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Prediction of plasma concentration–time curve of orally administered theophylline based on a scintigraphic monitoring of gastrointestinal transit in human volunteers

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Abstract

The plasma concentration–time profile of theophylline after oral administration in human volunteers was predicted using the individual gastrointestinal (GI) transit data monitored by a gamma scintigraphic technique. Theophylline was administered as aminophylline under fasted and fed condition, along with ^{99m}Tc-labeled diethylenetriamine-pentaacetic acid (DTPA), an unabsorbable marker to evaluate the GI transit by a gamma scintigraphic technique. Two healthy male volunteers participated under fasted and fed conditions in a crossover study. The GI transit was evaluated by dividing the GI tract to four segments, stomach, jejunum, ileum and cecum/colon. Under the fed condition, the GI transit pattern for each segment was confirmed to alter considerably, causing a delay in the gastric emptying mainly. Further, the plasma concentration curves of theophylline after oral administration were predicted using the GI-Transit-Absorption Model on the basis of individual GI transit parameters calculated by the fitting of the observed data to the GI-Transit Kinetic Model. The absorption rate constant in each segment and the pharmacokinetic parameters after intravenous administration used for the prediction were the values extrapolated from the data in rats and the ones normalized from the values in literatures, respectively. The plasma concentration–time curves for theophylline were well predicted using obtained individual GI transit parameters. The analysis using this method could estimate the variable absorption behavior governed by the GI transit in detail.

Keywords: Oral absorption; Gastrointestinal transit; Gamma scintigraphy; Human; GI-transit-absorption model; Prediction of absorption profile

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1. Introduction

The rate and extent of oral drug absorption from the GI tract are governed by two major factors, the permeability of gastrointestinal (GI) mucosa and the GI transit rate. Pharmacokinetic analysis for the plasma concentration–time curve of an orally administered drug is generally performed using a first-order absorption model from the whole GI tract, regarded as a single compartment. Since there are site-differences in the absorbability of drugs and the residence time (Stripp, 1965; Rebecca and Amidon, 1987; Gramatte, 1994) it is hard to analyze the absorption process from the GI tract in detail using such a simple model. Furthermore, the GI transit rate is changeable by various factors, e.g. individual differences (Davis et al., 1986), meals (Dressman et al., 1992), disease states (Snape et al., 1982) and so on, resulting in the remarkable alteration of absorption behavior of orally administered drugs.

In our previous papers (Sawamoto et al., 1997; Haruta et al., 1998), a novel method based on the GI transit kinetics was developed for estimating the absorption profiles of drugs administered orally as an aqueous solution. In those cases, the GI transit was evaluated as averaged values using phenol red as an unabsorbable marker. The validity and the utility of the prediction method have been demonstrated for model drugs with different absorption characteristics in rats. Furthermore, to evaluate the drug absorption process regulated by the GI transit more precisely, the prediction of the plasma concentration–time curve after oral administration was performed with each individual transit data using a gamma scintigraphy and it became possible to estimate the variable absorption behavior governed by the GI transit in detail in rats (Haruta et al., 2001).

In the present study, our prediction method for plasma concentration–time curve of orally administered drugs was applied to two healthy volunteers on the basis of the GI transit monitoring using a gamma scintigraphy, a non-invasive technique, under fasted and fed conditions in the crossover study. The use of gamma scintigraphy to monitor the GI transit in the experimental and clinical practice has been well established and utilized (Casey et al., 1976; Theodorakis et al., 1980; Harris et al., 1990; Digenis and Sandefer, 1991). This technique leads to evaluate GI transit and oral absorbability simultaneously in the same individual. As an absorbable drug without first-pass metabolism after oral administration (Ogiso et al., 1993), aminophylline was administered along with ^{99m}Tc-labeled diethylenetriamine-pentaacetic acid (^{99m}Tc-DTPA), an unabsorbable marker. The prediction of plasma concentration–time curves of theophylline in each individual was performed. In addition, the effect of the food on the absorption behavior was also investigated.

2. Materials and methods

2.1. Materials

Aminophylline (Neophylline® injection) was supplied by Eisai Ltd (Tokyo, Japan) and theophylline (Tokyo Kasei Kogyo Co, Tokyo, Japan) was obtained commercially. All other chemicals and reagents were analytical grade commercial products. ^{99m}Tc was obtained as sodium pertechnetate solution by elution of a generator, and ^{99m}Tc-DTPA was prepared using a kit containing calcium trisodium diethylenetriamine-pentaacetate and stannous chloride dihydrate (Daiichi Radioisotope Lab, Tokyo, Japan).

2.2. Volunteers

Two healthy male volunteers, non-smokers, aged 27 and 29 years participated in the study with written informed consent, which was approved by our local ethical committee at Miyazaki Medical College.

