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Analysis of the absorption characteristics of cimetidine with the use of the multi-segment absorption model

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Summary

Compartment model analysis is able to determine the mean transit time of drugs in the gastrointestinal tract, but it must be assumed that the movement of drugs is approximately first-order in the gastrointestinal tract, as reported previously. The multi-segment absorption model does not need such a first-order approximation. We applied this model to clarify the effects of metoclopramide and atropine on the absorption of cimetidine. The initiation times of absorption at the duodenum and the jejunum were decreased 0.5-fold by metoclopramide but increased 4-fold at the duodenum and 2-fold at the jejunum by atropine. The initiation time of absorption at the ileum was not changed in the cases of control and coadministration of metoclopramide when it was corrected for lag time. These findings were consistent with the results of intestinal motility measurement by γ-scintigraphy. Calculated plasma concentrations based on the multi-segment absorption model were well correlated to the observed values. Consequently, it was suggested that the multi-segment absorption model is reliable and that this model would be useful to analyze in detail the gastrointestinal absorption of drugs such as cimetidine, in which the optimal absorption site is the ileum.

Introduction

In order to achieve a satisfactory rate and extent of availability of a drug from controlled-release products, a knowledge of the transit time of the preparation through the small intestine is essential (Bechgaard, 1982). We (Kaneniwa et al., 1986a) have studied the absorption characteristics of cimetidine in rats by means of multi-compartment model analysis, in which the alimentary canal compartments were divided into the stomach, duodenum, jejunum and ileum. The movement of drug in the alimentary canal was presumed to be first-order in that work, and in fact the mean transit time ($t_{50\%}$) of cimetidine in the small intestine was similar to the values measured directly by using radioyttrium (Marcus and Lengemann, 1962) and dye (Okuma et al., 1985) in rats. Thus, it appears that such compartment model analysis is applicable to determine the mean transit time of drugs in the gastrointestinal tract.

On the other hand, metoclopramide increases the peristaltic motility of the gastrointestinal tract by stimulating the constriction of smooth muscle

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(Harrington et al., 1983) and it is sometimes given together with cimetidine (Gugler et al., 1981). In the previous report, we (Funaki et al., 1986a) studied the effect of metoclopramide on the mean transit time of cimetidine in the gastrointestinal tract and clarified that its effect was stronger at the upper site and disappeared at the lower site. However, the approximation of the movement of drugs in the gastrointestinal tract as a first-order rate process may not be valid under all physiological conditions. The multi-segment absorption model (Murata et al., 1985) does not require the first-order approximation for the movement of drugs in the gastrointestinal tract, and therefore, in the present study we applied this model to clarify the effects of metoclopramide and atropine on the absorption of cimetidine.

Materials and Methods

Materials

Cimetidine was obtained from Industrie Chimich Farmaceutiche Italiane (Italy). Metoclopramide was kindly supplied by Takeshima Pharmaceutical Co. (Tokyo, Japan). All other chemicals were of reagent grade.

Animal experiments and drug administration

Groups of 6 male Wistar rats weighing 230–280 g (9–11 weeks old) were fasted for 18 h before the experiment and a cannula (Atom disposable intravenous catheter 2Fr; Atom Co., Tokyo, Japan) was inserted into the femoral artery under light ether anesthesia. The dose of 25 mg/kg of cimetidine was dissolved in 1 ml of distilled water and it was administered orally through a gastric tube after awakening of the rats. Blood samples (ca. 0.25 ml) were collected periodically from the femoral artery into heparinized glass centrifuge tubes. Plasma was separated and kept frozen until analysis.

The doses of atropine sulfate and metoclopramide hydrochloride were 1 mg/kg and the drugs were dissolved in 1 ml of normal saline in both cases. Each dose was administered intraperitoneally 30 min prior to cimetidine administration.

Analytical method

Plasma samples were assayed by high-performance liquid chromatography as described previously (Kaneniwa et al., 1986b).

