*International Journal of Pharmaceutics*, 31 (1986) 119–123
Elsevier



IJP 01037

# Discontinuous absorption property of cimetidine

Tomoo Funaki, Sigeru Furuta and Nobuyoshi Kaneniwa

*School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo 142 (Japan)*

(Received November 5th, 1985)
(Modified version received January 15th, 1986)
(Accepted February 11th, 1986)

*Key words*: cimetidine – discontinuous absorption – biliary excretion – absorption site – compartment model

## Summary

The double-peaked plasma concentration profile of cimetidine reported by Walkenstein et al. (1978) was analyzed with the use of a discontinuous absorption model in the present study. The observed and calculated plasma concentrations were in good agreement with each other, suggesting the validity of the discontinuous absorption. The absorption rate constants $k_{a1}$, $k_{a2}$ and $k_{a3}$ appear to correspond to those at the duodenum, jejunum and ileum, respectively, and the ileum is considered to be the optimal absorption site of cimetidine in man. Pedersen and Miller (1980) analyzed the double-peaked plasma concentration profiles of cimetidine in terms of a model with enterohepatic circulation. However, discontinuous absorption seems more likely than enterohepatic circulation to account for the secondary peak of cimetidine because the biliary excretion rate of cimetidine was found to be insufficient (i.e. 2% in rats) to produce significant enterohepatic circulation in the present study. Our analysis suggests that when the drug is administered as a solid form, most of it is absorbed at the duodenum, but the fraction which is not dissolved in the duodenum dissolves during its passage through the jejunum and is absorbed at the ileum.

## Introduction

In the previous report, we (Kaneniwa et al., 1985b) showed that the optimal absorption site of cimetidine in rats is the ileum, although in the oral administration of cimetidine solution, the drug is mainly absorbed at the duodenum.

Pedersen and Miller (1980) analyzed the double-peaked human plasma concentration profiles of cimetidine reported by Walkenstein et al. (1978) in terms of a pharmacokinetic model with enterohepatic circulation to account for the appearance of the secondary peak in the plasma concentration profiles. However, no experimental evidence for enterohepatic circulation (or biliary excretion) in man has been reported, though McPherson and Lee (1977) reported that the biliary excretion of [$^{14}$C]cimetidine was almost 5% in rats.

On the other hand, it may be possible to analyze the double-peaked plasma concentration profiles with the use of a discontinuous absorption model (Zimmerman, 1983; Kaniwa et al., 1984), because cimetidine is well absorbed at the upper and lower regions of the intestine (Kaneniwa et al., 1985b). Consequently, to clarify the possibility of the time-dependent absorption process of cimetidine more clearly, the animal experimentation for the absorption properties of cimetidine from the

*Correspondence*: N. Kaneniwa, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo 142, Japan.

gastrointestinal tract was done. Secondly, the double-peaked plasma concentration profiles of cimetidine reported by Walkenstein et al. (1978) were analyzed with the use of a discontinuous absorption model in the present study.

## Materials and Methods

*Materials*

Cimetidine was obtained from Industrie Chimiche Farmaceutiche Italiane (Italy). All other chemicals were of reagent grade.

*Animal experiments*

Male Wistar rats weighing 230–280 g (9–11 weeks old) were fasted for 18 h before each experiment. In order to compare the absorption rates of cimetidine at various intestinal sites, a cannula (Atom disposable intravenous catheter 2Fr; Atom Co., Tokyo, Japan) was inserted into the femoral artery, and the small intestine was divided into three parts (i.e. duodenal, jejunal and ileac sections) following the previous report (Kaneniwa et al., 1985b). The dose of 25 mg/kg of cimetidine was dissolved in 0.5 ml of distilled water with the aid of a minimum amount of hydrochloric acid (the hydrochloric acid amounted to 0.085 w/v%), and the solution was administered into each ligated intestinal loop. Blood samples (ca. 0.25 ml) were collected periodically from the femoral artery into heparinized glass centrifuge micro-tubes and plasma was separated and kept frozen until analysis.

In order to measure the biliary excretion rate of cimetidine, a cannula (Atom disposable intravenous catheter 2Fr; Atom Co., Tokyo, Japan) was inserted into the bile duct. The dose of cimetidine used for experiments to measure the biliary excretion rate was 100 mg/kg, and it was dissolved in 1 ml of normal saline and distilled water for intravenous and oral administrations, respectively, with the aid of a minimum amount of hydrochloric acid (the hydrochloric acid amounted to 0.170 w/v%). Bile was collected for 9 h after the drug administration.

For each operation, the animals were anesthetized lightly with ether at suitable intervals as necessary during surgery. Fresh animals were used for each experiment.

*Analytical method*

Plasma and bile samples were assayed by high-performance liquid chromatography as described previously (Kaneniwa et al., 1985a).

