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RESEARCH PAPER

Comparative Study of Pharmacokinetic Parameters Between Clarithromycin and Erythromycin Stearate in Relation to Their Physicochemical Properties

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ABSTRACT

Pharmacokinetic parameters for clarithromycin (CAM) and erythromycin stearate (EMS) were obtained from a model including decomposition in the gastrointestinal tract. To confirm the accuracy of the parameters, various physicochemical properties of both drugs were examined.

The ratio of the in vivo *dissolution rate, the* in vivo *decomposition rate and the absorption rate between CAM and EMS were well correlated to the ratio of the* in vitro *intrinsic dissolution rate, the decomposition rate in the acidic solution, and partition coefficient, respectively.*

One of the reasons for the excellent absorption of CAM compared with that of EMS was the higher stability in the acidic solution and the higher partition coefficient of CAM.

These findings indicate that the ratio of the partition coefficient to the decomposition rate constant in acidic solution plays an important role in determining drug bioavailability for macrolide antibiotics.

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INTRODUCTION

Macrolide antibiotics are widely employed in the treatment of gram-positive infections and are used clinically for other purposes as well (1). However, it is known that the biological activity of macrolide antibiotics such as erythromycin (EM) rapidly diminishes in acidic media due to extensive acid-catalyzed transformation (2).

Therefore, erythromycin derivatives, erythromycin esters, and the sparingly soluble salt of EM have been developed to compensate for this disadvantage of EM. A salt of EM, erythromycin stearate (EMS), has been reported to be less acid-unstable than the free base (3).

Moreover, structurally modified macrolide antibiotics, such as clarithromycin (CAM), (4) roxithromycin, and azithromycin, with high stability in acidic conditions have recently been developed.

In the present study, we investigated the effect of the structural differences of EMS and CAM on their pharmacokinetic properties.

It is known that EM is degraded to erythromycin 6,9-hemiketal, and subsequently to anhydro erythromycin in acidic solution, as shown in Fig. 1 (a) (2).

In contrast, CAM is degraded via cleavage of the neutral cladinose sugar, and 6,9-hemiketal is not formed, as shown in Fig. 1 (b) (5). Thus, the products of decomposition of the two drugs in acidic solution differ, though the structure of EMS is similar to that of CAM. On the other hand, the degree and extent of decomposition in the gastrointestinal tract can play an important role in determining the bioavailability of these two drugs.

Therefore, comparative studies of chemical and physicochemical properties including dissolution rate constant, partition coefficient (n-octanol/phosphate buffer solution), and acidic stability of CAM and EMS were performed. Furthermore, using a pharmacokinetic model which takes into account the dissolution, the decomposition in the gastrointestinal tract, the absorption, and the elimination rates, pharmacokinetic parameters including the in vivo dissolution rate, the in vivo

