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Phase I Clinical Studies of S-1108: Safety and Pharmacokinetics in a Multiple-Administration Study with Special Emphasis on the Influence on Carnitine Body Stores

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S-1108, the prodrug of S-1006, was given to healthy volunteers three times a day (TID) for 8 days in a dose of 200 mg in a crossover placebo-controlled study. The safety of S-1108 and the pharmacokinetics of S-1006 and pivalic acid liberated from pivaloyloxymethyl ester of S-1108 were investigated. There were no abnormal symptoms or signs, as observed by physical and laboratory tests. The half-life and area under the concentration-time curve of S-1006 was reduced from 1.11 ± 0.17 h at the first dose to 0.87 ± 0.18 h at the last dose and from 7.30 ± 1.10 to 5.20 ± 0.85 μg · h/ml, respectively. However, there was no significant difference in the peak concentration between the two doses. Pivalic acid was found to be completely detoxified by conjugation with carnitine. The total urinary recovery of pivalic acid as pivaloylcarnitine was 98.7 ± 3.6%, resulting in an increase of daily carnitine urinary excretion two- to threefold the predose value. During the multiple administration of S-1108, the plasma carnitine concentration was reduced to and maintained at 50 to 70% of the control value, suggesting that there might be enough carnitine store in the body to detoxify the pivalic acid in a dose of 200 mg TID. Moreover, the reduced plasma carnitine was rapidly returned to the control value within a few days after the cessation of the administration of 200 mg TID.

S-1108 is a new oral cephem antibiotic that possesses a pivaloyloxymethyl ester group. It is easily deesterified in the intestine and converted to its active form, S-1006, which is highly active against a wide range of gram-positive and gram-negative bacteria except several bacteria such as *Pseudomonas aeruginosa* and enterococci. There are some other antibiotics that are esterified with a pivaloyloxymethyl group to increase the extent of absorption. These prodrugs, such as cefteram pivoxil, pivampicillin, and pivmecillinam, have already been used for the treatment of infectious diseases. The clinical efficacy, safety, and pharmacokinetics of these active forms were sufficiently investigated.

Recently, it has been reported that prodrugs having a pivaloxyloxymethyl ester group might promote myopathic carnitine deficiency in humans (4). However, the pharmacological, toxicological, and pharmacokinetic properties of metabolites liberated from these prodrugs have not been sufficiently investigated. It is well known (2, 9) that a prodrug having a pivaloyloxymethyl ester group is further metabolized to produce pivalic acid and formaldehyde. Pivalic acid is excreted in urine mainly as a conjugate with carnitine, resulting in a decrease of carnitine stores in the body, especially in the case of long-term therapy with these prodrugs (4–6, 11). The metabolism of S-1108 was studied, as shown in Fig. 1 (10a). As mentioned above, the liberated pivalic acid from S-1108 might reduce carnitine stores by the formation of pivaloylcarnitine. The purpose of this study is to investigate the safety of S-1108 and the pharmacokinetics of S-1006 and pivalic acid liberated in healthy volunteers following multiple oral administrations of S-1108 in a placebo-controlled crossover study. In particular, we studied the effects of the oral administration of S-1108 on the concentration in plasma and the urinary excretion of carnitine in the same healthy volunteers.

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MATERIALS AND METHODS

Materials. The chemical structures of S-1108 and its active form, S-1006, are shown in Fig. 1. They are both slightly soluble in water. In this study, S-1108 was supplied from Shionogi Research Laboratories as a tablet which contains 100 mg of the active substance. Placebo tablets were also prepared by Shionogi Research Laboratories.

Subjects. Eight healthy Japanese male volunteers participated in this study, which was approved by a local ethics committee. They were selected from many candidates after physical and laboratory examinations such as those for hematology, blood pressure, respiratory rate, blood chemistry, urinalysis, allergies to β-lactam antibiotics; an electrocardiogram and the Coombs test were also performed. They were given information about the purpose and methods of this study and the safety and efficacy of S-1108 before giving their informed written consents. The ages of the subjects ranged from 25 to 45 years (mean, 32 years), and their weights ranged from 50 to 77 kg (mean, 63 kg).

