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Clinical trial of risedronate in Japanese volunteers: a study on the effects of timing of dosing on absorption

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Abstract Because of its chemical structure, risedronate was thought to form a complex with divalent cations, e.g., Ca^{2+}, and to be likely to show changes in the efficiency of absorbance from the gastrointestinal tract according to the presence of food. Therefore, we conducted a crossover study using healthy Japanese adults to examine the effects of food intake on absorption after the oral administration of risedronate and to choose the best timing of regimen for risedronate. Using single doses of 5 mg risedronate, the following four dose times were investigated: (a) in the morning under a fasting condition without breakfast; (b) 30 min before breakfast; (c) 30 min after breakfast; and (d) 3 h after breakfast. The results showed that the C_{max} and AUC_{0-24} of the plasma risedronate concentrations and its cumulative urinary excretions decreased in the following order: fasting without breakfast >30 min before breakfast >3 h after breakfast >30 min after breakfast. In other words, it was demonstrated that the absorption of risedronate decreases due to the effects of food. Several adverse events, whose causality with risedronate was unknown or possibly related, were observed, including headaches, diarrhea, increased CK-BB, and an increased urinary β_2-microglobulin excretion rate, but none of these events was clinically significant, and none differed in frequency or severity from the events after a single oral administration. In consideration of the optimal practical timings required to administer risedronate for Japanese patients, therefore, it was found that ingesting the drug immediately after waking up in the morning, when the stomach is empty, was optimal, and that it was necessary to refrain from eating and drinking for at least 30 min after drug ingestion. Therefore, we determined that the optimal time for risedronate to be administered in Japanese patients is 30 min before breakfast.

Key words osteoporosis · risedronate (risedronate sodium hydrate) · NE-58095 · bisphosphonate

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Introduction

Osteoporosis is defined as a systemic bone disorder in which bone fragility is increased due to a reduction in bone mass and disruption of the microstructure of the bone, leading to an increased risk of fracture [1]. According to the Guidelines for the Treatment (Pharmacotherapy) of Osteoporosis, the estimated number of patients with osteoporosis is about 11 000 000 in Japan (in the year 2002); this number has increased along with the aging of Japanese society [2]. To diagnose and treat osteoporotic patients, useful diagnostic criteria and guidelines on the use of biochemical markers are proposed [3,4]. For the prevention of osteoporosis, it is considered essential to acquire and maintain higher maximum bone mass through diet and exercise. However, the development of a more effective therapeutic drug that can increase bone mass, enhance bone strength, and finally reduce bone fractures is anticipated for the treatment of osteoporosis.

Risedronate sodium (monosodium 1-hydroxy-2-pyridin-3-ylethylidenediphosphonate; hereafter risedronate) hydrate is a third-generation bisphosphonate compound discovered by Norwich Eaton Pharmaceutical (currently Procter & Gamble Pharmaceutical, P&GP). Risedronate, which was developed to enhance bone antiresorptive activity and reduce the calcification-inhibitory activity of early bisphosphonate compounds, has been verified in animal studies to potently inhibit bone resorption, in comparison with early bisphosphonate compounds [5,6].

In the United States, oral dose clinical trials of risedronate have been conducted since 1988. The phase I clinical trial, which consisted of a single oral dose study (0.25–40 mg) and a multiple oral dose study (5–30 mg once daily for 14 days) has been completed, and it was verified that risedronate is well tolerated.

A phase I clinical trial has also been conducted in Japan, and the results verified that risedronate is well

tolerated when administered orally at single doses of up to 20 mg.

Because of its chemical structure, risedronate was thought to form a complex with divalent cations, e.g., Ca^{2+}, and thus likely to show changes in the efficiency of absorbance from the gastrointestinal tract according to the presence of food [7]. Mitchell et al. investigated the effect of food on risedronate absorption in the United States. They found a comparable extent of risedronate absorption when the drug was administered either 0.5–1 h before breakfast or 2 h after dinner [8]. However, because we previously found that the extent of absorption of this drug in a fasting state might differ between the populations of Japan and the United Kingdom [9], which, like the U.S. population, contains large numbers of non-Japanese, we decided to conduct a study using Japanese adults. To determine the optimal timing for clinical administration of risedronate in Japan, we here examined the effects of timing of food intake on risedronate absorption from the gastrointestinal tract.

