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# Pharmacokinetic Analysis of the Effects of Different Foods on Absorption of Cefaclor

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**Cefaclor is an oral cephalosporin antibiotic which has a broad antibacterial spectrum. The purpose of this study was to investigate the effect of food on the absorption of cefaclor and to analyze kinetically the absorption process of this drug. Cefaclor was given to eight volunteers at five test times: after overnight fasting, after two rice meals (350 and 700 cal [1 cal = 4.184 J]), and after two bread meals (500 and 1,000 cal). Urinary recoveries of cefaclor and concentrations of the drug in plasma were determined for each administration. Areas under the concentration-time curves and urinary recoveries were not affected by food intake, but the maximum concentration of drug in serum was reduced and the time to maximum concentration of drug in serum was prolonged depending on the type and the quantity of the meal. The larger the quantity of the meal, the more the maximum concentration of drug in serum and the time to maximum concentration of drug in serum were affected. The rice meals affected the absorption process of cefaclor more than the bread meals. The concentrations of cefaclor in plasma following administration after overnight fasting were well fitted to a conventional one-compartment model with a first-order absorption process, but those after the other administrations were not fitted to the model. For the pharmacokinetic analysis of those data, it was necessary to introduce a transfer process from administration site to absorption site to the conventional model. The concentrations in plasma after rice and bread meals were best fitted to the model with a zero-order transfer process than to that with a first-order process. The velocity of the transfer process depended on the type and volume of the meal.**

Cefaclor is a cephalosporin antibiotic for oral use. It has a broad antibacterial spectrum against various gram-positive bacteria and gram-negative bacteria such as *Haemophilus influenzae* and *Klebsiella* species. In particular, it shows a strong antibacterial action within a short period, and it is known to be effective against various infections. Meanwhile, as to the effect of food on the absorption of oral antimicrobial agents, there are various reports (11).

Cephalosporin antibiotics also show various phenomena, as in cases in which absorption is not affected by food (1, 5), in which absorption is hindered by food intake (9, 10), or, on the contrary, in which absorption is accelerated by food intake (4, 12). Cefaclor was also reported to be affected by food intake (1, 3).

In our present study, accordingly, focus was put on how the absorption would be affected by food as well as on whether the absorption depends on the quantity and the type of food. Moreover, pharmacokinetic analyses including the effect of food on the absorption process were performed.

## MATERIALS AND METHODS

**Material.** Cefaclor capsules of 500 mg, which were commercially available, were supplied by Shionogi & Co., Ltd.

**Subjects.** Eight healthy male volunteers, who were considered to be suitable for the study from the results of the physical and laboratory examinations, participated in this study. They gave their informed written consent after being given an explanation of the purpose and method of the study and also the safety and efficacy of the drug. They had a mean ± standard deviation age of 34 ± 9 years, ranging from 25 to 46 years; a mean height of 169 ± 5 cm, ranging from 160 to 173 cm; and a mean body weight of 67 ± 7 kg, ranging from 56 to 74 kg. They were not allowed to take any drugs or alcohol for the course of the study.

**Study design.** A cefaclor capsule of 500 mg was given each morning after overnight fasting under the following conditions: first while fasting, then 30 min after a meal of rice (300 g of rice with 160 ml of bean paste soup, 20 g of pickles, and 200 ml of milk, totaling 700 cal [1 cal = 4.184 J]), and then 30 min after a meal of bread (one and one-half slices of bread with 10 g of margarine, one boiled egg, and 200 ml of milk, totaling 500 cal) each at intervals of one week. The volunteers were forbidden to eat or drink anything until 4 h after drug administration, when lunch was served to them. About half a year later, the drug was given again once 30 min after a meal of rice and once 30 min after a meal of bread, at the same interval. The volume of the rice meal was reduced to half (350 cal) of the previous volume, and the volume of the bread meal was increased to twice (1,000 cal) the previous volume.

**Collection of blood and urine samples.** Samples of blood were collected before administration and 0.5, 1, 1.5, 2, 3, 4, and 6 h after administration. The blood samples collected were immediately centrifuged under cooling, and the plasma obtained was stored in a frozen state at −20°C until measurement of drug concentration. Urine was collected every 2 h up to 6 h after administration, and after the volume was measured accurately, part of each portion was stored in a frozen state at −20°C until measurement of cefaclor concentrations. Since cefaclor in plasma was found to be stable at −20°C for at least 1 week, the concentration assay was carried out within one week after samples were taken.

**Assay method.** Concentrations of cefaclor in plasma and urine were measured by the bioassay method by using

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*Micrococcus luteus* ATCC 9341 as a test bacterium. The standard curves for the plasma and urine assays of cefaclor were linear in the range of 0.038 to 0.6 μg/ml. Plasma and urine samples were diluted with 0.1 M phosphate buffer until the concentration came into this range. The accuracy and precision of the standard curves were generally within 5%.

