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Pharmacokinetic analysis of discontinuous absorption process of ceftibuten in humans

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Summary

Ceftibuten is a new oral antibiotic currently under clinical investigation. Although this drug is readily absorbed in humans as well as in animals, the process of absorption is frequently observed to be discontinuous in humans. In order to clarify the mechanism of discontinuous absorption, the solubility properties and gastric emptying of the drug were investigated. Plasma concentrations of ceftibuten were determined using a modified compartment model in which dissolution in the gastrointestinal tract and gastric emptying were incorporated based on the results observed. The quality of the curve fitting achieved was comparable with that obtained when using the two-step discontinuous absorption model, thereby indicating how the two processes can cause the discontinuous absorption of ceftibuten.

Introduction

The plasma concentrations of a drug which is administered orally are usually analyzed kinetically, based on a one- or two-compartment model with a first-order absorption process. However, the absorption process of a number of drugs cannot be described by simple first-order kinetics: some drugs show discontinuous absorption with double peaks in the plasma concentration-time profile, depending on the physico-chemical properties of the drug and/or the gastrointestinal physiological condition of the animals including humans (Clements et al., 1978; Webster et al., 1981; Hammarlund et al., 1984; Lui et al., 1986).

The newly developed oral cephem antibiotic, ceftibuten, has a broad antibacterial spectrum and is absorbed well in humans and other animals (Hirano et al., 1986). The plasma concentration-time profiles of this drug in the absorption phase following oral administration to healthy volunteers show that the absorption process of this drug cannot be described by simple first-order kinetics as mentioned above.

For the pharmacokinetic analysis of drug concentration-time data during such a discontinuous

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absorption process, the discontinuous two-step absorption model (Suverkrup, 1979; Zimmerman, 1983) and multi-fraction absorption model (Murata et al. 1987) were developed, which appear to be able to describe the change in drug concentration during absorption fairly well. Thus, these models may characterize several possible factors (e.g., a different absorption rate constant along the gastrointestinal tract, and solubility characteristics) related to such discontinuous absorption. The discontinuous absorption process of ceftibuten was also suitable for analysis by the two-step absorption model. However, the pharmacokinetic parameters obtained from the model analysis could not help in clarification of the dominant mechanisms, since these parameters are composite rate constants of processes such as dissolution, gastric emptying and absorption. The problem as to whether a drug is absorbed discontinuously depends largely on its physico-chemical properties. Therefore, it is important to investigate the mechanism of discontinuous absorption for every drug which exhibits such a phenomenon.

The purpose of this study is the investigation of each stage of the process of discontinuous absorption of ceftibuten and examination of the possible underlying mechanisms.

Materials and Methods

Materials

Ceftibuten (chemical structure shown in Fig. 1) and ceftibuten sodium were supplied by Shionogi Research Laboratories. Capsules (JP XI size no. 2 for monkeys and size no. 9 for rats) were purchased from Japan Elanco Co. (Osaka, Japan).

Assay method

Plasma concentrations and the amount of ceftibuten remaining in the stomach and intestine were determined by an HPLC method using a Shimadzu LC-6A pump with a C-R3A integrator and an SPD-6AV detector (256 nm) (Nakashima et al., 1988).

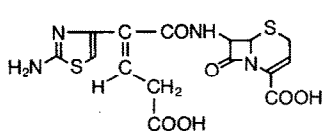


Fig. 1. Chemical structure of ceftibuten.

Single dose study in humans

Published results on the plasma concentrations of ceftibuten in humans in a phase I study (Nakashima et al., 1988) were used in this investigation. In the phase I study, ceftibuten (25, 50, 100 and 200 mg) was administered orally to six healthy male volunteers after overnight fasting with a 1-week interval between the different doses.

Experiments in rats

Ceftibuten and ceftibuten sodium in capsules were given orally to rats at a dose of 20 mg/kg. Blood samples of 0.5 ml were taken at 0, 15, 30, and 45 min, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6 and 8 h after dosing and immediately centrifuged for 15 min at 4°C. The plasma was frozen at below −70°C until assay.

Ceftibuten powder and aqueous solution were given orally to rats at the same dose. The amount of ceftibuten remaining in the stomach was determined immediately after dosing and at 15 and 30 min, 1, 2, 4 and 6 h following dosing. The ceftibuten in the stomach was extracted with water and aliquots were stored frozen at −70°C until assay.