Subjects and methods

Study design

The present study was conducted as one of the phase I studies at Bio-Iatric Center, the Kitasato Institute, between February 1993 and April 1993. The study protocol was approved by the Institutional Review Board before initiation of the study, and all patients gave their written informed consent before participating in the study, which was conducted in compliance with Good Clinical Practice and in accordance with the spirit of the Declaration of Helsinki. Because the single oral dose study revealed individual differences in gastrointestinal absorption, the 12 subjects were randomized into the four groups shown in Table 1. After overnight fasting, two 2.5-mg capsules were administered orally in a single dose with 150 ml water at one of the four administration times shown in Fig. 1. The present clinical trial was divided into stages I, II, III, and IV and conducted according to a crossover design with a washout period of at least 2 weeks. The meals for all groups were the same, and the breakfast on the day of administration contained 200 mg calcium.

Table 1. Randomization of subjects

	Stage			
Subject no.	I	II	III	IV
1, 2, 3	A	B	C	D
4, 5, 6	B	C	D	A
7, 8, 9	C	D	A	B
10, 11, 12	D	A	B	C

Administration timing: A, fasting without breakfast; B, 30 min before breakfast; C, 30 min after breakfast; D, 3 h after breakfast

Selection of subjects

The present clinical trial was conducted using healthy Japanese adult male volunteers aged 20–35 years, whose body weight was within 20% of ideal body weight obtained from (height − 100) × 0.9, and who showed no abnormalities at a medical checkup or by laboratory tests at screening. The following volunteers were excluded: those with anamnesis or complications from current diseases that were considered inappropriate for the present trial; those with allergies to drugs or other compounds; and those with a history of narcotic addiction and/or alcoholism. In addition, persons who were receiving drugs that are considered to affect the evaluation of the pharmacological actions of the study drug, e.g., other bisphosphonates, steroid hormones, vitamin D preparations, or calcitonin, as well as those who were enrolled in the clinical trial of another drug within 6 months before the onset of the present clinical trial, were excluded.

Dose selection

The dose for this study was determined to be 5 mg in consideration of the estimated clinical dose that had been determined from the results of clinical trials in the United States, where the developmental stage of the drug antecedes, and of the pharmacokinetically analyzable doses which meet the objectives of the present clinical trial. The drug was administered as two 2.5-mg capsules (manufactured by Norwich Eaton Pharmaceutical, Norwich, VA, USA).

Pharmacokinetic evaluation

Blood was collected from each subject before drug administration and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 h

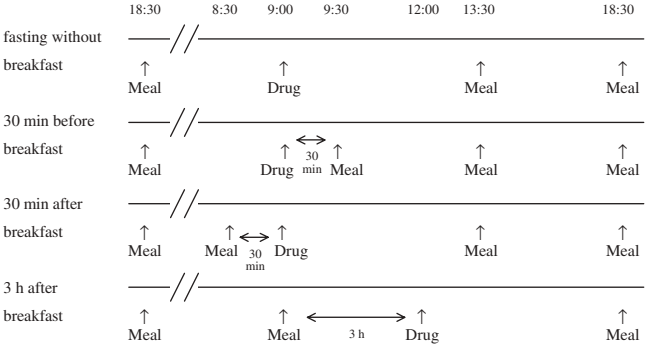

Fig. 1. Timing for administration and meal

after the dose in each stage. Urine was collected from each subject before drug administration, and was pooled over time intervals of 0–4, 4–8, 8–12, 12–24, 24–48, and 48–72 h after the dose in each stage. Also, 5 ml venous blood was obtained from the forearm of each subject (into a heparinized blood-collecting tube). The collected blood was immediately centrifuged (3000 rpm, 4°C, 10 min), and the separated plasma was cryopreserved at −20°C until measurement. Urine was collected at each time interval, and its volume was determined. Subsequently, a 50-ml portion from each specimen was collected and then cryopreserved at −20°C until measurement. SRL (Tokyo, Japan) measured the plasma concentrations of the risedronate according to enzyme-linked immunosorbent assay (ELISA) [10] and the urinary drug concentrations according to gas chromatography/mass spectrometry (GC/MS) (lower limit of quantification (LLQ), 10 ng/ml).

Safety assessment

Each of the measurements described below was conducted in each of the four stages according to the specified schedule.

During the study period, adverse event findings were reviewed during a medical examination conducted by an investigator. Adverse events were recorded by the subject into the specified form. A physical examination, electrocardiography, and laboratory tests, including hematology, blood chemistry, and urinalysis, were conducted at specified intervals (Table 2).

