Pharmaceutical Research, Vol. 25, No. 4, April 2008 (© 2007)
DOI: 10.1007/s11095-007-9469-z

Research Paper

Appearance of Double Peaks in Plasma Concentration–time Profile after Oral Administration Depends on Gastric Emptying Profile and Weight Function

Yukiko Metsugi,[1] Yoshihiro Miyaji,[1] Ken-ichi Ogawara,[1] Kazutaka Higaki,[1] and Toshikiro Kimura[1,2]

Received September 3, 2007; accepted October 2, 2007; published online October 23, 2007

Purpose. Mechanism for double-peak occurrence in plasma concentration profile after oral administration of drugs is controversial, although irregular gastric emptying would be an important factor. The objective of this study was to assess the effect of gastric emptying and a weight function, i.e. pharmacokinetics after reaching the systemic circulation, on the double-peak appearance in plasma concentration profiles.
Materials and Methods. Alprazolam, which generates irregular gastric emptying, was orally co-administered with theophylline to rats, and the plasma concentration profiles or absorption rates were compared between the two drugs. Both drugs are highly absorbable, but alprazolam is rapidly eliminated from plasma, while the elimination of theophylline is very slow.
Results. Oral administration of alprazolam generated the irregular gastric emptying profiles, resulting in multiple peaks in the absorption rate profiles of both drugs. The double peaks in the absorption rate profiles led to the double peaks in plasma concentration profiles for alprazolam, but not necessarily for theophylline. Simulation study clearly indicated that the slower elimination from plasma made the first peak less recognizable.
Conclusions. The irregular gastric emptying could be a main reason for the double peaks in plasma concentration profiles. However, the frequency of double-peak occurrence depends on the weight function, particularly the elimination rate, of each drug.

KEY WORDS: Absorption rate; Double peaks; Gastric emptying; Weight function.

INTRODUCTION

Oral absorption behavior is often very complex because many time-dependent and variable factors in the gastrointestinal tract would influence the drug absorption from the small intestine after oral administration (1,2). The double-peak phenomenon is a typical example indicating the complex kinetics of drug absorption after oral dosing. Double peaks in plasma concentration–time profiles have been often observed after oral administration for many drugs (3–18). Possible reasons for the double-peak phenomenon have also been proposed as follows: (a) the interaction between drugs and bile salts in the intestinal lumen (10,11), (b) the enterohepatic circulation (12,19), (c) the two different sites of drug absorption (13–16,20), (d) the irregular pattern of gastric emptying (3–9). However, these explanations are not definitive yet, or rather controversial. Particularly, several different reasons were proposed for the cases of ranitidine (17,21–23) and cimetidine (18–20,24). Since most drugs are mainly absorbed from the small intestine, but not from the stomach, gastric emptying is the rate-limiting step for drug absorption, particularly for drugs with high permeability and high solubility as classified in BCS class I (25). Therefore, an irregular pattern of gastric emptying may result in the irregular profile of absorption rate (3,9,18), even though some cases do not lead to the multiple peaks in plasma concentration–time profiles (18). Gastric emptying rate is significantly correlated with gastric motility (8,26,27), and the gastric motility is well known to be regulated by the migrating motor complex (MMC) under the fasted condition (28,29). On the other hand, the feedback mechanism influenced by the contents in the duodenal lumen regulates the gastric motility (29), resulting in the irregular contractions of the antrum (30). Thus, gastric emptying is affected by the amount and kinds of foods ingested (31–33). Therefore, the pattern of gastric emptying is often complicated dependent on the physiological and/or food conditions. Some drugs influence the gastric emptying (2,34,35). It was reported that alprazolam reduced the gastric motility and that double peaks were observed in plasma concentration–time profile after oral administration in rats (36).

However, there is some criticism saying that gastric emptying is not necessarily a critical factor for multiple peaks. The reason for the criticism is as follows: if gastric empting is a determining factor for multiple peaks, the multiple peaks should be observed for every drug, but they are not observed for every drug.

In the present study, in order to investigate the effect of gastric emptying on plasma concentration–time profile,

[1] Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Okayama University, 1-1-1 Tsushima-naka, Okayama, 700-8530, Japan.
[2] To whom correspondence should be addressed. (e-mail: kimura@pharm.okayama-u.ac.jp)

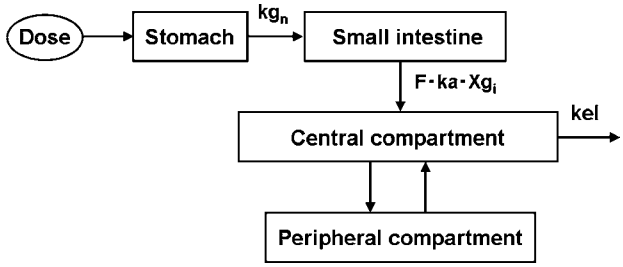

Fig. 1. Pharmacokinetic model for analyzing the absorption kinetics of alprazolam and theophylline after oral administration. *Dose*, intragastrically administered dose; kg_n, symbolic parameter showing variable gastric emptying behavior; *ka*, first-order absorption rate constant; *kel*, first-order elimination rate constant from central compartment; *F*, bioavailability; Xg_i, amount of drug in the small intestinal lumen.

irregular gastric emptying in rats was generated by the oral administration of alprazolam. Furthermore, theophylline was orally co-administered to assess the effect of the pharmacokinetics after reaching the systemic circulation, a weight function, on the shape of plasma concentration–time profile, because the elimination of theophylline from plasma is much slower than alprazolam (34,36,37). Then, the plasma concentration profiles were compared between alprazolam and theophylline. The importance of irregular gastric emptying profiles and the impact of weight function, particularly the elimination rate from plasma, for multiple peaks are discussed based on the experimental data and simulation study.

MATERIALS AND METHODS

Materials. Alprazolam was kindly supplied by formerly Upjohn Co. (now Pfizer) (Kalamazoo, MI). Theophylline and aminophylline (theophylline hemiethylenediamine complex) were purchased from Tokyo Kasei Kogyo Co. (Tokyo, Japan) and Sigma Chemical Co. (St. Louis, MO), respectively. All other chemicals and reagents were analytical grade commercial products.

Animals. Male Wistar rats (Japan SLC, Hamamatsu, Japan), maintained at 25°C and 55% humidity, were allowed free access to standard laboratory chow (Clea Japan, Tokyo) and water. After fasted for 12 h, they were allowed free access to standard laboratory chow and water for 8 h prior to the experiment. Rats weighing 210–280 g were randomly assigned to each experimental group. Our investigations were performed after approval by our local ethical committee at Okayama University and in accordance with "Principal of Laboratory Animal Care (NIH publication # 85–23)."

In Situ Closed Loop Study. To evaluate the first-order absorption rate constant, the absorption experiments were performed for 10-cm jejunal segment by a conventional *in-situ* closed loop method (38). Alprazolam (0.2 mg/ml) or aminophylline (0.5 mg/ml) in isotonic phosphate buffer (pH 6.5) was introduced into the jejunal segment at 0.5 ml. The first-order absorption rate constant (ka) was obtained by estimating the disappearance rate of drug from the lumen in 15 min.