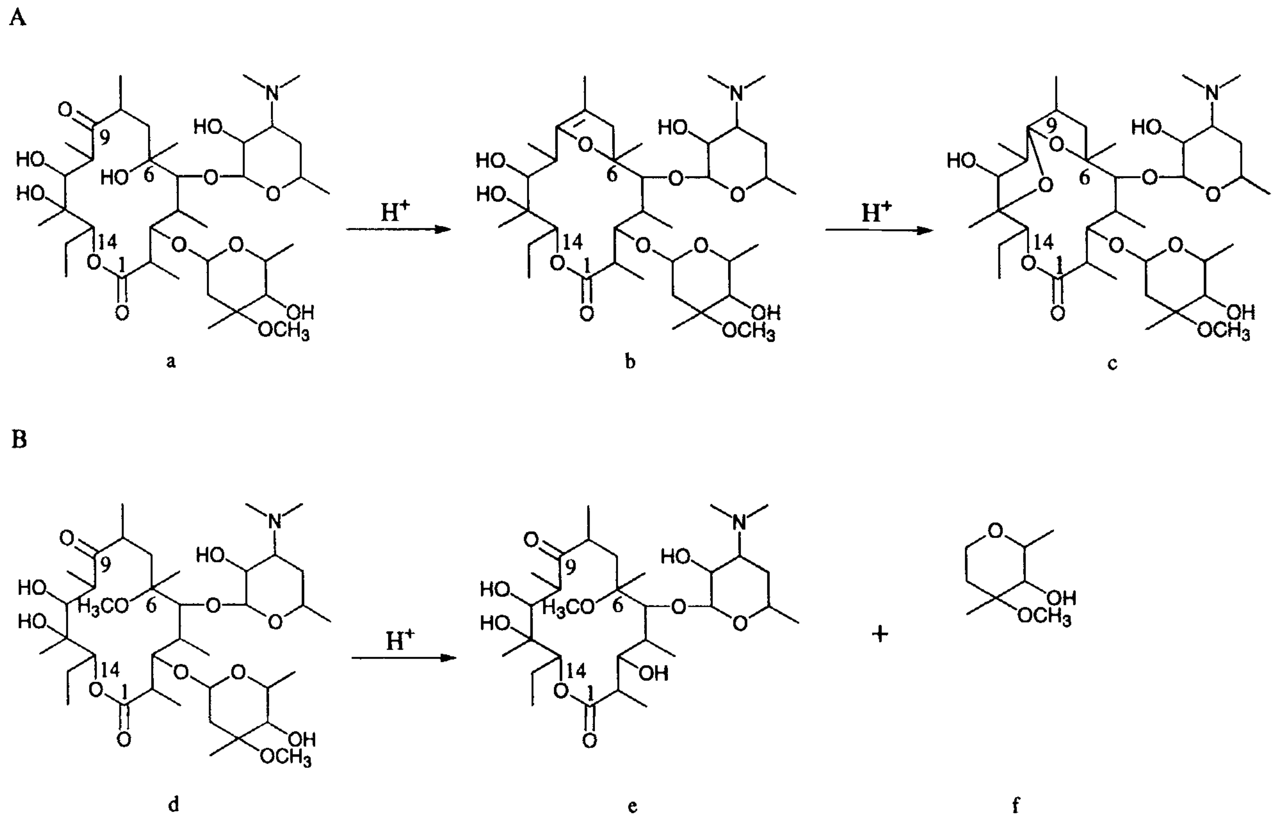

Figure 1. Mechanisms of degradation of CAM and EM in acidic solution A, EM; B, CAM. (a) EM, (b) erythromycin 6,9-hemiketal; (c) anhydroerythromycin; (d) CAM; (e) 5-O-desosaminyl-6-metylerythronolide; (f) cladinose.

decomposition rate, the absorption rate, and the elimination rate for CAM and EMS were determined. Then, the pharmacokinetic parameters obtained from the model were compared with the chemical and physicochemical properties.

MATERIALS AND METHODS

Materials

CAM and EMS were synthesized at Taisho Pharmaceutical Co., Ltd., Saitama, Japan. All other chemicals were of reagent grade and were used without further purification.

In Vivo Data

The present study used serum concentrations and urinary excretion values for CAM and EMS as reported by Saito et al. (6).

Assay of CAM and EMS

The concentrations of CAM and EMS were determined using the HPLC method. The operating conditions of HPLC for CAM and EMS were as follows. CAM: detector, UV absorption spectra; detector wavelength, 210 nm; column temperature, 50°C; flow rate, 1 ml/min; mobile phase, 1/15 M potassium dihydrogen phosphate:acetonitrile (13:7); EMS: detector, UV absorption spectra; detector wavelength, 204 nm; column temperature, 40°C; flow rate, 1 ml/min; mobile phase, pH 3.0 phosphate buffer:acetonitrile:sodium dodecyl sulfate (50:50:0.5).

Pharmacokinetic Model

The pharmacokinetic model including the dissolution rate, decomposition rate, absorption rate, and the rate of elimination from the central compartment is illustrated in Fig. 2.

In this model, the drug is dissolved from the formulation in the gastrointestinal tract, and the drug undergoes decomposition. The drug in solution is immediately absorbed at the same time, and the drug is thereby eliminated from the central compartment.

For the pharmacokinetic model in Fig. 2, the differential equations employed for calculations were as follows:

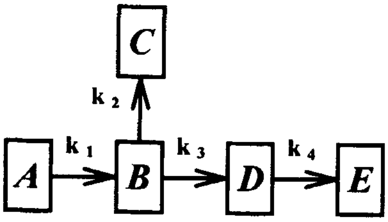

Figure 2. Pharmacokinetic model including dissolution, decomposition, absorption, and elimination in gastrointestinal tract.