Experiments in monkeys

A capsule of ceftibuten (100 mg) was given orally with 20 ml water to rhesus monkeys (body wt 4–6 kg) which were anesthetized with pentobarbital and placed in a monkey chair. The dissolution and transfer behaviors of the capsule and ceftibuten in the stomach were observed with a fiberscope (Olympus XP-10) attached to a camera (SC16-4) with light supply equipment (CLE-F10).

Absorption experiment using rat intestinal loop

The site of absorption of ceftibuten in the intestinal tract was established by the in situ loop method using rats. Under the conditions for anesthetization, intestinal loops of 20 cm were prepared by ligation at the upper, middle and lower parts of the intestine. Ceftibuten dissolved

in isotonic buffer of pH 6.5 was introduced into each loop at a dose of 20 mg/10 ml per kg. The drug remaining in the loop was determined after 30 min.

Pharmacokinetic analysis

Pharmacokinetic analysis of plasma concentration-time data of ceftibuten in volunteers following oral administration was performed with a NONLIN program (Metzler et al., 1974) using a conventional one-compartment model, a two-step absorption model and a modified compartment model which is shown in Fig. 2. According to the modified model, ceftibuten behaves as follows: Firstly, a small portion of ceftibuten is dissolved or dispersed in water, but not emptied, until the first lag time (τ_1). Secondly, the small portion is emptied according to first-order kinetics between the first and the second lag times (τ_1, τ_2). During this process, the plasma concentration is described by Eqn 1. Thirdly, ceftibuten as the unabsorbed fraction, which contains a larger proportion of the dose, is emptied from the stomach at the same time. After the second gastric emptying, the plasma concentration is described by Eqn 2.

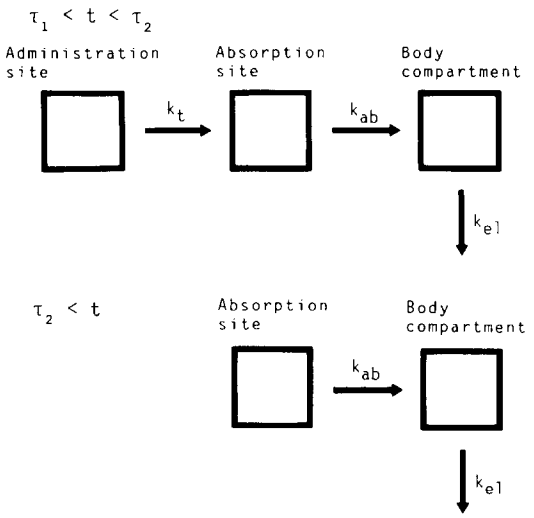


Fig. 2. Compartment model for ceftibuten following oral administration.

$$C = \frac{k_t k_{ab} fFD}{(k_{ab} - k_t)(k_{el} - k_t)V} e^{-k_t(t-\tau_1)} + \frac{k_t k_{ab} fFD}{(k_t - k_{ab})(k_{el} - k_{ab})V} e^{-k_{ab}(t-\tau_1)} + \frac{k_t k_{ab} fFD}{(k_t - k_{el})(k_{ab} - k_{el})V} e^{-k_{el}(t-\tau_1)} \quad (1)$$

$$C = \frac{k_{ab} FD^*}{(k_{ab} - k_{el})V} e^{-k_{el}(t-\tau_2)} - \frac{k_{ab} FD^*}{(k_{ab} - k_{el})V} e^{-k_{ab}(t-\tau_2)} + C^* e^{-k_{el}(t-\tau_2)} \quad (2)$$

where D is the dose and f is the fraction of the dose which is dissolved or dispersed in the gastric fluid until τ_2, F is the absorbed fraction of the dose, and k_t is the first-order rate constant of transfer from the site of administration to that of absorption, k_{ab} is the absorption rate constant during the entire absorption process, k_{el} and V are the elimination rate constant and the distribution volume, respectively, D^* $(= fDe^{-k_t(\tau_2 - \tau_1)} + (1-f)D)$ is the dose remaining in the stomach, and C^* is the plasma concentration at $t = \tau_2$.

