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Pharmacokinetic Characteristics of Ibandronate and Tolerability of DP-R206 (150 mg Ibandronate/24,000 IU Vitamin D_3) Compared to the Ibandronate (150 mg) Monotherapy in Healthy Adults

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Ibandronate (a bisphosphonate) is commonly used as an treatment of osteoporosis in combination with vitamin D. Monthly DP-R206-a novel, fixed-dose combination tablet (150 mg ibandronate/24,000 IU vitamin D_3)-was recently developed to enhance patient compliance. This open, randomized, two-period crossover study was conducted to compare the pharmacokinetics of ibandronate when administered as DP-R206 or 150 mg ibandronate to healthy adult volunteers. Each volunteer was randomly allocated to receive single-dose DP-R206 or ibandronate with a 28-day washout period between treatments. Blood samples were assessed using pharmacokinetic analysis. Plasma ibandronate concentrations were determined using liquid chromatography-tandem mass spectrometry. Safety and tolerability assessments were performed throughout the study. In total, 103 participants received the study drugs and 72 participants completed the study. The geometric mean ratios (DP-R206/ibandronate) of the maximum concentration (C_{max}) and the area under the plasma concentration time curve from time zero to the last concentration (AUC_{last}) values were 0.959 (90% CI: 0.820–1.120) and 0.924 (90% CI: 0.805–1.060), respectively. The frequencies of adverse events (AEs) and drug reactions were similar between treatment groups, and all AEs were recovered without sequalae. Ibandronate pharmacokinetics, tolerability, and safety are comparable when administered to healthy individuals, regardless if administered as DP-R206 or ibandronate.

ORIGINAL ARTICLE

Introduction

Bisphosphonate, which is already widely used to treat osteoporosis, has a chemically stable pyrophosphate structure. The structural characteristics allow bisphosphonate to bind to hydroxyapatite crystals, which have a high affinity for bone minerals.[1] Most especially, second- and third-generation bisphosphonates, which share a common P-C-P backbone and contain nitrogen on one side chain, contribute to osteoclast apoptosis by inhibiting farnesyl pyrophosphate synthase and promoting the isoprenylation of the Rab, Rac, and Rho proteins that control osteoclast activity.[1] Although the mechanism has not been directly clinically measured, drug effects can be indirectly assessed by measuring decreases in bone resorption-related biomarkers

(e.g., the amino- and carboxyl-terminal breakdown of type 1 collagen). Most bisphosphonate demonstrates the maximum inhibition of bone resorption within 3 months after drug administration, and this effect is maintained at a relatively constant level during treatment.[2] Compliance is one of the major factors that influence the oral administration of bisphosphonate, mainly due to inconvenient dosing methods and side effects. Patients need to maintain an empty stomach >2 hours before dosing and cannot lie down, drink, or eat any food for >30 minutes after receiving oral bisphosphonate. Also, commonly reported gastrointestinal adverse events directly influence compliance.[3,4] Ibandronate sodium, a third-generation bisphosphonate, can be administered once per month because it demonstrates a higher affinity for bone tissue than other bisphosphonates; therefore, it could markedly improve compliance.[6,7]

Meanwhile, the clinician's guide on treatment of osteoporosis by the National Osteoporosis Foundation highly recommends vitamin D intake in order to reduce the risk of bone fracture.[3] Vitamin D deficiency also reportedly increases the risk of bone fracture.[8,9] Also, because vitamin D is associated with the absorption of calcium, bone metabolism, muscle strength, and position balance, it might decrease the risk of falls.[10-12] Generally, the daily recommended dose of vitamin D is 400–800 IU, and patients >71 years should ingest 800 IU because of the high frequency of deficiency.[3,13,14] Also, additional vitamin D administration is recommended in order to maintain concentrations >30 ng/mL 25(OH)D in patients with osteoporosis.[3] Recent studies indicate that maintaining an adequate vitamin D concentration is an important factor that increases the efficacy of treatment of osteoporosis.[15,16]

Accordingly, a fixed drug combination-DP-R206 (150 mg ibandronate/24,000 IU vitamin D3)-was developed to increase the treatment effects of ibandronate and adherence. Therefore, the objective of this study was to investigate the pharmacokinetic (PK) characteristics of ibandronate when administered as DP-R206 or 150 mg ibandronate to healthy volunteers, as well as assess tolerability and safety.

