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Pharmacokinetic Evaluation of Omeprazole Suspension Following Oral Administration in Rats: Effect of Neutralization of Gastric Acid

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Abstract

In order to evaluate a clinical use of omeprazole suspension, we examined the pharmacokinetics of omeprazole after oral administration in rats. Although the administration of omeprazole suspension buffered by NaHCO3 solution did not produce a significant increase in the area under the concentration-time curve (AUC) value compared with non-buffered group, the administration of NaHCO3 buffer immediately after dosing of omeprazole suspension buffered by NaHCO3 caused a significant increase in the AUC value. These results suggest that the NaHCO3 treatment following the administration of omeprazole buffered suspension effectively decreased the degradation of the compound by gastric acid. Therefore, the successive administration of NaHCO3 solution after the omeprazole dosing seems to be a simple and useful method for the administration to patients who cannot receive tablets.

KEYWORDS: omeprazole, suspension, pharmacokinetics, rats

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Brief Note

Pharmacokinetic Evaluation of Omeprazole Suspension Following Oral Administration in Rats: Effect of Neutralization of Gastric Acid

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In order to evaluate a clinical use of omeprazole suspension, we examined the pharmacokinetics of omeprazole after oral administration in rats. Although the administration of omeprazole suspension buffered by $NaHCO_3$ solution did not produce a significant increase in the area under the concentration-time curve (AUC) value compared with non-buffered group, the administration of $NaHCO_3$ buffer immediately after dosing of omeprazole suspension buffered by $NaHCO_3$ caused a significant increase in the AUC value. These results suggest that the $NaHCO_3$ treatment following the administration of omeprazole buffered suspension effectively decreased the degradation of the compound by gastric acid. Therefore, the successive administration of $NaHCO_3$ solution after the omeprazole dosing seems to be a simple and useful method for the administration to patients who cannot receive tablets.

Key words: omeprazole, suspension, pharmacokinetics, rats

Omeprazole is a substituted benzimidazole that effectively suppresses gastric acid secretion by inhibiting H^+/K^+-ATPase in the parietal cell (1, 2). This inhibition is long-lasting, although omeprazole is rapidly eliminated from plasma (3). Thus, the time-dependent antisecretory effect of omeprazole is not correlated with the plasma concentration (3). However, the area under the plasma concentration-time curve (AUC) has been reported to be correlated to the degree of the inhibition (4).

Since omeprazole is unstable in acidic conditions (5), the compound is administered orally to patients as an enteric-coated tablet that is the only formulation on the market in Japan. For patients who have difficulty with tablets, omeprazole is given in the powder or suppository form. Recently, we reported that, in rats, omeprazole administered intrarectally undergoes metabolism by gut flora, and that about 60 % of the dose is degraded before absorption from the intestinal tract can occur (6). Thus, the powder or suspension form of omeprazole is preferred for these patients. However, the pharmacokinetics of the absorption of omeprazole suspension has not been systematically investigated. In the present study, therefore, we examine the pharmacokinetics of omeprazole suspension after oral administration in rats.

Male Wistar rats (Charles River Lab., Atsugi, Japan) each weighing 200-320 g were housed in the experimental animal center of Okayama University Medical School at a controlled ambient temperature of 22 ± 1°C with approximately 60 % relative humidity and with a 12-h light/12-h dark cycle (lights on at 07:00). Animals were allowed free access to food and water, except for a 12-h fast before experiments. Omeprazole (donated by Fujisawa-Astra Ltd. Osaka, Japan) was suspended in 0.5 % methylcellulose, and administered orally at a dose of 20 mg/kg. The animals were divided into six groups as follows: (a) non-buffered group receiving omeprazole suspension which was not buffered with $NaHCO_3$; (b) 0.2 % $NaHCO_3$ group receiving omeprazole suspension

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Table I Method for oral administration of omeprazole suspension in rats

Groups	Omeprazole suspension[a]		Treatment
	Buffering	pH Adjustment[b]	
Non-buffered	Not contained	Not adjusted	—
0.2% $NaHCO_3$	0.2% $NaHCO_3$	pH 9	—
2.5% $NaHCO_3$	2.5% $NaHCO_3$	pH 9	
H_2O post-dosed	2.5% $NaHCO_3$	pH 9	Oral administration of H_2O (3 ml/kg) immediately after omeprazole dosing
$NaHCO_3$ pre-dosed	2.5% $NaHCO_3$	pH 9	Oral administration of 2.5% $NaHCO_3$ (3 ml/kg) 5 min before omeprazole dosing
$NaHCO_3$ post-dosed	2.5% $NaHCO_3$	pH 9	Oral administration of 2.5% $NaHCO_3$ (3 ml/kg) immediately after omeprazole dosing

a: Omeprazole was suspended in 0.5% methylcellulose and administered at 20 mg/kg in a volume of 1 ml/kg.
b: pH of omeprazole suspension was adjusted by 1 N NaOH.