**Pharmacokinetic analyses.** Analyses of the mean and individual changes of concentrations in plasma with time were performed basically by means of a one-compartment model containing a first-order absorption process (model I). As for administration after a meal, a model including the transfer process from the stomach to the digestive tract was applied to the pharmacokinetic analysis. On the assumption that this transfer process is a first-order (model II) or a zero-order (model III) process, two models were developed. Plasma concentration is described by equation 1 for a first-order process and by equation 2 for a zero-order process:

$$t < \tau$$

$$C = 0$$

$$t \geq \tau$$

$$C = \frac{k_t k_{ab} FD}{(k_{ab} - k_t)(k_{el} - k_t)V} e - k_t(t - \tau) + \frac{k_t k_{ab} FD}{(k_t - k_{ab})(k_{el} - k_{ab})V} e - k_{ab}(t - \tau) + \frac{k_t k_{ab} FD}{(k_t - k_{el})(k_{ab} - k_{el})V} e - k_{el}(t - \tau) \quad (1)$$

$$t < \tau$$

$$C = 0$$

$$\tau \leq t < T \ (T = D/k_0)$$

$$C = -\frac{k_0 k_{ab} F}{k_{ab}(k_{el} - k_{ab})V} e - k_{ab}(t - \tau) - \frac{k_0 k_{ab} F}{k_{el}(k_{ab} - k_{el})V} e - k_{el}(t - \tau) + \frac{k_0 F}{k_{el} V}$$

$$t \geq T$$

$$C = \frac{k_{ab} X_T F}{(k_{el} - k_{ab})V} e - k_{ab}(t - T) + \frac{k_{ab} X_T F}{(k_{ab} - k_{el})V} e - k_{el}(t - T) + C_T e - k_{el}(t - T) \quad (2)$$

where $D$ is dose, and $F$ and $V$ are the extent of absorption and distribution volume, respectively. First-order rate constants for the transfer, absorption, and elimination processes are $k_t$, $k_{ab}$, and $k_{el}$, respectively. A zero-order rate for the transfer process is $k_0$, and $\tau$ is absorption lag time. $T$ is the time required for the zero-order transfer of whole drug from administration site to absorption site and is calculated as $D/k_0$. $C_T$ and $X_T$ are the concentration of drug in plasma and the amount of drug at the absorption site, respectively, which are values at a point where $t = T$.

The data for concentrations in plasma were fitted to these equations by means of the least-squares method by using the NONLIN program (6).

The elimination half-life was estimated by dividing 0.693 by the elimination rate constant ($k_{el}$). The area under the concentration-time curve from 0 to 6 h ($AUC_{0-6}$) was calculated by the trapezoidal rule method.

Akaike's information criteria (AIC) (13) were used for selecting an appropriate model which provides the best description of the concentrations in plasma after food intake among the three models as AIC = $n \cdot \ln SS + 2p$, where $n$ is the number of observations, p is the number of parameters, and SS is the residual sum of squares of the observed values. The best model is considered to give the lowest AIC value.

## RESULTS

The mean values and standard deviations of maximum concentrations of drug in plasma ($C_{max}$) were 14.8 ± 5.3 μg/ml with administration in a fasting state, 9.11 ± 2.19 μg/ml with administration after a rice meal of 350 cal, 5.91 ± 1.04 μg/ml after a rice meal of 700 cal, 7.88 ± 1.65 μg/ml after a bread meal of 500 cal, and 6.79 ± 2.11 μg/ml after a bread meal of 1,000 cal. The mean $C_{max}$ values of cefaclor under the four conditions in which subjects were fed were reduced to less than two-thirds of that under conditions in which subjects fasted. Thus, $C_{max}$ decreased when the drug was given after a meal with a greater decrease with an increase in food volume. However, this tendency to decrease was not necessarily in proportion to the caloric value of the food taken, and the effect of the food varied depending on the type of the food, too. Also, in the time ($T_{max}$) required for the drug to reach its maximum concentration in plasma, the mean value was within 1 h with administration in a fasting state, but the $T_{max}$ tended to be delayed with administrations after meals. However, there was little difference among $AUC_{0-6}$s for the five administrations. The mean cefaclor $AUC_{0-6}$s were 18.6 ± 3.6 μg · hr/ml under the fasting condition, 19.9 ± 2.6 and 16.6 ± 2.9 μg · hr/ml after rice meals (350 and 700 cal, respectively), and 15.4 ± 4.0 and 17.7 ± 3.7 μg · hr/ml after bread meal (500 and 1,000 cal, respectively), as shown in Table 1.