In Vivo Intravenous and Oral Administration Studies. One day before drug administration, the jugular vein of a rat was cannulated with vinyl tubing (i.d., 0.5×0.8 mm; Dural Plastics & Engineering, Australia) under ether anesthesia. In the case of oral administration, the solution containing both alprazolam (10.0 or 5.0 mg/ml) and aminophylline (2.0 mg/ml) was intragastrically administered at a volume of 2.5 ml/kg. For intravenous administration, the solution containing alprazolam (2.5 mg/ml) and aminophylline (1.0 mg/ml) in saline was administered into the tail vein at a volume of 1.0 ml/kg. Blood samples were periodically taken from the cannulated jugular vein. One hundred microliters of plasma obtained by centrifugation was deprotenized by 200 μl of methanol. The resulting supernatant was introduced into HPLC for the analysis of alprazolam and theophylline.

Analytical Method. Alprazolam and theophylline were determined by HPLC, which consists of a model LC-6A HPLC pump (Shimadzu, Kyoto, Japan), a model SIL-6A system controller (Shimadzu), and a model SPD-6A UV detector (Shimadzu) set at 222 nm for alprazolam, or set at 272 nm for theophylline. TSK-gel ODS-80TM (150×4.6 mm i.d., Tosoh Corporation, Tokyo) was used at room temperature. The mobile phase for alprazolam was 5 mM phosphate buffer (pH 7.2):acetonitrile (70:30, v/v) delivered at 1.0 ml/min, and that for theophylline was 5 mM acetate buffer (pH 4.5):acetonitrile (95:5, v/v) delivered at 1.0 ml/min. The standard curves of alprazolam (0.05–5 μg/ml) or theophylline (0.5–10 μg/ml) gave the coefficient of variation (CV) ranged from 0.07 to 8.24% or 0.77 to 8.59%, respectively. The squared correlation coefficient was over 0.995 for both drugs.

Pharmacokinetic Analysis. Pharmacokinetic model (Fig. 1) was used to analyze the absorption kinetics of alprazolam and theophylline after oral administration. The first-order kinetics was assumed except for the gastric emptying process, where variable emptying profiles were not necessarily dependent on the amount or concentration of drugs in the stomach were observed. The parameter, kg_n, just symbolically represents the variable gastric emptying behavior. *F*, ka, kel and Xg_i mean

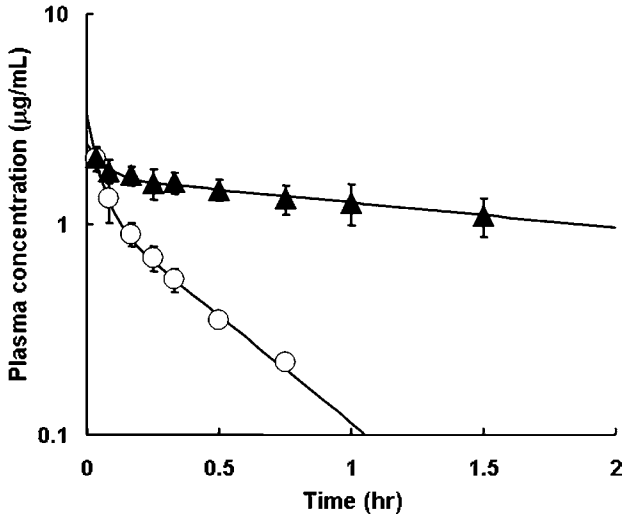

Fig. 2. Plasma concentration–time profiles of alprazolam and theophylline after intravenous administration of both drugs. Doses of alprazolam and theophylline were 2.5 and 1.0 mg/kg (aminophylline), respectively. Results were expressed as the mean with the bars showing S.D. of at least three experiments. Keys: *open circle*, alprazolam; *filled triangle*, theophylline.

Table I. Pharmacokinetic Parameters of Alprazolam and Theophylline After Intravenous Administration

Pharmacokinetic Parameters	Alprazolam	Theophylline
A (μg/ml)	2.14±0.69	0.750±0.399*
α (h^{-1})	23.3±10.4	16.62±9.53
B (μg/ml)	1.18±0.08	1.67±0.18**
β (h^{-1})	2.34±0.06	0.279±0.055**
AUC_{iv} (μg·h/ml)	0.61±0.06	6.27±1.67*
CL_{total} (l/h/kg)	4.15±0.37	0.128±0.031**
kel (h^{-1})	5.56±1.39	0.367±0.122**
Vd_{ss} (l/kg)	1.53±0.20	0.456±0.020**

Both alprazolam and theophylline were simultaneously administered. Dose of alprazolam was 2.5 mg/kg. Theophylline was dosed as aminophylline at 1.0 mg/kg. Results are expressed as the mean ± S.D. of at least 3 experiments. *$p<0.05$; **$p<0.01$ compared with alprazolam.

bioavailability, absorption rate constant, elimination rate constant and amount of drug in the small intestine, respectively. Pharmacokinetic parameters describing the plasma concentration–time profiles of alprazolam and theophylline after intravenous administration were obtained based on a two-compartment model by the non-linear least-squares regression program MULTI (39). The plasma concentration–time profile is generally expressed by the following equation:

$$Cp = A \cdot \exp(-\alpha \cdot t) + B \cdot \exp(-\beta \cdot t) \quad (1)$$

where α and β are rate constants for the distribution phase and elimination phase, respectively. A and B are hybrid constants shown as $D \cdot (\alpha \cdot k_{21})/Vc/(\alpha-\beta)$ and $D \cdot (k_{21}-\beta)/Vc/(\alpha-\beta)$, respectively. D, k_{21} and Vc mean dose, first-order rate constant from peripheral to central compartment and distribution volume in central compartment, respectively.

The value of F was calculated as the absolute bioavailability by the following equation:

$$F = \frac{D_{iv} \cdot AUC_{po}^{0\to\infty}}{D_{po} \cdot AUC_{iv}^{0\to\infty}} \quad (2)$$

where D_{iv} and D_{po} are doses of alprazolam or theophylline for intravenous and oral administration, respectively. AUC after oral administration from 0 time to infinity, $AUC_{po}^{0\to\infty}$, was calculated by trapezoidal rule and AUC after intravenous administration from 0 time to infinity,$AUC_{iv}^{0\to\infty}$, was calculated by $A/\alpha+B/\beta$. CL_{total}, total body clearance, was calculated by

