J. Pharm. Pharmacol. 1997, 49: 450–457
Received September 30, 1996
Accepted January 3, 1997

Prediction of the Plasma Concentration Profiles of Orally Administered Drugs in Rats on the Basis of Gastrointestinal Transit Kinetics and Absorbability

TAIJI SAWAMOTO, SHUNJI HARUTA, YUJI KUROSAKI, KAZUTAKA HIGAKI AND TOSHIKIRO KIMURA

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700, Japan

Abstract

A new method based on gastrointestinal transit kinetics has been developed for estimation of the absorption profiles of drugs administered orally as aqueous solutions. The utility of the method was evaluated in rats.

The gastrointestinal transit profile for each segment was estimated by in-vivo studies using phenol red, an unabsorbable marker. The gastrointestinal transit profile of phenol red was well explained by a linear gastrointestinal transit kinetic model with eight segments. We also introduced the absorption process into the gastrointestinal transit kinetic model and the plasma profile was predicted by the convolution method. The absorbability of drugs in each segment was assessed by an in-situ absorption study. The validity of the model was evaluated for model drugs with different absorption characteristics. The plasma profiles predicted for ampicillin, theophylline and cephalexin were in good agreement with those observed. The overestimated plasma profile of propranolol suggests that the low bioavailability of propranolol is a result of first-pass metabolism by the intestine wall and the liver, because the calculated absolute absorption is almost perfect. This proposed model is also suitable for estimation of segmental absorption, which is useful for the development of drug delivery systems.

We have demonstrated that the plasma profile of orally administered drugs can be predicted by use of gastrointestinal transit and segmental absorbability information and that this method is especially useful for estimating separately the effect of absolute absorption and first-pass metabolism on the bioavailability of drugs.

Because oral administration is the most convenient route for drug delivery, it is very important and useful for the development of novel drugs or novel dosage forms, or both, to be able to estimate the absorbability of drugs and to predict the plasma concentration profiles of drugs after oral administration. The absorbability of drugs has usually been estimated by in-situ re-circulation studies or in-situ closed-loop studies. The information obtained from these studies, e.g. absorption rate constants, ka, is the averaged value through the intestinal tract. There are, however, site differences in absorbability (Patel & Kramer 1986; Tukker & Poelma 1988) and the drug observed in the plasma is the sum of the amounts of drug absorbed from each segment. As for absorption after oral administration, the gastrointestinal transit of a drug is, furthermore, partly responsible for drug absorption and is influenced by the dosage conditions, for example, fed or fasted state (Dressman et al 1992). The absorbability and residence time in each segment are, therefore, major determining factors in drug absorption after oral administration and these factors are very important in the analytical estimation of drugs and the prediction of their plasma concentration profiles.

In this study we have developed a gastrointestinal transit kinetic model with the absorption process for analysis and prediction of the plasma concentration profile after oral administration of the aqueous drug solution in the fasted state. In this model the absorption parameters for each segment are incorporated into a linear first-order gastrointestinal transit kinetic model with eight segments. The absorption rate constant for each segment could be determined by a conventional in-situ closed-loop method and the gastrointestinal transit rate constant for each segment was calculated from in-vivo studies using phenol red, an unabsorbable marker. By use of the convolution method on gastrointestinal-transit rate-constant data and absorption rate-constant data we predicted the plasma profiles of four model drugs with different absorption characteristics: ampicillin as a poorly absorbable drug, cephalexin as a drug highly absorbed via carrier-mediated transport system, theophylline as a highly absorbable drug without first-pass elimination and propranolol as a highly absorbable drug with first-pass elimination after oral administration. The usefulness of this method of prediction is discussed.

Correspondence: T. Kimura, Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700, Japan.

Materials and Methods

Materials

Ampicillin sodium (Wako Pure Chemical, Osaka), aminophylline (Sigma, St Louis, MO), theophylline (Tokyo Kasei Kogyo, Tokyo), propranolol hydrochloride (Nacalai Tesque, Kyoto) and cephalexin (Sigma) were obtained commercially and used as supplied. Other chemicals and reagents were analytical grade commercial products.

Animals

Male Wistar rats, 200–220 g (Japan SLC, Hamamatsu), were fasted for 24 h before and during the experiment but were allowed free access to water.

Determination of gastrointestinal transit rate constant (k_i) for each segment

Phenol red solution was used as a non-absorbable marker for estimation of the gastrointestinal transit rate constant for each

segment. Phenol red solution (5 mL kg^{-1}) was administered into the stomach and rats were killed at appropriate times after administration. The whole gastrointestinal tract was removed and was divided into eight segments: stomach (s), duodenum (d), upper jejunum (uj), lower jejunum (lj), upper ileum (ui), lower ileum (li), caecum (ce) and large intestine (co). Each size (length) was: stomach, whole organ; duodenum, ca 6 cm; upper and lower jejunum, ca 20 cm; upper and lower ileum, ca 20 cm; caecum, whole organ; large intestine, colon to anus. Phenol red in each segment was washed out with saline and the amount recovered was measured colorimetrically at 560 nm. The gastrointestinal transit rate constant (k_i) for each segment (i) was calculated by use of the gastrointestinal transit kinetic model (Fig. 1) using a non-linear regression program, MULTI (FILT) (Yano et al 1989b).