2.3. In vivo study design

The study was performed for each subject under two different food conditions at an interval of a month. Under the fasted condition, each subject was dosed after a 12-h overnight fast. While, under the fed condition, each subject was dosed 1 h after a light breakfast consisting of a slice of bread, a scramble egg, two boiled sausages and a

glass of orange juice. Food was withheld for at least 5 h after the drug administration. Under each food condition, aminophylline (100 mg) was administered as the 30 ml of aqueous solution containing ^{99m}Tc-DTPA (4–5 mCi), followed by 70 ml of water. After the drug dosing, imaging was immediately undertaken with a subject on his back using a gamma camera (PRISM 2000, Picker Int, Cleveland, OH). Blood samples of 5 ml were drawn after 15, 30, 45, 60, 90, 120, 180, 240, 360 and 480 min through an intravenous catheter, and the serum was obtained for the determination of theophylline concentration.

2.4. Gamma scintigraphic imaging

Gamma scintigraphy, a non-invasive technique, was employed to measure the GI transit rate for each segment. An aqueous solution of ^{99m}Tc-DTPA, an unabsorbable compound, was prepared as a tracer passing through the GI tract. The gamma scintigraphic imaging was carried out for 480 min. For the first 60 min, imaging was continuously carried out at 2-min intervals under the dynamic planar condition, beginning immediately after dosing, and then imaging was carried out for 2 min each after 90, 120, 150, 180, 240, 300, 360, 420 and 480 min under the static planar condition. During the non-imaging time, subjects were allowed free action.

2.5. Determination of GI transit rate constant for each segment

GI tract was divided into four segments, i.e. stomach (s), jejunum (jej), ileum (ile) and cecum/colon (co). The radioactivity in each segment was then measured from each region of interest (ROI) using a mini super computer (ODDYSEY, Picker Int, Cleveland, OH), and the relative percent of radioactivity for each ROI versus time was generated. The GI transit rate constant (k_i) for each segment in the individual study was obtained from the fitting of the experimental GI transit data to the modified GI-Transit Kinetic Model (Haruta et al., 2001), a linear transit kinetic model incorporating a lag time factor in ileo–cecal region, using a non-linear regression program, MULTI (FILT) (Yano et al., 1988).

2.6. Estimation of absorption parameters for each segment in human

The absorption rate constant of theophylline for each GI segment in human, which is necessary for the prediction of the plasma concentration–time curve after oral administration, was estimated using absorption data of theophylline in rats according to Eq. (1), introduced by Yuasa (1998).

$$ka_{human} = 0.744 \cdot ka_{rat} \quad (1)$$

where ka_{human} and ka_{rat} represent the absorption rate constants in human and rats, respectively.

2.7. Pharmacokinetic parameters of theophylline after intravenous administration

Pharmacokinetic parameters for theophylline after intravenous bolus administration in human, which are used as a weight function for the convolution in the prediction method, were calculated from the data of 24 human subjects reported by Mitenko and Ogilvie (1972, 1973, 1974). They are not only normal volunteers but also asthmatic subjects. But the authors showed that the pharmacokinetic parameters in the group of asthmatic subjects were not significantly different from those in the group of normal volunteers (Mitenko and Ogilvie, 1974), where the plasma concentration profiles were analyzed by a two-compartment model and were expressed as $Cp = A\exp(-\alpha t) + B\exp(-\beta t)$. The parameters were normalized to the values at the dose of 1 mg/kg. The results are summarized in Table 1.

2.8. Analytical method

Blood samples were collected in heparinized tubes. Theophylline in the plasma was assayed by a fluorescence polarization immunoassay method, using an Abbott TDx (Abbott Lab, Chicago, IL). The coefficient of variation (CV) of the standard curve ranged from 3.09 to 3.21% and the squared correlation coefficient was over 0.997.

Table 1
Normalized pharmacokinetic parameters for theophylline after intravenous administration in human