Figure 1 shows urinary recoveries up to 6 h after administration. The mean recovery and its standard deviation up to 6 h after administration were 63.1% ± 6.9% with administration in a fasting state, 75.9% ± 4.3% and 67.4% ± 6.8% after rice meals (350 and 700 cal, respectively), and 71.6% ± 4.5% and 78.5% ± 6.7% after bread meals (500 and 1,000 cal, respectively). Thus, the administrations after meals did not lead to any decrease in urinary recovery. However, as shown in Fig. 1, for administrations after rice meals (700 cal) and after bread meals (1,000 cal), the urinary recoveries were considerably low up to 2 h after administration, but at 4 h after administration, there was little difference compared with urinary recovery under other conditions. These results indicated that although the absorption was slow in the early stage with an increase in food volume, there was little difference in eventual total absorption.

Figure 2 shows the fitting curves of mean concentrations

TABLE 1. Pharmacokinetic parameters of cefaclor in volunteers following an oral administration of 500 mg after overnight fasting and at 30 min after food intake

| Food | Subject | $k_0$[a] (mg/hr) | $T$[b] (hr) | $k_{ab}$ $hr^{-1}$ | $k_{el}$ $hr^{-1}$ | $V/F$ (liters) | $\tau$[c] (hr) | $t_{1/2}$[d] (hr) | $AUC_{0-6}$[e] (μg · hr/ml) |
|---|---|---|---|---|---|---|---|---|---|
| None | Mean[f] | | | 2.90 | 1.10 | 23.3 | 0.01 | 0.63 | 18.5 |
| | 1 | | | 16.64 | 1.43 | 10.4 | 0.00 | 0.48 | 25.3 |
| | 2 | | | 3.23 | 0.95 | 26.1 | 0.03 | 0.73 | 18.7 |
| | 3 | | | 15.70 | 1.09 | 28.7 | 0.99 | 0.64 | 16.2 |
| | 4 | | | 5.63 | 1.64 | 20.4 | 0.01 | 0.42 | 12.8 |
| | 5 | | | 6.38 | 1.12 | 23.5 | 0.43 | 0.62 | 20.2 |
| | 6 | | | 13.54 | 0.90 | 26.9 | 0.46 | 0.77 | 19.6 |
| | 7 | | | 7.37 | 1.13 | 27.4 | 0.40 | 0.61 | 17.4 |
| | 8 | | | 22.92 | 1.69 | 11.4 | 0.00 | 0.41 | 18.4 |
| | Mean | | | 11.41 | 1.24 | 21.9 | 0.29 | 0.59 | 18.6 |
| | SD | | | 6.82 | 0.30 | 7.2 | 0.35 | 0.14 | 3.6 |
| Rice (350 cal) | Mean[f] | 399 | 1.25 | 1.45 | 1.19 | 21.3 | 0.03 | 0.58 | 19.9 |
| | 1 | 566 | 0.88 | 4.77 | 1.12 | 21.5 | 0.50 | 0.62 | 21.4 |
| | 2 | 1,626 | 0.31 | 1.03 | 0.97 | 24.1 | 0.00 | 0.71 | 20.3 |
| | 3 | 426 | 1.17 | 2.12 | 1.18 | 19.2 | 0.53 | 0.59 | 22.8 |
| | 4 | 1,800 | 0.28 | 3.34 | 0.70 | 48.4 | 0.00 | 0.99 | 14.2 |
| | 5 | 725 | 0.69 | 4.23 | 0.82 | 28.1 | 0.29 | 0.85 | 21.5 |
| | 6 | 557 | 0.90 | 1.70 | 1.27 | 19.9 | 0.69 | 0.54 | 20.2 |