Determination of absorption rate constant (ka_i) for each segment (i)

The absorption experiments were performed for each segment described above by means of a conventional in-situ closed-loop method (Schanker et al 1957; Kakemi et al 1970). The initial concentrations (period of absorption experiment) for ampicillin, aminophylline, cephalexin and propranolol were 2 mg mL^{-1} (60 min), 0·5 mg mL^{-1} (5 min), 0·5 mg mL^{-1} (30 min) and 0·5 mg mL^{-1} (10 min), respectively. The first-order absorption rate constant was estimated by the rate of disappearance from the lumen.

Oral and intravenous administration of drugs

For study of oral administration, the right femoral artery was cannulated with vinyl tubing (0·5 × 0·8 mm i.d.; Dural Plastics & Engineering, Australia) under ether anaesthesia. Solutions of the model drugs (ampicillin-Na (30 mg kg^{-1}), aminophylline (5 mg kg^{-1}), propranolol (5 mg kg^{-1}) and cephalexin (5 mg kg^{-1})) were administered intragastrically to the rat using a gastric sonde. For study of intravenous administration, drugs were administered in solutions by bolus injection into the left femoral vein. The dosed rats were kept in restraining cages, with free access to water. Blood samples were periodically taken from the cannulated femoral artery.

Analytical method

Ampicillin, theophylline (Shiu et al 1988), propranolol (Kurosaki et al 1988) and cephalexin (Kimura et al 1983) were determined by reversed-phase HPLC with a Shimadzu (Kyoto) LC-3A chromatograph fitted with a 150 mm × 4·6 mm i.d. TSK-gel ODS-80TM column (Tosoh, Tokyo) and equipped with a Shimadzu SPD-6A UV detector or Shimadzu PF-535 fluorescence detector. The mobile phase, flow rate and operating wavelength of the detector were: for ampicillin, 16·7 mM phosphate buffer (pH 7·0)–methanol (2 : 1, v/v), 0·6 mL min^{-1} and 220 nm, respectively; for theophylline 5 mM acetate buffer (pH 4·8)–acetonitrile (9 : 1, v/v), 1·0 mL min^{-1} and 272 nm, respectively; for cephalexin 10 mM ammonium acetate–methanol (4 : 1, v/v), 0·8 mL min^{-1} and 260 nM, respectively; and for propranolol 20 mM ammonium chloride–0·05% phosphoric acid–acetonitrile (1 : 1 : 1, v/v), 0·8 mL min^{-1} and 314 nM (λ_{ex}) and 340 nm (λ_{em}), respectively. A Shimadzu C-R4A data module was used for quantitative analysis.

Briefly, plasma samples (100 μL) were deproteinized with methanol (200 μL) for ampicillin and cephalexin or with acetonitrile (100 μL) for theophylline and propranolol. After centrifugation at 3000 rev. min^{-1} for 10 min, the supernatant of the resulting mixture was filtered through a 0·45-μm pore-size membrane filter (Nihon Millipore Kogyo, Yonezawa) and injected on to the HPLC column.

Theory

Absorption kinetics containing gastrointestinal transit and absorption in each segment

If drug distribution in each intestinal segment can be defined as the well-stirred phase, the k_i value represents intestinal transit clearance, i.e. a hybrid parameter of the intestinal transit rate constant and the intestinal distribution volume per unit length. Further, absorption in each segment is assumed to be an apparent first-order process and the absorbability is represented by the absorption rate constant, which is supposed to be equivalent to the value obtained by dividing the absorption clearance by the intestinal distribution volume.

The transit of an unabsorbable drug from one segment to the next was approximated to follow first-order kinetics as shown in Fig. 1. The absorbable drug moves from a segment (i) to the next segment (i + 1) with segmental absorption (first-order absorption) as shown in Fig. 2. For a non-absorbable drug ($ka_i = 0$) gastric emptying rate and intestinal transit rate for each segment are represented by equations 1 and 2, respectively:

$$dX_s/dt = -(k_s + ka_s)X_s \quad (1)$$

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

$$dX_{i+1}/dt = X_i k_i - (k_{i+1} + ka_{i+1})X_{i+1} \quad (2)$$

where X, k and ka represent the amount, the transit rate constant and the absorption rate constant, respectively. The subscripts s and i indicate stomach and each intestine site, respectively.

Prediction of plasma concentration profile by the convolution method

An outline of the prediction method using convolution analysis is as follows. In Step 1, the profile of the amount of drug against time (X-time profile) in each segment is calculated by the convolution method (multi function convolution simulator

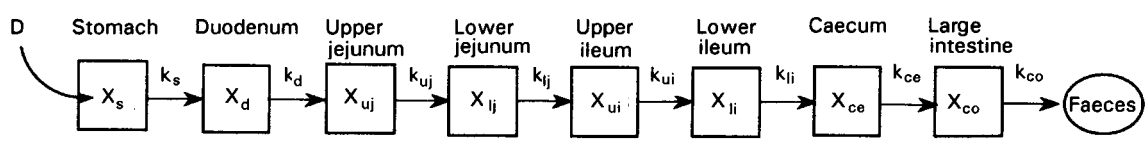

FIG. 1. Pharmacokinetic model of gastrointestinal transit. D Initially administered dose, X_i amount of drug in segment i, k_i first-order transit rate constant from segment i.

