Influence of Cimetidine on the Kinetics of Diazepam and Lorazepam

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The influence of cimetidine on the kinetics of two benzodiazepines, diazepam and lorazepam, after a single oral dose (diazepam 5 mg or lorazepam 2 mg) was studied in 8 healthy male Japanese volunteers using an experimental design with two Latin squares. Cimetidine coadministration, 800 mg/day, was begun 24 hr prior to the benzodiazepine dose and continued during the trial. Cimetidine significantly prolonged the elimination half-life ($P < 0.05$), increased the AUC ($P < 0.01$), and decreased the clearance of diazepam ($P < 0.01$), although it did not influence the peak plasma concentration, the time to reach peak concentration, and the volume of distribution of diazepam. However, cimetidine had a slight effect on the peak plasma concentration, the time to reach peak concentration, the elimination half-life, the AUC, the volume of distribution, and the clearance of lorazepam. The prolonged elimination half-life of diazepam with cimetidine coadministration was caused by decreased clearance of the drug. These results indicate that cimetidine influences differently the kinetics of diazepam and lorazepam due to the different metabolic characteristics of the two drugs, since lorazepam is directly biotransformed to glucuronide conjugates and diazepam is metabolized by reduction or oxidation prior to glucuronide conjugation.

Key words : diazepam, lorazepam, cimetidine, drug interaction, pharmacokinetics

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Since cimetidine, an H_2 receptor antagonist, specifically inhibits gastric acid secretion, it is now extensively used for the treatment of peptic ulcer. In treating peptic ulcer which is induced by stress, benzodiazepines are frequently coadministered with cimetidine due to the pathoetiological characteristics of the disease. However, cimetidine has been reported to impair hepatic drug metabolism and to prolong the effects of a number of coadministered drugs.¹⁾ Clearance of benzodiazepines such as diazepam,^{2,3)} desmethyldiazepam,^{4,5)} chlordiazepoxide,⁶⁾ alprazolam,⁷⁾ triazolam,⁷⁾ clobazam,⁸⁾ and nitrazepam,⁹⁾ which are metabolized by oxidation or reduction prior to glucuronide conjugation, has been reported to be decreased by coadministration of cimetidine. On the other hand, cimetidine has little effect on the clearance of oxazepam,^{4,10,11)} lorazepam,^{10,11)} temazepam,¹²⁾ which are mainly metabolized by glucuronide conjugation. Most of these experiments has been performed in the Western countries and never in Orientals such as Japanese. And most of these studies have been performed by an intravenous route of administration with benzodiazepines. Therefore, the present study was designed to evaluate the effects of cimetidine coadministration on the pharmacokinetics of diazepam and lorazepam by the intraindividual comparison after a single oral administration of diazepam or lorazepam in healthy male Japanese subjects.

Methods

The subjects were eight healthy male volunteers aged 21 to 26 years (mean $\pm$ S. D. = 23.5 $\pm$ 1.4 years). Mean body weight was 67.6 $\pm$ 7.3 kg (range : 58 to 83 kg). All subjects were extensively informed and gave written consent. Subjects were free of identifiable medical or psychiatric disease, and none had a history of

regular drug use.

Each subject ingested either diazepam or lorazepam with or without coadministration of cimetidine. The sequence of drug combination in 8 subjects was described in Tab. 1 (Experimental design using two Latin squares) and at least 3 weeks elapsed between trials. Each subject took 5 mg of diazepam (one 5-mg tablet) or 2 mg of lorazepam (two 1-mg tablets) between 08 : 15 and 08 : 30 A. M. with 180 ml of water after overnight fasting. Subjects kept fasting for 4 hr after each benzodiazepine dose, at which time they resumed their normal diet. On the day of cimetidine coadministration, subjects ingested 800 mg/day of cimetidine (Tagamet, Smith Kline & Fujisawa ; 200 mg just after each meal and just before going to bed), beginning 24 hr prior to benzodiazepine dosage and continuing during the trial. Heparinized venous blood samples were drawn into 10 ml green-stoppered Venoject 100 H tubes (Terumo Corp.) prior to the dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 33, 48 hr after dosing of both benzodiazepines and additionally obtained 57 and 72 hr after oral diazepam. Blood samples were immediately centrifuged and plasma were separated and kept frozen at -20°C until the time of assay. Total plasma concentrations of diazepam and N-desmethyldiazepam, the main metabolite of diazepam, or lorazepam were determined by electron-capture gas-liquid chromatography.^{13,14)}

Model-independent kinetic parameters of each benzodiazepine were determined. These were elimination half-life ($t_{1/2}$), peak plasma concentration (C_{max}), time to reach peak concentration (t_{max}), area under the plasma concentration-time curve from time zero to infinity ($\text{AUC}_{0-\infty}$), the volume of distribution ($V_{d_{\text{area}}}$), and the clearance (CL).

