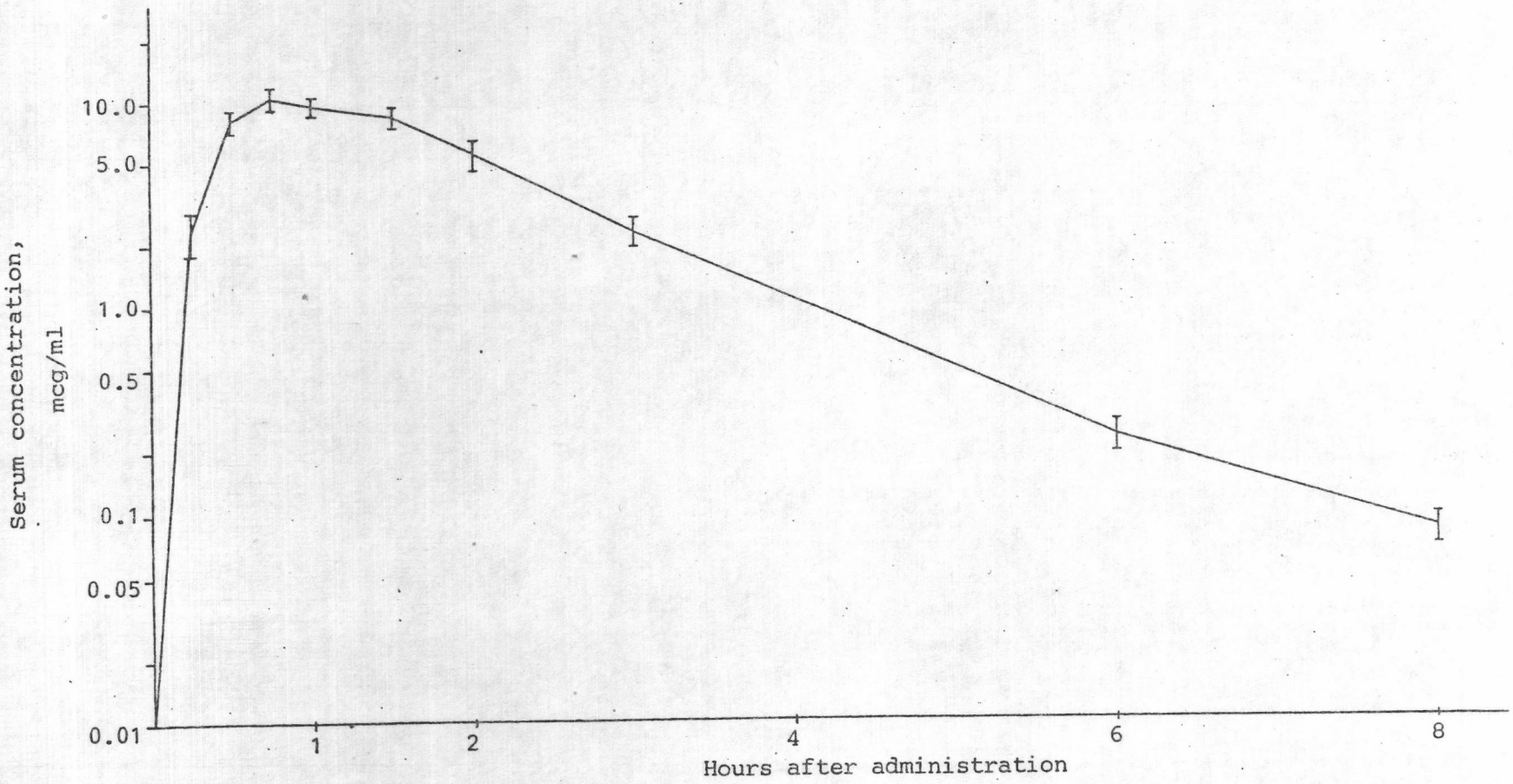

Figure 12 Mean ampicillin serum concentrations (± SEM) after oral administration of bacampicillin 800 mg; fasting state in 7 subjects.