Study design. Eight volunteers were randomly divided into two groups of four volunteers each. To each volunteer in the first group, two tablets of S-1108 were given with 100 ml of tap water three times a day (TID) at 9:00, 15:00, and 21:00, 30 min after meals for 8 consecutive days for a total of 22 doses. To four volunteers in the other group, two placebo tablets were given according to the same schedule as the S-1108-treated group. Volunteers were blinded as to which tablet was given at each time. They were not allowed to drink alcoholic or caffeine-containing beverages, to smoke,

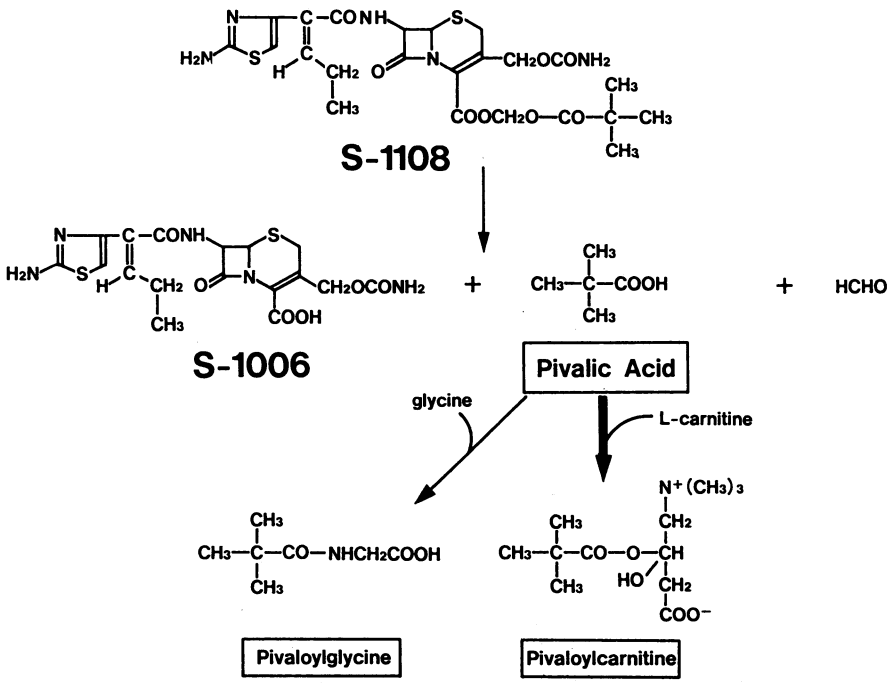

FIG. 1. Chemical structures of S-1108 and its metabolic pathway.

or to take any other medicine during the study. After a washout period of 1 month, the same study was carried out by exchanging the S-1108 tablet and placebo tablet between the two groups. This crossover study was conducted in the Shionogi Pharmacological Laboratory.

Clinical observations, physical tests, electrocardiograms, and laboratory tests. Clinical observations (subjective and objective symptoms) were performed just before each dosing: 2 h after the morning dose on the first, fourth, and sixth days and 24 h after the last dose. Physical tests were performed before and at 1, 2, 3, 4, and 6 h after the dose on the first and last days; at 8, 10, and 14 h on the first day; and before, 2, 6, 8, 12, and 14 h on the other days. Electrocardiograms were monitored and recorded (DS-1020; Fukuda Denshi) for 30 min before and at 1 day after the study. Laboratory tests (hematology, blood chemistry, and urinalysis) were performed before and 1 day, 1 week, and 2 weeks after the study.

Blood and urine samples. Five milliliters of blood was drawn before and at 1, 1.5, 2, 2.5, 3, 4, 5, and 6 h after the first and last doses. Additional blood samples were drawn at 8, 10, 12 h after the last dose. Blood samples were drawn just before the morning dose every day and at 2 and 4 h after the 10th and 16th doses. In addition, blood sampling was continued once daily for 7 days and at 2 weeks after the end of multiple dosings. All blood samples were collected into heparinized tubes and immediately centrifuged at 3,000 rpm for 15 min under cooling. The plasma was stored at −20°C until analysis.

Urine was collected just before the first dose; then as block samples at 0 to 2, 2 to 4, and 4 to 6 h after the first and last doses; and additionally at 6 to 8, 8 to 10, 10 to 12, and 12 to 24 h after the last dose. On the day after the last dose, urine was collected on the same schedule as that for the last-dose day. After every dose except the first and last doses, urine was collected for the dosing interval. From the second to sixth days and at 1, 2, and 3 weeks after the last dose day, urine was collected every 24 h. The volume of the urine sample was measured accurately, and then two 4-ml aliquots from each well-mixed block sample were stored at −20°C until the assay. Blood and urine were obtained on the same schedule for both S-1108 and the placebo tablets.