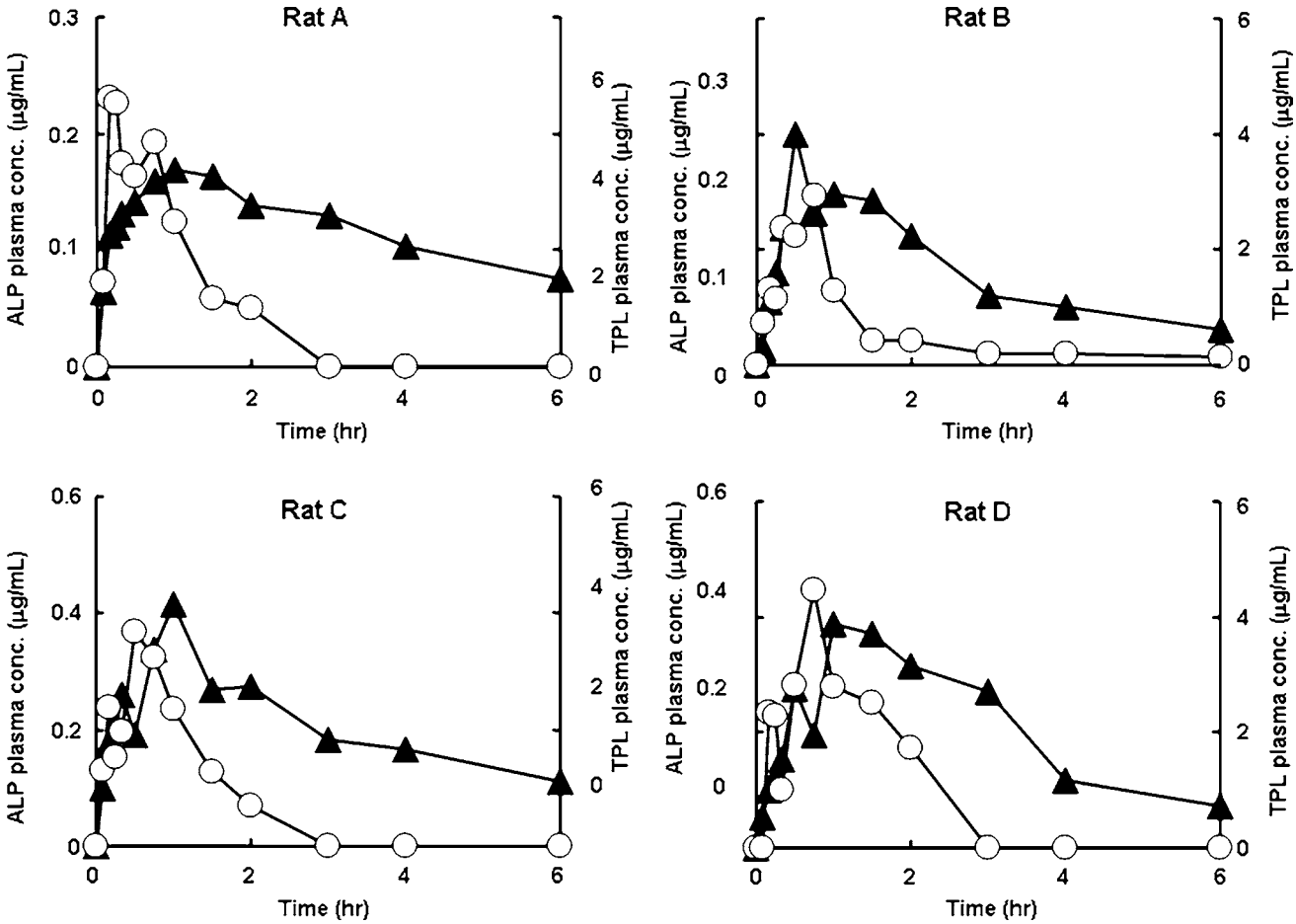

Fig. 3. Plasma concentration–time profiles of alprazolam (ALP) and theophylline (TPL) after oral administration in each rat. Dose of ALP was 12.5 mg/kg for rats A and B or 25 mg/kg for rats C and D. Dose of theophylline was 5 mg/kg as aminophylline. Keys: *open circle*, ALP; *filled triangle*, TPL.

Table II. Bioavailability of Alprazolam and Theophylline in Each Rat After Oral Administration

Rat	Alprazolam			Theophylline		
	Dose (mg/kg)	AUC_{po} (μg·h/ml)	*F*	Dose (mg/kg)	AUC_{po} (μg·h/ml)	*F*
A	12.5	0.258	0.085	5.0	23.37	0.818
B	12.5	0.136	0.045	5.0	12.32	0.431
C	25.0	0.450	0.075	5.0	17.55	0.615
D	25.0	0.570	0.094	5.0	16.61	0.582

Both alprazolam and theophylline were simultaneously administered. Dose of alprazolam was 12.5 or 25.0 mg/kg. Theophylline was administered as aminophylline at 5.0 mg/kg. AUC_{po} from 0 to infinity was calculated by trapezoidal rule.

$D_{iv}/AUC_{iv}^{0\to\infty}$. Vd_{ss}, distribution volume at steady state, was determined by $Vc\cdot(1+k_{12}/k_{21})$, where k_{12} is a first-order rate constant from central to peripheral compartment.

The absorption rate–time profiles were calculated by following Loo–Riegelman method (40) because the pharmacokinetics after intravenous administration was described by the two-compartment model for both alprazolam and theophylline.

In order to obtain the gastric emptying rate profiles, the remaining amount of alprazolam–time profiles in the small-intestinal lumen as an output function and the first-order absorption process as a weight function were utilized to perform the deconvolution with a multi-function convolution simulator (41). It was assumed that the absorption of alprazolam was rate-limited by gastric emptying (36). Here the remaining amount of alprazolam–time profiles in the small intestine were obtained by dividing the absorption rate–time profiles with $F\cdot ka$ of alprazolam. As both alprazolam and theophylline follow the identical profile of gastric emptying, the absorption rate profiles of theophylline as well as alprazolam were calculated utilizing the gastric emptying profile calculated above as an input function and the first-order absorption process of each drug as a weight function with the multi-function convolution simulator (41).

Finally, the plasma concentration profiles for both drugs were calculated utilizing the absorption rate–time profile as an input function and the equation describing the plasma concentration profiles after intravenous administration as a weigh function using the multi-function convolution simulator (41).