$$\frac{dA}{dt} = -\mathrm{k}_1 \cdot A \tag{1}$$

$$\frac{dB}{dt} = \mathrm{k}_1 \cdot A - \mathrm{k}_2 \cdot B - \mathrm{k}_3 \cdot B \tag{2}$$

$$\frac{dC}{dt} = \mathrm{k}_2 \cdot B \tag{3}$$

$$\frac{dD}{dt} = \mathrm{k}_3 \cdot B - \mathrm{k}_4 \cdot D \tag{4}$$

$$\frac{dE}{dt} = \mathrm{k}_4 \cdot D \tag{5}$$

where A, B, and C represent the amount of solid drug, dissolved drug, and decomposed drug, respectively. D and E represent, respectively, the amount of absorbed drug in the central compartment and the amount of drug eliminated from the central compartment. k_1, k_2, k_3, and k_4 represent the rate constants for dissolution, decomposition, absorption, and excretion, respectively.

The amount of drug in each compartment can be calculated with the following equations by Laplace transforms.

$$A = A_0 \cdot e^{-\mathrm{k}_1 t} \tag{6}$$

$$B = \frac{A_0 \cdot \mathrm{k}_1}{\mathrm{k}_1 - (\mathrm{k}_2 + \mathrm{k}_3)} \cdot \left(e^{(\mathrm{k}_2 + \mathrm{k}_3) \cdot t} - e^{-\mathrm{k}_1 t}\right) \tag{7}$$

$$C = \frac{A_0}{\mathrm{k}_1 - (\mathrm{k}_2 + \mathrm{k}_3)} \cdot \left(\mathrm{k}_2 \cdot e^{-\mathrm{k}_1 \cdot t} - \frac{\mathrm{k}_1 \cdot \mathrm{k}_2}{\mathrm{k}_2 + \mathrm{k}_3} \cdot e^{-(\mathrm{k}_2 + \mathrm{k}_3) \cdot t} + \frac{\mathrm{k}_1 \cdot \mathrm{k}_2}{\mathrm{k}_2 + \mathrm{k}_3} - \mathrm{k}_2\right) \tag{8}$$

$$D = \frac{A_0 \cdot \mathrm{k}_1 \cdot \mathrm{k}_3}{\mathrm{k}_1 - (\mathrm{k}_2 - \mathrm{k}_3)} \cdot \left(\frac{1}{\mathrm{k}_1 - \mathrm{k}_4} \cdot e^{-\mathrm{k}_1 \cdot t} - \frac{1}{(\mathrm{k}_2 - \mathrm{k}_3) - \mathrm{k}_4} e^{-(\mathrm{k}_2 - \mathrm{k}_3) \cdot t} + \left(\frac{1}{(\mathrm{k}_2 + \mathrm{k}_3) - \mathrm{k}_4} - \frac{1}{\mathrm{k}_1 - \mathrm{k}_4} \right) \cdot e^{-\mathrm{k}_4 \cdot t} \right) \tag{9}$$

$$E = \frac{A_0 \cdot \mathrm{k}_1 \cdot \mathrm{k}_3 \cdot \mathrm{k}_4}{\mathrm{k}_1 - (\mathrm{k}_2 + \mathrm{k}_3)} \cdot \left(\frac{1}{(\mathrm{k}_2 + \mathrm{k}_3) \cdot ((\mathrm{k}_2 + \mathrm{k}_3) - \mathrm{k}_4)} e^{-(\mathrm{k}_2 + \mathrm{k}_3) \cdot t} - \frac{1}{\mathrm{k}_1 \cdot (\mathrm{k}_1 - \mathrm{k}_4)} \cdot e^{-\mathrm{k}_1 \cdot t} - \frac{1}{\mathrm{k}_4 \cdot ((\mathrm{k}_2 + \mathrm{k}_3) - \mathrm{k}_4) \cdot (\mathrm{k}_1 - \mathrm{k}_4)} \cdot e^{-\mathrm{k}_4 \cdot t} - \frac{1}{\mathrm{k}_1 \cdot \mathrm{k}_4} + \frac{1}{(\mathrm{k}_2 + \mathrm{k}_3) \cdot \mathrm{k}_4} \right) \tag{10}$$

where A_0 is the initial value of A and is equivalent to the initial dose. Integrating Eq. (8) from $t = 0$ to infinite time, the total amount of decomposed drug in the gastrointestinal tract, C_m is given by

$$C_m = \frac{A_0 \cdot \mathrm{k}_2}{\mathrm{k}_2 + \mathrm{k}_3} \tag{11}$$

Therefore, F_S, the fraction of the dose absorbed, can be obtained as

$$F_S = \frac{A_0 - C_m}{A_0} \tag{12}$$

This equation can be rewritten as follows:

$$F_S = \frac{\mathrm{k}_3}{\mathrm{k}_2 + \mathrm{k}_3} \tag{13}$$

As can be seen from Eq. (13), F_S increases with decreasing k_2 and increasing k_3.