*Data analysis*

For testing of the pharmacokinetic model shown in Fig. 1, the data reported by Walkenstein et al. (1978) were used. These data were fitted to Eqn. 1 with the use of the non-linear least-squares program SALS (Nakagawa and Oyanagi, 1977) and the discontinuous absorption rate constants were obtained.

$$C = \frac{k_a \cdot F \cdot D(k_{21} - \lambda_1)}{V_1(k_a - \lambda_1)(\lambda_2 - \lambda_1)} e^{-\lambda_1(t - t_{lag})} + \frac{k_a \cdot F \cdot D(k_{21} - \lambda_2)}{V_1(k_a - \lambda_2)(\lambda_1 - \lambda_2)} e^{-\lambda_2(t - t_{lag})} + \frac{k_a \cdot F \cdot D(k_{21} - k_a)}{V_1(\lambda_1 - k_a)(\lambda_2 - k_a)} e^{-k_a(t - t_{lag})} \quad (1)$$

where C is the plasma concentration at time t, $\lambda_1$ and $\lambda_2$ are the exponential coefficients associated with the faster and slower processes, respectively, $k_{21}$ is the rate constant associated with movement of drug from compartment 2 to compartment 1, and $t_{lag}$ is a lag time. Further, we have $C = 0$ for $t < t_{lag}$, $k_a = k_{a1}$ for $t_{lag} \leqq t < t_1$, $k_a = k_{a2}$ for $t_1 \leqq t < t_2$, and $k_a = k_{a3}$ for $t \geqq t_2$, in which $t_1$ and $t_2$

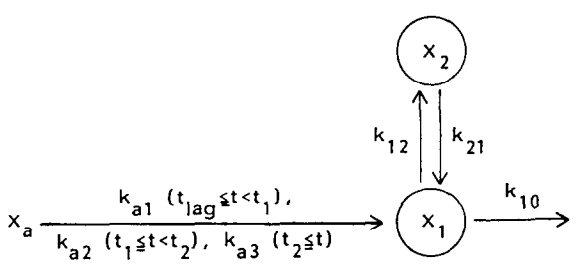



Fig. 1. Pharmacokinetic model for discontinuous absorption of cimetidine following oral administration. Compartments 1 and 2 are central and peripheral, respectively. The amount of drug is designated by X and k is the rate constant.

are the initiation time of second and third absorption processes, respectively.

## Results and Discussion

Pederson and Miller (1980) analyzed the double-peaked plasma concentration profiles of cimetidine reported in man by Walkenstein et al. (1978). Pederson and Miller (1980) speculated that the secondary peak of cimetidine was due to the release from a drug depot (i.e. the bile and hepatic parenchymal tissues). This speculation was based on the facts that the gallbladder released most of its bile content into the duodenum shortly after the intake of a meal, and the secondary peak coincided with the intake of food (2 h after the administration of drug) in most cases. However, a marked secondary peak was not observed in the case of intravenous administration when similar food was taken, and furthermore the secondary peak sometimes did not coincide with the intake of food. Pedersen and Miller (1980) referred to the report by Spence et al. (1977) as the basis for the enterohepatic circulation of cimetidine. However, Spence et al. (1977) measured only the biliary concentration of cimetidine in man, but did not report the amount of biliary excretion, and they concluded that the total amount of drug secreted in bile would not be enough to produce significant enterohepatic circulation.

The cumulative biliary excretion of cimetidine in rats is shown in Table 1. The ratio of the amount of biliary excretion to the dose of cimetidine in the intravenous route was somewhat lower than that in the oral route, and both were smaller than 2%. Although the values obtained in the present study were almost two-fifths of those reported in rats by McPherson and Lee (1977), if these results were applicable to man, it would be unreasonable to consider that the secondary peak of cimetidine is mainly attributable to enterohepatic circulation arising from biliary excretion. The difference of biliary excretion rate between the present results and McPherson and Lee's results might be due to the difference of analytical method used in the two studies.

We (Kaneniwa et al., 1985b) have already shown that the optimal absorption site of cimetidine solution is the ileum in rats, even though an oral dose of cimetidine solution is absorbed mainly at the duodenum. The absorption rate constants following administration of cimetidine into various ligated intestinal loops in rats are shown in Table 2. It is clear that the absorption of cimetidine is fast at the duodenum and ileum but slow at the jejunum. Thus, on administration of the solid form, incomplete dissolution may sometimes occur at

TABLE 1

CUMULATIVE BILIARY EXCRETION RATE (%) OF CIMETIDINE (DOSE: 100 mg/kg) FOLLOWING INTRAVENOUS (i.v.) AND ORAL (p.o.) ADMINISTRATION IN RATS (MEAN ± S.E.)