Elimination half-life was determined from the

Tab. 1 Schedule of Drug Ingestion in Each Subject

Subject	Trial			
	1st	2nd	3rd	4th
1	D	C-D	L	C-L
2	D	C-D	C-L	L
3	C-D	D	L	C-L
4	C-D	D	C-L	L
5	L	C-L	D	C-D
6	L	C-L	C-D	D
7	C-L	L	D	C-D
8	C-L	L	C-D	D

C, D, and L : cimetidine, diazepam, and lorazepam, respectively.

C-D or C-L : coadministration of cimetidine with diazepam or lorazepam, respectively.

Fig. 1 Schedule of drug ingestion and blood sampling. DZP, LZP, and CMZ : diazepam, lorazepam and cimetidine, respectively.

terminal linear segment of a semilogarithmic plot of plasma concentration versus time. $AUC_{0-\infty}$ calculation was performed according to the following equation,

$$AUC_{0-\infty} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2} (C_i + C_{i+1}) + C_n / K,$$

where C_i is the plasma drug concentration at the sampling time of t_i , K is the elimination rate constant and C_n means the plasma drug concentration at the last sampling time. The volume of distribution and the clearance were estimated by

$$V_{d \text{ area}} = \frac{D \cdot F}{K \cdot AUC_{0-\infty}}, \text{ and } CL = \frac{D \cdot F}{AUC_{0-\infty}},$$

where D is the dose administered and F is the extent of absorption of the drug.

Statistical evaluation of the data was per-

formed by the Student's paired t -test and the Wilcoxon matched-pairs signed-ranks test (two-tailed).

Results

The results were summarized in Tab. 2 and Figs. 2 and 3. Cimetidine did not influence on the peak plasma concentration, the time to reach peak concentration, the elimination half-life, the area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$), the volume of distribution, and the clearance of lorazepam (Tab. 2 and Fig. 3). Cimetidine had no significant effect on the peak plasma concentration, the time to reach peak concentration, and the volume of distribution of diazepam (Tab. 2 and Fig. 2). However, the elimination half-life of diazepam was significantly prolonged by coadministration of cimetidine ($P < 0.05$). Cimetidine significantly increased $AUC_{0-\infty}$ and significantly decreased the clearance of diazepam (both; $P < 0.01$) (Tab. 2).

Discussion

In the present study, it was demonstrated in Japanese men that cimetidine had significant effect on the diazepam kinetics, prolonging $t_{1/2}$ ($P < 0.05$), increasing $AUC_{0-\infty}$ ($P < 0.01$), and decreasing CL ($P < 0.01$) but had little effect on lorazepam kinetics. These findings are consistent with several recent reports published in the Western countries.^{2-4, 10, 11)}

Three half-lives are ideally necessary for the duration of blood sampling to calculate the half-life of a drug accurately. In the present study, the durations of blood sampling were approximately 1.5 half-lives for diazepam and 3 half-lives for lorazepam when ingested without cimetidine. Elimination half-life of diazepam in young Japanese has been demonstrated to be relatively long compared with that in European.¹⁵⁾ There-

Tab. 2 Influence of Cimetidine on the Kinetics of Diazepam and Lorazepam

	Diazepam		Lorazepam	
	with C	Control	with C	Control
Peak plasma concentration (ng/ml)	243.8±103.0	211.0±94.6	27.1±6.5	26.1±7.3
Time of peak (hr after dose)	0.56±0.18	0.69±0.26	1.75±1.16	1.75±0.71
Elimination half-life (hr)	77.6±26.4*	49.1±17.2	18.3±3.8	15.6±8.1
AUC _{0-∞} (μg·hr/ml)	7.03±2.51**	4.90±1.64	0.48±0.16	0.40±0.11
Vd _{area} (l/kg)	1.24±0.37	1.08±0.22	1.62±0.45	1.90±1.14
CL (ml/hr/kg)	12.0±4.6**	16.9±5.9	66.4±16.2	81.6±34.0

Values shown are means±standard deviations.

C : Cimetidine; AUC_{0-∞} : area under the plasma concentration-time curve from 0 to infinity after dosing.

Vd_{area} and CL : Volume of distribution and clearance of the drug. On Vd_{area} or CL estimation, F was taken as 1.0.

* : P<0.05; ** : P<0.01 when compared between with cimetidine and control by paired t-test.

Fig. 2 Effect of cimetidine coadministration on the plasma diazepam and N-desmethyldiazepam levels following a single oral administration of 5 mg diazepam. Each point is a mean value. ●—● and ■—■ : diazepam and N-desmethyldiazepam without cimetidine; ○—○ and □—□ : diazepam and N-desmethyldiazepam with cimetidine, respectively.