Data analysis

As the disposition of cimetidine in rats could be approximated by a two-compartment model (Kaneniwa et al., 1985), the pharmacokinetic models shown in Fig. 1 were used for the data analysis. Models A and B in Fig. 1 are the multi-segment absorption model and ordinary two-compartment model following oral administration, respectively. The mass-balances of the drug in the body at any time t for model A are given by:

$$\begin{aligned} dC/dt = &-(k_{12}+k_{10})C + k_{21}X_2/V_1 \\ &+ k_{a1}DF_1\, e^{-k_{a1}(t-T_1)}/V_1 \\ &+ k_{a2}DF_2\, e^{-k_{a2}(t-T_2)}/V_1 \\ &+ k_{a3}D(1-(F_1+F_2))\, e^{-k_{a3}(t-T_3)}/V_1 \end{aligned} \quad (1)$$

$$dX_2/dt = k_{12}CV_1 - k_{21}X_2 \quad (2)$$

where D is dose and V_1 is the distribution volume of the central compartment; T_1, T_2 and T_3 are the initiation times of absorption at the first (duodenum), second (jejunum) and third (ileum) segments, respectively, since the absorption of cimetidine from the stomach was negligible (Kaneniwa et al., 1986a); k_{a1}, k_{a2} and k_{a3} are the absorption rate constants in the segments indicated by the subscripts. Consequently, $k_{a3}=0$ at $t<T_3$, $k_{a2}=0$ at $t<T_2$ and $k_{a1}=0$ at $t<T_1$ under the condition of $T_1<T_2<T_3$. F_1, F_2 and F_3 are the available fractions of absorption at the first, second and third segments, respectively, and the sum of these was presumed to be unity in the present study since the bioavailability of cimetidine in rats is almost unity (Kaneniwa et al., 1985).

Data analysis was done with the use of the computer program SALS (Nakagawa and Oyanaagi, 1980) for non-linear least-squares analysis, and Eqns. 1 and 2 were solved by the

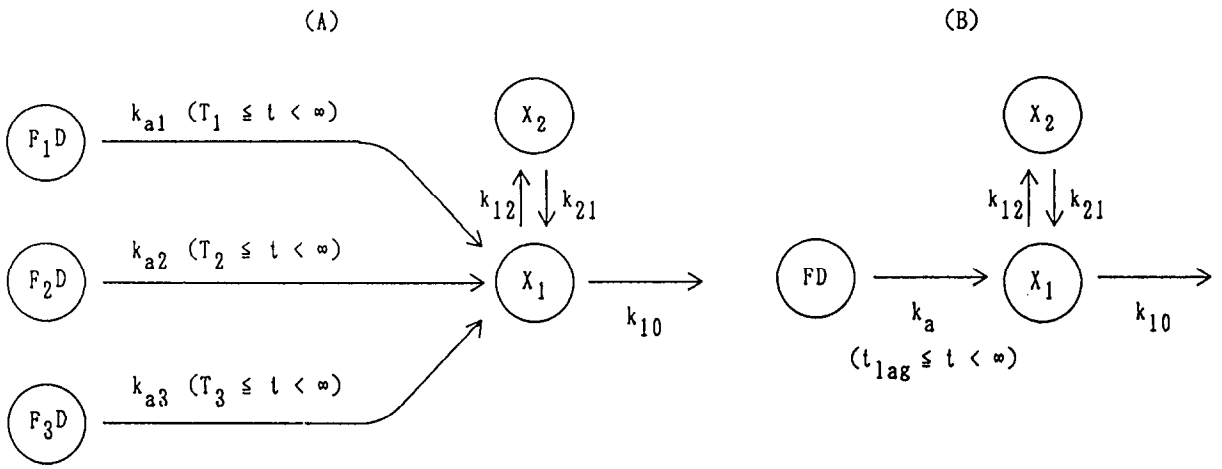

Fig. 1. Pharmacokinetic model for the absorption of cimetidine following oral administration. Compartments 1 and 2 are central and peripheral, respectively. The amount of drug is designated by X, and k is the rate constant. A: the multi-segment model, in which the length of time is $T_1 < T_2 < T_3$ and the total fraction of absorption is assumed to unity (i.e. $F_1 + F_2 + F_3 = 1$). B: the ordinary two-compartment model.

Runge-Kutta-Gill method. Previously reported values (Kaneniwa et al., 1985) of k_{12}, k_{21}, k_{10} and V_1 obtained from the i.v. data were used as the initial values for the analysis of model B, since the mean weight, species and age of subjects used for i.v. study were similar to those of the present study.