Subject	Age, sex	Disease	Dose (mg/kg)	Parameters at the dose of 1 mg/kg				Reference
				A (μg/ml)	B (μg/ml)	α (per h)	β (per h)	
C.A.	22, M	Normal	2.4	1.173	2.095	3.948	0.162	Mitenko and Ogilvie, 1973
W.W.	31, M	Normal	2.4	0.066	2.075	1.489	0.139	Mitenko and Ogilvie, 1973
P.R.	25, M	Normal	2.4	0.264	1.708	10.572	0.138	Mitenko and Ogilvie, 1973
M.R.	21, M	Normal	2.4	0.602	1.318	0.249	0.098	Mitenko and Ogilvie, 1973
C.S.	25, M	Normal	2.4	3.698	2.082	9.116	0.104	Mitenko and Ogilvie, 1973
C.W.[a]	24, M	Normal	2.4	2.560	1.904	6.186	0.242	Mitenko and Ogilvie, 1973
R.L.	30, M	Normal	2.4	5.543	2.521	9.942	0.194	Mitenko and Ogilvie, 1973
F.S.	22, M	Normal	2.4	5.296	2.111	5.423	0.177	Mitenko and Ogilvie, 1973
M.W.	19, M	Normal	2.4	0.118	2.339	4.108	0.166	Mitenko and Ogilvie, 1973
H.W.	34, M	Asthmatic	5.6	0.282	1.873	5.152	0.130	Mitenko and Ogilvie, 1973
V.W.[b]	53, F	Asthmatic	5.6	0.131	2.845	2.595	0.114	Mitenko and Ogilvie, 1973
A.G.	37, M	Asthmatic	5.6	2.414	2.030	4.744	0.171	Mitenko and Ogilvie, 1973
A.E.	43, F	Asthmatic	5.6	2.282	2.435	5.727	0.141	Mitenko and Ogilvie, 1973
V.M.	47, F	Asthmatic	5.6	5.807	2.597	13.519	0.241	Mitenko and Ogilvie, 1973
J.L.	43, M	Asthmatic	5.6	0.191	2.266	2.170	0.168	Mitenko and Ogilvie, 1973
T.S.	51, F	Asthmatic	5.6	3.134	2.548	8.017	0.166	Mitenko and Ogilvie, 1973
C.S.	25, M	Normal	2.4	2.744	2.358	5.830	0.099	Mitenko and Ogilvie, 1972
R.L.	30, M	Normal	2.4	5.801	2.463	8.350	0.190	Mitenko and Ogilvie, 1972
F.S.	22, M	Normal	2.4	5.569	2.183	4.890	0.183	Mitenko and Ogilvie, 1972
1	21, M	Normal	4	0.017	2.446	1.697	0.131	Mitenko and Ogilvie, 1974
2	22, M	Normal	4	1.176	2.214	2.212	0.131	Mitenko and Ogilvie, 1974
3	18, M	Normal	4	0.589	1.988	1.379	0.084	Mitenko and Ogilvie, 1974
4	21, M	Normal	4	1.555	1.941	5.462	0.129	Mitenko and Ogilvie, 1974
5	19, M	Normal	4	0.549	2.349	2.063	0.098	Mitenko and Ogilvie, 1974
Mean				2.148	2.196	5.202	0.150	
S.D.				2.100	0.327	3.352	0.042	

Plasma concentration–time profiles were expressed as $Cp = A\exp(-\alpha t) + B\exp(-\beta t)$.
[a] Subject showing the highest plasma profile.
[b] Subject showing the lowest plasma profile.

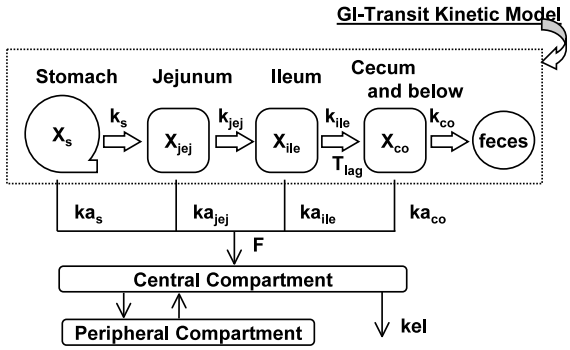

Fig. 1. GI-Transit-Absorption Model. GI-Transit-Absorption Model is a pharmacokinetic model containing a GI transit and an absorption process in each segment. D, initially administered dose; X_i, amount of drug in the segment i; k_i, first-order transit rate constant from the segment i; ka_i, first-order absorption rate constant for the segment i; T_{lag}, onset time to transit from the ileum to cecum; k_{el}, first-order elimination rate constant from central compartment; F, bioavailability without first-pass metabolism.

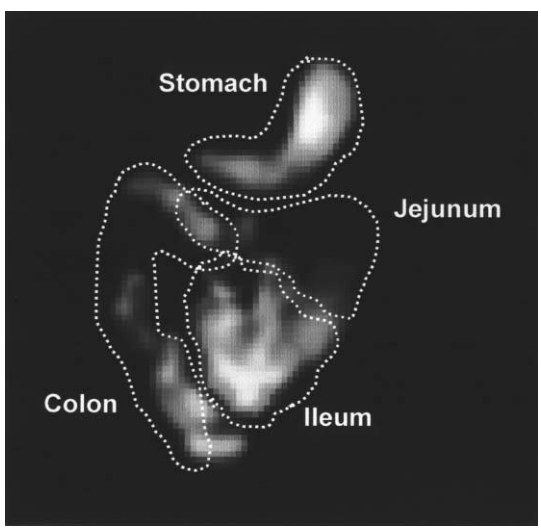

Fig. 2. Scintigraphic image of human GI tract and ROI of each GI segment. Scintigraphic image of whole GI tract was obtained by piling up each image of GI tract after oral administration of ^{99m}Tc-DTPA solution.

2.9. Statistical analysis

Statistical significance of the correlation between observed and calculated values of plasma concentration was determined by Pearson's method, which is the one to estimate the significance for the linear correlation by calculating Pearson's correlation coefficient.