Akaike's information criteria (AIC) (Yamaoka et al., 1978) were used for selecting an appropriate model which provides the best description of the experimental data from these three models as:

$$\mathrm{AIC} = n \ln \mathrm{SS} + 2p \quad (3)$$

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 model with the lowest AIC value is considered to be the best for the experimental data. These AIC values were statistically evaluated between each model using paired t-test.

Results

Plasma concentration-time data for ceftibuten in each of the six volunteers following oral administration of 200 mg are shown in Fig. 3. The fitted curves obtained by pharmacokinetic analysis of the data using a conventional one-compartment model with a first-order absorption process and absorption lag time as well as a two-step absorption model are also shown in Fig. 3. In the post-absorptive phase, a very good fit was obtained in every case. However, in the absorption phase four out of six cases revealed a discrepancy between the observed values and the fitted curves obtained using the conventional model in the early absorption phase of about 2 h as shown in Fig. 3. On the other hand, in these four cases, the plasma concentration-time data gave a better fit to the two-step absorption model. The same results were obtained with doses other than that of 200 mg (data not shown). These results suggest that the absorption rate constant varied along the intestine or that the whole dose was not transferred to the absorption site immediately. Therefore, the conventional one-compartment model cannot be used for analyzing the absorption kinetics.

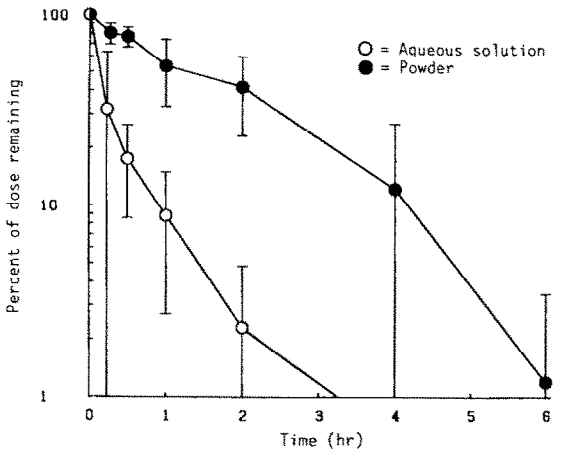


Fig. 4. Gastric emptying of ceftibuten in rats following an oral administration of 20 mg/kg ceftibuten as powder and aqueous solution formulations (mean ± S.D. of four experiments).

Fig. 4 shows the time courses of ceftibuten remaining in the stomach following oral adminis-

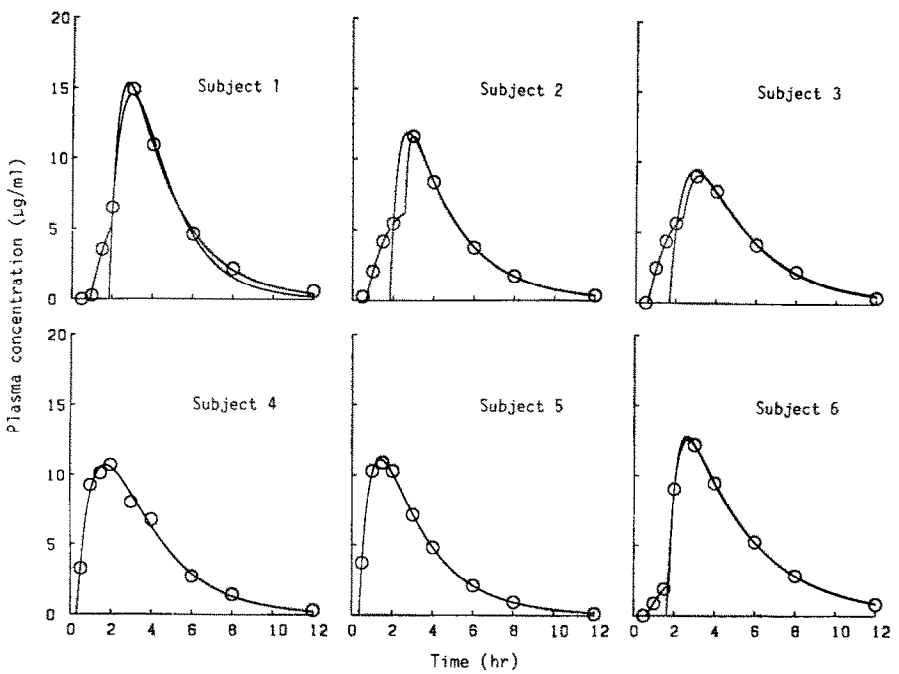


Fig. 3. Plasma ceftibuten concentration-time data and the fitted curves obtained using the conventional one-compartment and the two-step absorption models in volunteers following an oral administration of 200 mg.