If D_t, E_t, V, and F_U are defined as the drug concentration in serum at time t, the cumulative drug in urine from administration to time t, the apparent distribution volume, and the fraction of drug excreted in urine, respectively. D_t and E_t are given by

$$D_t = \frac{A_0 \cdot \mathrm{k}_1 \cdot \mathrm{k}_3}{(\mathrm{k}_1 - (\mathrm{k}_2 + \mathrm{k}_3)) \cdot V} \cdot \left(\frac{1}{(\mathrm{k}_1 - \mathrm{k}_4)} \cdot e^{-\mathrm{k}_1 \cdot t} - \frac{1}{((\mathrm{k}_2 + \mathrm{k}_3) - \mathrm{k}_4)} \cdot e^{-(\mathrm{k}_2 + \mathrm{k}_3) \cdot t} + \left(\frac{1}{((\mathrm{k}_2 + \mathrm{k}_3) - \mathrm{k}_4)} - \frac{1}{(\mathrm{k}_1 \cdot \mathrm{k}_4)} \right) \cdot e^{-\mathrm{k}_4 \cdot t} \right) \tag{14}$$

$$E_t = \frac{A_0 \cdot \mathrm{k}_1 \cdot \mathrm{k}_3 \cdot \mathrm{k}_4 \cdot F_U}{\mathrm{k}_1 - (\mathrm{k}_2 + \mathrm{k}_3)} \cdot \left(\frac{1}{(\mathrm{k}_2 + \mathrm{k}_3) \cdot ((\mathrm{k}_2 + \mathrm{k}_3) - \mathrm{k}_4)} \cdot e^{-(\mathrm{k}_2 + \mathrm{k}_3) \cdot t} - \frac{1}{\mathrm{k}_1 \cdot (\mathrm{k}_1 - \mathrm{k}_4)} \cdot e^{-\mathrm{k}_1 \cdot t} - \frac{\mathrm{k}_1 - (\mathrm{k}_2 + \mathrm{k}_3)}{\mathrm{k}_4 \cdot ((\mathrm{k}_2 + \mathrm{k}_3) - \mathrm{k}_4) \cdot (\mathrm{k}_1 - \mathrm{k}_4)} \cdot e^{-\mathrm{k}_4 \cdot t} - \frac{1}{\mathrm{k}_1 \cdot \mathrm{k}_4} + \frac{1}{(\mathrm{k}_2 + \mathrm{k}_3) \cdot \mathrm{k}_4} \right) \tag{15}$$

Pharmacokinetic Analysis

Pharmacokinetic parameters, obtained from the model shown in Fig. 2, were calculated by simultaneously fitting the individual serum concentration–time data and urinary excretion data for CAM and EMS administration in the fasting state, with the MULTI program using nonlinear least-squares regression analysis.

Stability in the Acidic Solution

About 0.035 g of EMS was dissolved in 100 ml of water. After 10 ml of this solution was added to 50 ml of hydrochloride solutions of several pHs at 37°C, portions of the solutions were withdrawn by a pipet at regular time intervals and the residual concentrations of EMS were quantified by the HPLC method.

The stability of CAM in acidic solution was obtained from data in the literature (7).

Partition Coefficient (n-Octanol–Phosphate Buffer)

The partition coefficient of EMS between n-octanol and the phosphate buffer solution was obtained using the concentration of EMS remaining in the phosphate buffer solution at room temperature. The partition coefficient of CAM between n-octanol and the phosphate buffer solution was obtained from data in the literature (7).

Stationary Disk Method for Dissolution Study

The stationary disk method was used to determine the dissolution rate constant per unit area. A drug disk with a diameter of 2 cm (surface area = 3.14 cm^2) was placed in the bottom of the vessel in a JP dissolution test (paddle method) apparatus, and the paddle was rotated at 100 rpm in pH 4.0 phosphate buffer solution. At appropriate intervals, 2 ml of sample solution was withdrawn and diluted with 1 ml of the pH 7.2 phosphate buffer solution. The drug concentration was determined by the HPLC method.