Fig. 3 Effect of cimetidine coadministration on plasma lorazepam levels following a single oral administration of 2 mg lorazepam. Each point is a mean value. ▲—▲ : lorazepam without cimetidine; △—△ : lorazepam with cimetidine.

fore, the duration of blood sampling for diazepam, especially in the case of cimetidine coadministration, might not be sufficiently long enough to get the accurate half-life, although it is enough for lorazepam. However, the estimated AUC_{0-72h} values were $3.52 \pm 0.97 \mu\text{g} \cdot \text{hr/ml}$ (mean ± S. D.)

for diazepam and $0.39 \pm 0.09 \mu\text{g} \cdot \text{hr/ml}$ for lorazepam in the case of cimetidine coadministration. They were $3.24 \pm 0.63 \mu\text{g} \cdot \text{hr/ml}$ for diazepam and $0.33 \pm 0.11 \mu\text{g} \cdot \text{hr/ml}$ for lorazepam when administered without cimetidine. These AUC_{0-72h} values correspond to $52.9 \pm 13.4\%$ of

the $AUC_{0-\infty}$ value for diazepam and $81.8 \pm 7.2\%$ for lorazepam in the condition of cimetidine coadministration, and $69.3 \pm 14.0\%$ for diazepam and $82.2 \pm 9.7\%$ for lorazepam when administered without cimetidine. Therefore, a substantial error could not be produced to determine the $AUC_{0-\infty}$ values as well as the elimination half-lives of these drugs in this study.

No difference was found in the estimated $V_{d_{area}}$ of diazepam between two experimental conditions as shown Tab. 2, assuming that F of diazepam with cimetidine was equivalent to that of diazepam without cimetidine. On the other hand, the CL of diazepam with cimetidine was significantly decreased as compared to that of diazepam without cimetidine. Therefore, the cimetidine-induced prolongation of the $t_{1/2}$ of diazepam in this study is strongly suggested to be caused by the reduction in CL of the drug. These results in this study were consistent with the previous report that the volume of distribution of

diazepam remains unchanged but the clearance is significantly reduced and the terminal half-life is significantly prolonged by the coadministration of cimetidine.¹⁾

Diazepam is mainly metabolized by the microsomal mixed function oxidases in the liver. In humans, the main pathway of diazepam biotransformation is *N*-desmethylation, yielding desmethyldiazepam. *N*-desmethyldiazepam is then oxidized at 3-position to convert oxazepam^{16,17)} (Fig. 4). Although oxazepam is eliminated almost entirely as glucuronide conjugates, it is partly biotransformed to several metabolites, such as quinazoline derivatives, hydroxydized derivative, and so on in the liver¹⁸⁾ (Fig. 4). A large portion (approximately 75% of administered dose) of lorazepam is conjugated with glucuronic acid and the glucuronide conjugate is rapidly excreted into urine, as in the case of oxazepam¹⁹⁾ (Fig. 4). However, a small portion of lorazepam is metabolized by hepatic oxidation

Fig. 4 Metabolic pathways of diazepam and lorazepam in humans. Larger arrows represent main metabolic pathways.

process and similar biotransformed derivatives are identified as in the case of oxazepam¹⁹⁾ (Fig. 4). Although cimetidine had little effect on the kinetics of lorazepam in this study as in other reports,^{10,11)} the minor change of lorazepam disposition induced by cimetidine in this study might be explained due to the difference of impairing hepatic drug oxidizing capacity in the two treatment conditions (Fig. 3). Further studies should be done to clarify this point.

Although it has been reported that cimetidine impairs the hepatic oxidative process from N-desmethyldiazepam to oxazepam (asterisk in Fig. 4),²⁻⁵⁾ this finding could not be exactly confirmed by the present study. However, plasma N-desmethyldiazepam concentrations tended to be lower up to 6 hr after dosing with cimetidine and this difference disappeared by 72 hr after dosing. This finding might suggest that the difference in plasma N-desmethyldiazepam concentrations in the earlier phase after dosing is created by the cimetidine-induced inhibition of the formation of N-desmethyldiazepam and the disappearance of this difference in the later phase is mainly produced by the cimetidine-induced inhibition of the metabolism of N-desmethyldiazepam and the reduced formation of this metabolite from diazepam depending on the decrease in plasma diazepam concentrations. From these results for the profile of plasma N-desmethyldiazepam concentrations, it has been suggested that cimetidine impairs the hepatic metabolism from diazepam to N-desmethyldiazepam in addition to hepatic oxidative process from N-desmethyldiazepam to oxazepam as reported previously.

Although further studies should be done measuring plasma N-desmethyldiazepam concentrations during longer period after dosing than in the present study to clarify the exact mechanism

of the interaction of benzodiazepines with cimetidine, the different effect of cimetidine on the kinetics of diazepam and lorazepam as indicated in this study may be of some clinical importance on cimetidine coadministration with benzodiazepines.

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