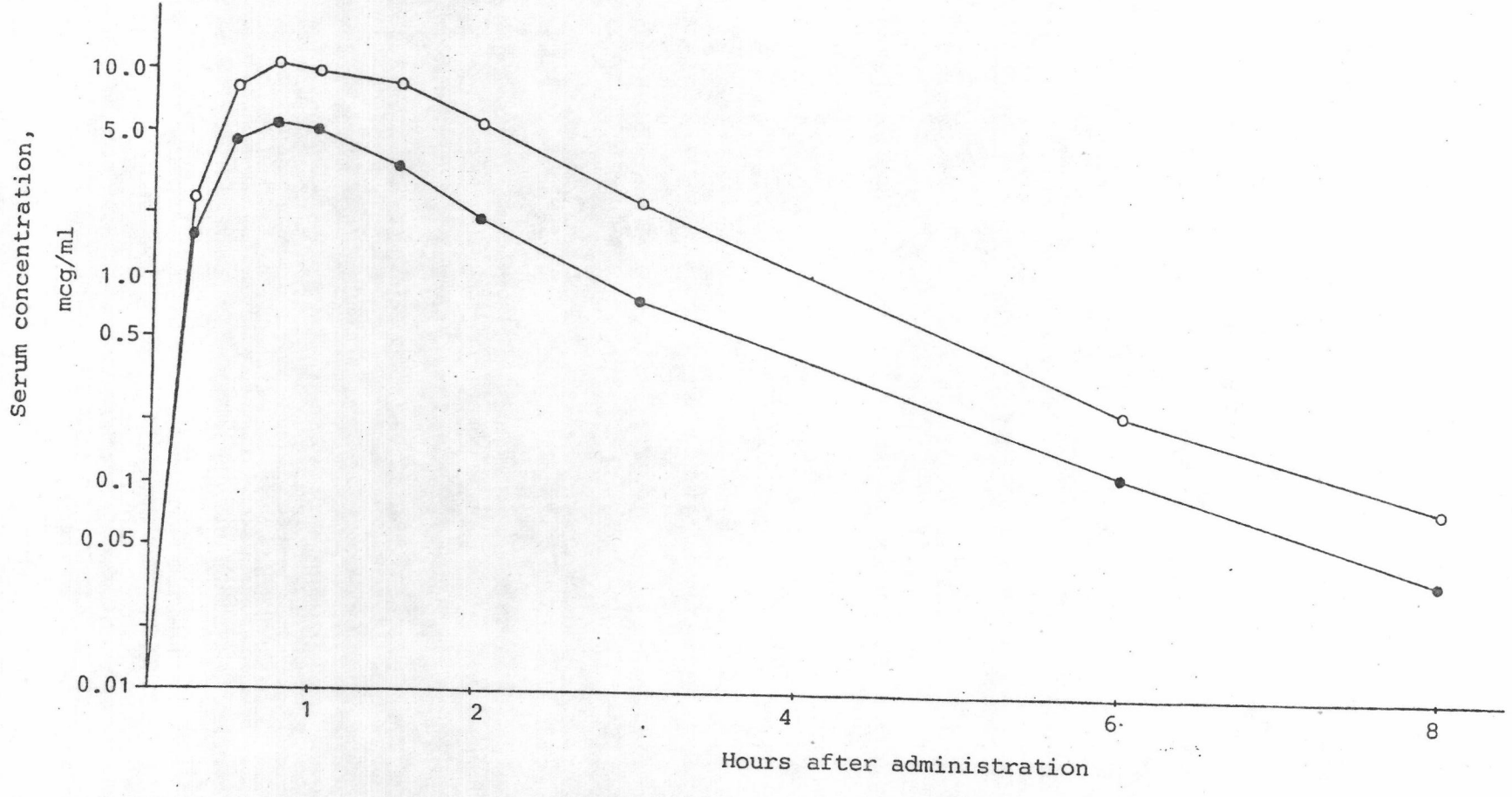

Figure 13 Mean ampicillin concentration profiles following oral administration of bacampicillin 400 mg ●——● and bacampicillin 800 mg o——o ; fasting state in 7 subjects.

Table 11 : Cumulative urinary excretion of ampicillin at the end of 8 hours after single oral administration of Bacampicillin 400 mg and Bacampicillin 800 mg; fasting condition in 7 subjects expressed as the percentage of dose.

Treatment / Subject no.	Cumulative urinary excretion 0-8 hours (% of dose)	
	Bacampicillin 400 mg	Bacampicillin 800 mg
01	49.32	45.07
03	89.17	99.09
04	77.13	57.78
07	52.73	28.83
08	65.54	56.73
11	75.80	43.45
12	56.81	47.36
Mean	66.62	54.04
SEM	5.14	8.34
CV	0.20	0.41