RESULTS AND DISCUSSION

Determination of Pharmacokinetic Parameters

Figure 3 shows serum concentrations and urinary excretions of CAM and EMS following administration of 200 mg to healthy volunteers (6). To clarify the difference in kinetic behavior between CAM and EMS, pharmacokinetic parameters were estimated by nonlinear least-squares regression analysis using serum concentration-time data and urinary excretion data. The pharmacokinetic parameters obtained are listed in Table 1.

The k_1 of CAM was about 50% greater than that of EMS. In contrast, the k_2 of EMS was about 10 times greater than that of CAM. The k_3 of CAM was about 7 times greater than that of EMS. The k_4 of EMS was about 3 times greater than that of CAM. To determine the time-course changes in the amounts of CAM and EMS in each compartment in Fig. 2, the pharmacokinetic parameters obtained were substituted into Eqs. (6) through (9). Figure 4 shows simulations of CAM- and EMS-time profiles in the gastrointestinal tract. For compartment B in the gastrointestinal tract, the amount of EMS was larger than that of CAM. The amount of the drug in compartment B is attributed to the balance of k_1, k_2, and k_3. EMS continues to exist in acidic conditions for long periods of time, since the k_3 is small. Moreover, EMS is readily degraded, since the k_2 of EMS is great. As a result, the amount of CAM was smaller than that of EMS in compartment C in the gastrointestinal tract. This result appeared to be due to the differences in absorption and degradation of CAM and EMS. Next, the relationship between the pharmacokinetic parameters obtained from the model for CAM and EMS, and the chemical and physicochemical properties were investigated.

Relationship Between the k_2 and Stability in the Acidic Solution

Table 2 shows the results of examination of the stability of CAM and EMS in acidic solution. CAM was about 300-fold more stable below pH 4.0 than EMS. In contrast, the in vivo k_2 obtained from the pharmacokinetic model for CAM was 10-fold more stable than that for EMS, as shown in Table 1. These findings suggest

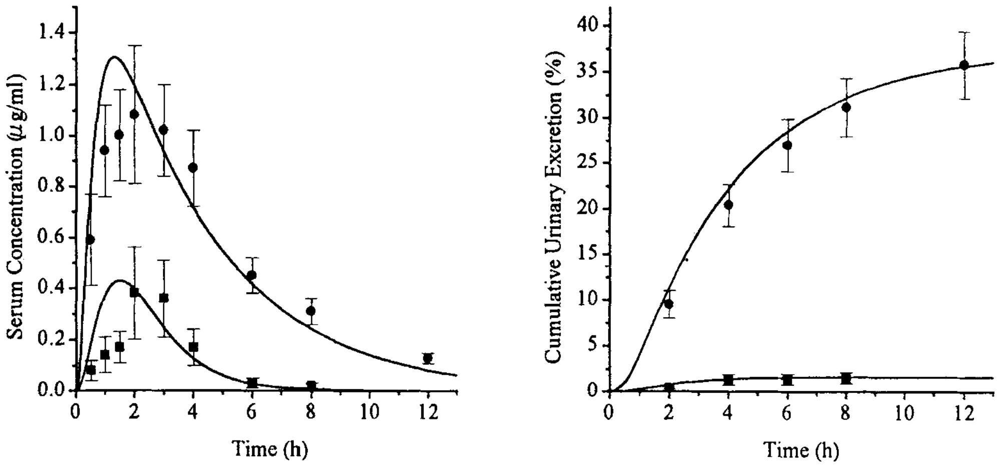

Figure 3. Serum concentration and urinary excretion for CAM and EMS following oral administration to healthy volunteers. Values are means ± SE. The solid lines were obtained by nonlinear least-squares regression analysis. Key: ●, CAM; ■, EMS.

Table 1

Pharmacokinetic Parameters for Single Oral Administration of CAM and EMS to Healthy Volunteers

Drug	k_1 (hr^{-1})	k_2 (hr^{-1})	k_3 (hr^{-1})	k_4 (hr^{-1})	$1/V$ ($liters^{-1}$)	F_U (%)
CAM	2.35 ± 1.64	0.10 ± 0.13	4.76 ± 2.69	0.27 ± 0.04	0.009 ± 0.003	38.2 ± 10.2
EMS	1.68 ± 1.27	1.02 ± 1.65	0.68 ± 0.29	0.82 ± 0.05	0.013 ± 0.006	4.1 ± 1.5

Results of CAM and EMS are expressed as the mean ± SD of 6 and 4, respectively.

