

Pharmacokinetic Interaction Study of Ranitidine and Daijokito in Healthy Volunteers

Yusuke Endo,* Yoshitaka Ishihara,* Satoshi Tsuno,* Akiko Matsuda,† Weibin Qian,* Norimasa Miura* and Junichi Hasegawa*

*Division of Pharmacotherapeutics, Department of Pathophysiological and Therapeutic Science, Tottori University Faculty of Medicine, Yonago 683-8503, Japan and †Department of Fundamental Nursing, School of Health Science, Tottori University Faculty of Medicine, Yonago 683-8503, Japan

ABSTRACT

Background Ranitidine is a histamine 2 receptor antagonist, and daijokito is a Kampo (Chinese herbal medicine as practiced in Japan) formula, which is traditionally used for treating constipation and digestive trouble. Previous study demonstrated that daijokito significantly affected the pharmacokinetics of ranitidine in rats; however, the doses of ranitidine and daijokito in that study were higher than in clinical practice. Therefore, we examined the pharmacokinetic interaction between ranitidine and daijokito in clinical practice doses in healthy volunteers.

Methods This was a randomized, open label, two-period crossover study in healthy volunteers ($n = 7$). Volunteers received administrations of either a single dose of ranitidine 300 mg, or ranitidine 300 mg in combination with daijokito extract granules 2.5 g. Plasma concentrations of ranitidine were measured over 12 h by LC/MS/MS method.

Results Plasma concentrations of ranitidine were lower with co-administration of daijokito compared with ranitidine alone. Co-administration of daijokito significantly decreased ranitidine area under the plasma concentration-time curve from 0 to 12 h (AUC_{0-12}) and maximum plasma concentration (C_{max}) with geometric mean (GM) ratio [90% confidence interval (CI)] for AUC_{0-12} of 0.609 (0.449, 0.826) and C_{max} of 0.515 (0.345, 0.771).

Conclusion Co-administration of ranitidine with daijokito resulted in a significant decrease in plasma level of ranitidine in healthy volunteers.

Key words daijokito; drug-drug interaction; pharmacokinetics; ranitidine

Ranitidine is a histamine 2 receptor antagonist that is widely used in the treatment of peptic ulcer, gastric mucosal lesion and in the control of acid secretion.^{1, 2} In addition, ranitidine is given as a proprietary drug for gastric pain and a heavy feeling in the stomach. It is also thought that the excretion amount of ranitidine unchanged body in urine is large, and ranitidine pharmacokinetic is influenced by renal function in the process of excretion. In cases like this, the dose of ranitidine should be adjusted depending on renal function.³

Daijokito is a Kampo formula, which is traditionally used as a purgative for clearing internal heat in the stomach and intestines and treating constipation.^{4, 5} It is composed of magnolia bark (*Magnolia officinalis*), rheum (*Rheum*), bitter orange (*Citrus aurantium*) and sodium sulfate.

Kampo formulas play an important role in modern medicine and are sometimes the preferred choice in an effective therapeutic approach to diseases that cannot be identified by a single etiology. According to the questionnaire, approximately 80% of physicians use Kampo formulas in general practice.⁶ Although concomitant therapy using western medicine and Kampo formulas is often provided for the purpose of enhancing therapeutic efficacy and decreasing the side effects,^{7, 8} there is insufficient information in the exact use or interaction of these therapies at the present time. A few studies have reported that Kampo formulas had some effect on the pharmacokinetics of drugs such as Warfarin and Ticlopidine hydrochloride.^{9, 10} Some studies focusing on the pharmacokinetic interaction between ranitidine and other medicines have been reported.¹¹ Even though there were no serious adverse interactions between the drugs and herbal prescription medications in patients,¹² there were still life-threatening herb-drug interactions in rats.¹³

Ranitidine is also used as an over-the-counter (OTC) drug and there are possibilities of its administration with daijokito in clinical practice. In an earlier preclinical