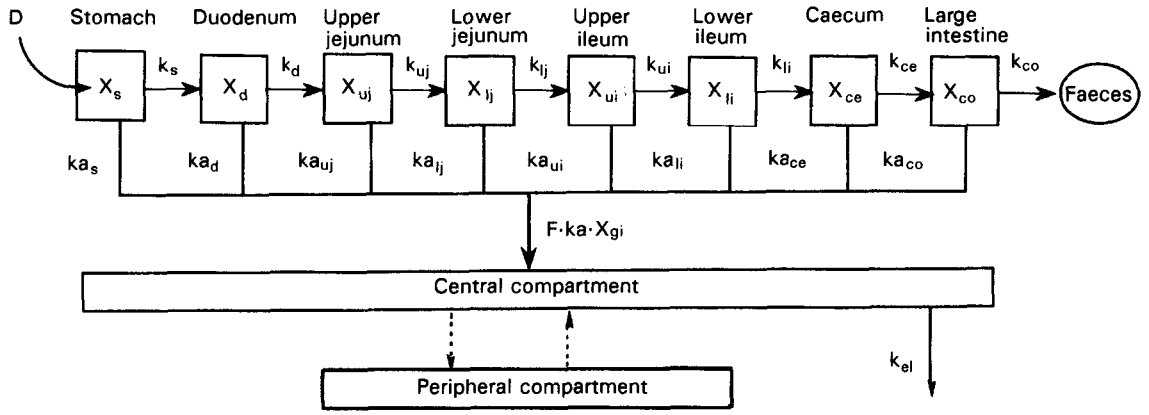

FIG. 2. Pharmacokinetic model containing gastrointestinal transit and absorption in each segment. D Initially administered dose, X_i amount of drug in segment i, k_i first-order transit rate constant from segment i, ka_i first-order absorption rate constant for segment i, k_{el} first-order elimination rate constant from central compartment, F bioavailability.

program; Yamaoka & Tanigawara 1984). The Laplace transform of the amount of drug in segment i+1 ($\tilde{X}_{i+1}(s)$) is described by equation 3:

$$\tilde{X}_{i+1}(s) = k_i\tilde{X}_i(s)/(s + k_{i+1} + ka_{i+1}) \quad (3)$$

That is, the fraction of the dose available for absorption in segment i+1 (F_{i+1}) can be given by equation 4 using its Laplace transform ($\tilde{f}_{i+1}(s)$):

$$\tilde{f}_{i+1}(s) = k_i\tilde{f}_i(s)/(s + k_{i+1} + ka_{i+1}) \quad (4)$$

In Step 2, the profile of absorption rate against time in each segment is calculated by using the X-time profile obtained in Step 1 and the absorption rate constant in each segment. The fraction of the dose absorbed (absolute absorption) from segment i (Fa_i) can be given by equation 5 using its Laplace transform ($\tilde{f}a_i(s)$).

$$\tilde{f}a_i(s) = ka_i\tilde{f}_i(s) \quad (5)$$

In Step 3, the profile of total absorption rate against time in the whole gastrointestinal tract is calculated as the sum of the absorption rate–time profiles obtained in Step 2.

In Step 4, prediction of the plasma concentration 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 transfer function, respectively. Plasma concentrations (Cp) of model drugs after intravenous administration were analysed by a two-compartment model using a non-linear least-squares program, MULTI (Yamaoka et al 1981). Laplace transform of the plasma concentration after oral administration $\tilde{C}p^{po}(s)$ is expressed using Laplace transform of the plasma concentration after intravenous administration ($\tilde{C}p^{iv}(s)$) as follows:

$$\tilde{C}p^{po}(s) = (D_{po}/D_{iv})(\tilde{f}a_s(s) + \sum_{i=d}^{co}\tilde{f}a_i(s))\tilde{C}p^{iv}(s) \quad (6)$$

The inverse Laplace transformation of equation 6 gives the predicted drug concentration in the plasma after oral administration without first-pass elimination in the intestinal epithelium or in the liver.

Several simulation studies were performed according to the procedure from Step 1 to 4 described above.

Results

Estimation of gastrointestinal transit

Figs 3 and 4 show the observed time-course of phenol red recovery in each segment after oral administration, and the fitting lines based on the gastrointestinal transit kinetic model, respectively. The calculated curves for phenol red remaining in each segment were in good agreement with the experimental data. Phenol red was not detected in the large intestine segment up to 10 h after oral administration. The k_i values for each segment are summarized in Table 1. The k_i values obtained by regression analysis were consistent with the values of the transit clearance in segment i ($CLgi_i$) calculated by use of equation 7:

$$k_i = CLgi_i = 100/AUCgi_i \quad (7)$$

where $AUCgi_i$ (%h), the area under the curve of observed recovery of phenol red dose (%) against time, was obtained by the trapezoidal rule. This coincidence strongly suggests that the gastrointestinal transit kinetic model is a sufficiently

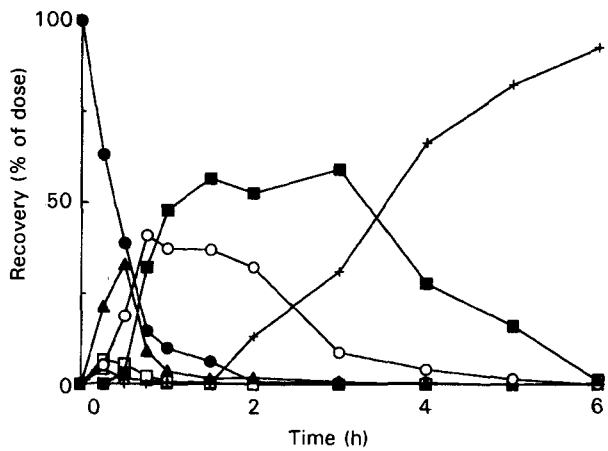

FIG. 3. Time-course of recovery of phenol red in each gastrointestinal segment after oral administration in rats. ● Stomach, △ duodenum, □ upper jejunum, ▲ lower jejunum, ○ upper ileum, ■ lower ileum, + caecum. Phenol red aqueous solution (5 mL kg^{-1}) was administered intragastrically. Results are the means from three experiments.