Initial values of absorption rate constant (k_{a1}, k_{a2} and k_{a3}) at each segment for the non-linear least-squares analysis were obtained from the experiments with ligated intestinal segments reported previously (Kaneniwa et al., 1986a; Funaki et al., 1986a). Initial values of initiation time (T_1, T_2 and T_3) for absorption and available fraction of absorption (F_1, F_2 and F_3) at each segment were calculated based on the results of multi-compartment model analysis in which the gastrointestinal tract was divided into the duodenal, jejunal and ileac segments (Kaneniwa et al., 1986a; Funaki et al., 1986a). Namely, T_1, T_2 and T_3 were roughly estimated from the mean transit time obtained by reversing the movement rate constant of drug in the gastrointestinal tract. F_1, F_2 or F_3 was estimated by dividing absorption rate constant by the sum of rate constants for absorption and movement of drug at each intestinal segment, in order of F_1, F_2 and F_3. Parameter values were restricted to within 10% deviation from these initial values for non-linear least-squares analysis. A weight of unity was employed in the present study.

The fraction absorbed (F_{abs}) for model A was calculated as follows:

$$\text{at } T_1 \leqq t < T_2 \quad F_{abs} = F_1(1 - e^{-k_{a1}(t-T_1)}) \tag{3}$$

$$\text{at } T_2 \leqq t < T_3 \quad F_{abs} = F_1(1 - e^{-k_{a1}(t-T_1)}) + F_2(1 - e^{-k_{a2}(t-T_2)}) \tag{4}$$

$$\text{at } T_3 \leqq t \quad F_{abs} = 1 - F_1 e^{-k_{a1}(t-T_1)} - F_2 e^{-k_{a2}(t-T_2)} - F_3 e^{-k_{a3}(t-T_3)}$$

$$(\text{i.e., } F_1 + F_2 + F_3 = 1) \tag{5}$$

The fraction absorbed for model B was calculated by means of Eqn. 6:

$$F_{abs} = 1 - e^{-k_a(t-t_{lag})} \tag{6}$$

Results and Discussion

Plasma concentration–time plots of cimetidine following oral administration to rats with coadministration of either metoclopramide or atropine are shown in Fig. 2 together with the control data. A detailed discussion of the effects of these drugs on the absorption characteristics of cimetidine has been presented previously (Kaneniwa et al., 1985). Solid lines in Fig. 2 show calculated values based on the multi-segment absorption model (Fig. 1A). These were well correlated to the observed values, suggesting that the model is reliable.

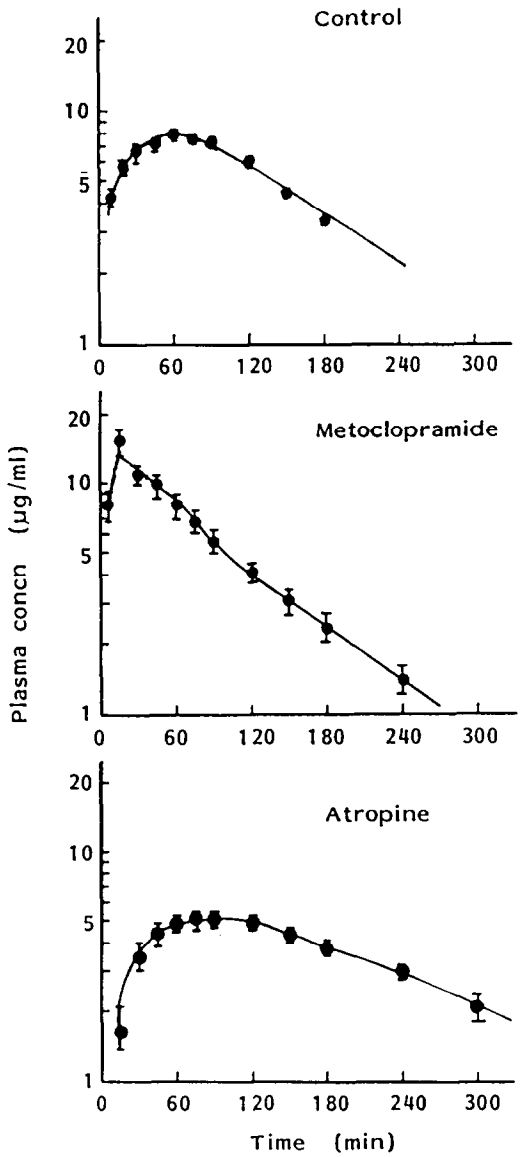

Fig. 2. Effects of metoclopramide and atropine on time courses of plasma concentration of cimetidine in rats following oral administration.