Assay methods. The concentrations of S-1006 in plasma and urine samples were determined by a high-performance liquid chromatography method by using a Shimadzu LC-6A pump equipped with a C-R3A integrator and a SPD-6AV detector. The plasma and urine samples were cleaned by using a Bond Elut C18 column. S-1006 in the eluted plasma sample of 100 μl was separated with a Cosmosil 5C18 column (4.6 by 150 mm) with a mobile phase of 50 mM phosphate-buffered saline (PBS; pH 6.0)–2 mM tetraoctylammoniumbromide (THAB) in CH_3CN (64:36) with a flow rate of 0.8 ml/min by using coumarin-3-carboxylic acid as an internal standard and was detected by UV radiation at 262 nm. S-1006 in the eluted urine sample of 10 μl was separated by using a Nucleosil 5C18 column (4.6 by 250 mM) with a Spheri 5C18 column (4.6 by 30 mm) as a guard column with a mobile phase of 50 mM PBS (pH 6.0)–8 mM THAB in CH_3CN-CH_3OH (70:27:3) with a flow rate of 1 ml/min by using the same internal standard. The detection limits were 0.1 and 0.5 μg/ml for plasma and urine, respectively, with a coefficient of variation of 7% for both.

The concentration of pivalic acid was determined by gas chromatography by a method described previously report (10b). The detection limits of pivalic acid were 0.2 and 0.5 μg/ml for plasma and urine, respectively. Coefficients of variation at the assay ranges were less than 8 and 3% for plasma and urine, respectively.

The pivaloylcarnitine concentration in plasma and urine was determined by a high-performance liquid chromatography method (4a). The detection limits of pivaloylcarnitine were 0.02 μg/ml for plasma and 1 μg/ml for urine. The coefficients of variation at the assay ranges were less than 4% for both.

Free and total carnitine concentrations in plasma obtained just before the morning dose and in 24-h urine samples (from 9:00 to 9:00) were determined by the method of Cederblad and Lindstedt (3) with modifications of the method of Parvin and Pande (8). The detection limits of carnitine were 6 and 25 nmol/ml, respectively, with a coefficient of variation of 5% for both.

Pharmacokinetic analysis of data. Concentrations in plasma of S-1006 and pivaloylcarnitine (i.e., converted pivalic acid) were fitted to a one-compartment model with first-order absorption and absorption lag time by nonlinear least-squares regression using the NONLIN program (7), with each concentration weighted equally. Individual and mean values were analyzed separately, depending on whether the sampling took place after the first or last dose, by using derived equations for a single dose and multiple doses with nonuniform dosing intervals, respectively. Pharmacokinetic parameters such as the elimination half-life ($t_{1/2}$) and the area under the concentration-time curve ($AUC_{0-\infty}$) resulting from each dose were calculated by using the estimated first-order elimination rate constant and the apparent distribution volume (V/F, with F as the extent of absorption) as follows: $t_{1/2} = \ln 2/k_{el}$ and $AUC = F \cdot dose/V \cdot k_{el}$. The renal clearance of S-1006 was calculated by dividing the amount excreted in urine in the period from 4 to 6 h by the concentration in plasma at 5 h, the mid-point of the urine collection period, for both the first and the last doses. The renal clearance of pivaloylcarnitine was also calculated by using the amount excreted in urine from 2 to 6 h and the concentration in plasma at 4 h after dosing for the first and last doses. The differences in these pharmacokinetic parameters between those taken after the first dose and the last dose were evaluated by using a paired t test ($P = 0.05$).

RESULTS

Tolerance and safety. Eight volunteers received S-1108 (200 mg TID for 8 days) and tolerated it well, both subjectively and objectively. No side effects and no abnormal values in physical and laboratory tests were observed throughout the study. There were no increases in phosphokinase, aldolase, or long-chain fatty acid concentrations.

Pharmacokinetics. (i) Concentration in plasma. Mean concentrations in plasma of S-1006 for eight volunteers are shown in Fig. 2. Peak values were observed at 2 h after both the first and the last doses, showing 2.08 ± 0.41 and 1.83 ± 0.45 (mean ± standard deviation) μg/ml, respectively. There was no significant difference between these values. The concentration in plasma plotted on a semilogarithm paper showed a monoexponential elimination in the postabsorption phase. Table 1 shows the pharmacokinetic parameters of S-1006 obtained by curve fitting to a one-compartment model by using the concentrations in plasma after the first and last doses. Data of subject 6 after the first dose could not be fitted to the compartment model because there was a plateau in the concentration from 1.5 to 4 h, suggesting absorption other than first-order kinetics occurred in this subject. Therefore, a paired t test of pharmacokinetic parameters was performed except for subject 6. The half-life ranged from 0.88 to 1.33 h after the first dose and from 0.63 to 1.19 h after the last dose; the half-life after the last dose was significantly shorter than that after the first dose. The calculated AUC after the last dose was significantly smaller than that after the first dose. The observed C_{max} tended to be smaller after the last dose, but the difference was not significant. Figure 2 also shows the curve simulated using the pharmacokinetic parameters estimated from data after the first dose. The observed values after the last dose were a little lower than the simulated ones.