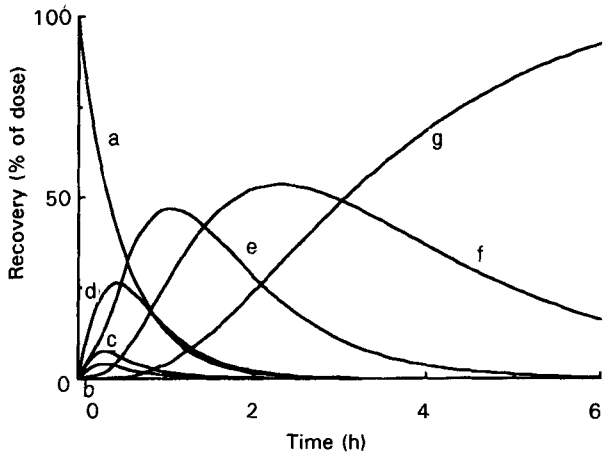

FIG. 4. Calculated time-course of phenol red recovery in each gastrointestinal segment. a. Stomach, b. duodenum, c. upper jejunum, d. lower jejunum, e. upper ileum, f. lower ileum, g. caecum. Solid lines were drawn using k_i values obtained from fitting by MULTI (FILT) (Table 1).

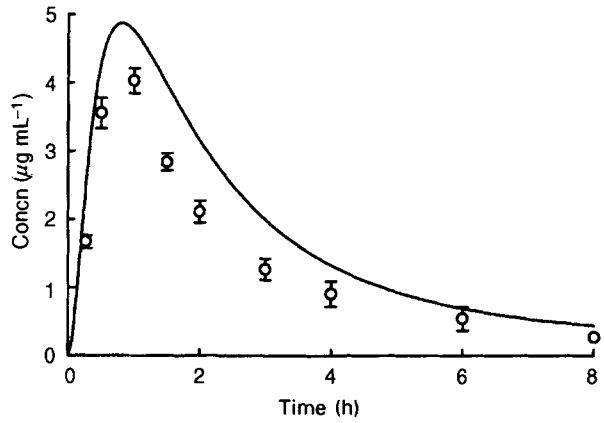

FIG. 5. Plasma concentration of ampicillin after oral administration. Ampicillin sodium was administered intragastrically as an aqueous solution at a dose of 30 mg kg^{-1}. Results are expressed as means, with the vertical bar showing the s.e. of four experiments. The predicted plasma concentration profile is shown by the solid line.

accurate representation of the entire gastrointestinal transit process. Table 1 also shows that k_i decreased along the intestinal tract from the upper (28·748 h^{-1}) to lower (0·464 h^{-1}) region, indicating that the transit rate differs considerably in each segment, although it depends on the estimated length of the intestine.

Prediction of plasma concentration after oral administration

The first-order absorption rate constants of the tested drugs in the eight segments are summarized in Table 2. Predicted plasma concentrations of the drugs after oral administration were calculated by use of equation 6 using the data in Tables 1 and 2.

Ampicillin. Ampicillin was chosen as a model drug poorly absorbable from the gastrointestinal tract and having no first-pass elimination (Yano et al 1989a). Plasma concentrations of this drug after oral administration reflect absorption from whole gastrointestinal tract and systemic elimination only. As shown in Fig. 5, the predicted curve for ampicillin agrees well with that obtained experimentally. Pharmacokinetic parameters calculated from the predicted plasma concentration profile are similar to those calculated from the experimental data (Table 3).

Table 1. Gastrointestinal transit rate constant (k_i; h^{-1}) for each segment.

Method	Stomach	Duodenum	Upper jejunum	Lower jejunum	Upper ileum	Lower ileum	Caecum	Large intestine
Gastrointestinal transit kinetic model*	2·031	28·748	18·066	4·206	1·162	0·464	–†	–†
Clearance‡	2·073 (0·114)	49·039 (4·436)	28·339 (7·726)	5·392 (0·803)	1·121 (0·161)	0·455 (0·044)	≪0·493§	–†

*The k_i value for each segment was obtained from fitting the experimental data in Fig. 3 to the gastrointestinal transit kinetic model (Fig. 1) by use of MULTI (FILT). †Not calculated. ‡The k_i value for each segment was calculated from the AUCgi in each segment and is represented as the mean, with s.e. from three experiments in parentheses. §As the AUCgi in the caecum will be much larger than the observed value, the substantial value of k_i for the caecum will be much smaller than the calculated value.

Table 2. Absorption rate constants (ka_i; h^{-1}) of model drugs for each segment.