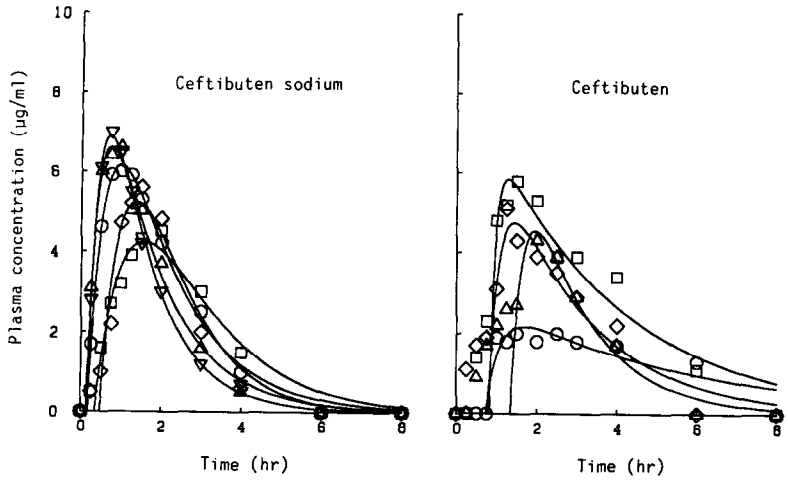


Fig. 5. Plasma concentration-time data of ceftibuten in rats following an oral administration of ceftibuten and ceftibuten sodium of 20 mg/kg in capsule.

tration of ceftibuten in powder and aqueous solution to rats. A remarkable difference is evident in gastric emptying between the two dosage forms. About 40% of the dose remained in the stomach 2 h following powder administration, whereas less than 5% was found at 2 h after solution administration. In the case of the solution, the drug seemed to be emptied according to first-order kinetics except for the initial 15 min postdose period. This might be related to the experimental procedure in that some portion of the solution could be forced into the intestine by the pressure due to dosing using a syringe.