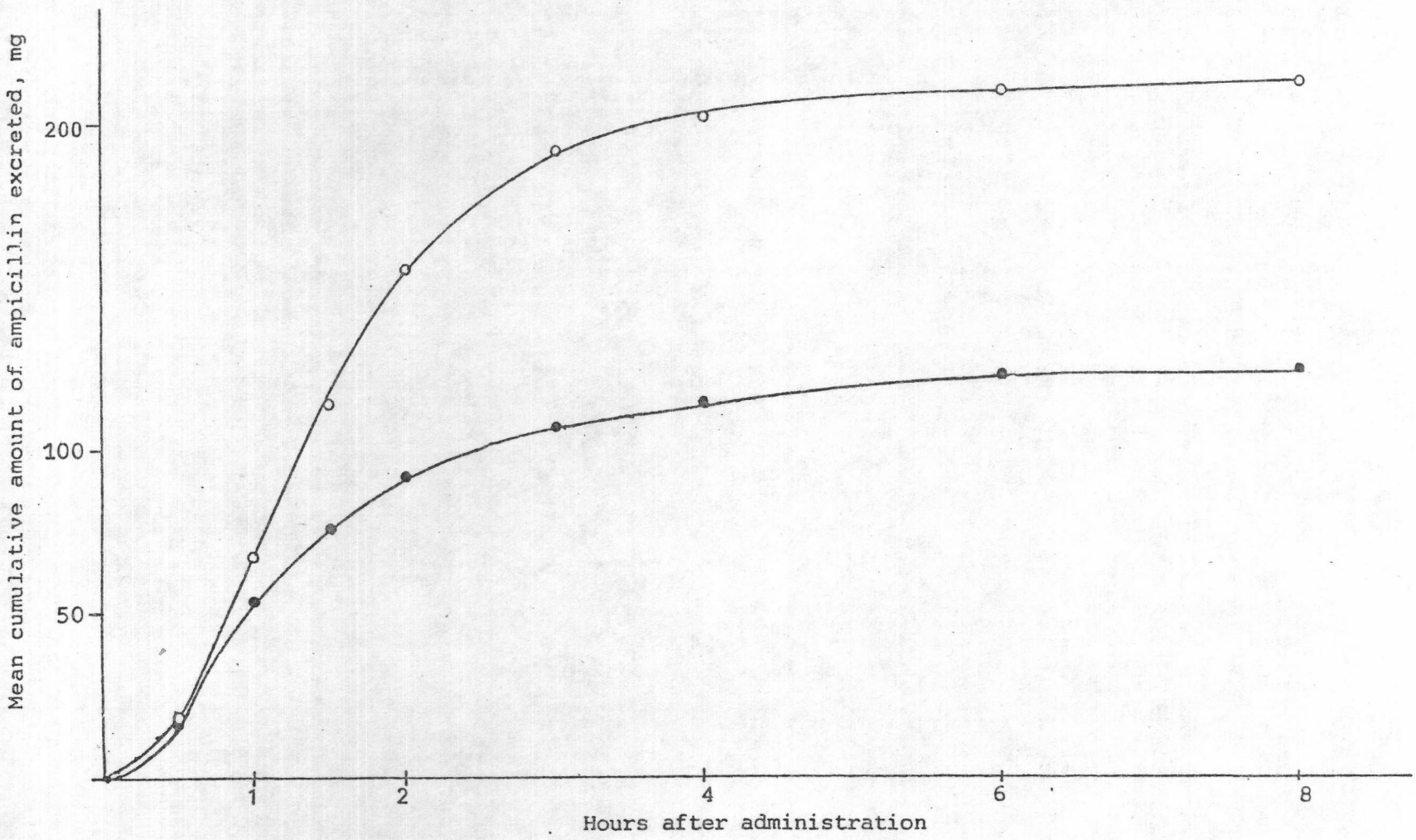

Figure 14 Cumulative urinary excretion of ampicillin after oral administration of bacampicillin 400 mg ●—● and bacampicillin 800 mg o—o in 7 subjects.

Table 12 : Non-modeling pharmacokinetic parameters after oral administration of Bacampicillin 400 mg and Bacampicillin 800 mg; fasting condition in 7 subjects

Drug	C_p (mcg/ml)			t_p (hr)			AUC_o^∞ (hr. mcg/ml)			% urinary recovery 0-8 hr.		
	Mean	SEM	CV	Mean	SEM	CV	Mean	SEM	CV	Mean	SEM	CV
Bacampicillin 400 mg (A_1)	5.64	0.61	0.28	0.75	0.13	0.47	9.27	0.81	0.23	66.62	5.14	0.20
Bacampicillin 800 mg (B)	11.26	1.26	0.30	1.11	0.14	0.34	22.36	2.40	0.28	54.04	8.34	0.41
Paird t-test[a]	$A_1 < B$			NS			$A_1 < B$			NS		

C_p mean individual peak serum levels

t_p mean individual time to peak

SEM Standard error of mean

CV Coefficient of variation

a significant at $p < 0.05$

NS not significantly different ($p > 0.05$)

Table 13 : Dose-bioavailability response of two progressive doses of ampicillin 250 and 500 mg in 14 fasting subjects and bacampicillin 400 and 800 mg in 7 fasting subjects

Drug	Dose mg	Dose-ratio	C_p	C_p-ratio	t_p	t_p-ratio	AUC_o^∞	AUC_o^∞-ratio	Total drug excreted in urine, mg	ratio	%UR	%UR-ratio
Ampicillin	250	1	2.04	1	1.68	1	5.51	1	82.54 ± 9.95	1	33.02	1
	500	2	3.93	1.93	1.71	1.01	10.97	1.99	154.99 ± 15.70	1.88	31.00	0.94
Bacampicillin	400	1	5.64	1	0.75	1	9.27	1	185.27 ± 15.43	1	66.62	1
	800	2	11.26	2.0	1.11	1.48	22.36	2.41	300.50 ± 46.39	1.62	54.04	0.81

C_p mean individual peak serum levels, mcg/ml

t_p mean individual time to reach the peak, hr

AUC_o^∞ mean area under the serum concentration-time curve from the time zero to infinity, hr. mcg/ml

%UR mean urinary recovery of ampicillin expressed as percentage of the dose

Table 14 : Serum pharmacokinetic parameters of ampicillin (Mean ± SEM) after oral administration of Bacampicillin 400 mg and 800 mg; fasting condition in 7 subjects