Drug	Stomach	Duodenum	Upper jejunum	Lower jejunum	Upper ileum	Lower ileum	Caecum	Large intestine
Ampicillin (n = 3)	–*	0·617 (0·052)	0·536 (0·017)	0·536 (0·017)	0·053 (0·010)	0·053 (0·010)	0·021 (0·002)	0·085 (0·017)
Aminophylline (n = 4)	–*	14·855 (1·757)	11·882 (0·117)	11·882 (0·117)	8·080 (0·117)	8·080 (0·117)	–*	–*
Cephalexin (n = 3)	–*	2·105 (0·066)	2·266 (0·065)	2·146 (0·107)	0·897 (0·037)	0·250 (0·023)	–*	–*
Propranolol (n = 3)	1·447 (0·138)	5·875 (0·189)	6·095 (0·127)	6·095 (0·127)	7·775 (0·242)	7·775 (0·242)	–*	–*

Absorption rate constants were obtained from conventional in-situ loop studies. Results are expressed as the mean, with s.e. in parentheses. *Not examined.

Table 3. Comparison of pharmacokinetic parameters predicted by the gastrointestinal transit-absorption model with observed data for four model drugs.

	Ampicillin		Theophylline		Cephalexin		Propranolol	
	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
Area under plasma concentration–time curve after oral administration (μg h mL^{-1})	14·6	10·0	29·3	29·4	11·0	9·4	2·08	0·67
Mean residence time after oral administration (h)	2·5	2·3	2·3	2·1	1·8	1·9	1·3	0·8
Fraction of dose available for absorption*	–	0·23	–	1·05	–	0·77	–	0·32
Fraction of dose absorbed†	0·33	–	1·04	–	0·90	–	1·01	–
Ratio of fraction of dose available to fraction absorbed	0·70	–	1·01	–	0·86	–	0·31	–

Predicted parameters were calculated from the data simulated by the convolution method on the basis of the gastrointestinal transit-absorption model. Observed values were obtained by calculation from mean experimental data. *$(D_{iv}/D_{po})(AUC_{po}(obs.)/AUC_{iv}(obs.))$. †$(D_{iv}/D_{po})(AUC_{po}(predict.)/AUC_{iv}(obs.))$.

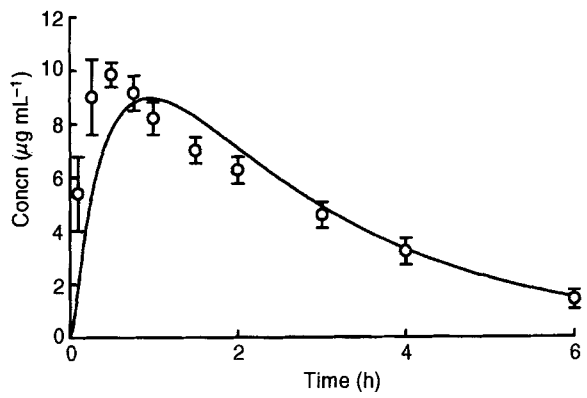

FIG. 6. Plasma concentration of theophylline after oral administration of aminophylline. Aminophylline was administered intragastrically as an aqueous solution at a dose of 5 mg kg^{-1}. Results are expressed as means, with the vertical bar showing the s.e. of four experiments. The predicted plasma concentration profile is shown by the solid line.

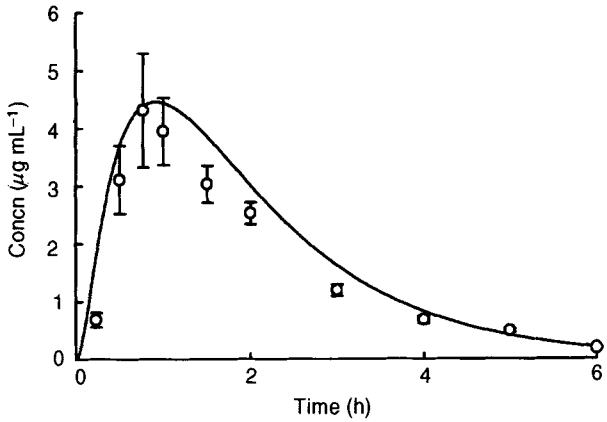

FIG. 7. Plasma concentration of cephalexin after oral administration. Cephalexin was administered intragastrically as an aqueous solution at a dose of 5 mg kg^{-1}. Results are expressed as means, with the vertical bar showing the s.e. of five experiments. The predicted plasma concentration profile is shown by the solid line.

Theophylline. Theophylline was examined as a drug absorbed rapidly from the gastrointestinal tract. Theophylline is characterized as a readily absorbable drug without first-pass elimination (Ogiso et al 1993). The predicted plasma concentration profile of theophylline after oral administration as aminophylline was in good agreement with experimental results (Fig. 6). As shown in Table 3, pharmacokinetic parameters calculated from the predicted profile are consistent with those calculated from the experimental data.

Cephalexin. The absorption of cephalexin was examined to assess the utility of this method for a drug absorbed via a carrier-mediated transport system (Miyazaki et al 1982; Kimura et al 1983; Nakashima et al 1984). Cephalexin is a readily absorbable and hepatic non-extractable drug (Speight et al 1972). Assuming first-order absorption in the model the plasma concentration and pharmacokinetic parameters predicted are in good agreement with the observed data (Fig. 7 and Table 3).

Propranolol. It is well known that orally administered propranolol is biotransformed by pre-systemic metabolism (Iwamoto & Watanabe 1985). Fig. 8 shows the predicted profile and the observed plasma concentration data for propranolol. Because this method of prediction gives the AUC value of drug in the absence of first-pass elimination, the difference between the predicted and the observed values of the AUC represents the contribution of first-pass elimination. The ratio of the first-pass elimination was predicted to be 70% (Table 3) which agrees with the reported value (70–80%; Iwamoto & Watanabe 1985).