| | 7 | 551 | 0.91 | 2.39 | 0.74 | 33.5 | 0.12 | 0.94 | 20.3 |
| | 8 | 814 | 0.61 | 1.18 | 1.07 | 23.7 | 0.36 | 0.65 | 18.9 |
| | Mean | 883 | 0.72 | 2.60 | 0.98 | 27.3 | 0.31 | 0.74 | 19.9 |
| | SD | 527 | 0.31 | 1.39 | 0.21 | 9.7 | 0.26 | 0.17 | 2.6 |
| Rice (700 cal) | Mean[f] | 202 | 2.48 | 1.75 | 0.97 | 30.6 | 0.23 | 0.71 | 16.6 |
| | 1 | 263 | 1.90 | 1.39 | 0.45 | 49.2 | 0.68 | 1.56 | 17.0 |
| | 2 | 337 | 1.49 | 1.48 | 0.95 | 30.4 | 0.14 | 0.73 | 17.4 |
| | 3 | 230 | 2.17 | 1.11 | 1.28 | 18.5 | 1.04 | 0.54 | 19.3 |
| | 4 | 161 | 3.11 | 4.11 | 2.06 | 19.0 | 0.05 | 0.34 | 12.8 |
| | 5 | 232 | 2.15 | 1.92 | 0.97 | 31.8 | 0.60 | 0.71 | 15.5 |
| | 6 | 255 | 1.96 | 1.63 | 1.10 | 21.1 | 1.40 | 0.63 | 21.4 |
| | 7 | 170 | 2.95 | 2.21 | 1.49 | 21.4 | 0.22 | 0.46 | 16.1 |
| | 8 | 202 | 2.47 | 2.00 | 1.72 | 22.7 | 0.40 | 0.40 | 13.4 |
| | Mean | 231 | 2.28 | 1.98 | 1.25 | 26.8 | 0.44 | 0.67 | 16.6 |
| | SD | 56 | 0.54 | 0.93 | 0.50 | 10.3 | 0.32 | 0.38 | 2.9 |
| Bread (500 cal) | Mean[f] | 720 | 0.69 | 1.66 | 0.99 | 33.0 | 0.30 | 0.70 | 15.4 |
| | 1 | 1,165 | 0.43 | 1.02 | 1.11 | 22.5 | 0.82 | 0.63 | 19.4 |
| | 2 | 1,529 | 1.33 | 0.33 | 1.36 | 22.5 | 0.48 | 0.51 | 16.5 |
| | 3 | 1,338 | 0.37 | 1.31 | 1.26 | 20.1 | 0.25 | 0.55 | 19.6 |
| | 4 | 822 | 0.61 | 3.17 | 2.64 | 16.7 | 0.40 | 0.26 | 11.3 |
| | 5 | 1,359 | 0.37 | 4.33 | 1.22 | 51.6 | 0.95 | 0.57 | 8.1 |
| | 6 | 504 | 0.99 | 4.02 | 0.73 | 41.8 | 0.12 | 0.95 | 16.6 |
| | 7 | 239 | 2.09 | 2.96 | 1.49 | 25.4 | 0.78 | 0.47 | 14.0 |
| | 8 | 823 | 0.61 | 5.48 | 0.88 | 31.2 | 0.56 | 0.79 | 17.9 |
| | Mean | 972 | 0.73 | 2.95 | 1.34 | 29.0 | 0.55 | 0.59 | 15.4 |
| | SD | 452 | 0.59 | 1.63 | 0.58 | 12.0 | 0.29 | 0.21 | 4.0 |
| Bread (1,000 cal) | Mean[f] | 555 | 0.90 | 0.96 | 0.95 | 28.5 | 0.60 | 0.73 | 17.7 |
| | 1 | 689 | 0.73 | 5.27 | 0.76 | 36.2 | 1.11 | 0.91 | 18.3 |
| | 2 | 253 | 1.98 | 2.49 | 0.84 | 31.7 | 1.04 | 0.83 | 18.4 |
| | 3 | 1,121 | 0.45 | 1.66 | 0.86 | 23.5 | 0.76 | 0.80 | 24.5 |
| | 4 | 265 | 1.89 | 3.10 | 1.01 | 35.1 | 0.16 | 0.69 | 14.0 |
| | 5 | 292 | 1.71 | 8.20 | 0.76 | 30.8 | 0.84 | 0.91 | 19.9 |
| | 6 | 1,025 | 0.49 | 0.91 | 0.97 | 28.1 | 0.44 | 0.72 | 17.3 |
| | 7 | 168 | 2.97 | 2.24 | 0.93 | 38.4 | 0.88 | 0.75 | 12.7 |
| | 8 | 174 | 2.87 | 12.82 | 4.26 | 7.6 | 0.97 | 0.16 | 16.6 |
| | Mean | 498 | 1.64 | 4.59 | 1.30 | 28.9 | 0.78 | 0.72 | 17.7 |
| | SD | 391 | 1.00 | 4.07 | 1.20 | 9.8 | 0.32 | 0.24 | 3.7 |