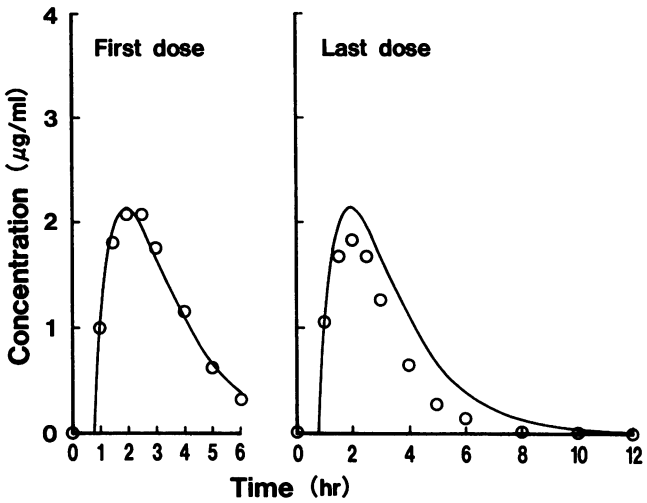

FIG. 2. Mean concentrations in plasma of S-1006 and its simulated curve following multiple administrations of 200 mg.

Mean concentrations in plasma of pivalic acid and pivaloylcarnitine, converted pivalic acid, are shown in Fig. 3. Most of the pivalic acid liberated from S-1108 was detected as pivaloylcarnitine after the first dose. However, the pivalic acid concentration gradually increased, even though it remained lower than the pivaloylcarnitine concentration. Table 2 shows the pharmacokinetic parameters of pivaloylcarnitine. There were no differences in the $t_{1/2}$, C_{max}, and AUC values between those taken after the first and the last doses. The $t_{1/2}$ of pivaloylcarnitine was longer than that of S-1006, and peak concentrations were observed later than those of S-1006. The concentration-time curve of pivaloylcarnitine simulated using the parameters estimated from first-dose data is also shown in Fig. 3, suggesting there are no differences between the observed and simulated values after the last dose. Concentrations in plasma of pivalic acid were too low to be analyzed pharmacokinetically.

Figure 4 shows the mean concentrations in plasma of carnitine throughout the study. When placebo tablets were given, the plasma carnitine concentrations were almost constant (about 60 nmol/ml). On the other hand, the administration of S-1108 reduced the plasma carnitine concentration significantly. The plasma carnitine concentration declined to values as low as 30 nmol/ml until the fourth day of the study, and this carnitine level was maintained during the multiple-administration period thereafter. After the end of administration, the concentration of carnitine in plasma was rapid to return to the normal value, and after a 4-day washout period there was no significant difference between the concentrations for the S-1108-treated and placebo-treated groups.

Urinary recovery. Figure 5 shows the mean urinary recovery of S-1006 within a dose interval (6 or 12 h) and the total recovery throughout the study. Each urinary recovery was about 30% and was almost constant throughout the study. The total recovery was 30.6 ± 1.7%. The renal clearances of S-1006 were 239 ± 61 and 285 ± 84 ml/min after the first and last doses, respectively. The renal clearance after the first dose tended to be smaller than that after the last dose, but the difference was not significant.

TABLE 1. Pharmacokinetic parameters of S-1006 after multiple administrations of 200 mg of S-1108

Dose no. and subject	V/E (liters)	$t_{1/2}$ (h)	τ (h)[a]	C_{max} (μg/ml)[b]	T_{max} (h)[b]	$AUC_{0-\infty}$ (μg · h/ml)[c]
1						
1	46.8	0.99	0.86	2.09	1.50	6.10
2	35.5	1.00	0.63	2.95	1.50	8.16
3	40.6	0.88	0.75	2.38	1.50	6.28
4	40.1	1.17	1.36	2.96	2.50	8.44
5	48.1	1.07	0.52	1.74	2.00	6.42
6				1.52	4.00	
7	54.3	1.32	0.77	1.87	2.50	7.03
8	44.1	1.33	1.12	2.48	2.50	8.69
Mean (SD)	44.2 (6.2)	1.11 (0.17)	0.86 (0.29)	2.25 (0.54)	2.25 (0.85)	7.30 (1.10)
Mean (8)[d]	48.9	1.26	0.77	2.08	2.00	7.41
22						
1	60.1	0.87	0.61	1.56	1.50	4.19
2	37.5	0.63	0.71	2.04	1.50	4.86
3	45.8	0.74	0.84	1.68	2.00	4.68
4	36.1	0.82	0.69	2.84	1.50	6.59
5	68.7	1.19	0.58	1.48	2.00	5.01
6	40.4	0.80	0.95	2.39	2.00	5.68
7	46.9	0.80	1.76	2.04	2.50	4.90
8	50.8	1.08	0.59	2.03	1.50	6.14
Mean (SD)	48.3 (11.3)	0.87 (0.18)	0.84 (0.39)	2.01 (0.45)	1.81 (0.37)	5.20 (0.85)
Mean (8)[d]	48.7	0.89	0.74	1.83	2.00	5.26