Determination	Bacampicillin 400 mg (A_1)	Bacampicillin 800 mg (B)	Paired-t test[a]
Peak serum concentrations (mcg/ml)	3.90 ± 0.38	9.37 ± 1.08	$A_1 < B$
Time to reach the peak (hr)	0.61 ± 0.04	0.70 ± 0.06	NS
Theoretical drug concentration at t_o extrapolated from the elimination phase (mcg/ml)	7.95 ± 1.00	24.17 ± 3.83	$A_1 < B$
Absorption rate constant, Ka (hr^{-1})	3.26 ± 0.28	2.70 ± 0.44	NS
Overall elimination rate constant, Ke (hr^{-1})	0.72 ± 0.03	0.74 ± 0.02	NS
Serum half-life, $t_{\frac{1}{2}}$ (hr)	0.97 ± 0.04	0.94 ± 0.02	NS
Area under the serum concentration curve from the time zero to infinity, AUC_o^∞ (hr. mcg/ml)	9.27 ± 0.81	22.36 ± 2.40	$A_1 < B$
Apparent volume of distribution, V_d (lit.)	40.91 ± 3.29	33.28 ± 4.55	NS
Total body clearance, Cl_T (lit./hr)	29.61 ± 3.20	24.22 ± 9.15	NS

a significant level at $p < 0.05$

NS not significantly different ($p > 0.05$)

Table 15 : Pharmacokinetic parameters calculated from urinary excretion data (Mean ± SEM) after oral administration of bacampicillin 400 and 800 mg in 7 fasting subjects

Parameters	Bacampicillin 400 mg	Bacampicillin 800 mg	Paired-t test[a]
Absorption rate constant, Ka (hr^{-1})	2.18 ± 0.25	2.14 ± 0.26	NS
Overall elimination rate constant, Ke (hr^{-1})	0.80 ± 0.04	0.78 ± 0.06	NS
	(0.97 ± 0.06)	(0.99 ± 0.07)	
Urinary excretion rate constant, ke (hr^{-1})	0.90 ± 0.12	1.30 ± 0.30	NS
Biological half-life, $t_{1/2}$ (hr)	0.88 ± 0.05	0.93 ± 0.08	NS
	(0.73 ± 0.04)	(0.72 ± 0.04)	

Note : The numbers outside parentheses calculated from urinary excretion rate plot while the numbers in parentheses obtained from the sigma-minus method

a significant level at $p < 0.05$

NS not significant different ($p > 0.05$)

5. The Influence of Food on Oral Absorption of Bacampicillin

The serum concentrations of ampicillin obtained after oral administration of bacampicillin 400 mg with meal in 7 subjects were presented in Table 16. The mean values with SEM were illustrated in Figure 15. The comparison with those obtained after oral administration of bacampicillin 400 mg in fasting condition were shown in Figure 16. The cumulative percentage of ampicillin excreted within 8 hours after administration of the two treatments were reported in Table 17 and illustrated in Figure 17.

5.1 Non-compartmental Modeling Pharmacokinetic Parameters

Table 18 revealed the non-modeling pharmacokinetic parameters generated following oral administration of bacampicillin 400 mg in fasting and non-fasting conditions. Statistical analysis showed no discernible difference in the peak serum levels, the AUC_o^∞ and the percentage urinary recovery. The time to reach the peak obtained after bacampicillin was administered with meal appeared to be slightly longer but it was not statistical significantly different.

5.2 Compartmental Modeling Pharmacokinetic Parameters

The pharmacokinetic parameters calculated from serum data were listed in Table 19. Statistical significant difference was not found for all parameters obtained after treatment A_1 and A_2 ($p < 0.05$). Inspection of Figure 16 showed that the serum concentration profiles were practically superimpossible. This

implied that the oral absorption of bacampicillin was evidently not affected by food.

The pharmacokinetic parameters calculated from urinary excretion data after the administration of bacampicillin 400 mg in fasting and non-fasting states were presented in Table 20. There were not significantly different in the absorption rate constant, the overall elimination rate constant and the biological half-life except, the slightly different in the urinary excretion rate constant obtained after oral administration of bacampicillin 400 mg in fasting and non-fasting states.

Table 16 : Serum concentrations of ampicillin (mcg/ml) after oral administration of Bacampicillin 400 mg with meal (Treatment A_2)in 7 subjects

Subject no. / Time (hr.)	02	05	06	09	10	13	14	Mean	SEM
0.25	1.07	0.40	1.43	0.36	3.94	1.54	0.06	1.26	0.50
0.5	5.04	3.73	6.53	2.89	8.10	6.07	0.09	4.64	1.00
0.75	5.78	6.78	7.58	4.91	13.89	6.56	0.82	6.62	1.47
1.0	5.88	7.82	5.20	5.71	8.90	6.28	1.40	5.79	0.86
1.5	2.72	6.32	2.78	4.60	3.62	4.18	2.06	3.75	0.54
2.0	1.67	3.99	1.51	2.22	2.33	3.06	1.99	2.39	0.33
3.0	0.81	1.48	0.64	1.02	0.73	0.96	1.48	1.02	0.13
6.0	0.10	0.13	0.08	0.09	0.45	0.11	0.14	0.16	0.05
8.0	0.03	0.04	0.02	0.04	0.08	0.04	0.04	0.04	0.0071