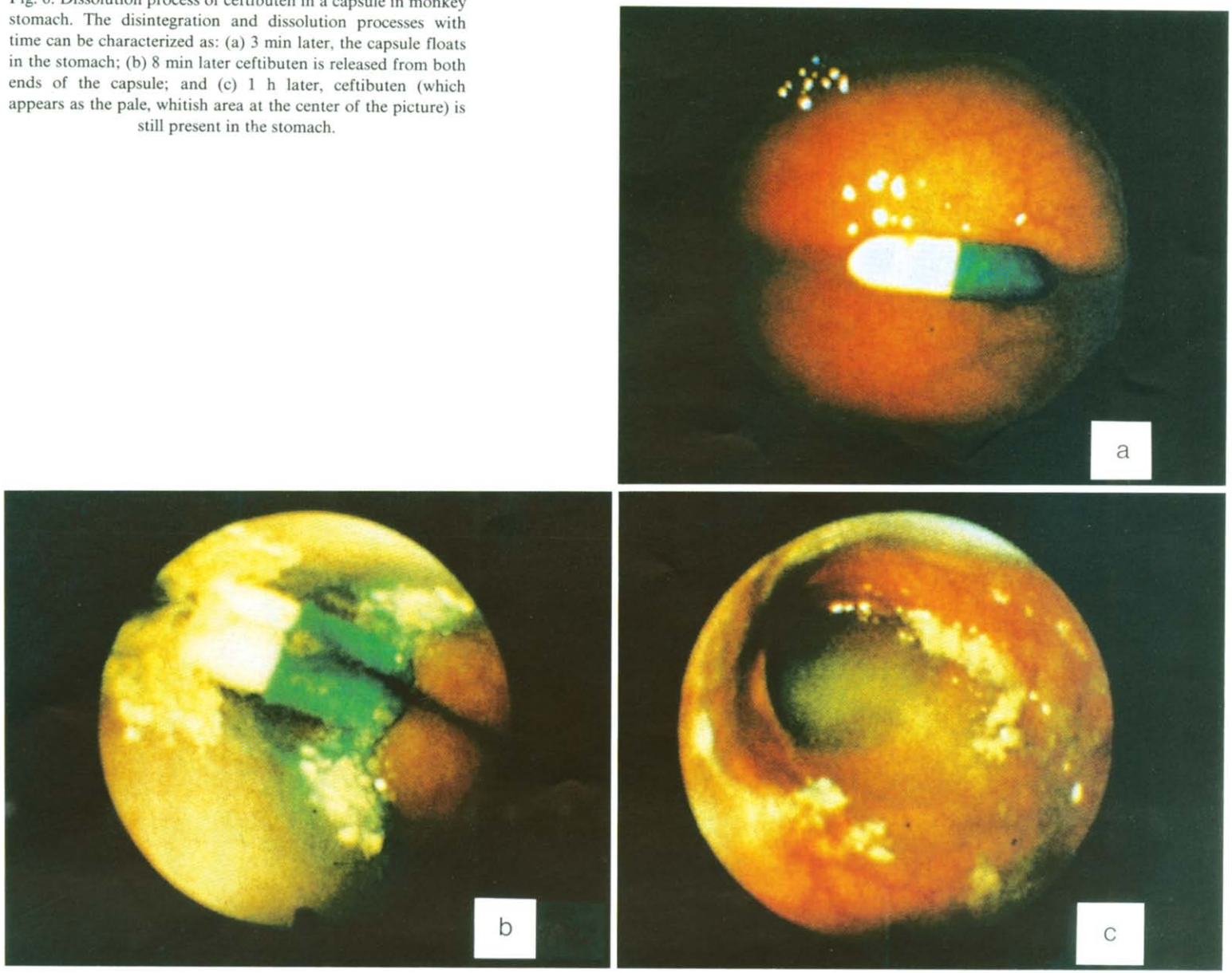
Plasma concentrations of ceftibuten following oral administration of ceftibuten and ceftibuten sodium in capsules to rats are plotted vs time in Fig. 5. The fitted curves for the conventional one-compartment model as a function of lag time are also shown in Fig. 5. After dosing with ceftibuten sodium, which is much more soluble in water than ceftibuten, the absorption process displayed less discontinuity even during the early absorption phase. On the other hand, in the case of ceftibuten, discontinuous absorption was observed (Fig. 5, right).

After the oral administration of one ceftibuten capsule to an anesthetized monkey, the capsule floated in the stomach for a while and then began to undergo degradation at both ends within 10 min, ceftibuten being subsequently released from the capsule. However, the drug was dissolved only to a limited extent, the major proportion of drug remaining at the bottom of the stomach even 2 h later. The dissolution patterns are visualized in Fig. 6. During the process of dissolution the pH value in the stomach was determined to be 2–4 and the concentration of ceftibuten in the gastric liquid was lower than 10 μg/ml.

The mean percentage values for the dose remaining in the intestinal loop obtained from in situ experiments on rats are shown in Fig. 7. Ceftibuten was absorbed very well over the first 30 min postdose. The statistical analysis (i.e., *t*-test) showed no significant difference in the mean absorption rates between the upper and middle intestine of the rats. There was a significantly ($p < 0.05$) greater amount remaining in the lower intestine as compared to the other two regions of the intestine. Ceftibuten absorption proceeded rapidly in the upper and middle parts of the intestine and slowly in the lower part.

The pH profile of ceftibuten solubility determined at 37 °C is shown in Fig. 8. The solubility of ceftibuten is about 100 μg/ml within the pH range 2–4 and about 3 mg/ml at pH 5, suggesting that ceftibuten is insoluble in the stomach due to the acidity, but dissolves quickly in the intestine.

Fig. 6. Dissolution process of ceftibuten in a capsule in monkey stomach. The disintegration and dissolution processes with time can be characterized as: (a) 3 min later, the capsule floats in the stomach; (b) 8 min later ceftibuten is released from both ends of the capsule; and (c) 1 h later, ceftibuten (which appears as the pale, whitish area at the center of the picture) is still present in the stomach.