Evaluation of absorption site in-vivo

The segmental difference in the absorbability of cephalexin was examined by an in-situ loop method (Fig. 9). The ka values for cephalexin in upper small intestine were larger than those in the lower intestine, indicating that absorbability is greater in the upper region. Fig. 9 also shows the substantial contribution of each segment to cephalexin absorption, as calculated by this proposed method. As is evident from the figure, the major absorption site of cephalexin in-vivo in the fasted state is clarified as below the lower jejunum.

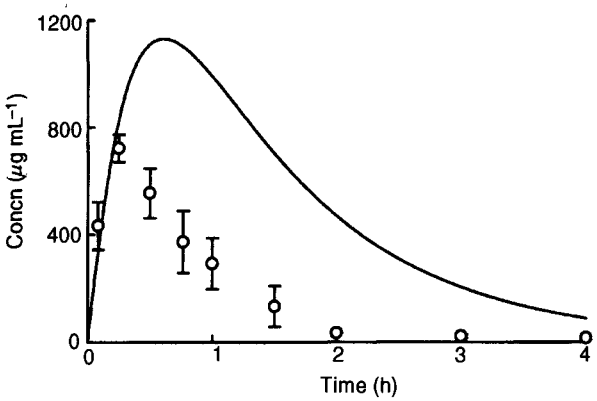

FIG. 8. Plasma concentration of propranolol after oral administration. Propranolol was administered orally as an aqueous solution at a dose of 5 mg kg^{-1}. Results are expressed as means, with the vertical bar showing the s.e. of five experiments. The predicted plasma concentration profile is shown by the solid line.

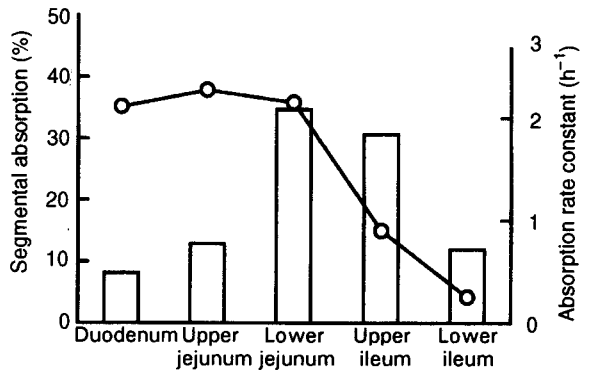

FIG. 9. Segmental absorption of cephalexin after oral administration in rats. The amount of cephalexin absorbed in each segment (histogram; %) was calculated by the convolution method, using gastrointestinal transit rate constant data (Table 1) and the absorption rate constant of cephalexin (Table 2; O, shown for comparison).

Discussion

The gastrointestinal absorption of drugs has been often evaluated by in-situ re-circulation perfusion or by the closed-loop method, and the correlation between the fraction of the dose absorbed in man and the membrane permeability determined from steady-state perfused rat intestinal segments can be useful for estimation of oral drug absorption in man irrespective of the mechanism of absorption (Amidon et al 1988). The absorption profile of orally administered drugs must, however, be determined not only by measurement of membrane permeability but also by determination of the residence time in each absorption site. Several efficient methods have been reported for estimation of the absorption of orally administered drug by analysis of gastrointestinal disposition after oral administration (gastrointestinal disposition analysis) in rats: the use of gastrointestinal transit kinetics based on a two-compartment model (stomach–small intestine; Yuasa et al 1989) and the use of the ratio of the faecally excreted proportion of tested drug dose to that of polyethylene glycol 4000 as a non-absorbable marker (Yuasa et al 1996). Analytical procedures have also been reported for determination of the plasma profile of a drug absorbed from successive absorption sites along the gastrointestinal tract (Oberle & Amidon 1987; Plusquellec & Houin 1994). The method developed in the current study is, however, simpler and can be easily applied to various analyses of absorption characteristics.

With regard to gastrointestinal transit rate in the fasting state, gastric emptying is reported to be almost complete by 1 h, and its half-life to be approximately 0·15 h (Scarpignato et al 1984). The gastric emptying rate estimated in this study was slightly lower and the half-life was 0·34 h, which would cause the slight delay of predicted T_{max}. A small amount of phenol red appeared in the caecum 2 h after administration; this corresponds to the gastrointestinal transit time because the estimated transit time to the caecum is supposed to be the gastrointestinal transit time of drugs in rats (Lennernas & Regardh 1993). The large intestine has, furthermore, been found not to contribute to drug absorption for least 10 h after oral administration. To estimate the contribution of the large intestine to drug absorption, further, longer-term studies must be conducted.

The low bioavailability of ampicillin depends on the low absolute absorption but not first-pass elimination. Accordingly, the bioavailability of this kind of drug could be improved by reducing the gastrointestinal transit rate, i.e. increasing the residence time in the gastrointestinal tract. This was confirmed by simulation analysis using small k_i values (results not shown).

It is well known that cephalexin is absorbed via a carrier-mediated transport system (Miyazaki et al 1982; Kimura et al 1983; Nakashima et al 1984). The K_m value for cephalexin in rat small intestine is, however, relatively high and we could not observe saturation of absorption up to 10 mM (Kimura et al 1983). This might be the reason why the plasma concentration profile was well predicted by first-order absorption.