3. Theoretical

3.1. GI-Transit-Absorption Model

GI-Transit-Absorption Model, a model that can predict in vivo absorption kinetics containing GI transit and absorption of drugs administered orally, is shown in Fig. 1. The whole GI tract is divided into four segments (stomach, jejunum, ileum and cecum/colon), and the drug disposition in each segment is defined as the well-stirred condition. An absorbable drug transits from a segment to the next segment with segmental absorption (first-order absorption). Gastric emptying rate and transit rate for each segment are represented by Eqs. (2)–(5), respectively. These equations can describe the GI transit of an unabsorbable drug, such as ^{99m}Tc-DTPA, when ka_i is defined as zero, corresponding to GI-Transit Kinetic Model.

For stomach:

$$\frac{dX_s}{dt} = -(k_s + ka_s)X_s \tag{2}$$

where at $t = 0$, $X_s = D_{po}$ (the dose of the orally administered drug).

For jejunum:

$$\frac{dX_{jej}}{dt} = k_s X_s - (k_{jej} + ka_{jej})X_{jej} \tag{3}$$

For ileum:

$$\frac{dX_{ile}}{dt} = k_{jej}X_{jej} - ka_{ile}X_{ile} \qquad (0 \le t \le T_{lag})$$

$$\frac{dX_{ile}}{dt} = k_{jej}X_{jej} - (k_{ile} + ka_{ile})X_{ile} \qquad (t \ge T_{lag}) \tag{4}$$

For cecum/colon:

$$\frac{dX_{co}}{dt} = k_{ile}X_{ile} - (k_{co} + ka_{co})X_{co} \qquad (t \ge T_{lag}) \tag{5}$$

where X, k and ka represent the amount, the transit rate constant and the absorption rate constant, respectively. T_{lag}, representing an onset time when the drug begins to transit from the ileum to cecum in the ileo-cecal region, was introduced to describe more precisely the characteristic motility in ileo–cecal region.

3.2. Prediction method

The prediction method using convolution analysis consists of four processes (Sawamoto et al., 1997). In step 1, the drug amount–time profile in each segment is calculated by the convolution method. In step 2, the absorption rate–time profile in each segment is calculated by using the drug amount–time profile in each segment, calculated in step 1. In step 3, the absorption rate–time profile in the whole GI tract is calculated as the sum of the absorption rate–time profiles of four segments obtained in step 2. In step 4, prediction of the plasma concentration–time curve of orally administered drug is performed by means of the convolution method. The total absorption rate–time data obtained in step 3 and pharmacokinetic parameters after intravenous administration correspond to the input function and the weight function, respectively. The inverse Laplace transformation of the obtained equation by the convolution program (Yamaoka and Tanigawara, 1984) gives the predicted plasma concentration profile after oral administration without the first-pass metabolism in intestinal epithelium and/or liver.

4. Results and discussion

The use of a gamma scintigraphy for the evaluation of GI transit has been well established and utilized in clinical practice (Casey et al., 1976; Theodorakis et al., 1980; Harris et al., 1990; Digenis and Sandefer, 1991). Thus, it is not difficult to introduce a gamma scintigraphic monitoring of the GI transit to our prediction method for the plasma concentration–time curve of orally administered drug in the human study. In the present study, we attempted to examine the effect of GI transit rate on the absorption kinetics of orally administered aminophylline.

Fig. 2 shows the scintigraphic image of the whole GI tract, obtained by piling up each image of the GI tract acquired after oral administration of ^{99m}Tc-DTPA, and each ROI located for four divided GI segments. The location of ROI for each segment was performed by referring to the previous report (Digenis et al., 1998). ROIs for

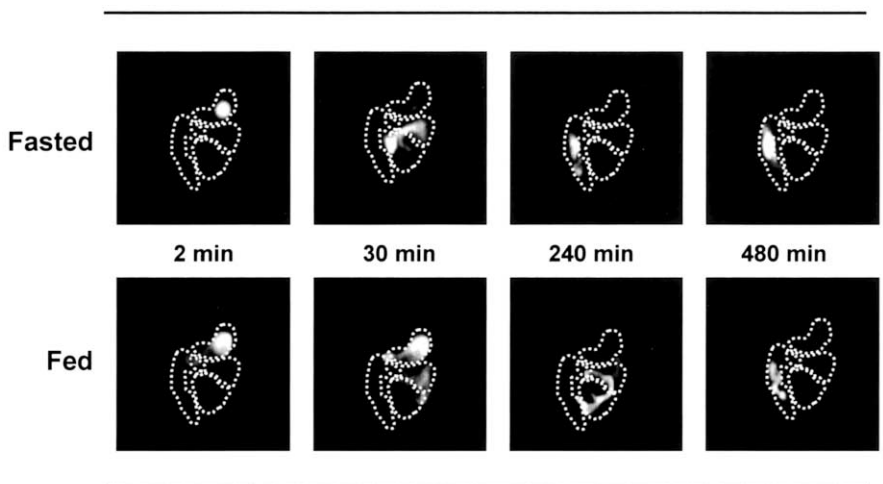

Fig. 3. Comparison of typical scintigraphic images of human GI tract after oral administration of ^{99m}Tc-DTPA solution under each food condition. Scintigraphic images of GI tract of Subject S.H. under both food conditions after oral administration of ^{99m}Tc-DTPA solution was picked up periodically. ROIs are shown by dotted lines.