Corresponding author: Yusuke Endo

y-endo@med.tottori-u.ac.jp

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Abbreviations: AE, adverse experience; AUC, area under the plasma concentration-time curve; AUC_{0-12} , area under the plasma concentration-time curve from 0 to 12 h; BMI, body mass index; CI, confidence interval; C_{max} , maximum plasma concentration; CYP, Cytochrome P450; FMO, flavin-containing monooxygenase; GER, gastric emptying rate; GM, geometric mean; k_e , elimination rate constant; %CV, percent coefficient of variance; T_{max} , time to reach maximum plasma concentration; $t_{1/2}$, elimination half-life

study of rats, when ranitidine and daijokito were co-administered, ranitidine plasma concentration was lower, and ranitidine $t_{1/2}$ was also delayed. It was demonstrated that daijokito significantly affected the pharmacokinetics of ranitidine.¹⁴ However, the doses of ranitidine and daijokito in this study were higher than in the human clinical setting, and it remains unclear whether the clinical practice dose of daijokito influenced the pharmacokinetics of ranitidine. The aim of this study was to evaluate the pharmacokinetic interaction between ranitidine and daijokito in a clinical practice dose in healthy volunteers in order to establish the potential clinical relevance of a preclinical study.

MATERIAL AND METHODS

Study population

The study was conducted in healthy male volunteers, 20–23 years old. Physical examination, laboratory tests and vital signs were conducted at screening. Volunteers with diarrhea, abnormalities in laboratory tests or drug hypersensitivity were excluded from this study. All volunteers provided written, informed consent prior to study initiation and final protocol was approved by Ethics Review Committee of Tottori University, Faculty of Medicine in Japan (Approval No. 1955). This clinical study was registered with the UMIN Clinical

Trials Registry (UMIN000013106), and was conducted in accordance with the ethical principles established in the Declaration of Helsinki and consistent with Ethical Guidelines for Clinical Research.

Study design and treatment

This study was a randomized, open label, two-period crossover design with two periods that were separated by at least a 5-day washout period (Fig. 1). During the study, volunteers received administrations of either ranitidine 300 mg (Treatment I), or ranitidine 300 mg in combination with daijokito extract granules 2.5 g (Treatment II) with water during fasting. Ranitidine (Zantac 150 mg tablet) and daijokito extract granules 2.5 g were purchased from GlaxoSmithKline & Co. (Tokyo, Japan) and Tsumura & Co. (Tokyo, Japan), respectively. For pharmacokinetic analyses of ranitidine, blood samples were collected at pre-dose and 0.5, 1, 1.5, 2, 4, 8 and 12 h post-dose on Day 1. Venous blood (5 mL) was collected into tubes and plasma samples were separated by centrifugation at 1,500 g and 4 °C for 10 min and stored frozen at –30 °C until analyzed. Urine samples also were collected at pre-dose (spot urine) and 0–12 h post-dose (pooled urine), and samples were immediately stored frozen at –30 °C until analyzed.

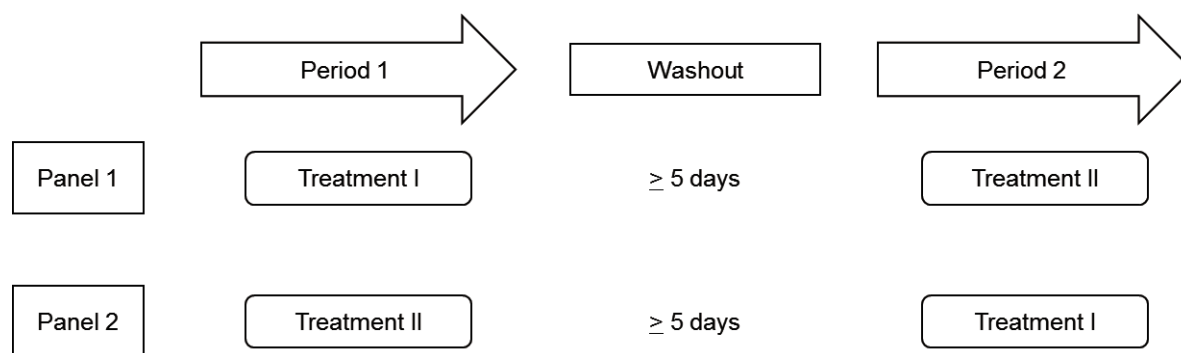


Fig. 1. Study design. Treatment I: Ranitidine 300 mg, Treatment II: Ranitidine 300 mg in combination with daijokito extract granules 2.5 g.