Methods

Subjects

We enrolled healthy Korean volunteers between 20–55 years of age. Medical histories, vital signs, physical examinations, laboratory tests, and electrocardiography (ECG) results were assessed in all volunteers, included volunteers who were negative for human immunodeficiency virus antibody, hepatitis B surface antigen, hepatitis C virus, and syphilis high quality reagin test. Exclusion criteria included clinically significant medical history, drug hypersensitivity, receiving any drugs that could induce or inhibit drug metabolism 30 days prior to dosing (e.g., barbiturates) and/or other prescription drugs 14 days prior to dosing, abnormal liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [rGT], alkaline phosphatase [ALP], total bilirubin >1.5x upper normal limit), abnormal parathyroid hormone, calcium, or phosphorus, <9 ng/mL 25(OH)D, and Cockroft-Gault creatinine clearance <80 mL/minute.

All subjects provided written informed consent prior to the study participation. This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). The institutional review boards (IRB) at Asan Medical Center and Chonbuk National University Hospital approved our protocol prior to starting this trial.

Study design

This study uses a randomized, open-label, single-dose, 2x2 crossover design. Each subject received the following 2 treatments in a randomly allocated sequence (RT or TR) with a 28-day washout between periods: single-dose 150 mg ibandronate (reference; R) or single-dose DP-R206 (test; T). The randomization code was generated using R® (version 2.10.1; R Foundation for Statistical Computing, Vienna, Austria). All subjects were admitted to the hospital on day 1 and discharged on day 2 after all blood samples were collected at 24 hours after dosing. On day 1, all subjects administered the study drug with 240 mL plain water on an empty stomach. Water was restricted for 2 hours after administration. Lunch and dinner were served 4 and 9 hours after administration, respectively. Participants had to remain in an upright sitting position for 1 hour after swallowing the study drug. After discharge, subjects participants visited the outpatient clinic for blood sample collection until 120 hours after dosing. Throughout the entire study period, alcohol, smoking, heavy exercise, and other drugs were not allowed, except concomitant drug(s) approved by the investigator.

Blood sample collection and bioanalysis of ibandronate

For the pharmacokinetic (PK) analysis, blood samples (7 mL) were collected prior to study drug administration and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 24, 32, 48, 72, and 120 hours after dosing. Each sample was collected in heparinized tubes. Plasma was obtained by centrifugation at 1800 g for 8 minutes at 4°C, immediately transferred to two Eppendorf tubes (0.8 mL), frozen at -70°C, and shipped to the Seoul Pharma Laboratory (Seoul, Korea) for analysis using an ibandronate concentration assay.

Plasma ibandronate concentrations were determined using validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Briefly, 300 μL plasma was added to 10 μL of the internal standard sample (ibandronate-d3 [8 μg/mL in water]), 200 μL sterile water, and 500 μL sodium bicarbonate buffer (10 mM; native pH). The mixture was then vortexed, and diazomethane in hexane and 2 mL methanol was added and allowed to evaporate. Then, added 50% acetonitrile and was injected into the HPLC-MS/MS system (HPLC system: Waters Alliance 2795 HT [Waters, US]; MS/MS system: Waters micromass Quattro Premier XE [Waters, US]). The column was

a Luna 3 μ HILIC 200 Å (2.0x100 mm; 3 μm), and the mobile phase consisted of ammonium formate buffer (5 mM; native pH): acetonitrile (8:92 [v/v]). The flow rate was maintained at 0.2 mL/minute. The calibration curves of each batch were linear over the range 0.5–500 ng/mL (r^2 >0.99) with intraday accuracy: 91.53–106.96%; precision: 0.19–2.03%; interday accuracy: 99.76–104.31%; precision: 1.33–10.85%.

Pharmacokinetic analysis

The PK characteristics of ibandronate were assessed by non-compartmental analysis of the actual sampling times (using Winnonlin® version 6.1; Pharsight, CA, US). Maximum concentration (C_{max}) and the time to reach C_{max} (T_{max}) values were directly obtained from the plasma concentration-time curves. The area under the plasma concentration time curve from time zero to the last concentration (AUC_{last}) was calculated using the linear trapezoidal method by increasing the period, and log/linear trapezoidal summation in the decreasing period. From the terminal slope, linear regression was used to estimate the elimination rate constants and obtain the AUC from time zero to infinity (AUC_{inf}) and the terminal half-life ($t_{1/2\beta}$). To compare the PK profiles of DP-R206 and ibandronate, the log-transformed individual C_{max} and AUC_{last} values were analyzed using mixed-effects analysis of variance (ANOVA, using SAS version 9.2; SAS Institute INC., NC, US). The treatment effects are shown as the geometric mean ratio (test/reference; DP-R206/ibandronate) and 90% confidence intervals (90% CI).