[a] Lag time for absorption.
[b] Observed value.
[c] Calculated by parameters as $AUC_{0-\infty}$ from each first and last dose.
[d] Mean concentrations in plasma of eight volunteers were analyzed.

Figure 6 shows the mean daily and whole urinary recoveries of total pivalic acid (free pivalic acid and its conjugates). The urinary recovery on the 8th day was for 6 h (the dose interval in the daytime) after the last dose. Daily urinary recoveries were about 90%, and the total recovery throughout the study was 95.5 ± 3.3%. This high urinary recovery suggested that pivalic acid, whether incorporated with or liberated from S-1108, was absorbed almost completely. However, there was no free pivalic acid detected in any urine sample. On the other hand, the urinary recovery of pivalic acid as pivaloylcarnitine was 98.7 ± 3.6%, which was comparable to the recovery of total pivalic acid. Renal clearances of pivaloylcarnitine were 118.1 ± 22.5 and 129.8 ± 26.1 ml/min after the first and last doses, respectively, without a significant difference between the two doses.

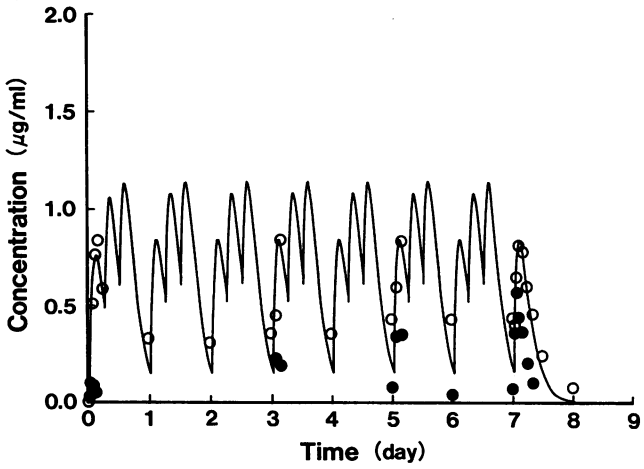

FIG. 3. Mean concentrations in plasma of pivalic acid (○) and pivaloylcarnitine (●) and the simulated curve of pivaloylcarnitine following multiple administrations of 200 mg.

Figure 7 shows the mean daily urinary excretion of carnitine in the S-1108-treated and placebo-treated groups throughout the study. In the placebo-treated group, the daily urinary excretion of total carnitine (free carnitine and its conjugates) was about 500 μmol and about half was free carnitine. However, during the multiple administration of S-1108, the daily urinary excretion of total carnitine increased to two to three times the no-dose value. Most of the excreted carnitine was in its conjugate form (pivaloylcarnitine). After the rebound to less than the normal value for 2 or 3 days after the completion of multiple administrations, it was restored to the normal value.

DISCUSSION

S-1108 was developed as a cephem antibiotic prodrug in order to improve the intestinal absorption of its active form, S-1006. Recently, such prodrugs that possess a pivaloyloxymethyl side chain have been reported to reduce the amount of carnitine in the body. It was reported that carnitine has important roles in fatty acid oxidation and the modulation of the acyl coenzyme A/coenzyme ASH ratio (1). Carnitine deficiency is found commonly in patients with metabolism disorders (10) such as acyl coenzyme A dehydrogenase deficiency and organic acidurias. Therefore, we conducted this multiple-administration study with special

TABLE 2. Pharmacokinetic parameters of pivaloylcarnitine after multiple administrations of 200 mg of S-1108