LC/MS/MS method for ranitidine

Concentrations of ranitidine in plasma and urine were determined using validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method (AB SCIEX QTRAP 5500; Takara Bio, Kusatsu, Japan). For plasma sample preparation, 3 volume of 0 °C methanol were added in 1 volume of plasma sample, and vortex, then centrifugation at 15,000 rpm and 4 °C for 17 min. Upper phase samples were diluted by adding water at 400 times. For urine sample preparation, 3 volume of 0

°C methanol were added in 1 volume of urine sample, and vortex, then centrifugation at 15,000 rpm and 4 °C for 17 min. Upper phase samples were diluted by adding water at 40,000 times. The calibration curves for plasma and urine by absolute calibration curve method were linear over the concentration range of 0.01 to 10.00 ng/mL ($r = 0.9998$ for plasma and $r = 0.9999$ for urine)

Pharmacokinetics analysis

Pharmacokinetic parameters of ranitidine were esti-

mated by non-compartmental methods using Microsoft Excel. The maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were directly obtained from the observed concentration-time data. The area under the plasma concentration-time curve (AUC) from zero point to last collection [area under the plasma concentration-time curve from 0 to 12 h (AUC_{0-12})] was calculated according to the liner trapezoidal rule. The terminal elimination rate constant (k_e) was estimated by liner terminal of the terminal portion of the In (concentration)-time curve, and the elimination half-life ($t_{1/2}$) was calculated as $0.693/k_e$ accordingly.

Safety and tolerability

Safety and tolerability were evaluated by monitoring the adverse experiences (AEs). Clinical laboratory assessment (clinical chemistry, hematology and urinalysis), vital signs and physical examination were performed at screening, pre-dose of first administration and end of study.

Statistical analysis

Summary statistics including geometric mean (GM), percent coefficient of variance (%CV), median, minimum and maximum were provided for ranitidine pharmacokinetic parameter. The differences of mean of log-transrated C_{max} , AUC_{0-12} , $t_{1/2}$ and urinary excretion between the ranitidine plus daijokito and ranitidine alone were back-transformed to estimate the GM ratios with the 90% confidence interval (CI). T_{max} , $t_{1/2}$ and urine excretion rate were compared using paired t test. Microsoft Excel was used to perform all statistical analyses.

RESULTS

Demographics and baseline characteristics

A total of 13 healthy male subjects submitted to a screening test, and 7 subjects were enrolled in this study. All of them completed the study without any deviation to the protocol and therefore used for pharmacokinetic analysis set. Four and 3 subjects were enrolled in Panel 1 and 2, respectively. Baseline characteristics of each Panel are shown in Table 1, and there were no differences between Panels.

Ranitidine pharmacokinetic parameters

Plasma concentrations of ranitidine were lower with co-administration of daijokito compared with ranitidine alone (Fig. 2). Co-administration of daijokito significantly decreased ranitidine AUC_{0-12} and C_{max} with GM ratio (90% CI) for AUC_{0-12} of 0.609 (0.449, 0.826) and C_{max} of 0.515 (0.345, 0.771) (Table 2 and Fig. 3). GM of ranitidine $t_{1/2}$ for co-administration of daijokito was 3.72

Table 1. Baseline characteristics

	Panel 1 (n = 4) (Treatment I to Treatment II)	Panel 2 (n = 3) (Treatment II to Treatment I)
Age (years)		
Average	21.8	20.7
SD	1.1	0.5
Minimum	20	20
Maximum	23	21
Height (cm)		
Average	170.0	171.0
SD	4.1	0.8
Minimum	164.0	170.0
Maximum	175.0	172.0
Weight (kg)		
Average	56.0	64.7
SD	4.7	7.4
Minimum	50.0	58.0
Maximum	63.0	75.0
BMI		
Average	19.3	22.1
SD	1.0	2.7
Minimum	18.3	19.6
Maximum	20.6	26.0
Concomitant disease		
None	4 (100%)	3 (100%)
Prior therapy		
None	4 (100%)	3 (100%)

BMI, body mass index.

h, and was comparable with ranitidine alone (3.23 h). In addition, median ranitidine T_{max} for co-administration of daijokito was 2.0 h, and slightly decreased compared with ranitidine alone (4.0 h).