| Time (min) | i.v. (n = 3) [a] | p.o. (n = 6) |
|---|---|---|
| 20 | 0.31 ± 0.06 | 0.10 ± 0.03 |
| 40 | 0.53 ± 0.11 | 0.21 ± 0.02 |
| 60 | 0.72 ± 0.15 | 0.43 ± 0.05 |
| 90 | 0.82 ± 0.17 | 0.61 ± 0.10 |
| 120 | 0.90 ± 0.17 | 0.79 ± 0.11 |
| 180 | 0.98 ± 0.18 | 1.18 ± 0.16 |
| 240 | 1.04 ± 0.19 | 1.44 ± 0.20 |
| 360 | 1.07 ± 0.19 | 1.68 ± 0.25 |
| 540 | 1.11 ± 0.19 | 1.73 ± 0.26 |

[a] n is the number of rats used.

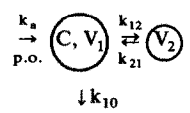
TABLE 2

ABSORPTION RATE CONSTANT FOLLOWING THE ADMINISTRATION OF CIMETIDINE (DOSE: 25 mg/kg) INTO THE LIGATED DUODENUM (i.d.), JEJUNUM (i.j.), AND ILEUM (i.i.) IN RATS [a] (n = 5; MEAN ± S.E.)

| | Ligated intestinal loop (ca. 10 cm) | | |
|---|---|---|---|
| | i.d. | i.j. | i.i. |
| $k_a$ ($h^{-1}$) | 1.260 ± 0.756 | 0.396 ± 0.040 | 1.968 ± 0.684 |

[a] Pharmacokinetic model for calculation of absorption rate constant:

$$C = (C_1)_{po} \cdot e^{-\lambda_1 \cdot t} + (C_2)_{po} \cdot e^{-\lambda_2 \cdot t} - \left((C_1)_{po} + (C_2)_{po}\right) \cdot e^{-k_a \cdot t}$$



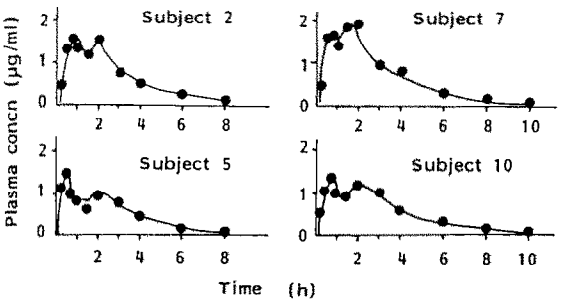



Fig. 2. Time courses of plasma concentration following oral administration of cimetidine fitted to the discontinuous absorption model. The data are taken from Walkenstein et al. (1978). The discontinuous absorption model is shown in Fig. 1. The curves were computer-fitted.

the duodenum, whereupon the solid dissolves slowly during its passage through the jejunum, and finally the dissolved drug is absorbed at the ileum. In such cases, double peaks may appear in the plasma concentration profile. By taking account of the solubility of cimetidine (11.4 mg/ml at 37°C) it is considered that the oral dosage form used by Walkenstein et al. (1978) would have been a suspension (300 mg/5 ml).

Pharmacokinetic analyses of discontinuous drug absorption profiles have been reported by a few workers (Zimmerman, 1983; Kaniwa et al., 1984). Hence, the plasma concentration profiles reported by Walkenstein et al. (1978) were analyzed in the present study based on the discontinuous absorption model shown in Fig. 1. As shown in Fig. 2, the observed and calculated plasma concentrations were in good agreement with each other, supporting the validity of the discontinuous absorption model shown in Fig. 1. The two component fit (i.e., $t_{lag}$, to $t_1$ and $t_1$ to $t_\infty$) could be fitted to Walkenstein's data (1978) and its residual sum of squares was similar to that in the case of the three component fit. AICs for the two component fit and the three component fit were $43.85 \pm 1.75$ and $39.80 \pm 3.06$, respectively. However, the computer-fitted line of the two component fit could not (or it was very difficult to) represent the trough of the blood concentration in each case, in other words, it could not show the double-peaked phenomenon.