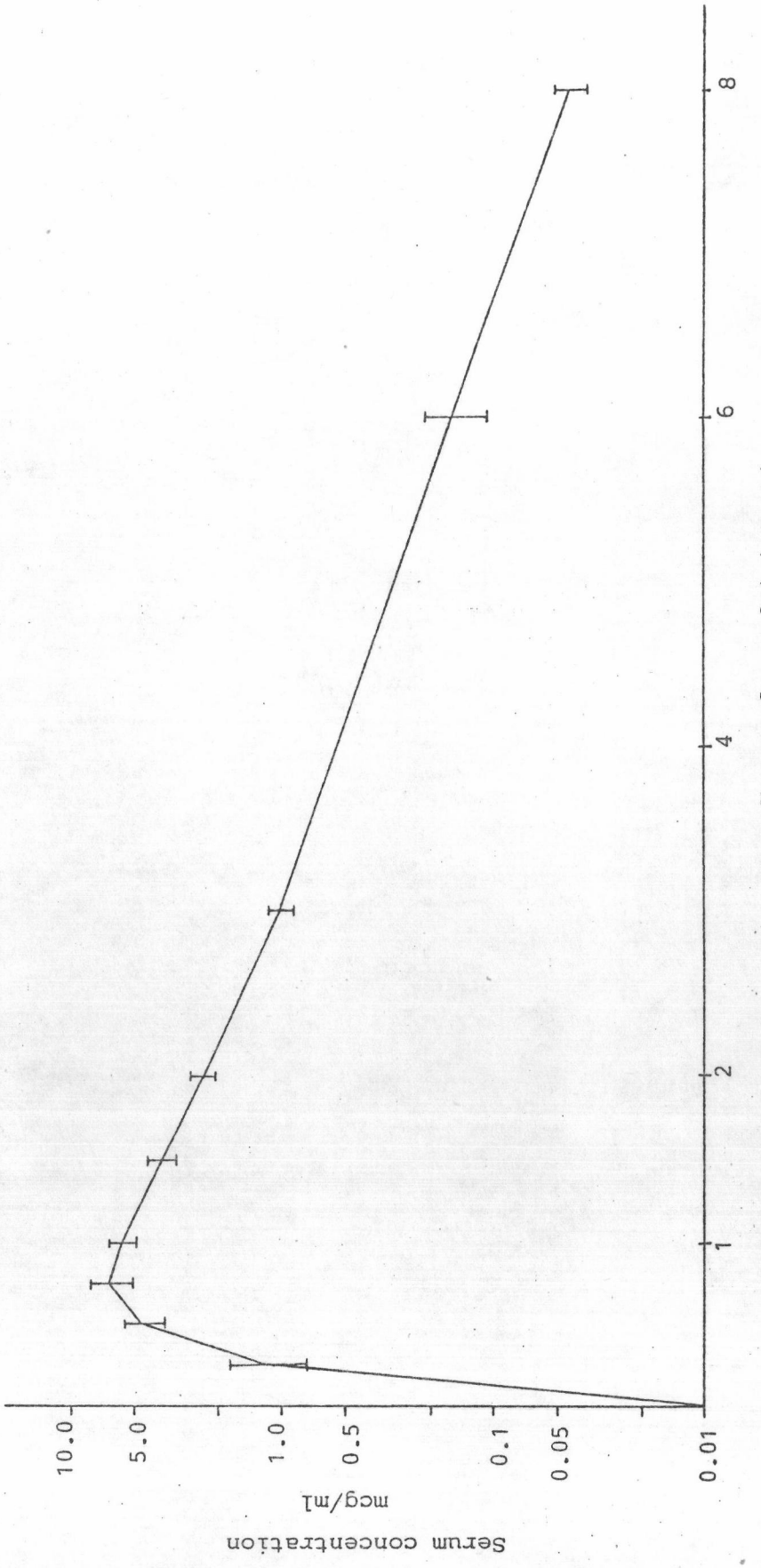

Figure 15 Mean serum levels of ampicillin (± SEM) after oral administration of bacampicillin 400 mg with meal in 7 subjects.