Ranitidine urinary excretion

Ranitidine is the drug of renal excretion type, so we evaluated ranitidine urinary excretion. GM (%CV) of ranitidine urine output for co-administration of daijokito was 14.2 mg (21.7), and significantly lower than ranitidine alone [29.3 mg (21.1)]. The rate of ranitidine excreted in urine for 12 h was significantly lower with co-administration of daijokito than ranitidine alone (Fig. 4).

Safety and tolerability

One subject who enrolled in Panel 1 (Treatment I to Treatment II) reported leucocyte increase at 12 h post-dose of Treatment II. Intensity was judged mild by the investigator. There were no clinically significant changes in other clinical laboratory assessments (clinical chemistry, hematology and urinalysis), vital signs or physical examination in either Panel.

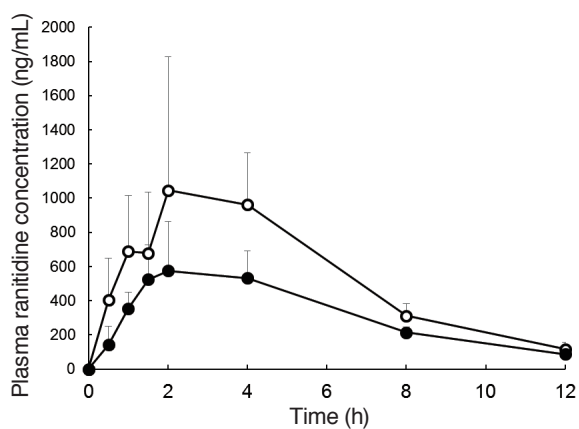


Fig. 2. Plasma concentration-time profiles of ranitidine. Open circles indicate the single dose of ranitidine ($n = 7$), and solid circles indicate co-administration of ranitidine and daijokito ($n = 7$). Each value is the mean value \pm SD.

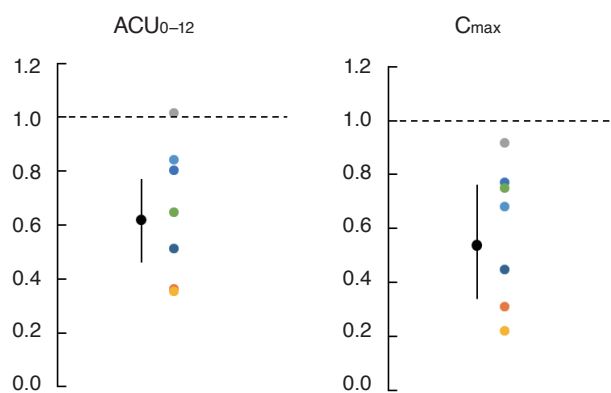


Fig. 3. Ratios of ranitidine AUC_{0-12} and C_{max} in each subject (ranitidine + daijokito/ranitidine) (color circles), and GM ratio and 90% CI (black circles).

AUC_{0-12} , area under the plasma concentration-time curve from 0 to 12 h; CI, confidence interval; C_{max} , maximum plasma concentration; GM, geometric mean.

Table 2. Pharmacokinetic parameters of ranitidine with and without daijokito

Pharmacokinetic parameters*	Ranitidine alone ($n = 7$)	Ranitidine + daijokito ($n = 7$)	GM ratio (90% CI)†
AUC_{0-12} (ng h/mL)	6917.7 (35.5)	3773.8 (23.4)	0.609 (0.449, 0.826)
C_{max} (ng/mL)	1110.5 (55.1)	572.4 (43.1)	0.515 (0.345, 0.771)
$t_{1/2}$ (h)	3.23 (24.0)	3.72 (27.3)	NA
T_{max} (h)	4.0 (2.0–4.0)	2.0 (1.5–4.0)	NA

*Values are GM (%CV) for AUC_{0-12} , C_{max} and $t_{1/2}$; median (range) for T_{max} .