Safety and tolerability analyses

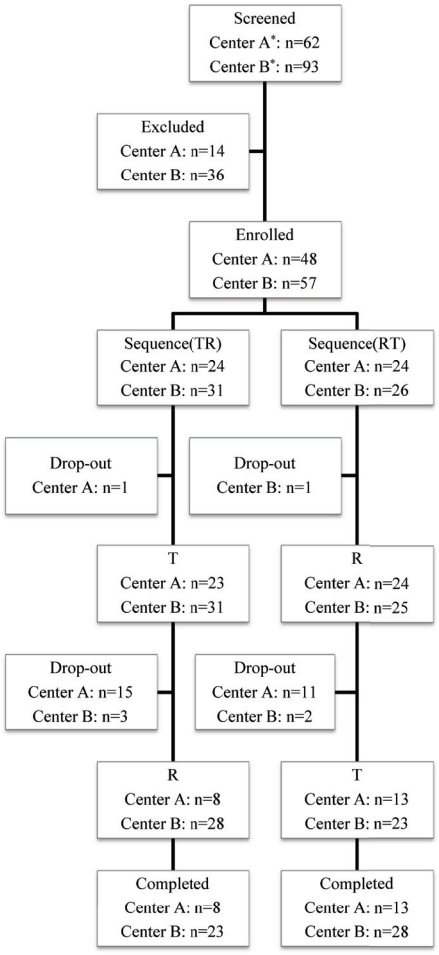
Safety and tolerability assessments included the regular monitoring of adverse events (AEs) and concomitant medications, as well as physical examination, vital signs, laboratory tests, and ECGs. The first admitted subject developed influenza-like symptoms at 1 day after drug dosing. These symptoms are sufficiently predictable based on previous studies on ibandronate, and the study protocol was revised to allow the preemptive administration of acetaminophen. At 14, 24, and 32 hours after study drug administration, a maximum of 2 acetaminophen ER (extended release) tablets could be administered according to the subjects' clinical symptoms. All AEs were intensively monitored because acetaminophen might increase the gastrointestinal irritation caused by the study drugs. All AEs were observed by unmasked investigators, and the participant's spontaneous reports were noted. The symptoms, signs, severity, time of onset, duration, course, outcomes, and relationship with the study drug were assessed (SAS version 9.2 and R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org) was used if any statistical analysis needed).

Results

This study was conducted at two centers: Asan Medical Center (AMC) (August–October 2011) and Chonbuk National University Hospital (January–March 2012).

Demographics

In total, 155 male volunteers were screened and 105 participants were enrolled (62 volunteers were screened and 48 subjects were enrolled at AMC; 93 volunteers were screened and 57 subjects were enrolled at Chonbuk National University Hospital). At AMC, 24 subjects were assigned two admission dates. At each admission date, participants were randomly assigned to two sequences (RT or TR) at a 1:1 ratio. At Chonbuk National University Hospital, 50 subjects were admitted and randomly assigned to two sequences (RT:TR=24:26), and 7 subjects were admitted at a 2:5 RT:TR randomization ratio. In total, 103 subjects were administered the study drug at least once, and 2 subjects withdrew consent before drug administration. Thirty-three subjects dropped out of the study, and 72 subjects completed the study (Fig. 1). Subjects either withdrew consent (10 subjects) or developed AEs (23 subjects). All AEs with dropout developed



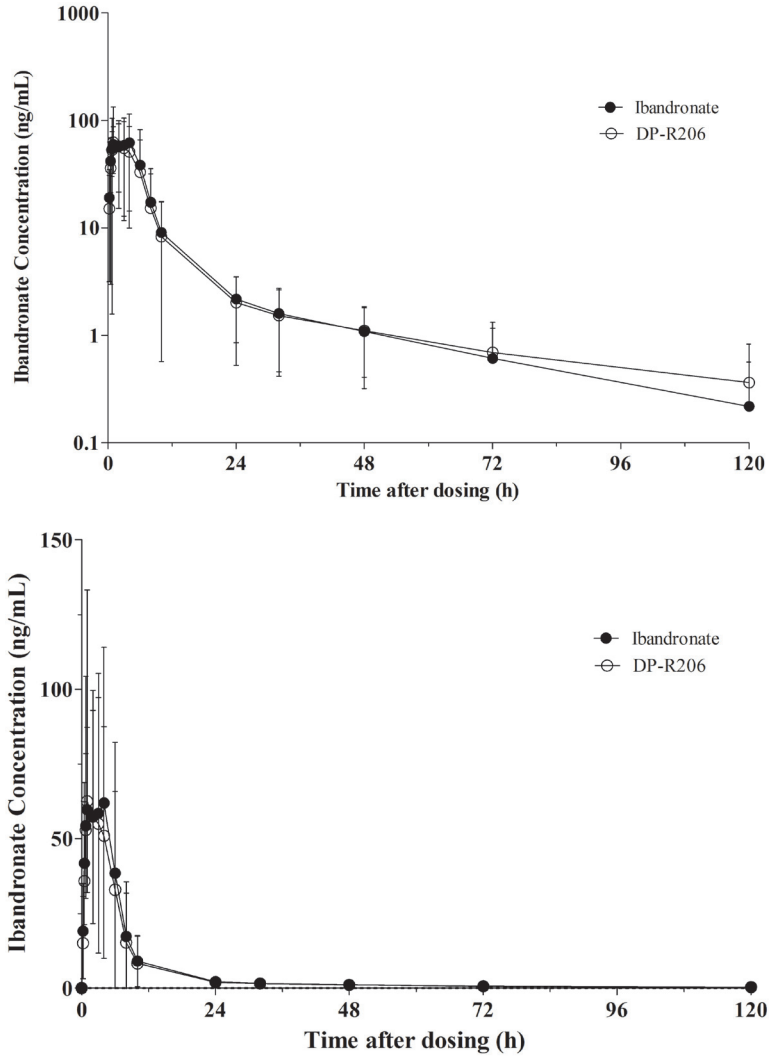
*Center A: Asan Medical Center; Center B: Chonbuk National University Hospital