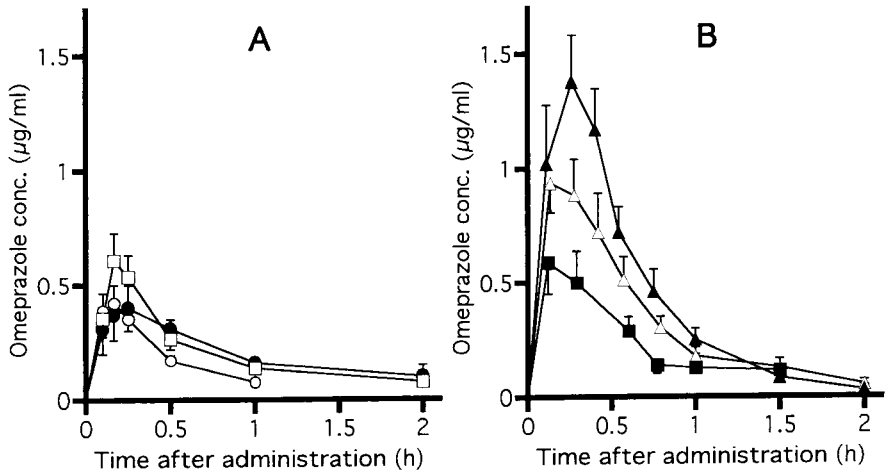

Fig. 1 Time course of plasma omeprazole concentration in rats. Omeprazole suspension was administered orally at a dose of 20 mg/kg. Each point indicates the mean ± SEM. **A**: (○), non-buffered group; (●), 0.2% $NaHCO_3$ group; (□), 2.5% $NaHCO_3$ group. **B**: (■), H_2O post-dosed group; (△), $NaHCO_3$ pre-dosed group; (▲), $NaHCO_3$ post-dosed group.

containing 0.2 % $NaHCO_3$ (pH 9); (c) 2.5 % $NaHCO_3$ group receiving omeprazole suspension containing 2.5 % $NaHCO_3$ (pH 9); (d) H_2O post-dosed group receiving H_2O (3 ml/kg) immediately after the administration of omeprazole suspension containing 2.5 % $NaHCO_3$ (pH 9); (e) $NaHCO_3$ pre-dosed group receiving 2.5 % $NaHCO_3$ solution (3 ml/kg) 5 min before the administration of omeprazole suspension containing 2.5 % $NaHCO_3$ (pH 9); (f) $NaHCO_3$ post-dosed group receiving 2.5 % $NaHCO_3$ solution (3 ml/kg) immediately after the administration of omeprazole suspension containing 2.5 % $NaHCO_3$ (pH 9) (Table 1). At various times after the administration, blood samples of 60 μl were collected from the tail vein, and the plasma concentrations of omeprazole were determined by high performance liquid chromatography, as described previously (7).

Pharmacokinetic parameters were obtained from the plasma concentration-time data of omeprazole for each animal, using a personal computer program for nonlinear least squares regression analysis (MULTI, Nankodo, Tokyo, Japan) (8). The maximum plasma concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were estimated from these pharmacokinetic parameters. The AUC values were calculated for 0–3 h period by the trapezoidal method. The mean residence time (MRT) was calculated by the model-independent moment

Table 2 Pharmacokinetic parameters of omeprazole suspension after oral administration in rats

Parameter	non-buffered (n = 5)	0.2% $NaHCO_3$ (n = 5)	2.5% $NaHCO_3$ (n = 5)	H_2O post-dosed (n = 5)	$NaHCO_3$ pre-dosed (n = 5)	$NaHCO_3$ post-dosed (n = 5)
C_{max} (μg/ml)	0.40 ± 0.06	0.42 ± 0.11	0.56 ± 0.10	0.61 ± 0.18	1.18 ± 0.20[a]	1.53 ± 0.26[b,d,f]
T_{max} (h)	0.16 ± 0.02	0.24 ± 0.04	0.19 ± 0.02	0.14 ± 0.02	0.12 ± 0.03[c]	0.21 ± 0.02
AUC (μg·h/ml)	0.24 ± 0.02	0.40 ± 0.09	0.48 ± 0.08	0.46 ± 0.09	0.70 ± 0.09[a]	0.87 ± 0.14[b,c,e]
MRT	0.47 ± 0.03	0.75 ± 0.08[b]	0.86 ± 0.10[a,e]	0.51 ± 0.09	0.68 ± 0.07[a]	0.52 ± 0.03[c]

Omeprazole suspension was administered orally at a dose of 20 mg/kg. Each value represents the mean ± SEM.
C_{max}: The maximum plasma concentration; T_{max}: The time to reach the maximum concentration; AUC: The area under the concentration-time curve; MRT: mean resistance time.
[a] $P < 0.05$ *vs.* non-buffered group. [b] $P < 0.01$ *vs.* non-buffered group. [c] $P < 0.05$ *vs.* 2.5% $NaHCO_3$ group.
[d] $P < 0.01$ *vs.* 2.5% $NaHCO_3$ group. [e] $P < 0.05$ *vs.* H_2O post-dosed group. [f] $P < 0.01$ *vs.* H_2O post-dosed group.

analysis using a personal computer program (9). The results were statistically evaluated by analysis of variance followed by Dunnett's test.