†GM ratio = ranitidine + daijokito/ranitidine.

AUC_{0-12} , area under the plasma concentration-time curve from 0 to 12 h; CI, confidence interval; C_{max} , maximum plasma concentration; GM, geometric mean; NA, not applicable; %CV, percent coefficient of variance; T_{max} , time to maximum plasma concentration; $t_{1/2}$, elimination half-life.

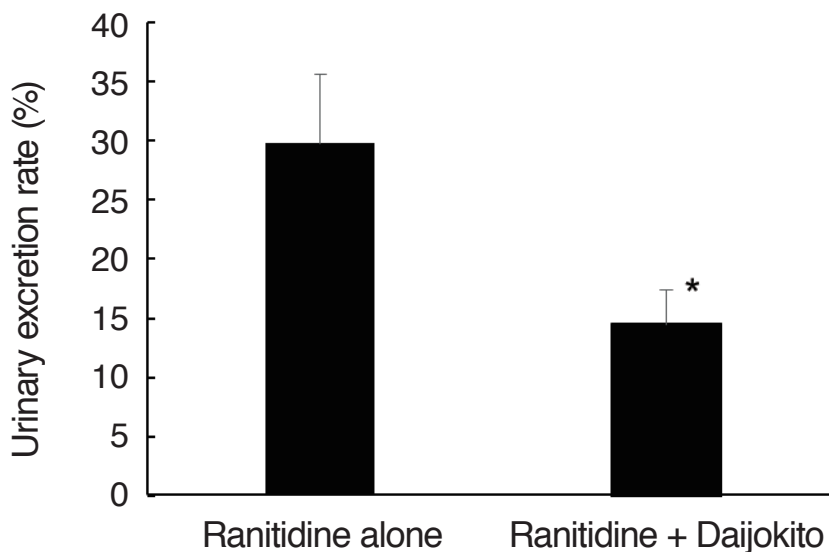


Fig. 4. GM (\pm SD) of the rate of ranitidine excreted in urine for 12 h. * $P < 0.05$ vs. ranitidine alone. GM, geometric mean.

DISCUSSION

The GM ratios (ranitidine + daijokito/ranitidine) (90% CI) of AUC_{0-12} and C_{max} were 0.609 (0.449, 0.826) and 0.515 (0.345, 0.771), respectively, and statistical significance was demonstrated. In an earlier preclinical study of rats, ranitidine mean concentration was 16.315 and 1.455 $\mu\text{g/mL}$ corresponding to ranitidine alone and ranitidine with daijokito, respectively, while ranitidine AUC_{0-12} was also 28.083 and 9.826 $\mu\text{g/L h}$, respectively.¹⁴ These clinical study results were consistent with the same previous preclinical study in rats,¹⁴ and showed the possibility of drug-drug interaction between ranitidine and daijokito in a clinical practice dose. In this study, plasma concentrations of ranitidine were lower with co-administration of daijokito compared with ranitidine alone, although inter-individual variability was wide. It has been reported that the effect of ranitidine on acid secretion does not show any significant variability, but inter-individual variability in bioavailability is wide.¹⁵ It has been also reported that a long antisecretory activity of ranitidine was observed, although the short half-life of the drug varies between 2 and 8 h.¹⁵ Additionally, it has been reported that ranitidine concentrations that produce 50% of the maximal effect are about 100 ng/mL and the maximal effect is reached at concentrations of about 600 ng/mL.¹⁶ Ranitidine $t_{1/2}$ was comparable between ranitidine alone and co-administration with daijokito, and ranitidine T_{max} under co-administration of daijokito slightly decreased compared with ranitidine alone in this study. In contrast to those data, after the addition of daijokito, ranitidine T_{max} was delayed with a longer half-life compared with ranitidine alone in rats.¹⁴

Ranitidine is affected by the first pass effect,¹⁷ and it is metabolized to its *N*- and *S*-oxides almost exclusively (more than 93%) by flavin-containing monooxygenase (FMO) and to desmethylranitidine by cytochrome P450 (CYP) 2C19, 1A2 and 2D6.¹⁸ Kampo formulas affect cytochrome P450 and then change the process of concomitant drug metabolism.^{19, 20} However, there is no report that daijokito could induce the activity of FMO, CYP2C19, 1A2 and 2D6 which metabolize ranitidine. In addition, the ranitidine elimination rate constant (k_e) of each subject in beta phase were similar between ranitidine alone and ranitidine with daijokito in this study; therefore we think that pharmacokinetic interaction might not be caused in the metabolism or excretion phase.