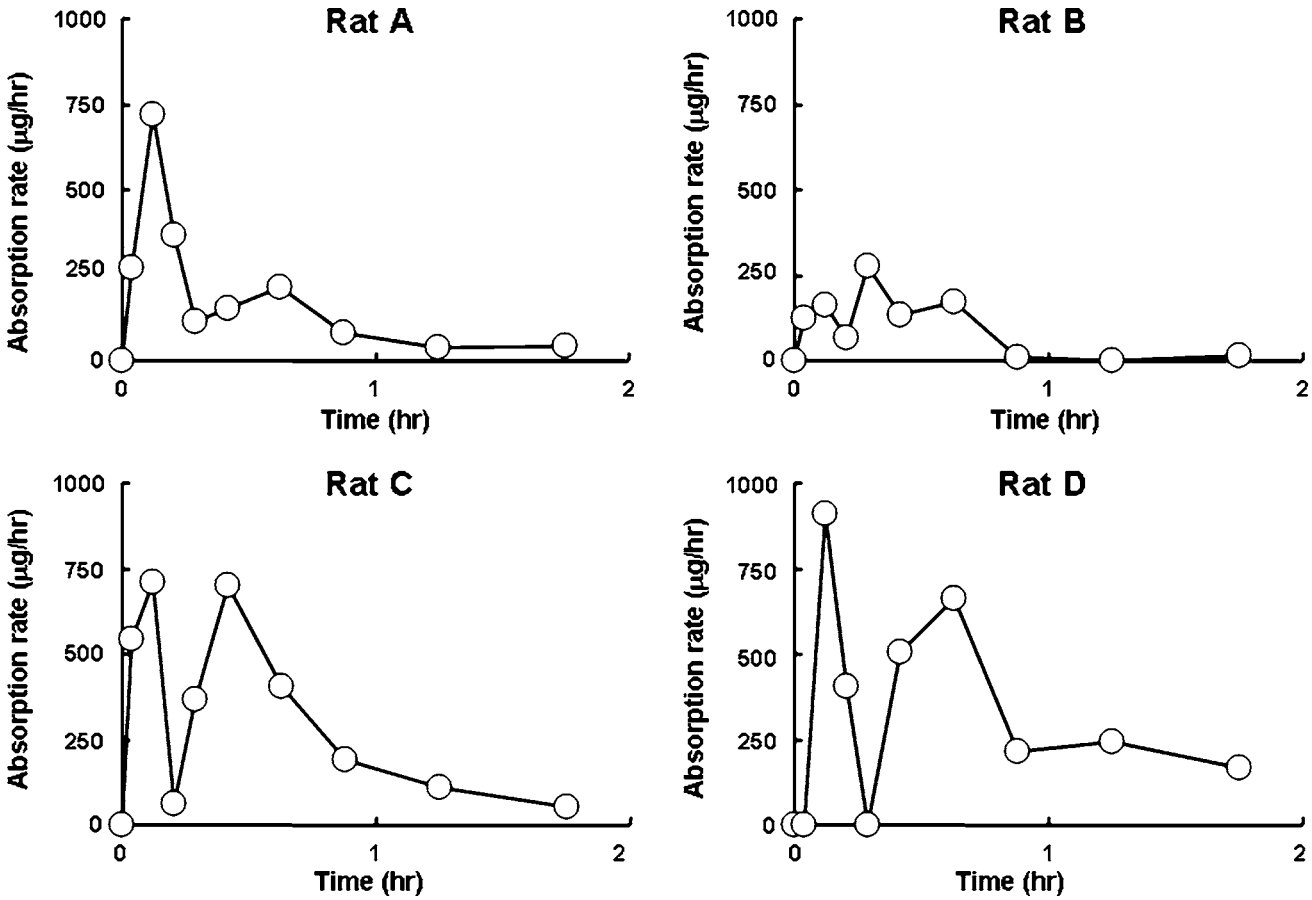

Fig. 4. Absorption rate–time profile of alprazolam after oral administration calculated by Loo–Riegelman method for each rat. Dose of alprazolam was 12.5 mg/kg for rats A and B or 25 mg/kg for rats C and D. Absorption rates were calculated by following Loo–Riegelman method.

Statistical Analysis. Results are expressed as the mean± S.D. of at least three experiments. Statistical significance in the differences of the means was determined by Student's *t*-test. Statistical significance of the correlation between observed and calculated values of plasma concentration was determined by Pearson's method.

RESULTS AND DISCUSSION

For various drugs, the occurrence of multiple peaks in plasma concentration profiles is related with gastric emptying (3–9,18,22,36). As the gastric emptying of drugs is physiologically regulated by gastric motility (28–33), the same effect of gastric emptying on the absorption behavior must be expected for most drugs, except for drugs with pharmacological effect to change the motility of gastrointestinal tract (34–36). However, multiple peaks are observed for some drugs, but not for other drugs. That is the reason why double-peak issue is still controversial. The present study provides some answers for this problem by paying attention to the pharmacokinetics after reaching the systemic circulation.

Alprazolam was selected as a model drug, because the drug reduces the gastric motility by its muscle relaxant effect and provides double peaks in plasma concentration profiles after being orally dosed (35,36). Alprazolam is highly absorbable and rapidly eliminated from the plasma (36). Theophylline is also highly absorbable (34), but its elimination from plasma is very slow (34,37), which is the reason why theophylline was chosen as another model compound. Fig. 2 shows the plasma concentration–time profiles of alprazolam and theophylline after intravenous administration of both drugs. The pharmacokinetic parameters obtained are summarized in Table I. CL_{total}, Vd_{ss} and kel values were significantly smaller for theophylline than alprazolam and the value of β for theophylline was also much smaller than that for alprazolam.

Fig. 3 shows the plasma concentration–time profiles of both drugs after oral administration in each rat, and the pharmacokinetic parameters are listed in Table II. Alprazolam provided an irregular shape in its plasma profile with double peaks for all the rats examined. Although alprazolam was administered at two different doses (12.5 mg/kg for rats A and B, 25 mg/kg for rats C and D), there was no large difference in the plasma concentration–time profiles between the two doses. On the other hand, theophylline showed no sharp peaks and the slow and gentle elimination profile in rat A, while double peaks were clearly observed for alprazolam. In other subjects, plasma concentration profiles of theophylline tended to be irregular, but seemed to be smoother than those of alprazolam.

Next, the absorption rate–time profiles were calculated for alprazolam by utilizing the pharmacokinetic parameters (Table I)

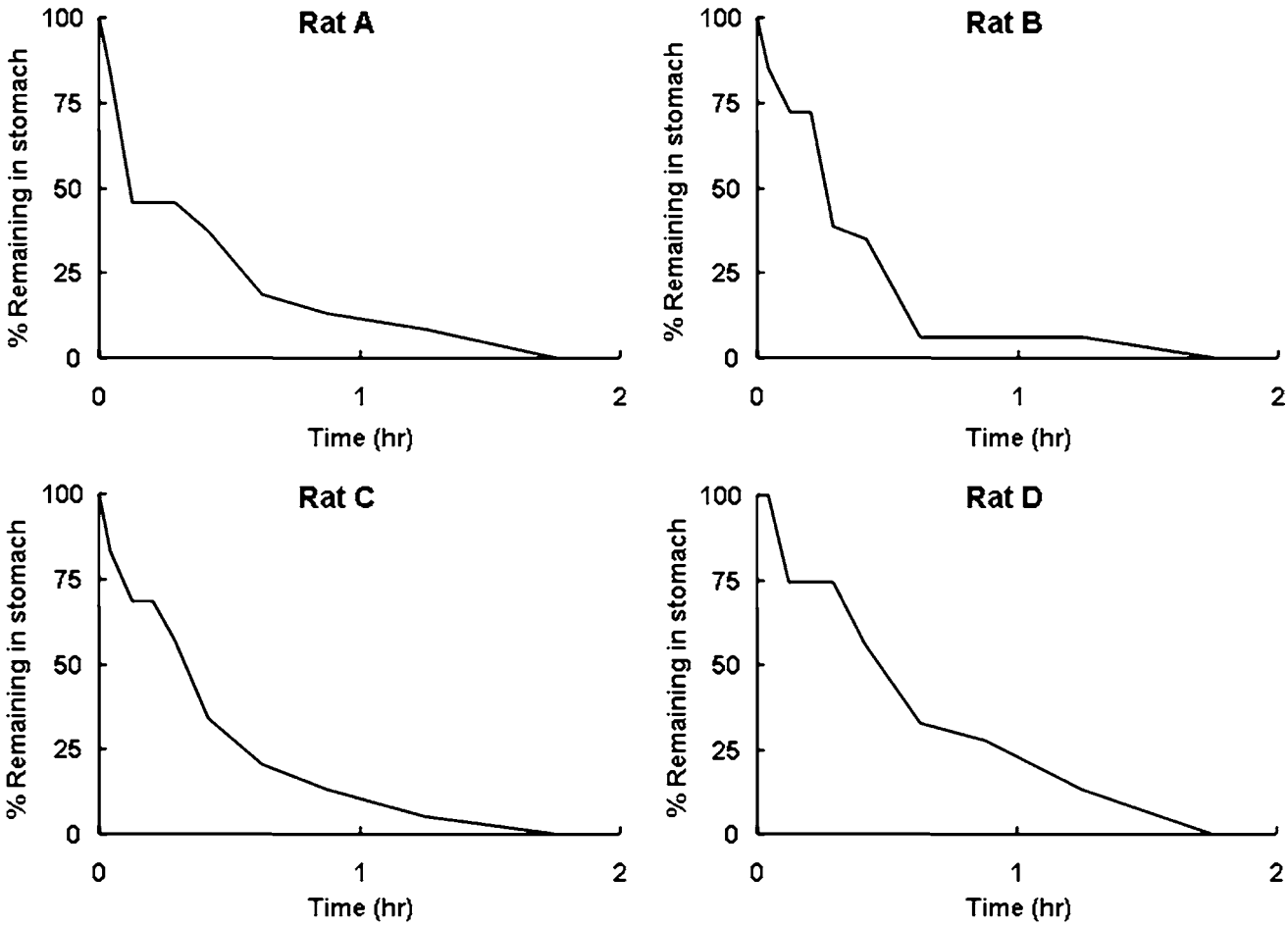

Fig. 5. Gastric emptying profile after oral administration calculated based on absorption behavior of alprazolam in each rat. Deconvolution was performed to calculate the gastric emptying profiles by following the procedure described in the section of "Pharmacokinetic analysis."