[a] Zero-order transfer rate constant from the stomach to the absorption site.
[b] Time required for the zero-order transfer of whole drug from the stomach to the absorption site.
[c] Absorption lag time.
[d] $t_{1/2}$, half-life.
[e] Calculated by trapezoidal rule.
[f] Mean concentrations in plasma were used to estimate parameters.

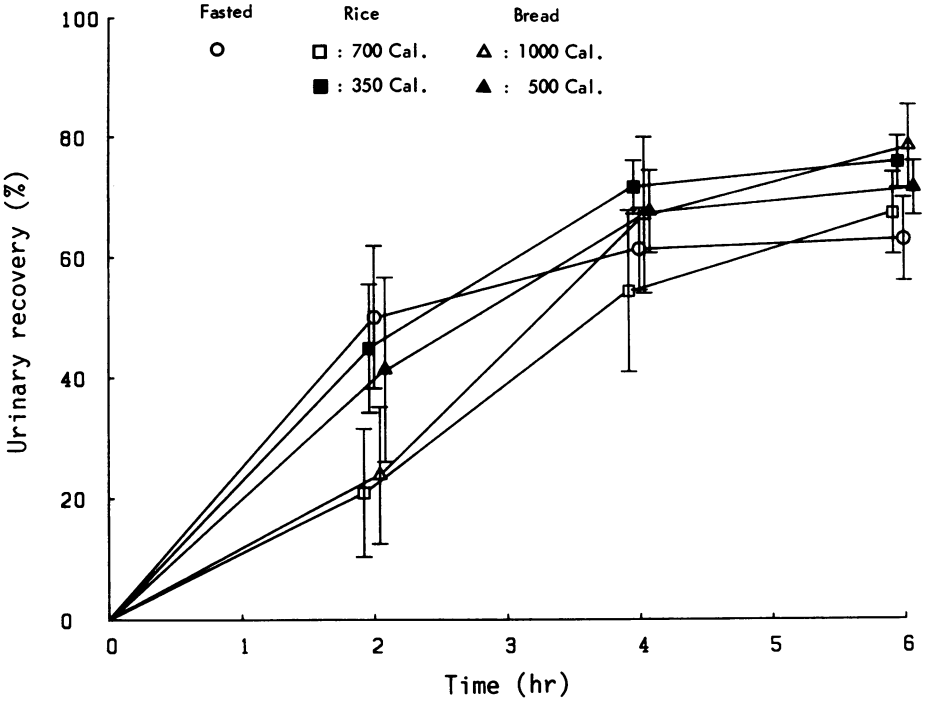


FIG. 1. Urinary recoveries of cefaclor in volunteers following an oral administration of 500 mg after overnight fasting and at 30 min after food intake.

in plasma to a conventional one-compartment model containing a first-order absorption process. Sufficient fitting was obtained for data for administration in a fasting state. For administration after meals, however, the fitting seemed to be not necessarily sufficient even when absorption lag time was taken into consideration, especially for poor fits in the absorption phase. Therefore, these results indicate that it is reasonable to introduce another process into an absorption

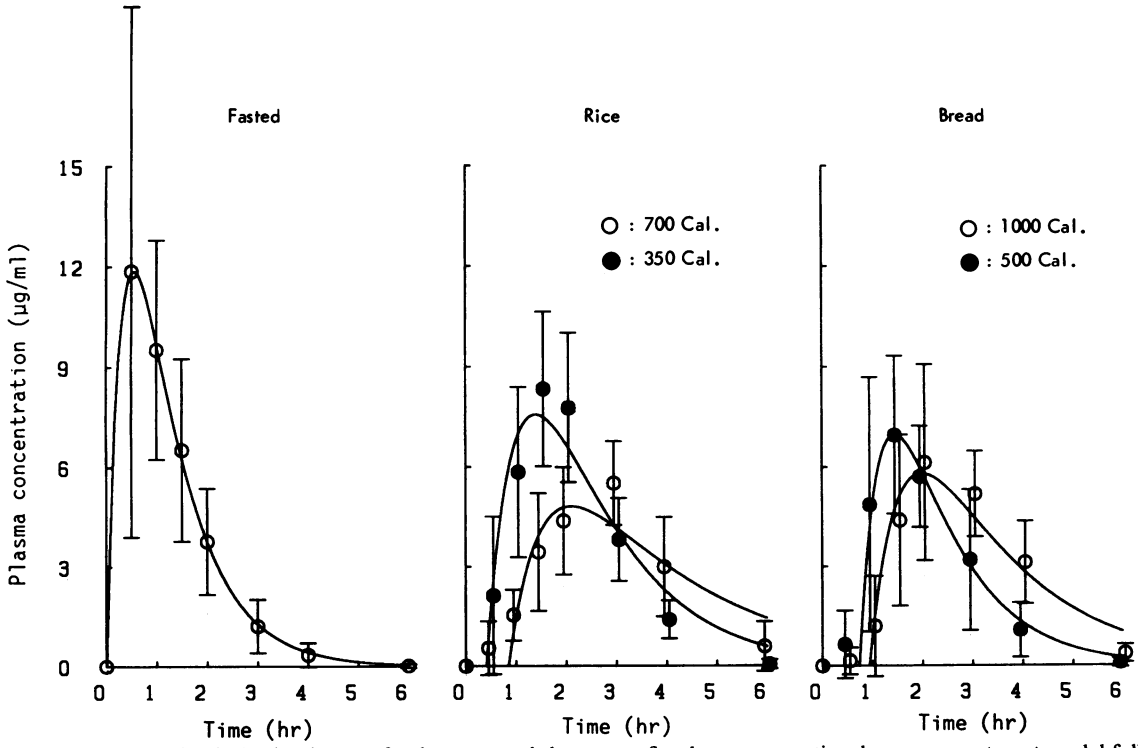


FIG. 2. Concentrations of cefaclor in plasma of volunteers and the curves fitted to a conventional one-compartment model following an oral administration of 500 mg after overnight fasting and at 30 min after food intake.