Pharmacokinetic parameters based on models A and B are shown in Table 1. It would be more pharmacokinetically correct to assess distributional microconstants from the same subject population. This may best be accomplished by using the simpler model, model B, to fit the control individual data if the absorption can be presumed to be a single first-order rate process. If the absorption cannot be described only by a single first-order rate process, estimation of distributional microconstants by using model B might be biased. However, it was impossible to include distributional microconstants as parameters for non-linear least-squares analysis of model A because the numbers of observed points exceeded those of parameters of curve-fitting. As can be seen in Table 1, there was only a significant difference between control and coadministration of metoclopramide for the value of k_{12}. This may be due to the assumption of a single first-order rate process for the absorption or the effect of metoclopramide on the disposition of cimetidine. However, as the contribution of F_1 fraction to the overall absorption is very large even in model A in each case, it may be reasonably safe to apply distributional microconstants obtained from model B to model A.

As described above, T_1, T_2 and T_3 are considered to be the initiation times for absorption at the duodenum, jejunum and ileum, respectively. The value of T_1 was increased 4-fold by atropine and the value of T_2 was decreased 2-fold by metoclopramide compared to the control. On the other hand, the values of T_3 minus T_1 were almost the same in the cases of control and coadministration of metoclopramide. This may be interpreted in terms of the following facts: (1) the effect of metoclopramide on the motility of the gastrointestinal tract decreases during passage to the lower intestinal regions (Harrington et al., 1983); and (2) the intestinal motility data obtained by gamma scintigraphy indicate that the ileum acts as a buffer

TABLE 1

Effects of metoclopramide and atropine on the absorption characteristic of cimetidine in rats [a]

Parameter	Model A [b]			Parameter	Model B		
	Control	Metoclopramide	Atropine		Control	Metoclopramide	Atropine
k_{a1} (min^{-1})	0.0203 ±0.0006	0.0822 [c] ±0.015	0.0105 [c] ±0.0011	k_{12} (min^{-1})	0.1039 ±0.0057	0.1325 [c] ±0.095	0.0998 ±0.0066
k_{a2} (min^{-1})	0.0091 ±0.0003	0.0108 [c] ±0.0002	0.0055 [c] ±0.0003	k_{21} (min^{-1})	0.0699 ±0.0091	0.0586 ±0.0052	0.0587 ±0.0084
k_{a3} (min^{-1})	0.0330 ±0.0001	0.0271 [c] ±0.0002	0.0320 ±0.0002	k_{10} (min^{-1})	0.0385 ±0.0016	0.0379 ±0.0022	0.0409 ±0.0028
F_1	0.865 ±0.008	0.955 [c] ±0.015	0.833 ±0.021	V_1/F [d] (ml/kg)	455.5 ±23.2	477.0 ±49.3	429.8 ±9.7
F_2	0.143 ±0.001	0.039 [c] ±0.002	0.132 [c] ±0.003	k_a (min^{-1})	0.0165 ±0.0009	0.0937 [c] ±0.0173	0.0082 [c] ±0.0010
T_1 (min)	2.48 ±0.12	1.70 ±0.46	10.43 [c] ±0.82	t_{1ag} (min)	1.68 ±0.07	2.17 ±0.46	9.30 [c] ±0.95
T_2 (min)	35.10 ±1.56	15.90 [c] ±0.42	73.44 [c] ±1.08				
T_3 (min)	168.5 ±3.24	160.5 ±6.54	193.4 [c] ±5.16				
AIC	47.87 ±2.82	69.52 ±6.37	52.75 ±4.95	AIC	48.73 ±5.92	64.40 ±7.89	48.22 ±7.29
SS	32.92 ±9.11	439.70 ±337.34	46.83 ±21.22	SS	123.61 ±91.92	452.61 ±360.48	65.24 ±28.36

[a] Results are mean ± S.E., $n = 6$.

[b] Distributional microconstants used for analysis, i.e. k_{12}, k_{21}, k_{10} and V_1/F, are the same as in model B. See text for details.

[c] Statistically different from the control ($P < 0.05$).

[d] F is the available fraction of absorption.

region for the material entering from above (Davis et al., 1984). Although atropine had no effect on the absorption characteristics of intraduodenally administered cimetidine in the previous report (Funaki et al., 1986a), the value of T_2 following orally administered cimetidine with coadministration of atropine was increased 2-fold compared to the control in the present study. Further, there was a significant difference between control and coadministration of atropine for the value of T_3. This is consistent with the finding of Ruwart et al. (1979) that atropine decreased the small intestinal transit time of orally administered solution but did not change that of intraduodenally administered solution. These results may be explained by the fact that the decreased gastric-emptying rate induced by atropine administration affects strongly the small intestinal transit time at the upper site (Davis et al., 1984; Ruwart et al., 1979; Christensen et al., 1985).