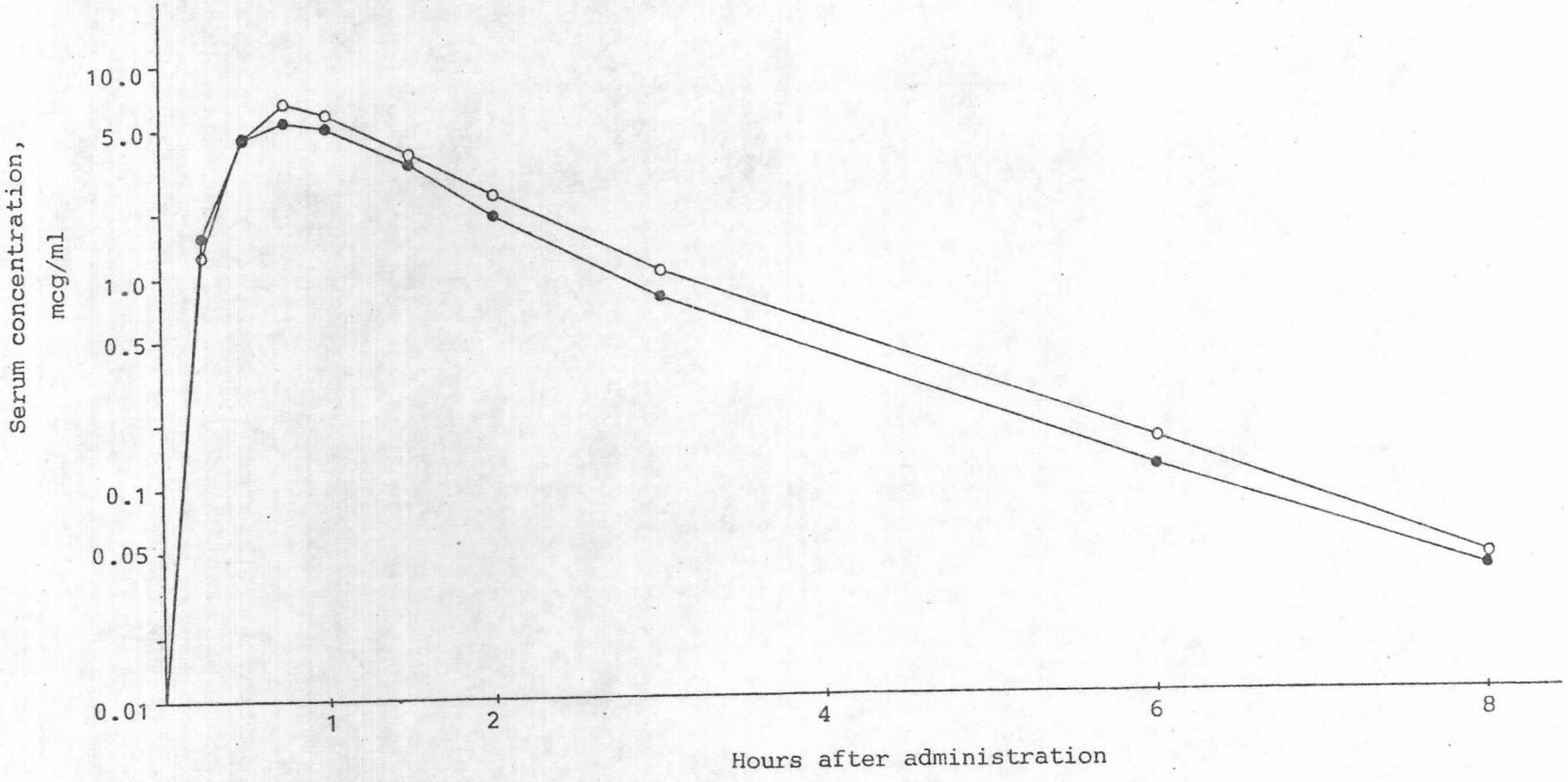

Figure 16 Mean ampicillin serum concentrations after oral administration of bacampicillin 400 mg in fasting ●—● and non-fasting state o—o in 7 subjects.

Table 17 : Cumulative urinary excretion of ampicillin at the end of 8 hours after single oral administration of Bacampicillin 400 mg, fasting condition and Bacampicillin 400 mg with meal in 7 subjects expressed as the percentage of dose.

Treatment / Subject no.	Bacampicillin 400 mg, fasted condition	Bacampicillin 400 mg, with meal
02	51.37	38.07
05	88.70	96.68
06	34.33	42.04
09	61.53	68.62
10	44.33	53.16
13	69.40	37.59
14	57.88	65.05
Mean	58.22	57.32
SEM	6.68	8.09
CV	0.30	0.37