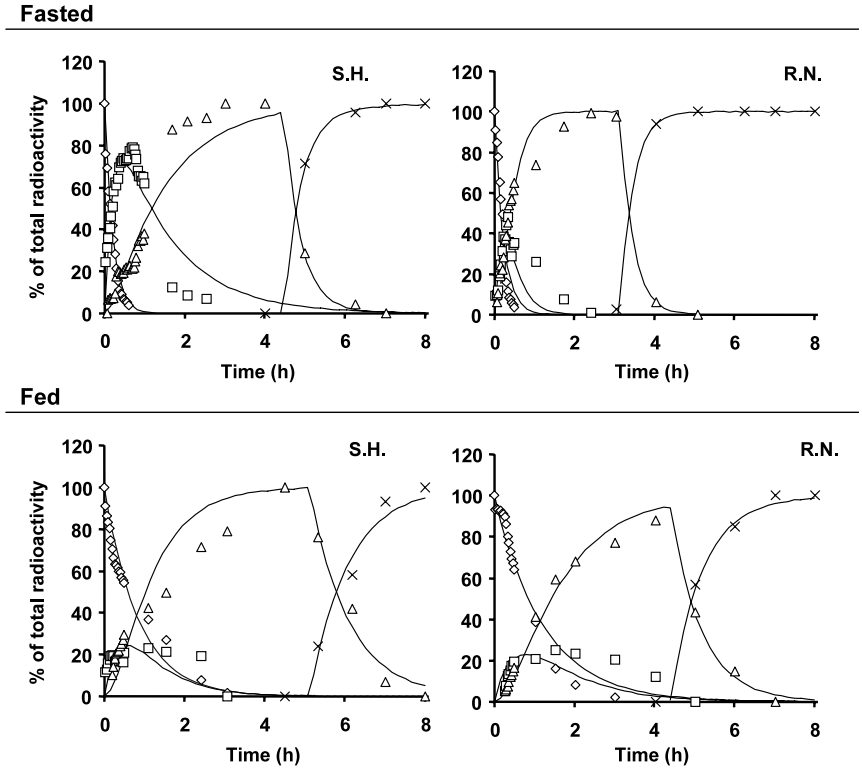

Fig. 4. Observed and calculated time courses of the remaining percent of dosed total radioactivity for each GI segment after oral administration of ^{99m}Tc-DTPA solution in human volunteers. Observed time courses of the remaining percent of dosed total radioactivity in each GI segment are expressed as follows: (◇) stomach; (△) jejunum; (□) ileum; (+) cecum/colon. Calculated time courses of the percent of dosed total radioactivity in each GI segment are expressed by solid lines by using k_i values obtained from the fitting by MULTI (FILT) program.

the stomach and cecum/colon were readily identified by their characteristic anatomical shapes, respectively. On the other hand, ROIs for the jejunum and ileum were located by drawing a vertical or diagonal midline that approximately bisects the field of the whole small intestine since the line of demarcation for the small intestine is not clear.

To compare the difference in GI transit behavior between both food conditions, typical scintigraphic images of GI tract under both food conditions were monitored periodically (Fig. 3). As is evident from the figure, the GI transit pattern considerably altered by the food condition. At 2-min post dose, almost the entire dosed radioactive marker existed in the stomach under both food conditions, and the relative size of a scintigraphic image of the stomach under the fed condition indicated the characteristic gastric shape after meals. At 30 min post dose, almost all of the radioactive marker dosed under the fasted condition was emptied from the stomach and existed in the small intestine, mainly ileum, while the marker dosed under the fed condition still remained in the stomach. After 240 min, the entire radioactive marker dosed under the fasted condition already reached to the cecum and colon, while the marker dosed under the fasted condition still existed in the small intestine, mainly ileum. At 480 min post dose, almost the entire dosed radioactive marker has reached to the colon (mainly ascending colon) under both food conditions. Particularly, the radioactive marker dosed under the fed condition was slightly

observed in the transverse colon, suggesting that the intestinal motility below the cecum under the fed condition might be rather higher than that under the fasted condition.