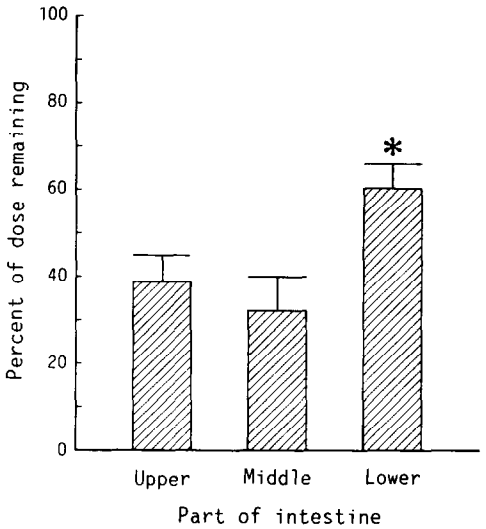


Fig. 7. Mean (±S.D.) percentages of ceftibuten remaining in the intestinal tract loop of rats at 30 min ($n = 4$, * $p < 0.05$).

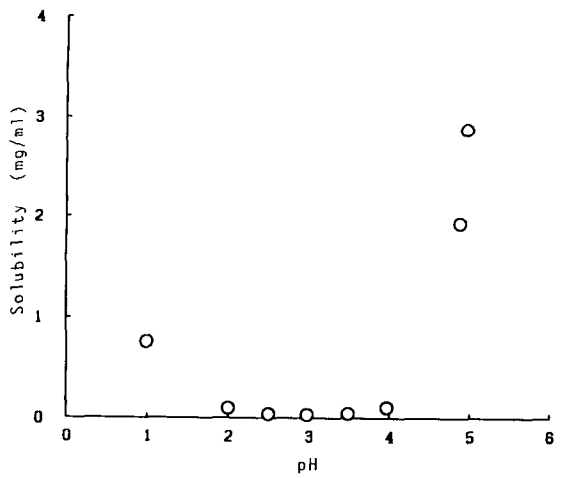


Fig. 8. Solubility of ceftibuten in 0.9% sodium chloride solution at 37 °C.

The results of pharmacokinetic analysis of the plasma concentration-time data obtained in phase I studies using the modified model are depicted in Fig. 9, with the exception of subjects 4 and 5 whose data were in conformity with the conventional model. The pharmacokinetic parameters are listed in Table 1. The half-life of ceftibuten was 1.5–2 h (i.e., identical to that obtained using a conventional model). The first lag time at which

TABLE 1

Pharmacokinetic parameters of ceftibuten in volunteers following an oral administration

Dose (mg)	Subject no.	k_t (h^{-1})	k_{ab} (h^{-1})	k_{el} (h^{-1})	$t_{1/2}$ (h)	V/F (l)	τ_1 (h)	τ_2 (h)	f
25	2	0.446	2.852	0.495	1.40	8.13	0.27	1.89	0.75
	3	0.429	0.675	0.913	0.76	6.27	0.50	3.58	0.25
	4	0.448	3.070	0.531	1.31	8.18	0.36	1.97	0.77
	5	0.164	2.821	0.836	0.83	5.26	0.21	2.77	0.52
50	1	1.727	3.585	0.444	1.56	7.64	0.18	2.66	0.54
	2	0.787	5.371	0.327	2.12	10.61	0.01	0.97	0.37
	3	0.709	2.389	0.416	1.66	8.51	0.07	1.96	0.72
	6	1.281	3.922	0.377	1.84	7.85	0.51	1.99	0.45
100	2	0.781	2.066	0.436	1.59	10.29	0.03	1.95	0.27
	3	1.321	1.355	0.420	1.65	9.45	0.58	2.78	0.33
	4	1.002	0.626	0.577	1.20	6.43	0.59	1.67	0.38
	6	0.549	1.979	0.365	1.90	8.81	0.52	2.35	0.84
200	1	0.529	1.776	0.455	1.52	7.06	0.62	1.94	0.66
	2	0.447	2.007	0.400	1.73	9.68	0.22	1.97	0.78
	3	1.384	1.722	0.341	2.03	11.87	0.38	2.34	0.61
	6	1.095	2.589	0.300	1.15	11.13	0.50	1.73	0.25

k_t, k_{ab} and k_{el}, first-order rate constants of transfer, absorption and elimination processes, respectively; $t_{1/2}$, elimination half-life; V, distribution volume; F, absorbed fraction; τ_1, τ_2, lag times for gastric emptying; and f, dose fraction dissolved or dispersed in gastric fluid until τ_2.