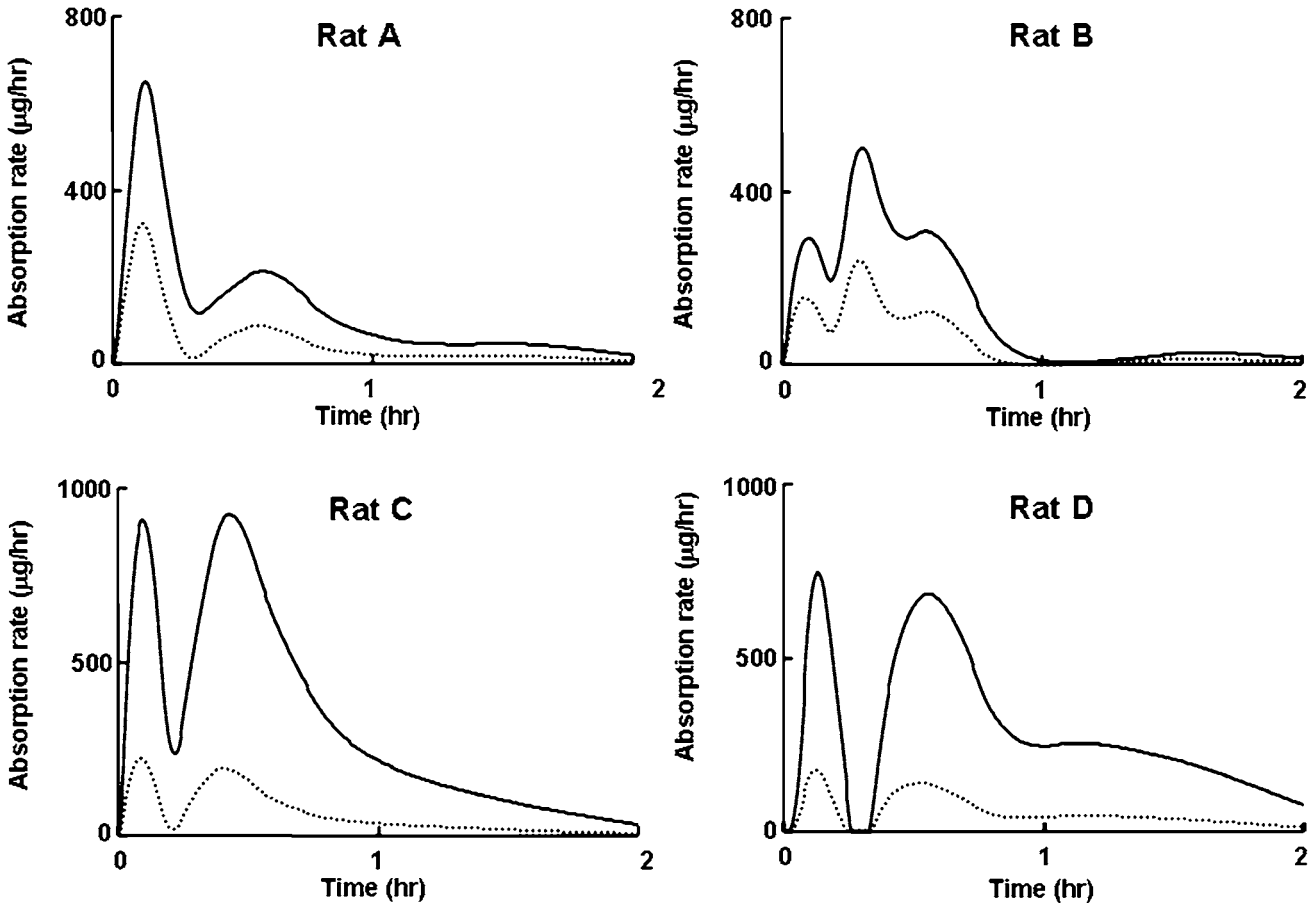

Fig. 6. Absorption rate–time profiles of alprazolam and theophylline calculated based on gastric emptying profiles. Convolution was performed to calculate the absorption rates for both alprazolam and theophylline based on the gastric emptying–time profiles shown in Fig. 5 by following the procedure described in the section of "Pharmacokinetic analysis." Keys: *solid line*, alprazolam; *broken line*, theophylline.

as a weight function according to Loo–Riegelman method (40). Fig. 4 clearly shows that there were double peaks in the absorption rate–time profiles in all subjects, indicating that the input of alprazolam from the small intestine to the blood circulation was interrupted at least once during the entire process of absorption after oral administration.

\The gastric emptying profiles of alprazolam after oral administration were obtained by deconvolution (Fig. 5). Here the remaining amount of alprazolam–time profiles in the small intestine were utilized as an output function, which were obtained by dividing the absorption rate–time profiles (Fig. 4) with $F \cdot$ ka of alprazolam. The value of ka for alprazolam was determined as 7.52± 0.09 h^{-1} (n=5) by *in-situ* closed loop study and F values are listed in Table II. The low bioavailability of alprazolam is attributed to the extensive metabolism due to cytochrome P450 3A subfamily in the liver (36,42). The obtained profile of gastric emptying indicates that the gastric emptying did not simply follow a first-order kinetics, but was interrupted and/or attenuated during the entire process for each subject. Similar irregular profiles of gastric emptying were also reported in several cases (3,9,26).

As the gastric emptying–time profile should be identical for both alprazolam and theophylline in each rat, the absorption rate–time profiles of theophylline were simulated by utilizing the gastric emptying profile (Fig. 5) as an input function and the first-order absorption process as a weight function (Fig. 6). The value of ka for theophylline (11.89±0.35 h^{-1}, n=5) was obtained by *in-situ* closed loop study and F value for each rat is shown in Table II. The calculated profiles of the absorption rate for theophylline are shown together with those for alprazolam (Fig. 6). The figure clearly indicates that the input rates of theophylline into the blood circulation had multiple peaks similar to those of alprazolam.