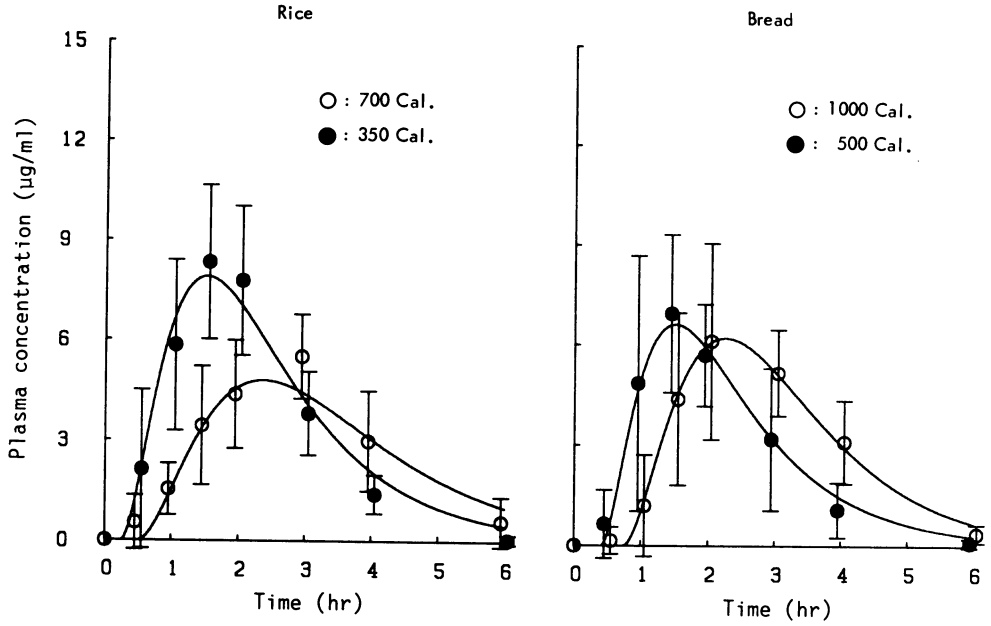


FIG. 3. Concentrations of cefaclor in plasma of volunteers and the curves fitted to a one-compartment model with a first-order transfer process following an oral administration of 500 mg at 30 min after food intake.

process in analyzing the drug disposition following administration after meals.

Figures 3 and 4 show the fitting curves of mean concentrations in plasma after each meal to equations 1 and 2, respectively. With equation 1, comparatively good fitting was obtained for administrations after bread meals, but the fitting still seemed to be insufficient for administrations after a meal of rice. On the other hand, it is obvious that satisfactory fitting to equation 2 was obtained for administrations after rice meals as well as bread meals. Pharmacokinetic parameters for these analyses of the mean and individual concentrations in plasma are shown in Table 1 together with those for administration in a fasting state.

Table 2 shows AIC values for fittings of the mean and individual concentrations in plasma to each model. The concentrations in plasma after rice meals were best fitted to model III. On the other hand, the mean concentrations in plasma after bread meals were best fitted to models II and III. However, it was found that the individual concentrations in plasma after bread meals were best fitted to model III.

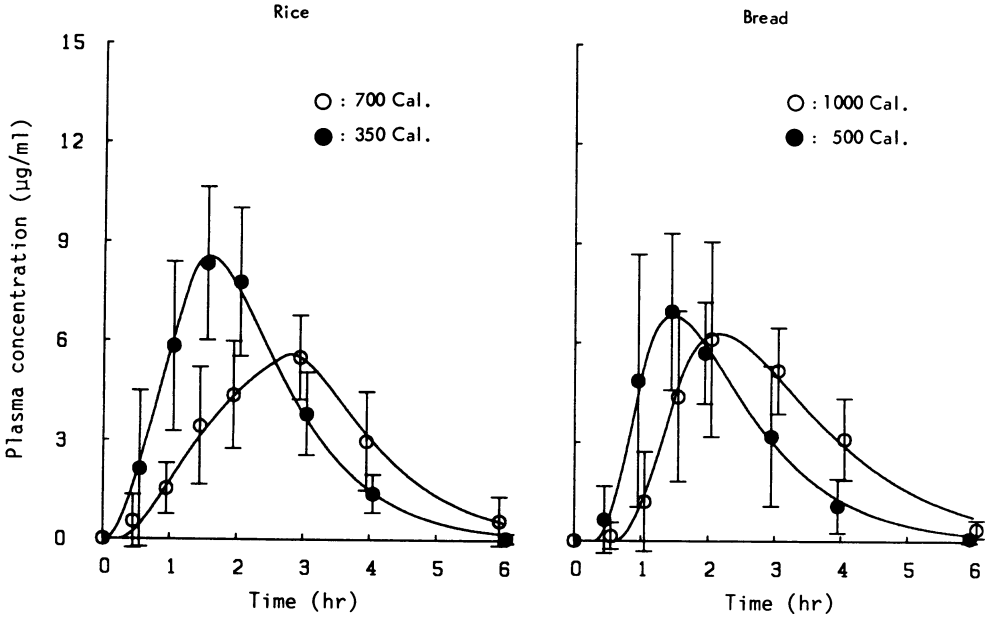


FIG. 4. Concentrations of cefaclor in plasma of volunteers and the curves fitted to a one-compartment model with a zero-order transfer process following an oral administration of 500 mg at 30 min after food intake.