TABLE 2

Akaike's information criteria for the conventional, two-step absorption and modified model analyses of ceftibuten concentrations

Dose (mg)	Subject no.	Model		
		Conventional	Two-step	Modified
25	2	2.22	−22.47	−21.86
	3	−17.69	−36.24	−29.92
	4	2.44	−19.09	−16.35
	5	−5.43	−27.15	−17.80
50	1	27.80	1.76	5.14
	2	−1.71	−1.07	0.63
	3	20.82	−27.96	−31.90
	6	16.90	−13.77	−16.92
100	2	13.63	−4.80	−9.86
	3	19.54	−19.94	−33.16
	4	−1.19	−5.39	13.83
	6	23.06	−3.08	0.83
200	1	31.02	12.71	13.17
	2	35.87	−11.33	3.62
	3	37.32	−15.72	−7.05
	6	21.18	−30.55	−34.44
		$p < 0.01$		NS
		$p < 0.01$		

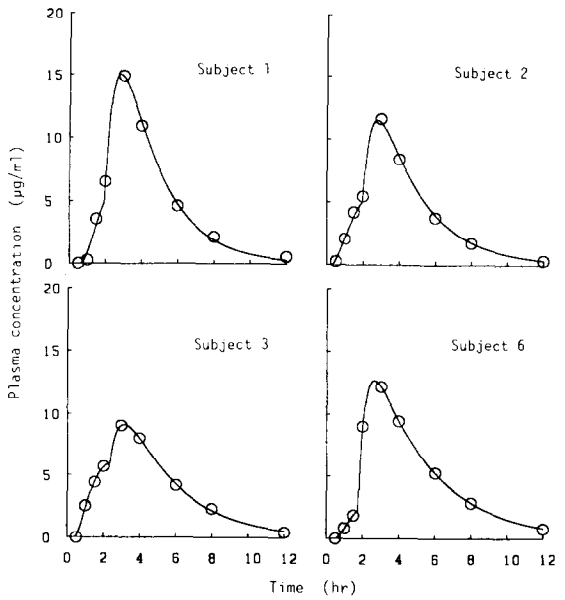


Fig. 9. Plasma ceftibuten concentration-time data and the fitted curves obtained with the modified compartment model in volunteers following an oral administration of 200 mg.

the absorption of drug begins after capsule degradation was estimated to be 30 min. The second lag period, during which a large proportion of the dose moves to the absorption site, was estimated as 2–3 h.

The AIC values for the three models are shown in Table 2. AIC values for the newly modified model were significantly ($p < 0.01$) lower than those for the conventional model, but slightly greater as compared to the two-step absorption model, although there was no significant difference between the two (Table 2).

Discussion

Discontinuous absorption of ceftibuten has frequently been demonstrated in the early absorption phase following oral administration to humans and rats. With respect to this phenomenon, a number of pharmacokinetic models have been de-

veloped, and several possible mechanisms have been suggested, for example, differing absorption rates according to the particular part of the intestine (Brockmeier et al., 1986; Funaki et al., 1986; Plusquellec et al., 1987), enterohepatic recycling (Veng-Pedersen, 1981) and rates of dissolution in the stomach and gastric emptying (Oberle and Amidon, 1987). The most probable cause of the difference in absorption rate along the intestine is the process of discontinuous absorption. In fact, the data on the discontinuous absorption of ceftibuten resulted in a good fit to the two-step absorption model with a slow first phase followed by a faster second phase of absorption. However, the results of in situ studies of ceftibuten absorption using an intestinal loop in rats indicated that a greater rate of absorption was observed in the upper and middle parts of the intestine. These results are inconsistent with the absorption rate constants determined for the two-step absorption model in which early slow absorption is followed by later rapid absorption. Therefore, it is not appropriate to conclude that the discontinuous absorption pattern of ceftibuten observed in humans was caused simply by variations in the rate of absorption along the intestine. This is because an absorption rate constant in the two-step absorption model does not necessarily correspond to a mean, real absorption rate constant from the intestine, but, rather, is a composite rate constant of dissolution, gastric emptying and/or absorption process. Therefore, further insights into the absorption rate constants are necessary.