Finally, plasma concentration–time profiles of both alprazolam and theophylline were calculated by performing convolution. Here the absorption rate profiles (Fig. 6) and pharmacokinetics after intravenous administration (Fig. 2 and Table I) were utilized as an input function and a weight function, respectively. As shown in Fig. 7, the simulated curve for alprazolam agreed remarkably with the observed plasma profile including the double peaks and irregular shape for each rat, indicating that the calculation error should be very small in the processes of deconvolution and convolution. Comparing absorption rate profiles (Fig. 6) with plasma concentration profiles (Fig. 7) for alprazolam, double peaks in absorption rate profiles led to the double peaks in plasma concentration profiles for rats A, C and D. In rat B, however, the clear multiple peaks were not observed in the plasma profile even though the absorption rate profile had multiple peaks. These results suggest that the irregular profiles of gastric emptying and absorption rate do not always result in the multiple peaks in plasma profile and that the time period and extent of interruption of absorption seems to be

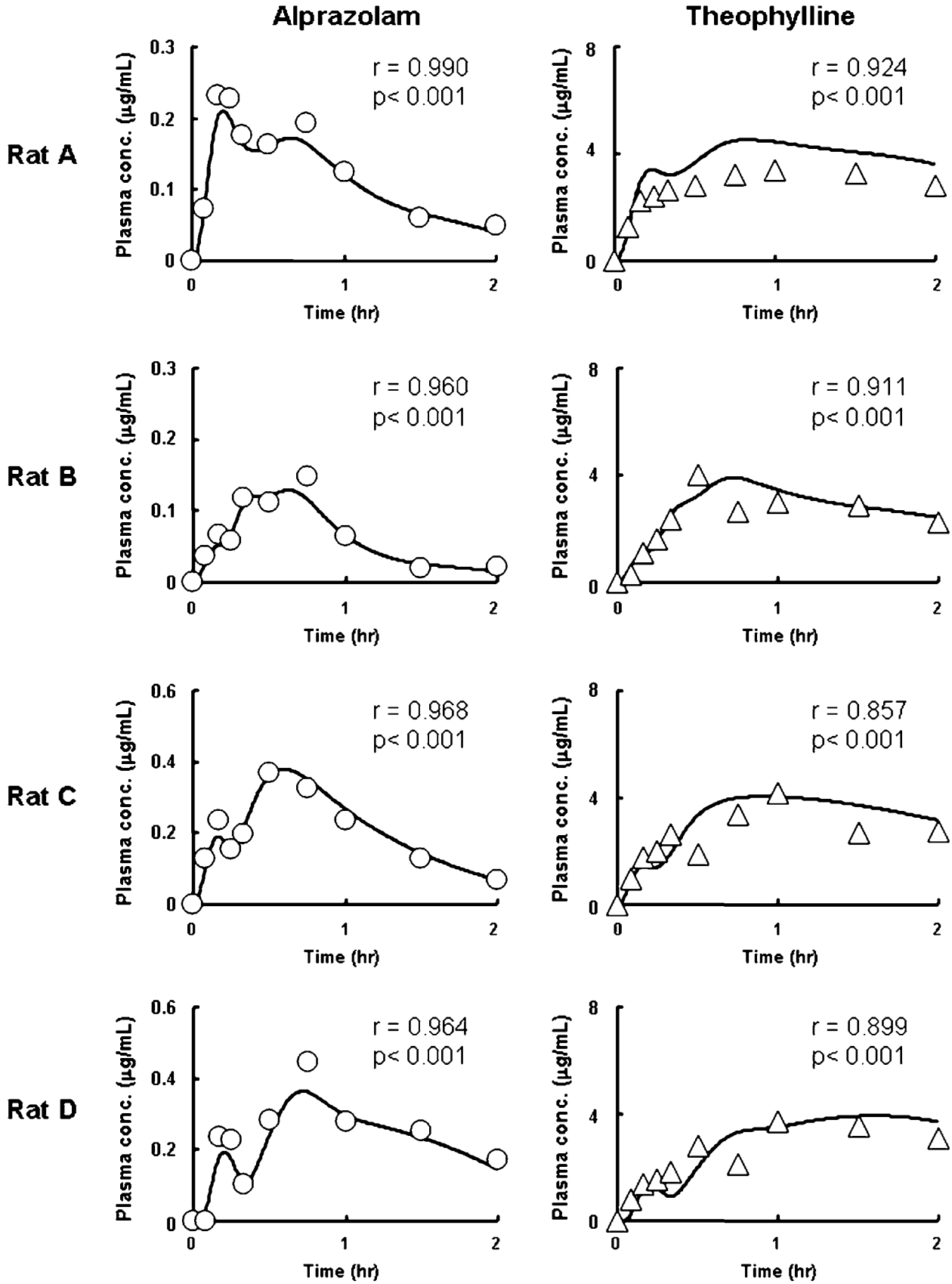

Fig. 7. Plasma concentration–time profiles for alprazolam and theophylline calculated based on gastric emptying profiles. Plasma concentration profiles were calculated with convolution method based on the absorption rates profiles shown in Fig. 6 by following the procedure described in the section of "Pharmacokinetic analysis." Statistical significance of correlation between observed and calculated values were examined by Pearson's method. Keys: *open circle*, observed values; *solid line*, calculated values.

important for the appearance of double peaks in plasma profile as suggested in the previous reports (3,9,18). The simulation curves for theophylline were also in good agreement with the observed plasma concentration profiles. When alprazolam was compared with theophylline in terms of plasma concentration profile, the shape of the profile was quite different each other. The change in plasma concentration was gentler for theophylline compared with alprazolam because theophylline is eliminated from plasma much more slowly than alprazolam (Table I). Therefore, the double peaks observed for alprazolam almost disappeared for theophylline in rat A even though both drugs had the identical time profile for absorption rates (Fig. 6). In rats C and D, the plasma concentration–time profiles of theophylline showed more gradual change than those of alprazolam. Therefore, it is difficult to recognize the appearance of double peaks in the plasma profile. These results experimentally suggest that the slower elimination from the plasma decreases the frequency of double-peak appearance in plasma concentration–time profiles.

In Fig. 8, rat C was taken as an example for the simulation study. The value of β was increased from 0.03 to 23.4 h^{-1} to calculate the plasma concentration time–curve of alprazolam. Fig. 8c shows the observed data and simulation curve for alprazolam, having clear double peaks in the profile. When the value of β was increased to 23.4 h^{-1}, the first peak was isolated from the second one more clearly and the double peaks became more remarkable (Fig. 8d). On the other hand, Fig. 8a and b shows that the decrease of β to 0.03 and 0.28 h^{-1}, which is the β value of theophylline, makes the first peak smaller compared with the second one, and tends to vanish the double peaks in the plasma concentration–time profiles. The simulation study clearly indicates that the shape of the plasma concentration–time profiles is affected by the change in a weight function even though the input function is not changed, and that the slower elimination from plasma makes the shape of plasma profile smoother and makes the first peak less recognizable. In the present study, we experimentally and theoretically succeeded to indicate the importance of gastric emptying as well as weight function for the double-peak appearance in plasma concentration–time profiles after oral administration of drugs.