Dose no. and subject	V/F (liters)	$t_{1/2}$ (h)	τ (h)[a]	C_{max} (μg/ml)[b]	T_{max} (h)[b]	$AUC_{0-\infty}$ (μg · h/ml)[c]
1						
1	26.5	1.65	0.94	0.728	3.00	4.05
2	25.2	2.60	0.82	1.030	4.00	6.69
3	21.5	1.68	0.87	0.958	3.00	5.08
4	27.8	3.08	1.75	0.973	4.00	7.20
5	41.8	3.92	0.83	0.725	4.00	6.09
6	50.4	7.45	1.50	0.774	4.00	9.61
7	30.7	2.38	1.62	0.824	4.00	5.04
8	37.9	4.71	1.67	0.908	4.00	8.08
Mean (SD)	32.7 (9.8)	3.43 (1.93)	1.25 (0.42)	0.865 (0.118)	3.75 (0.46)	6.48 (1.81)
Mean (8)[d]	29.7	2.63	0.94	0.841	4.00	5.74
22						
1	38.3	2.62	0.62	0.627	4.00	4.44
2	24.6	2.10	0.60	0.823	3.00	5.55
3	31.3	2.90	0.86	0.869	3.00	6.02
4	42.7	3.81	0.55	0.786	3.00	5.80
5	58.0	4.62	0.65	0.754	3.00	5.18
6	50.3	5.33	0.91	0.935	4.00	6.89
7	25.5	2.26	1.64	0.855	4.00	5.75
8	61.7	6.54	0.75	0.970	3.00	6.89
Mean (SD)	41.6 (14.2)	3.77 (1.60)	0.82 (0.35)	0.827 (0.108)	3.38 (0.52)	5.82 (0.82)
Mean (8)[d]	33.6	3.08	0.64	0.811	3.00	5.96

[a] Lag time for absorption.
[b] Observed value.
[c] Calculated by parameters as $AUC_{0-\infty}$ from each first and last dose.
[d] Mean concentrations in plasma of eight volunteers were analyzed.

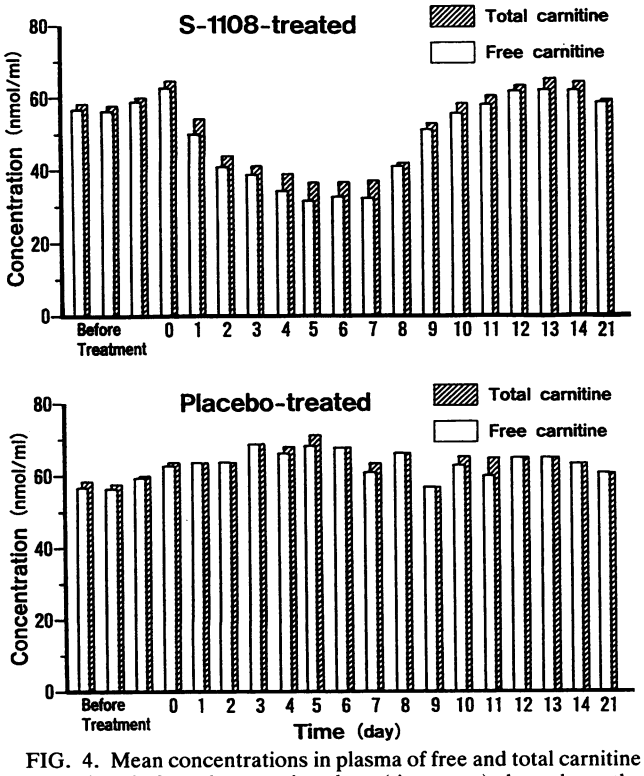

FIG. 4. Mean concentrations in plasma of free and total carnitine at 9:00, just before the morning dose (time zero) throughout the study.

attention to the safety of S-1108 during and after the study. The safety of S-1108 was assessed in this placebo-controlled crossover study in which two groups of four volunteers each received 200 mg of S-1108 orally TID for 8 days. The results indicated that S-1108 gives rise to no abnormalities in symptoms or in physical and laboratory tests, suggesting that S-1108 is safe and can be well tolerated in humans. The plasma carnitine concentration, however, decreased significantly, as reported previously (4–6, 11). This reduction is discussed later.

The pharmacokinetic analysis of the S-1006 concentration in plasma showed that the half-life of S-1006 was about 1 h. However, it was found that the $t_{1/2}$ and AUC became a little shorter and smaller after multiple administrations for 7 days.