Ceftibuten was considered to be insoluble in the stomach on the basis of its pH-dependent solubility as shown in Fig. 7. This insolubility in acidic gastric fluid was verified by determination of the ceftibuten concentration in gastric liquid following oral administration of ceftibuten in monkeys (< 10 μg/ml) and by detection of the ceftibuten powder remaining in the stomach of monkeys at 2 h after administration using a fiberscope. On the basis of the solubility of ceftibuten in vivo as well as in vitro, it is reasonable to postulate that the drug dissolves only to a very limited extent in the human stomach even when taking into account the anesthetization effect in the experiment on monkeys. Therefore, the slow increase in plasma concentration of ceftibuten during the early phase of the absorption process observed in volunteer studies appears to be due to the slow solubility caused by stomach acidity. In other words, the small proportion of the ceftibuten dose, which was dissolved or dispersed in the stomach after degradation of the capsule, was emptied from the stomach with the liquid. This assumptive explanation appears to be supported by data reported elsewhere showing that gastric emptying is a first-order process (Hunt and Stubb, 1975; Meyer et al., 1976; Moore et al., 1984). Early, first-order gastric emptying of such a type would have resulted in slow absorption with a slow increase in plasma concentration. After a period of first-order gastric emptying, almost all of the ceftibuten remaining in the stomach would have been emptied by gastric peristalsis at the same time to the absorption site where the pH value is appropriate (probably in the small intestine) for dissolution of the drug. This process would have resulted in a rapid increase in plasma concentration in the later phase of the absorption process. This suggests that the low solubility of this antibiotic and its gastric emptying behavior should be the major factors governing the discontinuous absorption process. In fact, the experimental data gave no indication of such a discontinuous phenomenon occurring following the oral administration of ceftibuten solution or ceftibuten sodium to rats.

The discontinuous absorption data on ceftibuten gave a good fit to the modified model in which these major factors had been incorporated. Since ceftibuten was given after an overnight fast, the stomach should have been in a fasting state. During the fasting state, stomach motor activity, referred to as the interdigestive myoelectric complex, recurs approximately every 2 h (Code and Marlett, 1975). The complex is composed of four phases. Phase 3 starts at 1.5–2 h of this cycle and sweeps even indigestible solids out of the stomach. The second lag time corresponds to the beginning of phase 3. Phase 3 motor activity may empty remaining drug. In clinical studies, subjects 2 and 3 showed discontinuous absorption at all doses, whereas others (subjects 1, 4 to 6) displayed this phenomenon depending on the dose. The drug

might be given to subjects during different phases of the interdigestive myoelectric complex after overnight fasting. Therefore, the different phases may lead to inter- and intra-individual differences in the appearance of the discontinuous absorption process. In addition, the inter- and intra-individual differences in gastric acidity may constitute of the possible factors that produce the variation in drug absorption.

The AIC values showed the two-step absorption model to be slightly superior to the newly modified model regarding the quality of fit of the data.

However, as mentioned before, the model does not provide a suitable explanation of the causes for discontinuous absorption of ceftibuten. On the other hand, comparably good curve fits were obtained using the modified model in which the factors deserving the solubility of ceftibuten and the process of physiological gastric emptying had been incorporated. These results suggest that ceftibuten would have been absorbed discontinuously via the mechanisms as described before.

Drugs of solubility comparable with that of ceftibuten may also show such a discontinuous absorption pattern in humans. For example, sulfisoxazole (Kaplan et al., 1972) and nalidixic acid (Ogata et al., 1984), which display the same low solubility in acidic medium and high solubility in alkaline medium as ceftibuten, have been reported to yield an absorption pattern similar to that of ceftibuten studied herein. Our newly modified model for characterizing the discontinuous absorption of ceftibuten in humans may be applicable for analysis of the absorption properties of other drugs similar to ceftibuten.

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