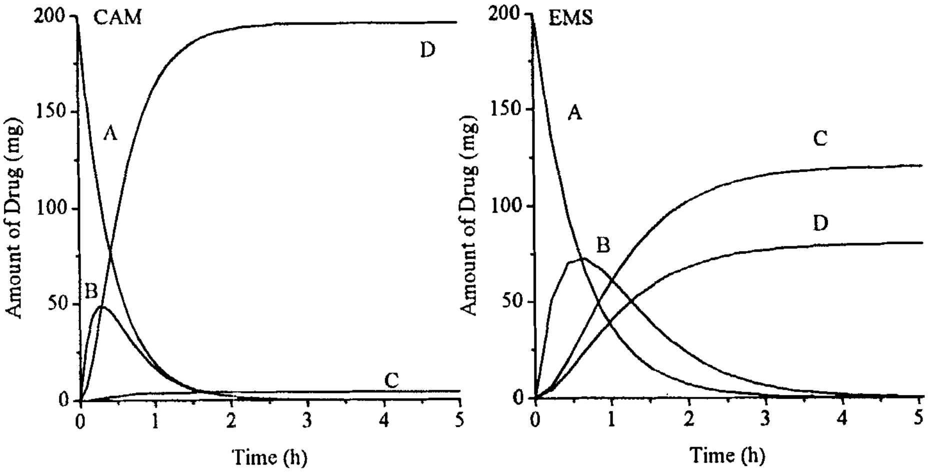

Figure 4. Simulation curves of CAM- and EMS-time profiles in gastrointestinal compartment Key: A, B, and C are the amounts of solid drug, dissolved drug, and decomposed drug, respectively. D is the amount of absorbed drug in central compartment.

Table 2

The Decomposition Rate Constants and Half-Lives for Decomposition of EMS and CAM in Acidic Solutions

	EMS		CAM		
pH	K_d (hr^{-1})	$t_{½}$ (hr)	K_d (hr^{-1})	$t_{½}$ (hr)	K
2.61	25.2	0.028	0.102	6.715	247
3.09	8.64	0.080	0.029	23.333	298
3.43	4.14	0.168	0.012	56.618	345
3.62	2.52	0.273	7.2×10^{-3}	92.400	350
3.96	1.08	0.642	3.1×10^{-3}	224.708	348
4.38	0.54	1.277	1.0×10^{-3}	671.512	554
5.92	0.06	14.80	1.9×10^{-5}	36783.440	3158

K is the ratio of the decomposition rate constant of CAM to that of EMS.

that one reason for the excellent absorption of CAM may be its stability in acidic solution, since, as can be seen from Eq. (13), the fraction of the dose absorbed increased with decreasing k_2.

However, the ratio (K) of the decomposition rate constant of CAM to that of EMS obtained in vivo was much greater than that obtained in vitro.

In order to clarify the differences between in vivo and in vitro results, we performed the stability test under conditions similar to those of gastric fluid. The pH and volume of gastric fluid are said to vary from pH 1.2 to 7.6 (8) and from 25 to 50 ml (9), respectively. Therefore, the 200 mg of CAM or EMS was dispersed in 50 ml of the solution adjusted by 0.1 N HC1 and shaken for 1 hr. The amounts of the drug remaining and the pH of the solutions were determined, and the results are shown in Table 3.

The pH of each solution was increased after 1 hr. The increase in pH may have been be due to the buffer effect of CAM and EMS. These findings suggest that the in vivo k_2 of both drugs in the gastrointestinal tract, especially that of EMS, should be smaller than the in vitro decomposition rate constant (k_{dec}) in the acidic buffer solution.

The logarithms of in vitro k_{dec} for CAM and EMS versus pH are plotted in Fig. 5. The relationship between log k_{dec} and pH was linear, and the following equations for CAM (7) and EMS were obtained.

$$\text{CAM:} \quad \log (k_{dec}) = -1.13\text{pH} - 1.59 \qquad r = 0.999 \tag{16}$$

$$\text{EMS:} \quad \log (k_{dec}) = -0.96\text{pH} + 3.91 \qquad r = 0.998 \tag{17}$$

The in vivo k_2 values obtained from the pharmacokinetic model for CAM and EMS were equivalent to in vitro k_{dec} at about pH 2.5 and about pH 4.0 obtained using Eqs. (16) and (17), respectively. This finding suggests that CAM and EMS decomposed in the stomach.