Fig. 4 shows both the observed time courses of the relative percent of radioactivity in each GI segment determined by the gamma scintigraphic study and the theoretical curves based on the modified GI-Transit Kinetic Model with a lag time factor in the ileo-cecal region. It is reasonable to put a lag time in the ileo-cecal region, since there is a valve, which would contribute to gut homeostasis by optimizing retention of chyme in the small intestine until digestion is complete (Wilding, 2000). As is evident from the figure, the theoretical curve of radioactivity for each GI segment, which was obtained from the fitting analysis, was in good agreement with the observed data in all the individual studies ($0.957 \leq r \leq 0.977$, $P < 0.001$). The corresponding GI transit parameters are summarized in Table 2, but GI transit rate constants thus calculated have been found to be quite useful for the description of the GI transit of a drug after oral administration. However, the transit rate constants thus calculated merely for the ileum do not reflect the actual transit of drugs, because of introducing a lag time factor to the ileo–cecal region (Haruta et al., 2001). The GI transit clearance (CLg_i), therefore, was employed to discuss the GI transit. CLg_i represents the transit clearance in the segment i calculated model-independently with the equation: $CLg_i = 100/AUCR$ (Sawamoto et al., 1997; Haruta et al., 1998, 2001), where AUCR indicates the area under the percent of dosed total radioactivity versus time curve, and the values are also summarized in Table 2. Under the fasted condition, the gastric emptying of the radioactive marker in both subjects completed by 1-h post dose, resulting in the gastric emptying clearances of 4.619 and 4.237 per h. And once the radioactive marker began to enter the cecum at approximately 3-h post dose, the cecum and colon were very rapidly filled with the entire radioactive marker until 5–7 h post dose. Similar profiles were reported by Digenis et al. (1998) and they indicated that the ileo-cecal valve regulated the transit from the ileum to the colon and that the time to reach the colon was around 3–5 h. On the other hand, under the fed condition, gastric emptying clearances decreased to 1.171 and 0.815 per h for each subject, resulting in the prolongation of the time for all of radioactive marker dosed to reach the cecum and colon. There is, however, no

Table 2
Gastrointestinal transit parameter for each segment

Subject	Food condition	Stomach	Jejunum	Ileum	Cecum and below	T_{lag} (h)
S.H.	Fasted					
	k_i (per h)	4.853	0.721	2.429	–[a]	4.485
	CLg_i (per h)	4.619	0.729	0.297	–	–
	Fed					
	k_i (per h)	1.174	2.451	1.040	–[a]	5.121
	CLg_i (per h)	1.171	2.467	0.209	–	–
R.N.	Fasted					
	k_i (per h)	4.413	4.156	3.085	–[a]	3.138
	CLg_i (per h)	4.237	4.331	0.334	–	–
	Fed					
	k_i (per h)	0.815	1.862	1.357	–[a]	4.411
	CLg_i (per h)	0.815	1.873	0.291	–	–

The GI transit rate constant for each segment and a lag time in the ileo-cecal region were obtained from the fitting of the experimental data to GI-Transit Kinetic Model by using MULTI (FILT) program (Yano et al., 1988). CLg_i, the transit clearance in segment i, was calculated by 100/AUCR (Haruta et al., 2001). AUCR means the area under the percent of dosed total radioactivity versus time curve for each segment calculated by the trapezoidal rule.

[a] Not calculated.