As ka value is larger than kel value for many drugs including alprazolam and theophylline, the decline of plasma

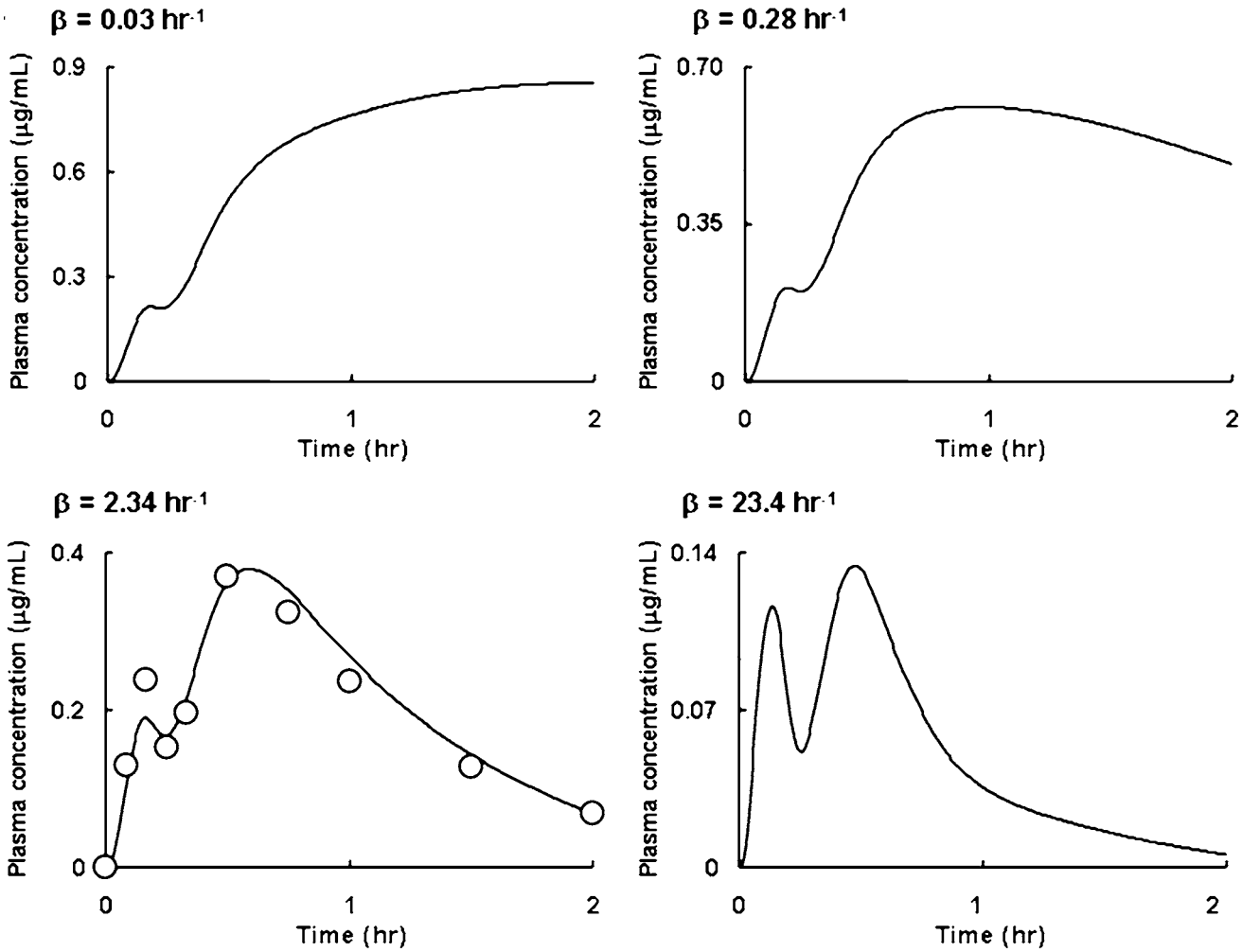

Fig. 8. Effect of elimination rate constant on appearance of double peaks in plasma concentration–time profile. Plasma concentration–time profile was simulated based on plasma concentration data of alprazolam in rat C by utilizing β values of 0.03, 0.28 (theophylline), 2.34 (alprazolam) and 23.4 h^{-1}. Other pharmacokinetic parameters used were those for alprazolam in rat C. Keys: *open circle*, observed concentration of alprazolam in rat C; *solid line*, simulated lines.

concentration is governed by the elimination rate after reaching a maximal concentration. Therefore, the slower elimination from plasma results in the dilution of double-peak phenomenon in plasma concentration profile as shown in the present study. On the other hand, in the case of a drug, of which kel value is larger than ka value, the decline of plasma concentration is regulated by its absorption rate. Therefore, the double peaks in the absorption rate profiles are likely to be reflected to the appearance of double peaks in plasma concentration profiles. This is the case for the simulation curve in Fig. 8d, where it was assumed that kel (54.6 h^{-1}) was larger than ka (7.52 h^{-1}). The shape of the simulated plasma concentration profile was very similar to that of absorption rate profile shown in Fig. 6 (Rat C). In any case, the weight function, particularly the elimination rate of drug is important for the appearance of double peaks in plasma concentration profiles.

CONCLUSIONS

Irregular gastric emptying caused irregular absorption rate profiles, which could be linked to the appearance of double peaks in plasma concentration–time profiles. However, the frequency or probability of double-peak occurrence in plasma concentration–time profiles depend on the weight function of each drug even if drugs are emptied from stomach by following the same irregular pattern.