Relationship Between k_3 and Partition Coefficient

Dressman et al. (10) reported that the absorption potential, calculated using the partition coefficient for the solution at pH 6.5, appeared to correlate strongly with the fraction absorbed for orally administered compounds. Moreover, Hansh et al. (11) reported that partition coefficients were correlated with the degree of absorption and the biological effects of the drugs. As shown in Table 4, the partition coefficients for CAM below pH 6.5 were higher than those for EMS. The ratio of the partition coefficient at pH 6.5 for CAM to that for EMS was equivalent to the ratio of the absorption rate constant obtained using the pharmacokinetic model. These findings suggest that another reason for the excellent absorption of CAM may be attributable to the superiority of the partition coefficient for CAM in the solution at pH 6.5 compared to that for EMS, since the fraction of the dose absorbed was increased by increasing k_3, as shown in Eq. (13).

From these results, the main determining factor of the absorption ratio may be the balance of the partition coefficient to the stability in acidic solution.

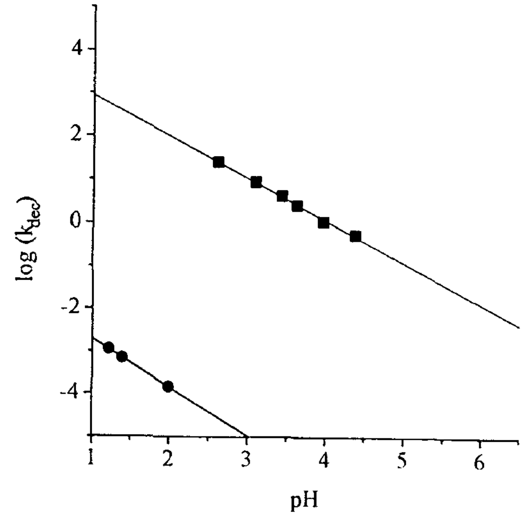

Figure 5. The relationship between pH and log (k_{dec}). Key: ●, CAM; ■, EMS.

Table 3

Stability and pH of CAM and EMS in Acidic Solutions (Hydrochloric Acid)

	After 1 hr			
	CAM		EMS	
Initial pH	pH	Remaining (%)	pH	Remaining (%)
2.5	6.68	98.8	3.21	6.8
3.0	7.03	93.8	7.28	73.8
3.5	7.25	97.6	7.61	71.2
4.25	7.57	95.2	8.30	91.6
4.5	7.65	98.5	8.66	92.0

Table 4

Partition Coefficient (n-Octanol/Phosphate Buffer Solution) of CAM and EMS

	Partition Coefficient		
pH	CAM	EMS	K
4.0	4.89	2.13	2.3
6.0	7.19	2.05	3.5
6.5	17.5	3.11	5.6
8.0	48.0	59.6	0.8

K is the ratio of the partition coefficient of CAM to that of EMS.

Relationship Between k_1 and Dissolution Rate Constant

The dissolution rate constants per unit area for CAM and EMS were determined by the stationary disk method in the buffer solution at pH 4.0. The concentration of EMS was not determined, since EMS was rapidly degraded in the buffer solution below pH 3.5. Under the sink condition, if diffusion is the rate-determining step for dissolution, dissolution on a constant surface should obey zero-order kinetics. Also, if the decomposition of CAM and EMS obeys first-order kinetics in acidic solution, the model can be illustrated as shown in Fig. 6, where drug is dissolved from a stationary disk with a constant surface in acidic solution, and the drug solution simultaneously undergoes decomposition. For the model in Fig. 6, the differential equation employed for the calculation was as follows:

$$\frac{dM}{dt} = k_0 - k_{dec}M \tag{18}$$

where M represents the amount of drug solution in the dissolution medium, and k_0 and k_{dec} represent the dissolution rate constant per unit area and the in vitro decomposition rate constant, respectively.