TABLE 2. AIC for the compartment model analyses of cefaclor concentrations in plasma

| Food | Subject | AIC for model: | | |
|---|---|---|---|---|
| | | I | II | III |
| None | Mean[a] | −9.83 | | |
| | 1 | −4.34 | | |
| | 2 | 13.41 | | |
| | 3 | 17.20 | | |
| | 4 | −13.23 | | |
| | 5 | 20.57 | | |
| | 6 | 12.47 | | |
| | 7 | −4.00 | | |
| | 8 | −2.24 | | |
| | Mean | 4.98 | | |
| | SD | 12.37 | | |
| Rice (350 cal) | Mean[a] | 19.11 | 14.78 | −8.34 |
| | 1 | −25.14 | −6.67 | −9.44 |
| | 2 | 5.92 | 8.25 | 8.53 |
| | 3 | 19.02 | 28.92 | 7.15 |
| | 4 | −3.46 | −4.53 | 0.09 |
| | 5 | −5.99 | 3.68 | 8.66 |
| | 6 | 14.68 | 17.25 | −2.03 |
| | 7 | 12.66 | 14.60 | 8.61 |
| | 8 | 16.39 | 10.14 | 9.58 |
| | Mean | 4.26 | 8.96 | 3.89 |
| | SD | 15.00 | 11.68 | 6.94 |
| Rice (700 cal) | Mean[a] | 17.85 | 14.49 | −5.42 |
| | 1 | 23.63 | 20.15 | 16.85 |
| | 2 | 25.65 | 20.39 | 17.72 |
| | 3 | 26.48 | 16.81 | 7.94 |
| | 4 | 16.21 | 14.85 | 8.19 |
| | 5 | 23.66 | 26.59 | 11.24 |
| | 6 | 27.56 | 18.17 | 13.16 |
| | 7 | 13.20 | 15.22 | −4.73 |
| | 8 | 14.52 | 16.64 | −16.96 |
| | Mean | 21.36 | 18.60 | 6.68 |
| | SD | 5.77 | 3.82 | 11.84 |
| Bread (500 cal) | Mean[a] | 7.44 | 2.40 | −5.84 |
| | 1 | 6.18 | 8.14 | 6.85 |
| | 2 | −4.26 | −0.47 | −6.29 |
| | 3 | −5.38 | −2.01 | −0.54 |
| | 4 | 10.64 | 12.00 | −6.77 |
| | 5 | −26.61 | −22.09 | −16.43 |
| | 6 | 12.16 | 16.82 | 14.05 |
| | 7 | 20.71 | 22.20 | 6.27 |
| | 8 | 10.41 | 12.60 | 10.39 |
| | Mean | 2.98 | 5.90 | 0.94 |
| | SD | 14.74 | 13.93 | 10.28 |
| Bread (1,000 cal) | Mean[a] | 10.96 | −4.06 | −2.77 |
| | 1 | −22.02 | −7.34 | 7.66 |
| | 2 | 20.92 | 22.39 | 7.07 |
| | 3 | −13.51 | −12.68 | −14.69 |
| | 4 | 23.46 | 22.78 | 11.08 |
| | 5 | 10.59 | 16.05 | 6.14 |
| | 6 | 8.50 | 10.66 | 10.65 |
| | 7 | 19.34 | 18.13 | 5.68 |
| | 8 | 8.27 | 7.57 | 3.02 |
| | Mean | 6.94 | 9.69 | 4.58 |
| | SD | 16.46 | 13.31 | 8.21 |

[a] Mean concentrations in plasma were analyzed.

## DISCUSSION

Concerning absorption of cefaclor, it was well known that cefaclor was sufficiently absorbed in humans. In this study, it was found that the absorption rate of cefaclor was affected by food during the first three treatments. It was interesting to investigate whether the change in quantity of food has any effect on that food effect. Therefore, additional experiments with two other different quantities of food were performed. In administration after meals, the $C_{max}$s were lower than that obtained for administration in a fasting state, and $T_{max}$s were longer for administration after meals. Thus, the absorption of cefaclor was affected by food intake. These results were consistent with previously published data (1). However, in urinary recovery and AUC up to 6 h after administration, there was not much effect by the food. Therefore, it is considered that the absorption is delayed by food intake, but food does not affect the extent of absorption, although the statistical significance of differences between treatments could not be evaluated because this study was not randomized about the treatment.