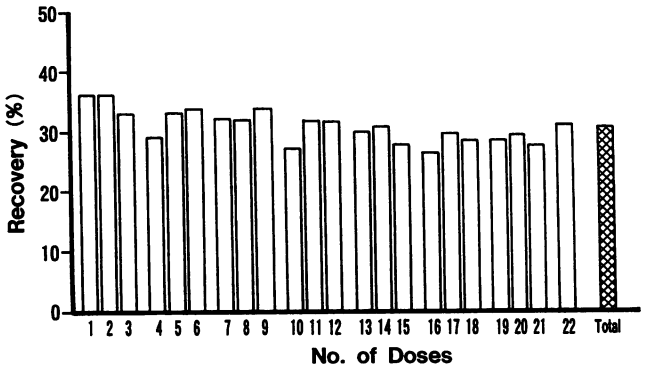

FIG. 5. Mean recoveries in urine of S-1006 following multiple administrations of 200 mg.

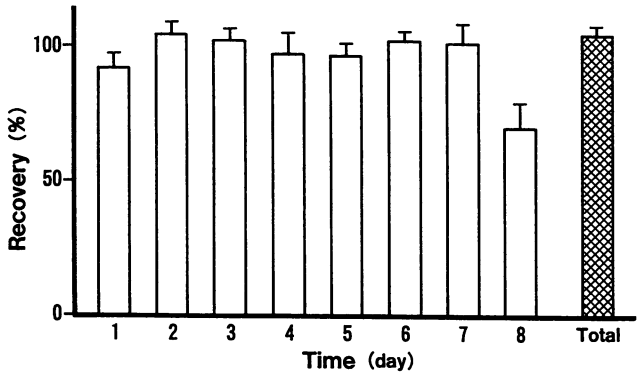

FIG. 6. Mean recoveries in urine of pivalic acid following multiple administrations of 200 mg.

These changes were supposedly caused by accelerated urinary excretion and/or the extent of reduced absorption. As shown in Fig. 5, the urinary recovery of S-1006 on the first day was a little greater than those on other days. However, on the second day and thereafter, the urinary recovery remained constant, suggesting that the extent of absorption was somewhat reduced compared with that on day 1, but it was not affected further by multiple administrations. It is reasonable to consider that absorption on day 1 happened to be better than that on the other days. On the other hand, renal clearance of S-1006 after the last dose was slightly higher than that after the first dose. Therefore, the differences in the AUC and the half-life between the first and last doses might be a reflection of better absorption on the first day and the acceleration of renal excretion after the last dose. However, the differences in concentrations in plasma after the last dose between the observed and simulated values are small, as shown in Fig. 2. These results imply that the changes in the extent of absorption and renal clearance were so small that the concentration in plasma could not be affected during multiple administrations.

Pivalic acid, which is incorporated in S-1108 as a pivaloyloxymethyl group, is liberated easily from S-1108 in the gastrointestinal tract or in the absorption process of S-1108. The urinary recovery rate of as high as 95% shows that pivalic acid was absorbed completely. On the other hand,