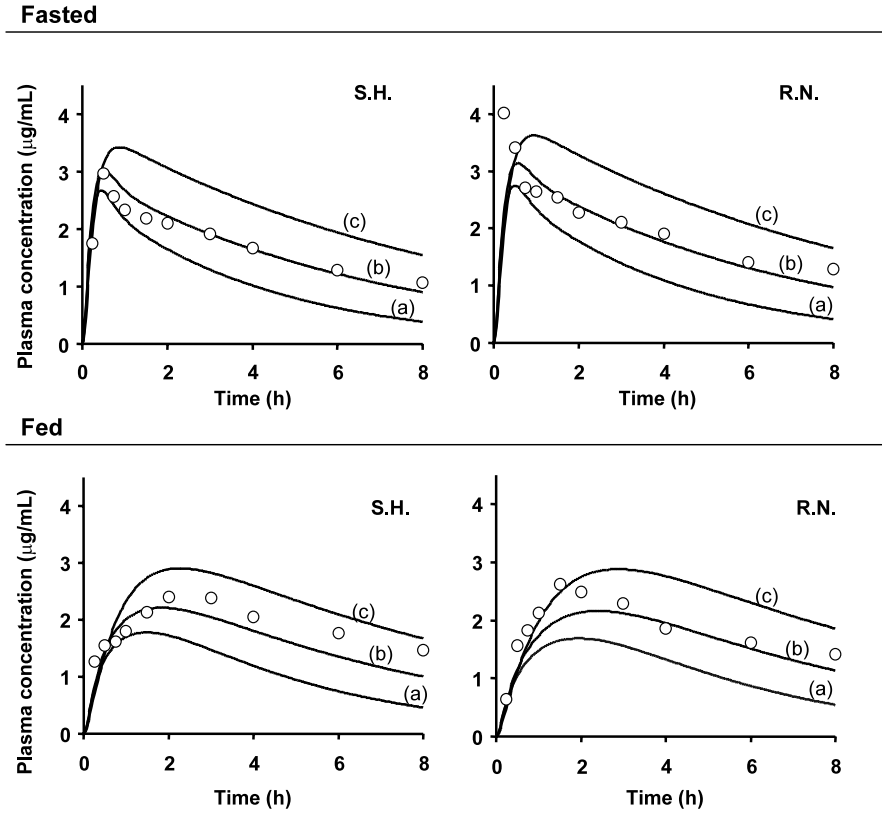

Fig. 5. Plasma concentration profiles of theophylline after oral administration of aminophylline in human volunteers. Theophylline was administered at the dose of 85 mg (100 mg)/body as aminophylline. Prediction of plasma concentration profile of theophylline after oral administration of aminophylline, which is shown by solid line, was performed using three different sets of weight functions, i.e. (a) pharmacokinetic parameters obtained from a subject with the lowest plasma profile, (b) pharmacokinetic parameters averaged from data of 24 subjects and (c) pharmacokinetic parameters obtained from a subject with the highest plasma profile after intravenous administration of theophylline.

apparent effect of food on the transit parameters for the jejunum and ileum. This observation is supported with other report, where the food intake and dosed formulation delay the gastric emptying rate but not affect the small-intestinal transit rate (Davis et al., 1986). Davis et al. (1986) also reported that the rapid gastric emptying was often observed in a fasted state, but even a light meal delayed emptying, where the transit time ranged from 10 to 100 min. These values are comparable with our data, 13–14 min in the fasted state and 50–74 min in the fed state. This is also the case for the small-intestinal transit. Based on the k_i value for the ileum, the transit times are between 180 and 202 min in the fasted state and are between 206 and 288 min in the fed state, comparing with 240–300 min by Davis et al. (1986). The values of $GE_{50\%}$ and $SITT_{50\%}$, the times to empty 50% of gastric contents and of intestinal contents, respectively, presented by Wilding (2000), also gave similar values in the rate constant with our results (Table 2).

To predict the plasma concentration–time curve after oral administration, the absorption rate constant of theophylline for each GI segment in human is needed. Although, in the rat study, absorption rate constants of theophylline were obtained by performing a conventional in situ closed loop method for each GI segment (Sawamoto et al., 1997; Haruta et al., 1998, 2001),

it is hard to estimate directly the corresponding absorption parameter for each GI segment in human. Therefore, the absorption rate constants in human were calculated using the absorption rate constants of theophylline obtained in rats (Sawamoto et al., 1997) according to the relationship between ka_{human} and ka_{rat} reported by Yuasa (1998), as described in the Methods section. The equation, $ka_{human} = 0.744\ ka_{rat}$, was introduced from the difference in the surface area and luminal volume of the small intestine between human and rats, based on the relationship of the permeability between human and rat reported by Amidon et al. (1988). The absorption rate constants obtained for human GI segments are as follows; stomach (unabsorbable), jejunum (8.84 per h) and ileum (6.01 per h). Then, the plasma concentration–time curve of theophylline after oral administration of aminophylline was estimated for each study using the ka values for human and individual GI transit rate constants in the fasted and fed conditions, according to our prediction method. The predicted plasma concentration–time curves of theophylline are shown in Fig. 5, together with the observed data and calculated pharmacokinetic parameters are summarized in Table 3. The disposition parameters of theophylline after intravenous administration in human, which were used as a weight function in the convolution analysis, were data of 24 subjects cited from literatures (Mitenko and Ogilvie, 1972, 1973, 1974) (Table 1). Considering the interindividual variation of the disposition parameters, the prediction was performed using three different sets of weight functions, i.e. pharmacokinetic parameters averaged for 24 subjects ($Cp = 2.15e^{-5.20t} + 2.20e^{-0.15t}$), the ones for the highest plasma profile ($Cp = 2.56e^{-6.19t} + 1.90e^{-0.24t}$) and the ones for the lowest plasma profile ($Cp = 0.13e^{-2.60t} + 2.85e^{-0.11t}$), which are normalized at the dose of 1 mg/kg. The plasma concentration–time curves predicted using the averaged parameters as the weight function are in good agreement with the observed data in all the individual studies ($0.725 \le r \le 0.960$, $P < 0.05$). Lower Cp_{max} and larger T_{max} in the plasma concentration–time curves under the fed condition were observed than under the fasted condition (Fig. 5). This effect of food conditions on the plasma concentration–time curve is caused by the alteration of the GI transit behavior, mainly gastric emptying. Fig. 6 shows the amount of theophylline versus time profiles in the stomach and small intestine, which were simulated using k_i and ka_i values obtained in the present study. Three cases except for S.H. under fasted condition indicate that the gastric emptying rate determines the absorption rate of theophylline, in which a greater value of k_s results in a greater absorption rate of theophylline.