Management of subjects

From 17 h before administration until termination of the present clinical trial, the subjects were admitted to Bio-Iatric Center, the Kitasato Institute, under the conditions listed below. The intake of caffeine- and alcohol-containing beverages and of beverages containing a large quantity of Ca, Fe, or P, as well as smoking, exercise, food intake, and the use of other drugs, were prohibited. The subjects were under the constant supervision of the subinvestigator. At the termination of the trial, the subjects were discharged unless they showed an important health abnormality. A poststudy medical checkup (medical history, physical examination, electrocardiography, and laboratory tests) was conducted 1 week after administration of the final dose.

Analysis of data

Based on the time-course of the actual plasma drug concentrations in each subject, the maximum plasma concentration (C_{max}), the time to reach the maximum plasma concentration (T_{max}), and the area under the plasma concentration–time curve up to 24 h after administration (AUC_{0-24}) were calculated according to the trapezoidal method. In addition, the half-life ($t_{1/2}$) in plasma was calculated by linear regression analysis with log-transformed plasma concentrations from T_{max} up to 8 h.

The urinary concentrations and urine volumes were used to calculate the urinary excretion amounts, and the total urinary excretion amounts up to 72 h after administration were taken as the cumulative urinary excretion.

A paired *t* test was conducted for the pre- and postadministration values of the data on safety, e.g., body weight, blood pressure, pulse rate, and body temperature, and laboratory tests. Values of $P < 0.05$ were considered to indicate statistical significance.

Results

Subjects' background factors

The subjects were 20–32 years in age (mean ± SD, 23.0 ± 3.4 years), 158.8–183.5 cm in height (172.0 ± 7.7 cm), and 49.8–71.1 kg in body weight (61.3 ± 7.4 kg). One subject chose to drop out of the study for personal reasons. Therefore, the data from this subject, consisting of his body weight, blood pressure, pulse rate, body temperature, laboratory tests, and pharmacokinetics (which were not abnormal), were excluded from the

Table 2. Schedule of clinical tests

	Groups A, B, C	Group D
Physical examination	Baseline, 24, 48, 72 h	Baseline, 21, 45, 69 h
Body weight	Baseline, 72 h	Baseline, 69 h
Electrocardiography	Baseline, 24 h	Baseline, 21 h
Hematology Blood chemistry Urinalysis	Baseline, 24, 72 h	Baseline, 21, 69 h

Administration timing: A, fasting without breakfast; B, 30 min before breakfast; C, 30 min after breakfast; D, 3 h after breakfast

Table 3. Pharmacokinetic parameters in plasma concentration and urinary excretion amount of risedronate after single oral administration at different dose times in relationship to breakfast in healthy volunteers at a dose of 5 mg

Dosage timing	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-24} (ng·h/ml)	$t_{1/2}$ (h)	Total urinary excretion amount (μg)
Fasting without breakfast	2.85 ± 1.46	1.36 ± 0.78	10.42 ± 6.20	1.52 ± 0.25	36.29 ± 19.43
30 min before breakfast	2.11 ± 1.25	0.86 ± 0.23	3.83 ± 2.27	1.16 ± 0.41	16.08 ± 10.63
30 min after breakfast	0.19 ± 0.13	3.56 ± 1.42	0.67 ± 0.51	3.63 ± 2.25	2.13 ± 2.55
3 h after breakfast	0.38 ± 0.23	2.27 ± 0.65	1.52 ± 1.50	2.61 ± 1.16	4.65 ± 4.78

Each value represents mean ± SD (n = 11)

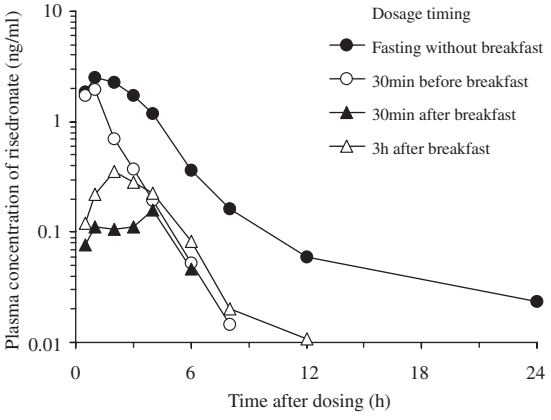

Fig. 2. Plasma concentration–time profiles of risedronate after single oral administration at different dose times in relationship to breakfast in healthy volunteers at a dose of 5 mg (each item of data represents the mean of 11 subjects)