As described above, by use of our method the drug concentration in plasma and the absolute absorption can easily be predicted from the data obtained by widely used in-situ closed-loop studies. Prediction of plasma concentration profiles at various doses is useful for determining how long the effective level can be maintained and whether the plasma concentration exceeds the toxic level.

The proposed method also gives us a variety of information about drug absorption. Firstly, segmental drug absorption in-vivo can be estimated. Cephalexin is well known to be strongly absorbed in the upper small intestine (Maekawa et al 1977). We also recognized that the absorbability of cephalexin is greater in the upper small intestine than in the lower (Fig. 9). At the same time, however, this proposed method suggested that in the fasted state the major absorption site of cephalexin in-vivo should be below the lower jejunum (Fig. 9), which would be attributed to much higher rate of transit in the upper small intestine than in the lower. Information about segmental absorption will be applicable to the development of site-specific and gastrointestinal-transit-controlled drug delivery systems.

Secondly, we can estimate absolute absorption. The effect of absolute absorption and first-pass elimination on the bioavailability of orally administered drug can be separately evaluated, as for propranolol. The information is useful for the screening and the characterization of new drugs in research and development.

Table 4. Prediction, by the gastrointestinal transit-absorption model, of the effect of gastric emptying rate on the pharmacokinetic parameters of theophylline.

Transit rate constant in the stomach (h^{-1})	1·015	2·031	4·062
Area under plasma concentration–time curve after oral administration (μg h mL^{-1})	28·2	29·3	29·7
Time to reach maximum plasma concentration (h)	1·50	0·97	0·57
Maximum plasma concentration (μg mL^{-1})	7·24	8·95	10·55

Parameters were calculated from data simulated by the convolution method on the basis of the gastrointestinal transit-absorption model.

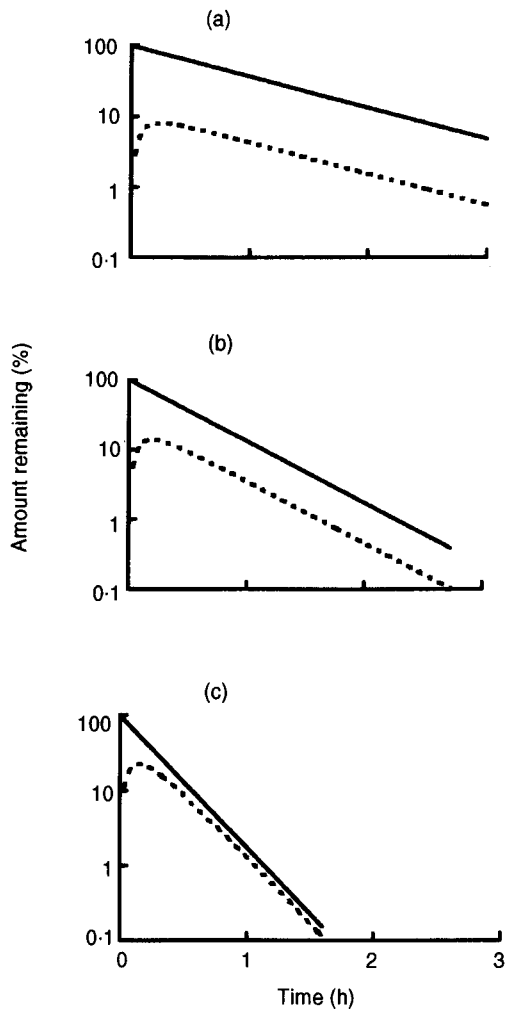

FIG. 10. Simulation of the amount of theophylline remaining in the stomach (—) and small intestine (- - -) for various gastric emptying rates after oral administration of aminophylline. a. $k_s = 1{\cdot}015\ h^{-1}$, b. $k_s = 2{\cdot}031\ h^{-1}$, c. $k_s = 4{\cdot}062\ h^{-1}$.

Thirdly, we can estimate the effect of gastric emptying rate on the plasma concentration of drugs after oral administration. The gastric emptying rate is influenced by physiological conditions, disease states, co-administered drugs and food taken simultaneously. Table 4 shows kinetic parameters predicted for theophylline for different gastric emptying rates ($k_s = 1{\cdot}015$, $2{\cdot}031$ and $4{\cdot}062\ h^{-1}$, respectively). It is recognized that T_{max} and Cp_{max} are influenced simultaneously by gastric emptying rate. Fig. 10 shows the dependence on time of the calculated amount of theophylline in the stomach and in the intestine for three different gastric emptying rates. These results indicate that the absorption of theophylline is limited by the gastric emptying rate.

Our method can, furthermore, aid understanding of the influence of gastrointestinal transit on drug absorption. A variety of information can be obtained by introducing a new process into the model or changing k_i and ka_i values flexibly. This method of prediction would be applicable to the development of new formulations by incorporating factors relating to dissolution rate, residence profile, etc. In conclusion, this method might be a useful tool for providing a variety of information enabling safe and certain oral administration of a drug, although further studies of gastrointestinal transit profile should be performed under different physiological conditions.