TABLE 3

PHARMACOKINETIC PARAMETERS FOLLOWING ORAL ADMINISTRATION OF CIMETIDINE [a,b]

| Parameter | Subject | | | | mean ± S.E. |
|---|---|---|---|---|---|
| | 2 | 5 | 7 | 10 | |
| $k_{a1}$ ($h^{-1}$) | 0.654 | 0.466 | 0.668 | 0.528 | 0.579 ± 0.049 |
| $k_{a2}$ ($h^{-1}$) | 0.401 | 0.184 | 0.456 | 0.300 | 0.335 ± 0.060 |
| $k_{a3}$ ($h^{-1}$) | 1.644 | 0.303 | 0.749 | 0.427 | 0.781 ± 0.303 |
| $\lambda_1$ ($h^{-1}$) | 2.040 | 1.904 | 2.720 | 1.124 | 1.947 ± 0.327 |
| $\lambda_2$ ($h^{-1}$) | 0.340 | 0.446 | 0.407 | 0.994 | 0.547 ± 0.151 |
| $k_{21}$ ($h^{-1}$) | 0.679 | 0.285 | 0.748 | 0.981 | 0.678 ± 0.145 |
| $t_{lag}$ (h) | 0.10 | 0.03 | 0.17 | 0.03 | 0.08 ± 0.03 |
| $t_1$ (h) | 1.25 | 0.50 | 0.75 | 0.75 | 0.81 ± 0.16 |
| $t_2$ (h) | 1.80 | 1.51 | 1.01 | 1.60 | 1.48 ± 0.34 |
| $V_1/F$ (L) | 42.18 | 24.06 | 28.18 | 47.88 | 35.58 ± 5.64 |

[a] The discontinuous absorption model is shown in Fig. 1.
[b] The data are taken from Walkenstein et al. (1978).

The pharmacokinetic parameters obtained by this analysis are shown in Table 3, in which mean $k_{a3}$ is larger than mean $k_{a1}$ and mean $k_{a2}$ is the smallest among them. This tendency is similar to the results obtained in ligated rat intestinal loops (Table 2). Consequently, it appears that $k_{a1}$, $k_{a2}$ and $k_{a3}$ are the absorption rate constants at the duodenum, jejunum, and ileum, respectively, and that the ileum is also the optimal absorption site in man. Walkenstein et al. (1978) used 12 subjects, but the subjects which were excluded from the present study could be analyzed more suitably by the ordinary two-compartment model (shown in Table 2), because they showed no marked secondary peak.

The discontinuous absorption process described above can account well for the secondary peak of plasma concentration reported by Walkenstein et al. (1978). Namely, an oral dose is absorbed mainly at the duodenum, while the residual fraction of undissolved drug is dissolved during its passage through the jejunum and absorbed at the ileum.

## References

Burland, W.L., Duncan, W.A.M., Hesselbo, T., Mills, J.C., Sharpe, P.C., Haggie, S.J. and Wyllie, J.H., Pharmacological evaluation of cimetidine, a new histamine $H_2$-receptor

antagonist, in healthy man. Br. J. Clin. Pharmacol., 2 (1975) 481–486.

Griffiths, R., Lee, R.M. and Taylor, D.C., Kinetics of cimetidine in man and experimental animals. In Proceedings of the Second International Symposium on Histamine $H_2$-Receptor Antagonists, Excerpta Medica, Amsterdam, The Netherlands, 1977, pp. 81–84.

Kaneniwa, N., Funaki, T., Furuta, S. and Watari, N., Influence of gastric emptying rate on the absorption of cimetidine in rats. Yakugaku Zasshi, 105 (1985a) 966–972.

Kaneniwa, N., Funaki, T., Furuta, S. and Watari, N., study of absorption site of cimetidine, J. Pharmacobio-Dyn., 9 (1986) 321–326.

Kaniwa, K., Aoyagi, N. and Ogata, H., Use of PKM-MULTI program for fitting discontinuous absorption profiles using a micro-computer. J. Pharmacobio-Dyn., 7 (1984) 900–909.

McPherson, F.J. and Lee, R.M., Biliary excretion and metabolism of $^{14}$C-cimetidine following oral administration to male and female rats. Experientia, 33 (1977) 1139–1140.

Nakagawa, T. and Oyanagi, Y., Program system 'SALS' for nonlinear least-squares fitting in experimental sciences. In Abstracts of International Conference on Statistics, Tokyo, November 1979, pp. 19–22.

Pedersen, P.V. and Miller, R., Pharmacokinetics and bioavailability of cimetidine in humans. J. Pharm. Sci., 69 (1980) 394–398.

Spence, R.W., Celestin, L.R., de la Guardia, R., MacMullen, C.A. and McCormick, D.A., Biliary secretion of cimetidine in man. In Proceedings of the Second International Symposium on Histamine $H_2$-Receptor Antagonists, Excerpta Medica, Amsterdam, The Netherlands, 1977, pp. 81–84.

Walkenstein, S.S., Dubb, J.W., Randolph, W.C., Westlake, W.J., Stote, R.M. and Intoccia, A.P., Bioavailability of cimetidine in man. Gastroenterology, 74 (1978) 360–365.

Zimmerman, J.J., Use of Metzler's NONLIN program for fitting discontinuous absorption profiles. J. Pharm. Sci., 72 (1983) 138–142.