On the other hand, the values of k_{a1} and k_{a2} following metoclopramide administration were increased and this might be due to the increase of intestinal blood flow at the upper site (Funaki et al., 1986a). The value of T_2 following metoclopramide administration was decreased 0.5-fold in addition to the 4-fold increase of k_{a1} as compared with the control. As a result, the value of F_1 was increased. The decrease of k_{a1} and k_{a2} compared to the control following atropine administration may be attributed to diffusion of the drug due to the increase of gastric residence time by

atropine, since atropine had no effect on the absorption in the ligated duodenal loop experiment (Funaki et al., 1986a). Therefore, the decreases of k_{a1} and k_{a2} may be apparent ones resulting from the fitting process. The value of T_2 following atropine administration was increased 2-fold as compared with the control but the value of k_{a1} was decreased, and consequently the value of F_1 was almost unchanged.

When compared to model B, the values of sum of k_{a1} amd k_{a2} for coadministration of metoclopramide is similar to that of k_a of model B. This may be partly explained by the rapid absorption of cimetidine produced by metoclopramide. On the other hand, in the cases of control and coadministration of atropine the value of T_1 is almost similar to that of t_{1ag} of model B; however, the value of k_a of model B is one-fifth smaller than that of k_{a1} in each case. In the present study the mean value of residual sum of squares (SS) for model A was considerably smaller compared with that of model B in each case, while, the mean value of AIC (Yamaoka et al., 1978) for model A was slightly larger than that of model B. However, there were no significant differences between both models A and B for the values of AIC (Yamaoka et al., 1978) and SS for statistical information. Furthermore, interestingly the values of k_{a3} are the largest ones among k_{a1}, k_{a2} and k_{a3} and almost the same in the cases of control and coadministration of atropine. This was in good agreement with the fact that the optimal absorption site of cimetidine is the ileum (Kaneniwa et al., 1986a). Based on this result, it appears that the movement of drugs in the gastrointestinal tract and permeation through the wall proceed simultaneously, but no work has been done on this problem except for our reports (Kaneniwa et al., 1986a; Funaki et al., 1986a).

In the present study, analysis was done with the use of the multi-segment absorption model, which does not require the assumption of first-order movement of drug in the gastrointestinal tract. A comparison of fraction absorbed according to the present method (model A) and the ordinary method (model B) is shown in Table 2. In the ordinary method, the overall absorption process (i.e. movement and membrane permeation) was assumed to be a single first-order rate process and the inverse relationships between mean absorption time and k_a in model B were observed in the previous report (Kaneniwa et al., 1986c). The difference of fraction absorbed in each case was minimal in both methods. Although the statistical values of AIC and SS were not significantly different between both models A and B in the present

TABLE 2

Comparison of the fraction absorbed calculated by the multi-segment model (A) and ordinary two-compartment model (B)

Time (min)	Control		Metoclopramide		Atropine	
	A	B	A	B	A	B
5	0.0431	0.0533	0.2269	0.2329	0	0
10	0.1225	0.1283	0.4723	0.5199	0	0.0057
15	0.1941	0.1973	0.6350	0.6995	0.0390	0.0457
20	0.2589	0.2609	0.7445	0.8119	0.0796	0.0840
30	0.3702	0.3733	0.8672	0.9263	0.1547	0.1561
45	0.5124	0.5107	0.9383	0.9819	0.2536	0.2538
60	0.6249	0.6180	0.9619	0.9956	0.3380	0.3401
75	0.7101	0.7017	0.9711	0.9989	0.4113	0.4165
90	0.7749	0.7671	0.9758	0.9997	0.4832	0.4840
120	0.8624	0.8581	0.9813	1	0.5992	0.5966
150	0.9144	0.9135	0.9848	1	0.6860	0.6845
180	0.9437	0.9473	0.9898	1	0.7511	0.7533
240	0.9716	0.9804	0.9958	1	0.8645	0.8392
300	0.9852	0.9927	0.9981	1	0.9211	0.9078

study, use of the multi-segment absorption model might be better to obtain more detailed information on cimetidine absorption. Because the optimal absorption site of cimetidine is the ileum (Kaneniwa et al., 1986a).

Knowledge of mean transit time through the small intestine is essential for the design of controlled-release products giving a satisfactory rate and extent of drug availability, as described in the Introduction. Recently, discontinuous absorption profiles of some drugs have been reported (Zimmerman, 1983; Kaniwa et al., 1984; Funaki et al., 1986b), and the present method may also be useful for the analysis of such profiles.

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