References

Amidon, G. L., Sinko, P. J., Fleisher, D. (1988) Estimating human oral fraction dose absorbed: a correlation using rat intestinal membrane permeability for passive and carrier-mediated compounds. Pharm. Res. 5: 651–654

Dressman, J. B., Berardi, R. R., Elta, G. H., Gray, T. M., Montgomery, P. A., Lau, H. S., Pelekoudas, K. L., Szpunar, G. J., Wagner, J. G. (1992) Absorption of flurbiprofen in the fed and fasted state. Pharm. Res. 9: 901–907

Iwamoto, K., Watanabe, J. (1985) Dose-dependent presystemic elimination of propranolol due to hepatic first-pass metabolism in rats. J. Pharm. Pharmacol. 37: 826–828

Kakemi, K., Sezaki, H., Konishi, R., Kimura, T., Okita, A. (1970) Effect of bile salts on the gastrointestinal absorption of drugs. II. Mechanism of the enhancement of the intestinal absorption of sulfaguanidine by bile salts. Chem. Pharm. Bull. 18: 1034–1039

Kimura, T., Yamamoto, T., Mizuno, M., Suga, Y., Kitade, S., Sezaki, H. (1983) Characterization of aminocephalosporin transport across rat small intestine. J. Pharmacobiodyn. 6: 246–253

Kurosaki, Y., Takatori, T., Kitayama, M., Nakayama, T., Kimura, T. (1988) Application of propranolol to the keratinized oral mucosa: avoidance of first-pass elimination and the use of 1-dodecylazacycloheptan-2-one (Azone) as an absorption enhancer of bioadhesive film-dosage form. J. Pharmacobiodyn. 11: 824–832

Lennernas, H., Regardh, C. G. (1993) Regional gastrointestinal absorption of the beta-blocker pafenolol in the rat and intestinal transit rate determined by movement of ^{14}C-polyethylene glycol (PEG) 4000. Pharm. Res. 10: 130–135

Maekawa, H., Takagishi, Y., Iwamoto, K., Doi, Y., Ogura, T., Ito, M., Kitamura, K., Fujimoto, H. (1977) Cephalexin preparation with prolonged activity. Jpn J. Antibiot. 30: 631–638

Miyazaki, Y., Ohtani, K., Umeniwa, K., Arita, T. (1982) Intestinal absorption of several β-lactam antibiotics. III. Competitive inhibition behavior among zwitterionic β-lactam antibiotics in the rat intestinal absorption. J. Pharmacobiodyn. 5: 555–563

Nakashima, E., Tsuji, A., Kagatani, S., Yamana, T. (1984) Intestinal absorption mechanism of amino-β-lactam antibiotics. III. Kinetics of carrier-mediated transport across the rat small intestine in-situ. J. Pharmacobio.-Dyn. 7: 452–464

Oberle, R. L., Amidon, G. L. (1987) 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

Ogiso, T., Iwaki, M., Tanino, T., Okuyama, K., Uno, S. (1993) Effect of mexiletine on elimination and metabolic conversion of theophylline and its major metabolites in rats. Biol. Pharm. Bull. 16: 163–167

Patel, V. S., Kramer, W. G. (1986) Allopurinol absorption from different sites of the rat gastrointestinal tract. J. Pharm. Sci. 75: 275–277

Plusquellec, Y., Houin, G. (1994) Pharmacokinetic compartmental model with n sites of absorption along the gastrointestinal tract. Arzneim. Forsch. 44: 679–682

Scarpignato, D., Girone, M. G., Tirelli, F., Bertaccini, G. (1984) Inhibition of gastric emptying and secretion by pirenzepine and atropine in rats. Eur. J. Pharmacol. 101: 193–200

Schanker, L. S., Shore, P. A., Brodie, B. B., Hogben, C. A. M. (1957) Absorption of drugs from the stomach. I. The rat. J. Pharmacol. Exp. Ther. 120: 528–539

Shiu, G. K., Sager, A. O., Velagapudi, R. B., Prasad, V. K., Skelly, J. P. (1988) The effect of food on the absorption of controlled-release theophylline in mini-swine. Pharm. Res. 5: 48–52

Speight, T. M., Brogden, R. N., Avery, G. S. (1972) Cephalexin: a review of its antibacterial, pharmacological and therapeutic properties. Drugs 3: 9–78

Tukker, J. J., Poelma, F. G. J. (1988) Site-dependent absorption in the rat intestine. Abstract, Third Int. Conf. on Drug Absorption, Edinburgh, pp 45

Yamaoka, K., Tanigawara, Y. (1984) Deconvolution. In: Introduction to Pharmacokinetic Analysis by Microcomputer. Nankodo, Tokyo, pp 91–112

Yamaoka, K., Tanigawara, Y., Nakagawa, T., Uno, T. (1981) A pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobiodyn. 4: 879–885

Yano, Y., Yamaoka, K., Aoyama, Y., Tanaka, H. (1989a) Two-compartment dispersion model for analysis of organ perfusion system of drugs by fast inverse Laplace transform (FILT). J. Pharmacokin. Biopharm. 17: 179–202

Yano, Y., Yamaoka, K., Tanaka, H. (1989b) A nonlinear least squares program, MULTI (FILT), based on fast inverse Laplace transform for microcomputer. Chem. Pharm. Bull. 37: 1035–1038

Yuasa, H., Iga, T., Hanano, M., Watanabe, J. (1989) Relationship between the first-order intestinal absorption rate constant in-vivo and the membrane permeability clearance in a perfusion system: an intragastric administration method in-vivo. J. Pharmacobiodyn. 12: 264–271

Yuasa, H., Kuno, C., Watanabe, J. (1996) Evaluation of the fractional absorption of D-xylose by analysis of gastrointestinal disposition after oral administration in rats. Biol. Pharm. Bull. 19: 604–607