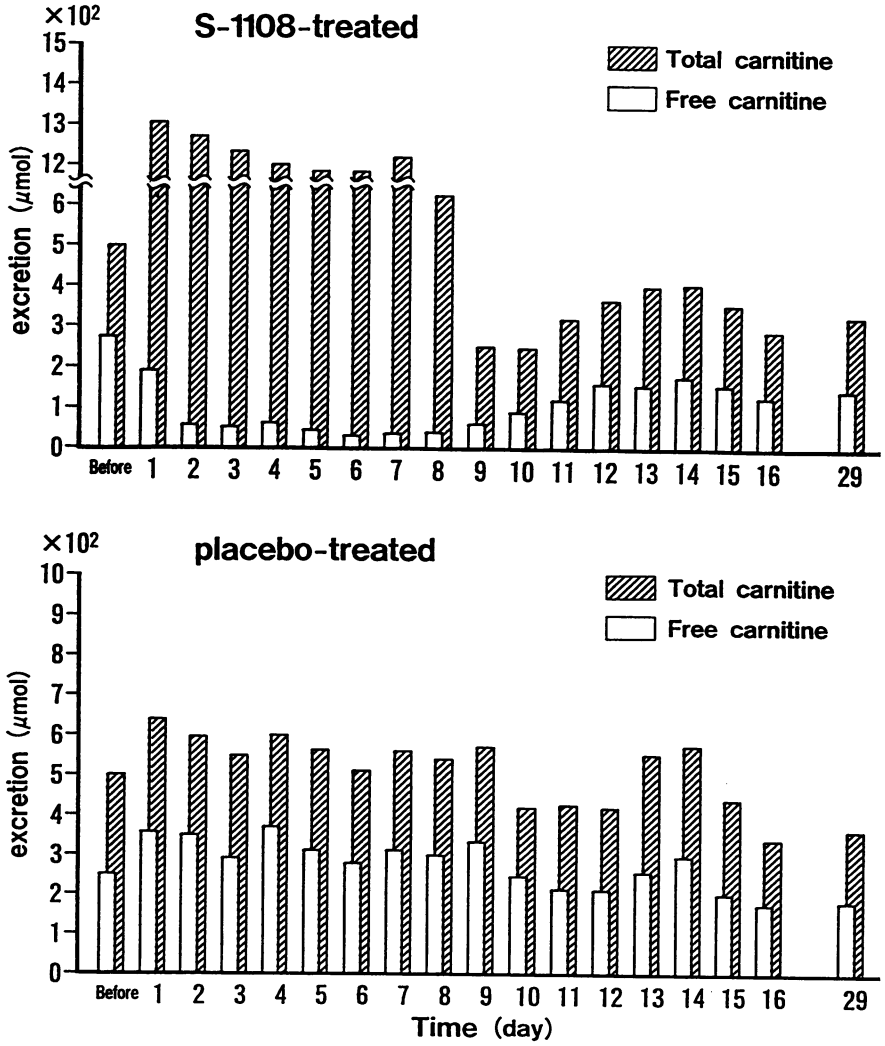

FIG. 7. Mean daily recoveries in urine of total and free carnitine throughout the study.

the extent of absorption of S-1108, about 30% as estimated from the urinary recovery, suggested that 30% or more of the pivalic acid was absorbed as S-1108 and the rest was absorbed as free pivalic acid. Because of the coincidence in urinary recoveries of total pivalic acid and pivaloylcarnitine, pivalic acid was considered to be excreted quantitatively in urine as pivaloylcarnitine. Moreover, the renal clearance of pivaloylcarnitine did not change during multiple administrations. These results indicated that pivalic acid was detoxified with carnitine and completely excreted in urine, even though there was some increase in the pivalic acid concentration during multiple administrations. This increase in the pivalic acid concentration seemed to be due to the decrease of carnitine, which conjugates with pivalic acid. However, the high urinary recovery of pivalic acid was maintained throughout the multiple-administration study, which suggested that the detoxification capacity of carnitine was not saturated and that it remained enough for the multiple administrations of 200 mg of S-1108 TID. These speculations may be supported by the fact that urinary excretion of total carnitine increased to two- to threefold the predose value (500 μmol), and the carnitine concentration in plasma of 30 to 40 nmol/ml, which corresponds to 50 to 70% of the control carnitine concentration, was maintained during multiple administrations, as shown in Fig 4 and 7.

The daily urinary excretion of free carnitine was about 250 μmol without any administration of S-1108 and decreased to less than 100 μmol during the multiple-administration study. On the other hand, most of the total carnitine excreted in urine during the administration was acylcarnitine, the majority of which was pivaloylcarnitine. In other words, endogenous carnitine was preferentially used to detoxify pivalic acid by conjugation. Therefore, the concentration of carnitine in plasma decreased in response to the administration of S-1108. During multiple administrations of 200 mg of S-1108 TID, the carnitine concentration in plasma decreased gradually to 50 to 70% of the normal value over 4 days and reached a steady state thereafter. As with many drugs and endogenous compounds, the carnitine concentration in plasma at steady state must be in equilibrium with that in the extravascular fluid and many tissues. The low carnitine concentration in plasma during multiple administrations implies a comparable reduction of carnitine stores in the body. However, the fact that 50 to 70% of the control carnitine concentration in plasma could be maintained throughout multiple administrations suggested that there might be enough carnitine stores in the body to overcome the increase in pivalic acid liberated from S-1108 even at a dose of as high as 200 mg TID. Moreover, the reduction in the carnitine concentration in plasma recovered to the control level 3 days after the cessation of multiple administrations. This recovery to the normal value implies that the reduced carnitine body stores returned to the normal store condition in accordance with the equilibrium theory. However, Holme et al. (4) reported a reduction of the total carnitine concentration in plasma to 20 nmol/ml and less than 20 nmol/ml following multiple administrations of 2 and 1.2 g of pivampicillin and pivmecillinam per day, respectively. These antibiotics are pivaloyloxymethylesters, and their daily doses corresponded to 4,300 and 2,700 μmol of pivalic acid, respectively. Also, 600 mg of S-1108 corresponds to 1,000 μmol. This difference in the amount of pivalic acid included in those daily doses caused different carnitine reductions. Probably, the degree of carnitine reduction might depend on the dose of S-1108 and the duration of the therapy. Therefore, it is necessary to be careful during the administration of S-1108 to patients with carnitine deficiency or at a dose higher than 200 mg or an administration longer than 1 week.

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