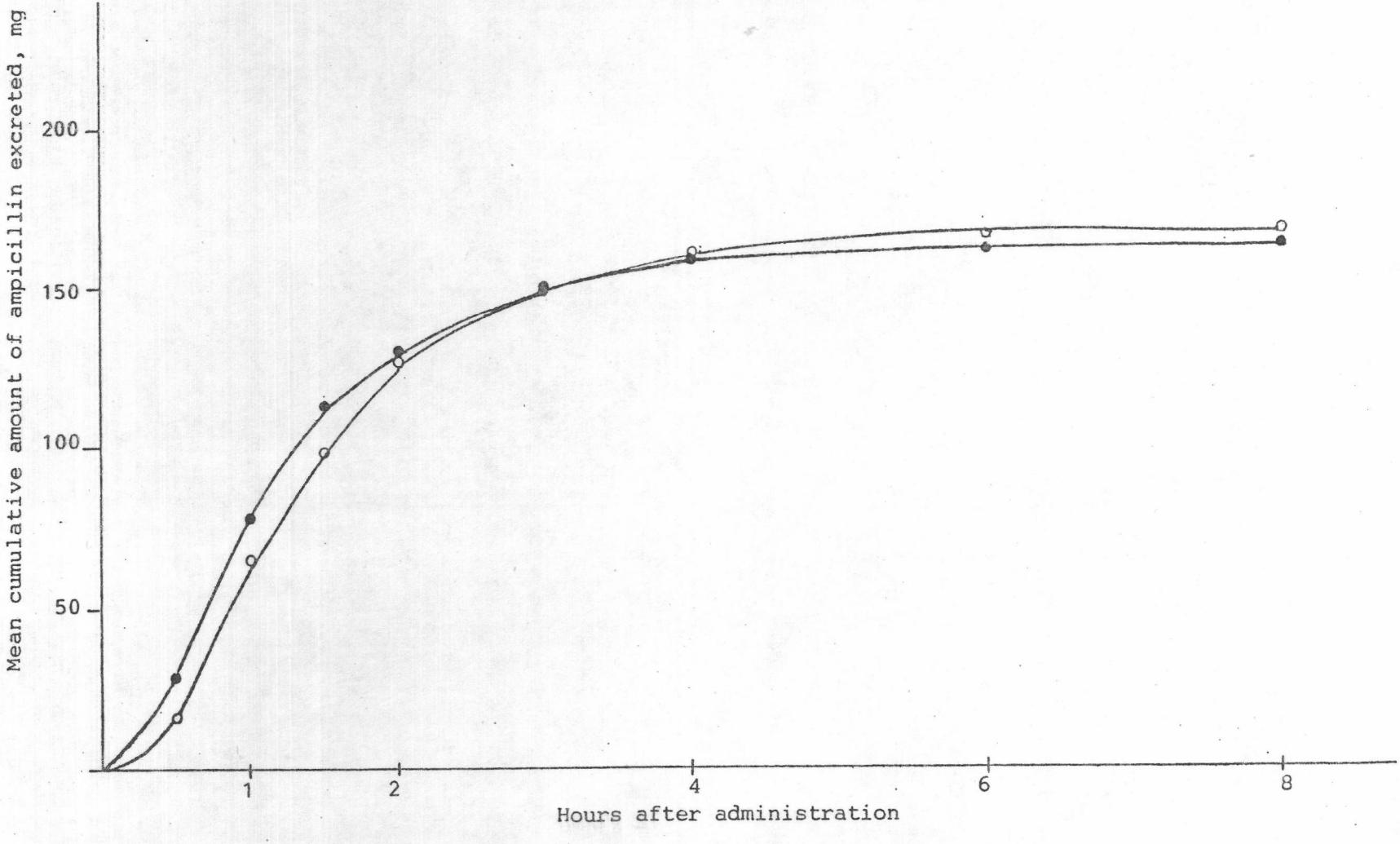

Figure 17 Cumulative urinary excretion of ampicillin after oral administration of bacampicillin 400 mg in fasting ●——● and non-fasting state o——o in 7 subjects.

Table 18 : Non-modeling pharmacokinetic parameters after oral administration of Bacampicillin 400 mg fasting and non-fasting condition in 7 subjects.

Drug	C_p (mcg/ml)			t_p (hr.)			AUC_o^∞ (hr. mcg/ml)			% urinary recovery 0-8 hr.		
	Mean	SEM	CV	Mean	SEM	CV	Mean	SEM	CV	Mean	SEM	CV
Bacampicillin 400 mg fasting state	6.33	0.48	0.20	0.89	0.05	0.15	10.59	0.89	0.22	58.22	6.68	0.30
Bacampicillin 400 mg with meal	7.07	1.34	0.50	0.96	0.10	0.28	11.46	1.31	0.30	57.32	8.09	0.37
Paired t-test[a]	NS			NS			NS			NS		

C_p mean individual peak serum levels

t_p mean individual time to peak

SEM standard error of mean

CV coefficient of variation

a significant level at $p < 0.05$

NS not significantly different ($p > 0.05$)

Table 19 : Serum pharmacokinetic parameters of ampicillin (Mean ± SEM) after oral administration of Bacampicillin 400 mg; fasting and non-fasting condition in 7 subjects.

Determination	Bacampicillin 400 mg fasting state (A_1)	Bacampicillin 400 mg with meal (A_2)	Paired t-test[a]
Peak serum concentrations (mcg/ml)	5.02 ± 0.49	4.80 ± 1.03	NS
Time to reach the peak (hr)	0.58 ± 0.04	0.74 ± 0.14	NS
Theoretical drug concentration at t_o extrapolated from the elimination phase (mcg/ml)	9.93 ± 1.05	11.04 ± 1.29	NS
Absorption rate constant, Ka (hr^{-1})	3.55 ± 0.50	3.14 ± 0.75	NS
Overall elimination rate constant, Ke (hr^{-1})	0.73 ± 0.03	0.72 ± 0.02	NS
Serum half-life, $t_{1/2}$ (hr)	0.96 ± 0.04	0.97 ± 0.04	NS
Area under the serum concentration curve from the time zero to infinity, AUC_o^∞ (hr. mcg/hr)	10.59 ± 0.89	11.46 ± 1.31	NS
Apparent volume of distribution, V_d (lit.)	34.96 ± 3.36	33.34 ± 4.66	NS
Total body clearance, Cl_T (lit/hr)	25.14 ± 2.18	23.72 ± 2.83	NS

a significant level at $p < 0.05$

NS not significantly different ($p > 0.05$)

Table 20 : Pharmacokinetic parameters calculated from urinary excretion data (Mean ± SEM) after oral administration of bacampicillin 400 mg in fasting and non-fasting states in 7 subjects