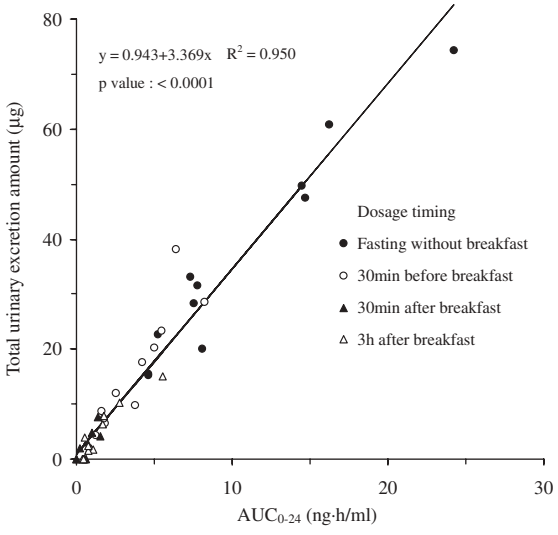

Fig. 3. Correlation between plasma AUC_{0-24} and urinary excretion amount after single oral administration of 5 mg of risedronate at different dose times in relationship to breakfast in healthy volunteers at a dose of 5 mg (The line and equation inserted show the results of linear regression analysis)

statistical analyses. Neither subjective symptoms nor objective findings were found in this subject.

Pharmacokinetic evaluation

The time-courses of the mean plasma concentrations after the single oral administration of risedronate were studied at four time points based on when the subjects ate breakfast, i.e., fasting without breakfast, 30 min before breakfast, 30 min after breakfast, and 3 h after breakfast (Fig. 2). The plasma concentrations of risedronate in the "fasting without breakfast" group demonstrated a time-course at levels that were higher than those in the other time point administration groups. The plasma concentration profiles of risedronate demonstrated relatively lower levels in the two postbreakfast administration groups. Table 3 shows the pharmacokinetic parameters for each administration group. Similar to AUC_{0-24}, the cumulative urinary excretion was also affected by food, and decreased in the following order: fasting without breakfast >30 min before breakfast >3 h after breakfast >30 min after breakfast. The cumulative urinary excretion for each subject, which is one of the parameters for systemic exposure in vivo, was plotted versus the AUC_{0-24} value, another parameter for systemic exposure. A linear correlation was observed.

Assessment of safety

Adverse events whose causality with risedronate was unknown or possibly related were abdominal pain, a feeling of having an enlarged abdomen, itching, epigastric pain, headache, and diarrhea (Table 4).

Abnormal changes in the laboratory values, whose causality with risedronate was unknown or possibly related, were positive-turned c-reactive protein (CRP), increased creatine kinase (CK), increased urinary leukocyte, positive-turned urinary ketone bodies in the qualitative assay, leukocytosis, increased glutamic-

Table 4. Summary of adverse events

Group	Fasting without breakfast	30 min before breakfast	30 min after breakfast	3 h after breakfast
Number of subjects	11	11	12	12
Number of subjects with drug-related adverse events[a] (%)	0	4 (36.4)	2 (16.7)	3 (25.0)
Number of drug-related adverse events	0	4	2	4
Stage				
Stage I				
Headache		1		
Stage II				
Abdominal pain		1		
Diarrhea				1[b]
Epigastric pain				1[b]
Headache				1
Stage III				
Feeling of enlarged abdomen		1		
Stage IV				
Headache		1	2	
Itching				1

[a] Subjects who experienced one or more adverse events were counted only once
[b] These events occurred in the same patient

pyruvic transaminase (GPT), increased CK-BB, and increased CK-MB (Table 5).