Figure 1 shows the time-course of plasma omeprazole concentration after oral administration in each group. The plasma concentration of omeprazole in the non-buffered group increased rapidly, reached a maximum at about 10 min, and became undetectable by 1 h after the administration. Similar rapid increases in plasma concentrations were obtained in the other groups with the maximum being reached at about 7–14 min; however, plasma concentrations were detectable for up to 2 h. Table 2 summarizes the pharmacokinetic parameters of omeprazole suspension after oral administration. The AUC values in the 0.2 % $NaHCO_3$ and 2.5 % $NaHCO_3$ groups were higher than in the non-buffered group, but the difference was not statistically significant. The MRT values in the 0.2 % $NaHCO_3$ and 2.5 % $NaHCO_3$ groups were significantly higher than in the non-buffered group ($P < 0.01$ and $P < 0.05$, respectively). The H_2O post-dosed group had an AUC value similar to the 2.5 % $NaHCO_3$ group but a significantly decreased MRT value ($P < 0.05$). In the $NaHCO_3$ pre-dosed group, C_{max}, AUC and MRT values were significantly higher than in the non-buffered group ($P < 0.05$), whereas T_{max} value in the $NaHCO_3$ pre-dosed group was significantly lower than in the 2.5 % $NaHCO_3$ group ($P < 0.05$). The $NaHCO_3$ post-dosed group showed significant increases in C_{max} and AUC values compared with the non-buffered group ($P < 0.01$), H_2O post-dosed group ($P < 0.01$ and 0.05, respectively) and the 2.5 % $NaHCO_3$ group ($P < 0.01$ and $P < 0.05$, respectively). The MRT value in the $NaHCO_3$ post-dosed group was significantly lower than in the 2.5 % $NaHCO_3$ group ($P < 0.05$).

Omeprazole is a potential inhibitor of gastric acid secretion (10), and is effective for intractable peptic ulcer that fails to respond to histamine H_2 receptor antagonists (11). Recently, proton pump inhibitors (PPI) including omeprazole have been used in combination with antibiotics to try to eradicate *Helicobacter pylori* (12, 13), which is involved in the pathogenesis of gastritis and peptic ulcer (14). Thus, PPI will probably be used more frequently, and so it seems that an occasion increases for administrating the PPI to patients who cannot receive tablets.

In the present study, we examined the clinical use of omeprazole suspension. In the first place, the effect of $NaHCO_3$ buffer on the bioavailability of omeprazole suspension was investigated. The AUC values in the 0.2 and 2.5 % $NaHCO_3$ groups were 1.7 and 2 times higher than in the non-buffered group, but the difference was not statistically significant. This suggests that the addition of $NaHCO_3$ did not sufficiently prevent degradation of omeprazole in the stomach. The MRT values in the $NaHCO_3$-buffered groups were significantly higher than in the non-buffered group. One explanation is that omeprazole in the non-buffered group was eliminated from plasma within 1 h due to rapid degradation in the stomach, whereas the addition of $NaHCO_3$ buffer decreased degradation of omeprazole and prolonged the MRT value.

We further examined the effect of administration of $NaHCO_3$ buffer before or after dosing of omeprazole buffered suspension. The AUC values in the $NaHCO_3$ pre-dosed and $NaHCO_3$ post-dosed groups were 1.5 and 1.8 times higher than in the 2.5 % $NaHCO_3$ group, respectively, while the AUC value in the H_2O post-dosed group was similar to that in the 2.5 % $NaHCO_3$ group.

These results indicate that neutralization of gastric acid is essential for improvement of the bioavailability of omeprazole, although it is still possible that the $NaHCO_3$ treatment increases absorption of omeprazole from the gastrointestinal tract. It appears that the $NaHCO_3$ pretreatment effectively decreased the degradation of omeprazole in the stomach, although partial degradation still occurs. However, the administration of $NaHCO_3$ buffer after omeprazole dosing accelerates gastric transit of the compound, thereby effectively reducing the degradation by gastric acid. Thus, post-treatment with the $NaHCO_3$ buffer is useful when the omeprazole suspension is administered to patients who cannot receive tablets.

In conclusion, the present study showed that the administration of $NaHCO_3$ solution following the dosing of omeprazole in buffered suspension attenuates effectively degradation of omeprazole in the stomach and causes an increase in systemic availability of the compound. The treatment of $NaHCO_3$ solution after omeprazole administration is a simple and useful method for administrating to patients who cannot receive tablets.

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