Parameters	Bacampicillin 400 mg fasting state (A_1)	Bacampicillin 400 mg with meals (A_2)	Paired-t test[a]
Absorption rate constant, Ka (hr^{-1})	2.52 ± 0.43	2.11 ± 0.49	NS
Overall elimination rate constant, Ke (hr^{-1})	0.78 ± 0.04	0.82 ± 0.05	NS
	(0.94 ± 0.07)	(0.98 ± 0.06)	
Urinary excretion rate constant, ke (hr^{-1})	1.24 ± 0.18	0.89 ± 0.22	$A_1 > A_2$
Biological half-life, $t_{1/2}$ (hr)	0.91 ± 0.05	0.94 ± 0.08	NS
	(0.75 ± 0.04)	(0.72 ± 0.04)	

Note : The numbers outside parentheses calculated from urinary excretion rate plot while the numbers in parentheses obtained from the sigma-minus method

a significant level at $p < 0.05$

NS not significantly different ($p > 0.05$)

6. Comparison of the Pharmacokinetic Parameters Obtained from Serum Concentration Profiles with Those Obtained from Urinary Excretion Data

By the semilogarithmic plot of the urinary excretion rate versus time and the method of sigma-minus, some relevant pharmacokinetic parameters were obtained and presented in Table 9, 15, 20. The statistical comparisons between the results obtained from serum data and urinary excretion data were presented in Table 21. The Student's t test showed no significant difference in the absorption rate constants calculated from serum data and urinary excretion data after the oral administration of bacampicillin 400 mg with meal, ampicillin 250 and 500 mg ($p < 0.05$). Following bacampicillin 400 and 800 mg, there was significant difference in absorption rate constants obtained from serum data and urinary excretion data at $p < 0.05$ however, when the significant level changed to $p > 0.01$ the difference between the two values could not be detectable. Some discrepancies in overall elimination rate constants and the biological half-lives obtained after oral administration of bacampicillin 400 and 800 mg were noted. Additionally, the parameters calculated using the semilogarithmic plot of urinary excretion rate versus time were more closely resembled those calculated from serum data than those obtained from the sigma-minus method.

Table 21 : Statistical comparison of some pharmacokinetic parameters obtained from serum data with those obtained from urinary excretion data

Drug	Absorption rate constant, Ka (hr^{-1})		Overall elimination rate constant, Ke (hr^{-1})			Serum half-life, $t_{\frac{1}{2}}$ (hr)		
	Serum (S)	Urine (U_1)	Serum (S)	Urine (U_1)	Urine (U_2)	Serum (S)	Urine (U_1)	Urine (U_2)
Bacampicillin 400 mg (A_1)	3.40 ± 0.28	2.35 ± 0.24	0.72 ± 0.02	0.79 ± 0.03	0.96 ± 0.04	0.97 ± 0.03	0.90 ± 0.03	0.74 ± 0.03
Paired t-test[a]	$S > U_1$ ($p < 0.05$) NS ($p > 0.01$)		$S < U_1 < U_2$			$S > U_1 > U_2$		
Bacampicillin 400 mg with meal (A_2)	3.14 ± 0.75	2.14 ± 0.26	0.72 ± 0.02	0.78 ± 0.06	0.99 ± 0.07	0.97 ± 0.04	0.93 ± 0.08	0.72 ± 0.04
Paired t-test[a]	NS		NS between S, U_1 $S < U_2$			NS between S, U_1 $S > U_2$		
Bacampicillin 800 mg (B)	2.70 ± 0.44	2.11 ± 0.49	0.74 ± 0.02	0.82 ± 0.05	0.98 ± 0.06	0.94 ± 0.02	0.94 ± 0.08	0.72 ± 0.04
Paired t-test[a]	$S > U_1$ ($p < 0.05$) NS ($p > 0.01$)		$S < U_1 < U_2$			NS between S_1, U $S < U_2$		

Table 21 : (Continued)

Drug	Absorption rate constant, Ka (hr^{-1})		Overall elimination rate constant, Ke (hr^{-1})			Serum half-life, $t_{\frac{1}{2}}$ (hr)		
	Serum (S)	Urine (U_1)	Serum (S)	Urine (U_1)	Urine (U_2)	Serum (S)	Urine (U_1)	Urine (U_2)
Ampicillin 250 mg (C)	1.37 ± 0.15	1.44 ± 0.15	0.71 ± 0.02	0.68 ± 0.05	0.88 ± 0.06	0.99 ± 0.03	1.10 ± 0.08	0.84 ± 0.06
Paired t-test[a]	NS		NS between S, U_1 $S < U_2$			NS between S, U_1 $S > U_2$		
Ampicillin 500 mg (D)	1.17 ± 0.08	1.19 ± 0.08	0.63 ± 0.04	0.63 ± 0.06	0.79 ± 0.06	1.15 ± 0.07	1.23 ± 0.11	0.94 ± 0.06
Paired t-test[a]	NS		NS between S, U_1 $S < U_2$			NS between S, U_1 $S > U_2$		

a significant level at $p < 0.05$

NS not significantly different by the Student's t test

S parameters calculated from serum data

U_1 parameters calculated from urinary excretion rate plot

U_2 parameters calculated from sigma-minus method