In analyzing the disposition of cefaclor, as shown in Fig. 2, sufficient fitting was not obtained with the one-compartment model containing the so-called first-order absorption process, with the exception of administration in a fasting state. In particular, fitting was not sufficient in the absorption phase. The absorption lag times after meals were longer than 0.5 h, at which time cefaclor was detected in plasma. Also, in cumulative curves of urinary recoveries (Fig. 1), urinary excretions were low in the early stages following administrations after meals, but it came up to the level of excretion seen for the administration in a fasting state until 4 h after administration. From these results, it is considered that, when the drug is given after meal, the transfer of the drug from the stomach to the absorption site (mainly intestine) is not as fast as that seen for the administration in a fasting state and that this delay in transfer is caused by the interaction with the contents (mostly food) in the stomach. Therefore, it is necessary to introduce a transfer process from the stomach to the intestine for analyzing concentrations in plasma following administrations after meals. We mean a complex process of dissolution and transfer by the transfer process, because dissolution and transfer processes cannot be distinguished from each other. These two processes might happen at same time. The problem is what kind of mode we should give to this transfer process. The mode of gastric emptying has been clarified considerably, as mentioned below. On the other hand, there is no information about the dissolution of cefaclor in the gastrointestinal tract when it contains food. So we discussed the transfer process in relation to the gastric emptying. Concerning gastric emptying, it is known that when the contents of the stomach are in a liquid state, the contents are emptied out generally with the first-order rate process (2, 7, 8). Therefore, we first analyzed the concentrations in plasma according to equation 1, which was derived from the model assumed to have a first-order transfer process. As seen in Fig. 2, comparatively good fitting was obtained for the mean concentrations in plasma after bread meals, but fitting was still insufficient for that after rice meals. Regarding solid contents, it is reported that the solid contents are emptied out with the zero-order process (7), in contrast to the first-order emptying of liquid contents. Therefore, we assumed a model in which the transfer process was set as a zero-order process. Then, the concentrations in plasma were analyzed according to the equation 2 derived therefrom. As shown in Fig. 4, it is obvious that satisfactory fitting was obtained for administration after a meal of rice as well as after a meal of bread. AIC values (Table 2) show that the individual and mean concentrations in plasma after rice meals were best fitted to model III. Also, the individual concentrations in plasma after bread meals were best fitted to model III, even though the mean concentrations in plasma were fitted equally to models II and III. Therefore, the results of the individual data analyses

were discussed thereafter. The difference in fitting between using models II and III seemed to be due to the transfer of the meal as solid, not as liquid, that is, fluidity of stomach contents. This was because when bread or rice was taken, the fluidity of the contents of the stomach was comparatively low, and consequently, the drug was emptied out of the stomach at a rate near that of the solid contents of the stomach, that is, a zero-order rate. Moreover, as regards solubility of cefaclor, 1 g of cefaclor is dissolved in 93 ml of water, suggesting that cefaclor is sparingly soluble in water. Therefore, the undissolved cefaclor is most likely to be emptied out of the stomach together with the contents of the stomach when cefaclor is taken after a meal. The time ($T$) required for the gastric emptying of the drug was dependent on the type and volume of food, as shown in Table 1. For administration after a bread meal, when the volume of food was doubled, the $T$ also became twice as long, suggesting that the gastric emptying took place at a certain fixed rate. When the drug was taken after taking rice, the $T$ was not necessarily in proportion to the volume of the food taken, which was considered to be due to a difference in fluidity of the contents of the stomach between bread and rice meals. Comparison of $T$ between rice and bread meals shows that the $T$ with rice is relatively longer than that with bread, independent of caloric value. The rice meal affected the absorption process of cefaclor more than the bread meal, because $T$ was considered to be zero in the fasting state, especially in the case of double volumes of rice. This indicated that the gastric emptying of the drug varies, depending on the type of food. Therefore, when a drug which is very soluble in the stomach is taken, it is promptly emptied out of the stomach together with the water in the stomach. In such a case, the gastric emptying of the drug is little affected by the food. On the other hand, in a case of a drug such as cefaclor, the gastric emptying seems to be influenced by the volume and type of food. In this study, effects of rice and bread meals on the absorption of cefaclor could be analyzed by using model III for healthy volunteers. However, these effects might change, depending on the patients. Especially for patients with gastrointestinal disease such as peptic ulcer, gastritis, gastrectomy, ileus, and so on, it might be necessary to develop another model.

As seen in Table 1, the absorption rate constant ($k_{ab}$) obtained for administrations after meals is smaller than that for administration in a fasting state in the cases of both rice and bread meals. This is because the absorption rate of cefaclor has decreased as a result of its having been mixed with the contents of the digestive tract. Food is not likely to have a direct influence on the elimination half-life, and the results shown in Table 1 support this. Also, almost the same values were obtained for AUCs for the five administration times, which indicates that the extent of absorption of cefaclor is not affected by food.

We conclude the following. The absorption of cefaclor was delayed, but the extent of absorption was not affected by food intake.

The gastric emptying of the contents of the stomach might vary depending on the volume and type of the food taken, for example, first-order or zero-order kinetics. When cefaclor, whose solubility in the stomach is low, was taken after rice or bread meals, the concentration in plasma was analyzed by using a model with a zero-order transfer process.

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