On the other hand, AUC values under both food conditions were almost same (Table 3), but this is reasonable. As reported previously (Haruta et al., 1998), AUC, an extent of bioavailability, is not affected by the delay of the GI transit in the case of a well-absorbable drug like as theophylline, because it is almost completely absorbed even under the condition where GI transit is fast such as the fasted condition.

The GI transit parameters in each subject can be estimated without accompanying affliction us-

Table 3
Pharmacokinetic parameters of theophylline after oral administration of aminophylline in two human volunteers

Subject	Food condition	AUC (μg h/ml)		
		Low[a]	Mean[b]	High[c]
S.H.	Fasted			
	Predicted	9.23	13.65	19.13
	Observed		13.40	
	Fed			
	Predicted	8.92	12.99	18.03
	Observed		15.11	
R.N.	Fasted			
	Predicted	8.95	14.55	20.38
	Observed		14.58	
	Fed			
	Predicted	9.23	13.33	18.41
	Observed		14.72	

Predicted AUCs were calculated from the data simulated by the convolution method based on the GI-Transit-Absorption Model. The prediction was performed using three different sets of weight function, i.e., pharmacokinetic parameters with the lowest plasma level[a], the ones averaged from the data of 24 subjects[b] and the ones with the highest plasma level[c] (Table 1) after intravenous administration of theophylline. The parameters were normalized at the dose of 1 mg/kg.

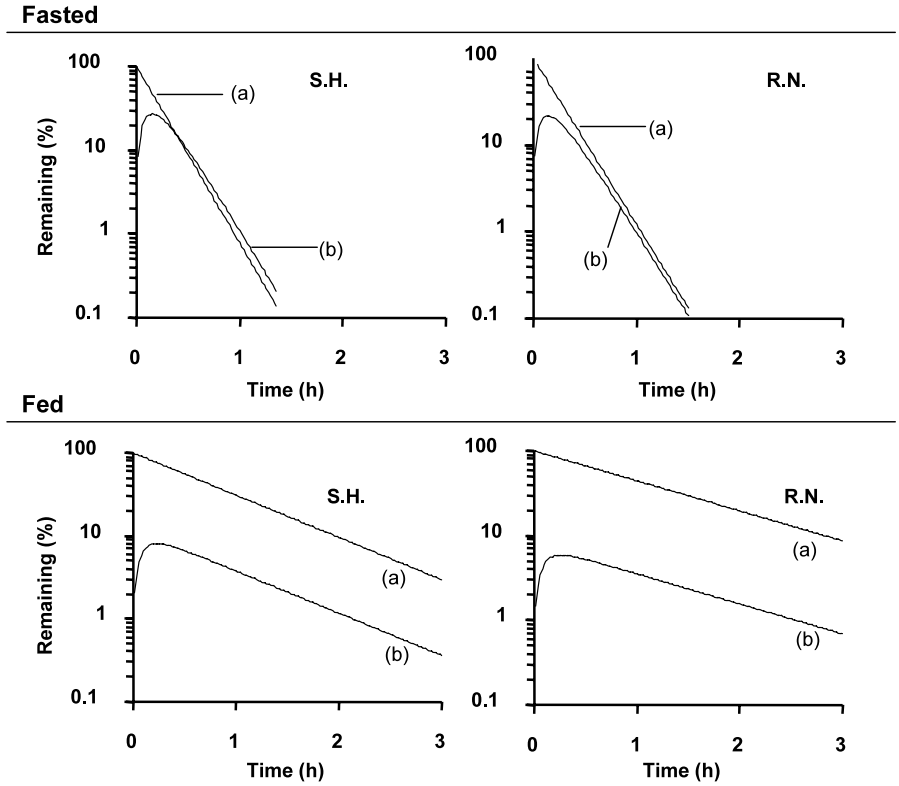

Fig. 6. Simulation of theophylline amount remaining in stomach and small intestine after oral administration of aminophylline in each GI transit condition. Time courses of theophylline remaining in the stomach (a) and small intestine (b), which were simulated by the convolution method, are expressed by solid lines, respectively.

ing a gamma scintigraphic technique. Using the segmental absorption data in rats, which can be easily obtained experimentally or from literatures, and the pharmacokinetic parameters after intravenous administration in human, which can be obtained through literature reference, the plasma concentration profile for the concerned drug in the individual would be predicted with the corresponding GI transit condition.

In the present study, we showed only two volunteers' data, because it has been being very difficult to perform human study, especially for a basic research in Japan. Therefore, we cannot mention the conclusion from the viewpoint of statistics. However, the present results suggest that our method using the GI-Transit-Absorption Model and gamma scintigraphic technique is a useful tool to analyze the drug absorption behavior and the effect of GI transit on it in human. This method could offer the beneficial information for the drug development and to perform the safer and more sufficient dosage regimen for the individual patient in the clinical practice.

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