In this study, ranitidine AUC_{0-12} was lower with co-administration of daijokito compared with ranitidine alone. In addition, the rate of ranitidine excreted in urine for 12 h was significantly lower with co-administration of daijokito than ranitidine alone, and this is thought to

be due to a low ranitidine absorption rate under co-administration of ranitidine and daijokito. Ranitidine $t_{1/2}$ was comparable between ranitidine alone and co-administration with daijokito. Therefore, it seems more likely that the process of absorption can be an influence to ranitidine pharmacokinetics under the co-administration of daijokito.

Pharmacokinetic interaction in the absorption process is caused by complex formation, change of pH in the stomach, gastrointestinal tract motility change, and transporter-mediated mechanism. Change in gastrointestinal tract motility is one of the main factors, and it depends on changes in gastric emptying rate (GER). In general, GER is increased, and then absorption rate becomes faster, while the amount of absorption is increased. Kampo formulas like rikkunshito and hangeshyashinto have the effect of accelerating the gastric tract,³² and the amount of concomitant drug that is absorbed from the intestine is changed. The absorbed amount of ranitidine for 12 h was decreased under co-administration of daijokito in this study, and daijokito is used for constipation and might change the ability of gastrointestinal tract motility; therefore the possibility that GER might be changed cannot be denied.

In the intestine, both P-glycoprotein and CYP3A4 are expressed in epithelial cells and cooperatively work as a barrier to orally administered drugs. Most substrates of CYP3A4 and P-glycoprotein overlap and these two proteins together function as an absorption barrier against xenobiotics by their coordinate tissue localization and co-inducibility.²¹ The administration of P-glycoprotein or CYP3A4 substrates with their other substrates, such as talinolol, digoxin, midazolam change the absorbed amount or maximum concentration of substrates.²²⁻²⁴ These are typical examples of pharmacokinetic interaction in intestinal drug absorption. In addition, some furanocoumarins in grapefruit affect the activities of P-glycoprotein and/or CYP3A4, resulting in alteration of the pharmacokinetics of western drugs.²⁵ Ranitidine is a P-glycoprotein substrate, and it was found that oral bioavailability of ranitidine was influenced at the intestinal absorption phase.²⁶ P-glycoprotein is a 170–180 kDa membrane glycoprotein that mediates the active, outward transport of a variety of mainly lipophilic compounds from cells.²⁷ P-glycoprotein is also widely expressed in normal tissues, including epithelial cells in the gastrointestinal tract and kidney tubules and endothelial cells at the blood-brain barrier.^{28, 29} Ranitidine could act as a substrate for intestinal P-glycoprotein and it has been suggested that the balance between absorption and secretory mechanisms is a factor in determining intestinal absorption needs as a routine consideration

even for compounds expected to have a predominantly paracellular route of absorption.³⁰ Ranitidine and daijokito were administered simultaneously, so it is thought that pharmacokinetic interaction via p-glycoprotein activation by daijokito could not be induced; however Yu CP et al. reported that rheum, one of component of daijokito, activated the function of p-glycoprotein.³¹

Co-administration of ranitidine and daijokito was well tolerated, and no safety issues were identified during the study. One subject who enrolled in Panel 1 (Treatment I to Treatment II) reported leucocyte increase at 12 h post-dose of Treatment II. The AE was minimal deviation of reference interval, and might be due to dehydration.

In summary, although the pharmacokinetic interaction of ranitidine and daijokito were demonstrated in this study, only a single dose of ranitidine and daijokito was evaluated. Therefore further data is needed to extrapolate more evidence in clinical practice. However, these data call attention to the risk of ineffectiveness of ranitidine in concomitant use of ranitidine and daijokito in clinical practice.

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The authors declare no conflict of interest.

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