Discussion

Comparison of the plasma concentrations among the groups suggested that the gastrointestinal absorption of risedronate is evidently affected by food intake. As shown in Fig. 2, the "30 min before breakfast" group showed a time-course vis-a-vis the plasma concentrations of risedronate that was similar to that in the "fasting without breakfast" group up to the time of food intake onset at 30 min after administration. However, the former group exhibited an acute decrease in subsequent plasma concentration values beginning at 1 h postdosing; namely, the C_{max} of both groups were almost the same, but the AUC_{0-24} of both groups was obviously different. Therefore, the intake of breakfast at 30 min after administration was strongly suggested to have affected the gastrointestinal absorption of risedronate, thus causing a decrease in absorption after the food was eaten. Furthermore, both the two postbreakfast groups showed low AUC_{0-24} values and low cumulative urinary excretions. In addition, the "30 min after breakfast" group, in which larger gastric contents were considered to exist than in the "3 h after breakfast" group, showed greater effects caused by food intake and exhibited the lowest C_{max} value, AUC_{0-24} value, and cumulative urinary excretion among all the administration groups. These results demonstrated that administration at fasting without breakfast is the optimal regimen for the absorption of risedronate. However, the regimen to reproduce the "fasting without breakfast" group requires administration without breakfast in the morning and continued fasting thereafter, which is not appropriate in practical clinical use in Japan. The best alternate regimen could be to eat breakfast at least 30 min after dosing. In conclusion, we determined that risedronate should be administered to Japanese patients at least 30 min before breakfast.

The good correlation between AUC_{0-24} values and cumulative urinary excretion amounts suggests that the renal clearance of risedronate was constant throughout this study. Risedronate is thought not to be metabolized in animals or humans, similar to other bisphosphonates. Therefore, the effects of food on the bioavailability of risedronate could not be caused by its excretion or metabolism, but only by its intestinal absorption.

In contrast, Mitchell et al. [8] reported that dosing either 0.5 h before breakfast or 2 h after dinner (the evening meal) resulted in a comparable absorption in the U.S. population. There were several differences in the conditions of the present study (Japan, JP) and U.S. study (US), such as in the numbers of subjects, the dosages administered, the types of meals eaten, the method used for analyzing the pharmacokinetic parameters, and the formulations used. Therefore, it is not possible to precisely compare results from both studies. In our previous report, we found that the extent of absorption of this drug might differ between the Japanese and the United Kingdom populations [9]. That is, there may be differences in gastrointestinal absorption between Japanese and non-Japanese individuals. Daily therapeutic doses of other bisphosphonates, such as etidronate and alendronate for Japanese patients, are

Table 5. Summary of laboratory tests

Group	Fasting without breakfast	30 min before breakfast	30 min after breakfast	3 h after breakfast
Number of subjects	11	11	12	12
Number of subjects with drug-related adverse events[a] (%)	6 (54.5)	7 (63.6)	2 (16.7)	3 (25.0)
Number of drug-related adverse events	9	10	2	3
Stage				
Stage I				
Increased CK-BB	1			
Leukocytosis		1[b]		
Positive-turned CRP		1[b]		
Stage II				
Increased CK-BB	1[c]	3[d]		
Increased CK-MB	1[c]	1[d]		1
Leukocytosis	1			
Stage III				
Increased CK-BB	2[e]			
Increased CK-MB	1[e]			
Increased GPT		1		
Stage IV				
Increased CK-BB	1[f]	1[g]		
Positive-turned CRP	1[f]			
Increased CK-MB		1[g]	1	1
Increased CK		1		
Increased urinary leukocytes		1[g]		
Sediments				
Increased GPT			1	
Positive-turned urinary ketone bodies				1

[a] Subjects who experienced one or more adverse events were counted only once
[b–g] Subjects who experienced one or more adverse events were counted once in each event
CK-BB, creatine kinase-BB; CRP, c-reactive protein; CK-MB, creatine kinase-MB; GPT, glutamic-pyruvic transaminase

half the amount of those for non-Japanese patients. Bisphosphonates are thought to show a decrease in absorption because of the formation of a complex with divalent cations, e.g., Ca^{2+}, which are contained in food and beverages, in the gastrointestinal tract [11]. It is not yet known why Japanese absorb bisphosphonates differently from non-Japanese, but we considered that the difference may be due to different environmental conditions in the gastrointestinal tracts of each population, such as residual amounts of divalent cations, which vary because of the different diets consumed by these populations.

A previous clinical trial of alendronate indicated a decrease by up to about 40% in the absorption rate when ingesting the drug with coffee and orange juice as compared with the value when ingesting the drug with water [12]. The absorption of risedronate, like that of alendronate, is expected to be similarly inhibited by ingestion with coffee, tea, juice, and other beverages. Therefore, we conclude that not only should restrictions be applied to food when doses are administered, but also to the beverage used to administer the dose.

Regarding the assessment of safety, some adverse events and laboratory test changes were found, but none of these was clinically significant.

With respect to absorption and practicality, the results of the present study indicate that it is optimal for Japanese patients to ingest the drug with water upon awakening (fasting condition), and to avoid food and other beverages for at least 30 min after dosing.

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