The amount of drug can be calculated using the following equation:

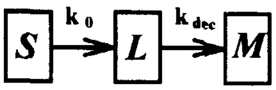

Figure 6. Dissolution model including dissolution and decomposition in acidic solution. Key: S is amount of solid drug with constant surface; L is dissolved drug in dissolution medium; M is amount of drug in dissolution medium.

$$M = \frac{k_0}{k_{dec}}(1 - e^{-k_{dec}\cdot t}) \tag{19}$$

M_t and V_m are the concentration of drug at time t and the volume of dissolution medium. Therefore,

$$M_t = M/V_m \tag{20}$$

M_t is given by:

$$M_t = \frac{k_0}{k_{dec}\cdot V_m}(1 - e^{-k_{dec}\cdot t}) \tag{21}$$

Figure 7 shows the dissolution profiles for CAM and EMS in acidic solution. The dissolution rate constants per unit area (k_0) were then calculated from the dissolution profiles in acidic solution for CAM and EMS by substituting the in vitro k_{dec} value into k_{dec} in Eq. (21), with the MULTI program (12) using nonlinear least-squares regression analysis. The k_0 (1.02×10^{-3} min^{-1}/cm^2) for CAM was about 3 times greater than that (0.35×10^{-3} min^{-1}/cm^2) for EMS.

The ratio of the dissolution rate constant per unit area (k_0) in the buffer solution at pH 4.0 for CAM to that for EMS was equivalent to that for the dissolution rate constant (k_1) obtained using the pharmacokinetic model. This finding suggests that the in vivo k_1 was correlated with the k_0 in the buffer solution.

Furthermore, the effect of the in vivo dissolution rate on the serum concentration–time profiles was estimated over the range from 0.78 to 7.05 hr^{-1} for CAM. The two limits of this range were one-third and 3 times the

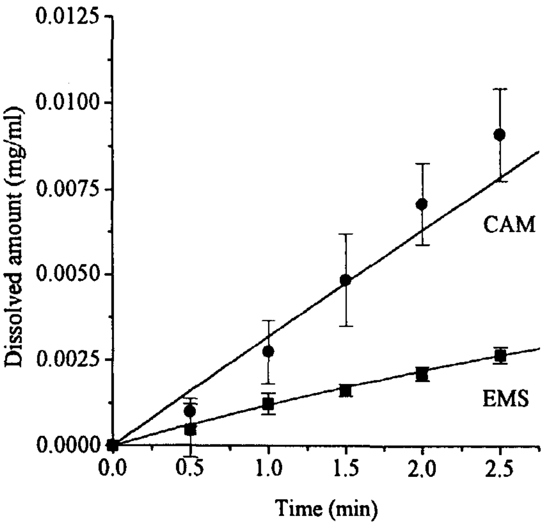

Figure 7. Dissolution profiles for CAM and EMS in acidic solution. Key: ●, CAM; ■, EMS.

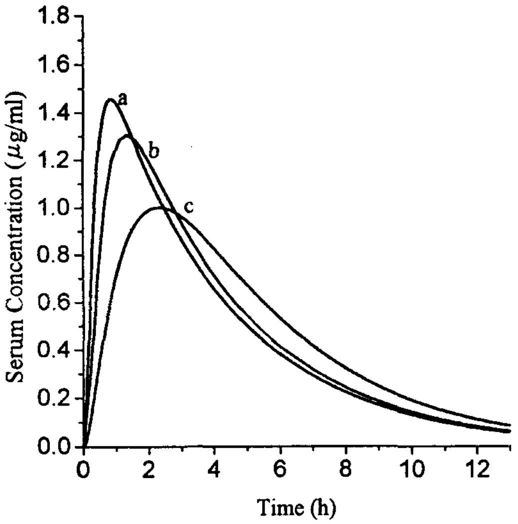

Figure 8. Effect of in vivo dissolution rate constant (k_1) on the serum concentration-time profiles for CAM. Key: a, 7.05 hr^{-1}; b, 2.35 hr^{-1}; c, 0.78 hr^{-1}.

k_1 of CAM, respectively. The results are shown in Fig. 8. The dissolution rate of the drug influenced both of the maximum serum concentration (C_{max}) and the time (T_{max}). However, the absorption ratio was not affected by the rate of dissolution.

CONCLUSIONS

The intrinsic dissolution, stability in acidic solution, and lipophilicity of CAM were superior to those of EMS. In order to clarify the differences in bioavailability between CAM and EMS, pharmacokinetic parameters including the in vivo dissolution rate constant, the in vivo decomposition rate constant, and the in vivo absorption rate constant were compared with chemical and physicochemical properties, including the dissolution rate constant per unit area, stability in acidic solution, and partition coefficient, respectively.

We found that the structural difference between EMS and CAM affected the chemical and physicochemical properties of the two drugs. Of these properties, the stability in acidic solution and the partition coefficient played the most important roles in determining the bioavailability. In particular, the absorption ratio is attributed to the balance of the rate constants of two properties.

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