REFERENCES

1. K. Higaki, S. Yamashita, and G. L. Amidon. Time-dependent oral absorption models. *J. Pharmacokin. Phrmacodyn.* **28**:109–128 (2001).
2. T. Kimura, and K. Higaki. Gastrointestinal transit and drug absorption. *Biol. Pharm. Bull.* **25**:149–164 (2002).
3. J. A. Clements, R. C. Heading, W. S. Nimmo, and L. F. Prescott. Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmacol. Ther.* **24**:420–431 (1978).
4. W. D. Mason, N. Winer, G. Kochak, I. Cohen, and R. Bell. Kinetics and absolute bioavailability of atenolol. *Clin. Pharmacol.* **25**:408–415 (1979).
5. W. N. Charman, M. C. Rogge, A. W. Boddy, W. H. Barr, and B. M. Berger. Absorption of danazol after administration to different sites of the gastrointestinal tract and the relationship to single- and double-peak phenomena in the plasma profiles. *J. Clin. Pharmacol.* **33**:1207–1213 (1993).
6. J. B. Dressman, R. R. Berardi, G. H. Elta, T. M. Gray, P. A. Montgomery, H. S. Lau, K. L. Pelekoudas, G. J. Szpunar, and J. G. Wabner. Absorption of flurbiprofen in the fed and fasted states. *Pharm. Res.* **9**:901–907 (1992).
7. J-P. Reymond, J-L. Steimer, and W. Niederberger. On the dose dependency of cyclosporin A absorption and disposition in healthy volunteers. *J. Pharmacokin. Biopharm.* **16**:331–353 (1988).
8. E. Lipka, I-D. Lee, P. Langguth, H. Spahn-Langguth, E. Mutschler, and G. L. Amidon. Celiprolol double-peak occurrence and gastric motility: nonlinear mixed effects modeling of bioavailability data obtained in dogs. *J. Pharmacokin. Biopharm.* **23**:267–286 (1995).
9. G. A. Digenis, E. P. Sandefer, R. C. Page, and W. J. Doll. Gamma scintigraphy: an evolving technology in pharmaceutical formulation development—Part 2. *Pharm. Sci. Technol. Today* **1**:160–165 (1998).
10. H. Lennernäs, and C-G. Regårdh. Evidence for an interaction between the β-blocker pafenolol and bile salts in the intestinal lumen of the rat leading to dose-dependent oral absorption and double peaks in the plasma concentration–time profile. *Pharm. Res.* **10**:879–88 (1993).
11. T. Yamaguchi, T. Oida, C. Ikeda, and Y. Sekine. Intestinal absorption of a β-adrenergic blocking agent nadolol. . *Chem. Pharm. Bull.* **34**:4259–4264 (1986).
12. J-E. Peris-Ribera, F. Torres-Molina, M. C. Garcia-Carbonell, J. C. Aristorena, and J. M. Pla-Delfina. Pharmacokinetics and bioavailability of diclofenac in the rat. *J. Pharmacokin. Biopharm.* **14**:615–633 (1986).
13. R. F. Bergstrom, D. R. Kay, T. M. Harkcom, and J. G. Wagner. Penicillamine kinetics in normal subjects. *Clin. Pharmacol. Ther.* **30**:404–413 (1981).
14. Y. Plusquellec, G. Campistron, S. Staveris, J. Barre, L. Jung, J. P. Tillement, and G. Houin. A double-peak phenomenon in the pharmacokinetics of veralipride after oral administration: a double-site model for drug absorption. *J. Pharmacokin. Biopharm.* **15**:225–239 (1987).
15. D. Brockmeier, H. G. Grigoleit, and H. Leonhardt. The absorption of piretanide from the gastrointestinal tract is site-dependent. *Eur. J. Clin. Pharmacol.* **30**:79–82 (1986).
16. H. Lennernäs, and C. G. Regårdh. Regional gastrointestinal absorption of the beta-blocker pafenolol in the rat and intestinal transit rate determined by movement of ^{14}C-PEG 4000. *Pharm. Res.* **10**:130–135 (1993).
17. R. Miller. Pharmacokinetics and bioavailability of ranitidine in humans. *J. Pharm. Sci.* **73**:1376–1379 (1984).
18. R. L. Oberle, and G. L. Amidon. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. *J. Pharmacokin. Biopharm.* **15**:529–544 (1987).
19. P. Veng-Pedersen, and R. Miller. Pharmacokinetics and bioavailability of cimetidine in humans. *J. Pharm. Sci.* **69**:394–398 (1980).
20. N. Piyapolrungroj, Y. S. Zhou, C. Li, G. Liu, E. Zimmermann, and D. Fleisher. Cimetidine absorption and elimination in rat small intestine. *Drug Metab. Dispos.* **28**:65–72 (2000).
21. G. Mullersman, V. P. Gotz, W. L. Russell, and H. Derendorf. Lack of clinically significant *in vitro* and *in vivo* interactions between ranitidine and sucralfate. *J. Pharm. Sci.* **75**:995–998 (1986).
22. A. B. Suttle, and K. L. R. Brouwer. Gastrointestinal transit and distribution of ranitidine in the rat. *Pharm. Res.* **12**:1316–1322 (1995).
23. K. S. Reynolds, M. H. Song, W. D. Heizer, C. B. Burns, D. A. Sica, and K. L. R. Brouwer. Effect of pancreatico-biliary secretions and GI tract time on the absorption and pharmacokinetic profile of ranitidine in humans. *Pharm. Res.* **15**:1281–1285 (1998).
24. V. Mummaneni, G. L. Amidon, and J. B. Dressman. Gastric pH influences the appearance of double peaks in the plasma concentration–time profiles of cimetidine after oral administration in dogs. *Pharm. Res.* **12**:780–786 (1995).
25. G. L. Amidon, H. Lennernäs, V. P. Shar, and J. R. Crison. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.* **12**:413–420 (1995).
26. R. L. Oberle, T-S. Chen, C. Lloyd, J. L. Barnett, C. Owyang, J. Meyer, and G. L. Amidon. The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroenterol.* **99**:1275–1282 (1990).
27. N. Takamatsu, L. S. Welage, Y. Hayashi, R. Yamamoto, J. L. Barnett, V. P. Shah, L. J. Lesko, C. Ramachandran, and G. L. Amidon. Variability in cimetidine absorption and plasma double peaks following oral administration in the fasted state in humans: correlation with antral gastric motility. *Eur. J. Pharm. Biopharm.* **53**:37–47 (2002).
28. S. K. Sarna. Cyclic motor activity; Migrating motor complex. *Gastroenterol.* **89**:894–913 (1985).
29. H. C. Kutchai. The gastrointestinal system. In R. M. Berne, and M. N. Levy (eds.), *Physiology*, 4th ed, Mosby, St. Louis, 1998, pp. 589–674.
30. G. S. Hebbard, W. M. Sun, F. Bochner, and M. Horowitz. Pharmacokinetic considerations in gastrointestinal motor disorders. *Clin. Pharmacokinet.* **28**:41–66 (1995).
31. L. A. Houghton, Y. F. Mangnall, and N. W. Read. Effect of incorporating fat into a liquid test meal on the relation between intragastric distribution and gastric emptying in human volunteers. *Gut* **31**:1226–1229 (1990).

32. C. Feinle, D. Grundy, B. Otto, and M. Fried. Relationship between increasing duodenal lipid doses, gastric perception, and plasma hormone levels in humans. *Am. J. Physiol.* **278**:R1217–1223 (2000).
33. J. T. McLaughlin, L. E. A. Troncon, J. Barlow, L. J. Heggie, and D. G. Thompson. Evidence for a lipid specific effect in nutrient induced human proximal gastric relaxation. *Gut* **43**:248–251 (1998).
34. S. Haruta, N. Iwasaki, K. Ogawara, K. Higaki, and T. Kimura. Absorption behavior of orally administered drugs in rats treated with propantheline. *J. Pharm. Sci.* **87**:1081–1085 (1998).
35. M. J. Fargeas, J. Fioramonti, and L. Bueno. Time-related effects of benzodiazepines on intestinal motility in conscious dogs Journal. *J. Pharm. Pharmacol.* **36**:130–132 (1984).
36. Y. Wang, A. Roy, L. Sun, and C. E. Lau. A double-peak phenomenon in the pharmacokinetics of alprazolam after oral administration. *Drug Metab. Dispos.* **27**:855–859 (1999).
37. S. Y. Yu, H. C. Chung, E. J. Kim, S. H. Kim, I. Lee, S. G. Kim, and M. G. Lee. Effects of acute renal failure induced by uranyl nitrate on the pharmacokinetics of intravenous theophylline in rats: the role of CYP2E1 induction in 1,3-demethyluric acid formation. *J. Pharm. Pharmacol.* **54**:1687–19692 (2002).
38. L. S. Schanker, P. A. Shore, B. B. Brodie, and C. A. M. Hogben. Absorption of drugs from the stomach. I. The rat. *J. Pharmacol. Exp. Ther.* **120**:528–539 (1957).
39. K. Yamaoka, Y. Tanigawara, Y. Nakagawa, and T. Uno. A pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharmacobio-Dyn.* **4**:879–855 (1981).
40. J.C.K. Loo, and S. Riegelman. New method for calculating the intrinsic absorption rate of drugs. *J. Pharm. Sci.* **57**:918–928 (1968).
41. K. Yamaoka and Y. Tanigawara. Deconvolution. In: Introduction to Pharmacokinetic Analysis by Microcomputer, Nankodo, Tokyo, 1984, pp. 91–112.
42. L. L. von Moltke, D. J. Greenblatt, J. S. Harmatz, and R. I. Shader. Alprazolam metabolism *in vitro*: studies of human, monkey, mouse, and rat liver microsomes. *Pharmacol.* **47**:268–276 (1993).