Figure 1. Allocation of the subjects to study groups

Table 1. Demographic characteristics of the enrolled subjects

		RT (n=49)	TR (n=54)	Total (n=103)	p
Age (yr)		24.71±2.75	24.70±3.49	24.71±3.15	0.694*¶
Weight (kg)		70.24±8.73	71.71±8.03	71.01±8.37	0.579†¶
Height (cm)		174.62±4.92	175.15±4.59	174.90±4.73	0.376†¶
Drinking‡	Yes	63.3% (31)	61.1% (33)	62.1% (64)	0.822§
	No	36.7% (18)	38.9% (21)	37.9% (39)	
Smoking‡	Yes	38.8% (19)	33.3% (18)	35.9% (37)	0.565§
	No	61.2% (30)	66.7% (36)	64.1% (66)	
Caffeine‡	Yes	61.2% (30)	55.6% (30)	58.3% (60)	0.560§
	No	38.8% (19)	44.4% (24)	41.7% (43)	

Subjects who administered the study drug at least once were included in this analysis. *Mann-Whitney U test, †T-test, ‡% (numbers of participants), §Chi-square test, ¶Shapiro-Wilk test for normality check were conducted. The p-value was <0.05 for age, while p-value>0.05 for weight and height parameters each.



during period 1.

Mean subject age, height, and weight were 24.7 years, 174.9 cm, and 71.0 kg, respectively. Age, height, weight, and alcohol, nicotine, and caffeine consumption were not statistically different between groups (Table 1).

Pharmacokinetic analysis

PK parameters were determined using the ibandronate concentration data obtained from the 72 subjects who complete the study. The plasma concentration-time profiles for ibandronate are shown in Figure 2. The mean (standard deviation [SD]) C_{max} value was 90.64 (54.72) ng/mL after the single-dose administration of ibandronate (reference drug), while 87.70 (74.52) ng/mL was determined for DP-R206 (test drug). Both drugs demonstrated median T_{max} values of 2 hours (range 0.5–6.0 hours). The mean (SD) AUC_{last} value was 530.66 (349.96) ng·hour/mL for ibandronate and 482.80 (325.34) ng·hour/mL for DP-R206. The mean (SD) AUC_{inf} values were 549.24 (366.76) and 501.43 (349.59) ng·hour/mL for ibandronate and DP-R206, respectively (Table 2).

The mixed-effects model considered sequence, period, treatment, trial center, interactions between period and trial center (period x trial center), and interactions between treatment and

Figure 2. Mean plasma ibandronate concentration-time curves (semilog (upper) and linear (lower) scale)

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Table 2. Pharmacokinetic parameters

PK parameter	Summary statistics	Ibandronate (150 mg)	DP-R206*
C_{max} (ng/mL)	Arithmetic mean SD CV (%)	90.64 54.72 60.4	87.70 74.52 85.0
AUC_{last} (ng/mL)	Arithmetic mean SD CV (%)	530.66 340.96 65.9	482.80 325.34 67.4
AUC_{inf} (ng·hr/mL)	Arithmetic mean SD CV (%)	549.24 366.76 66.8	501.43 349.59 69.7
T_{max} (hr)	Median Minimum Maximum	2.00 0.50 6.00	2.00 0.50 6.00
$t_{1/2}$ (hr)	Mean SD CV (%)	32.38 15.29 47.21	30.76 16.52 53.71

*DP-R206: fixed-dose 150 mg ibandronate/24,000 IU vitamin D_3

trial center (treatment x trial center) as fixed effects; admission date to the trial center and subjects nested in the admission date of the trial center were considered random effects. The log-transformed C_{max}, AUC_{last}, and AUC_{inf} values were analyzed using ANOVA. None of the differences in terms of fixed effects or admission dates were statistically significant (p>0.05). The geometric mean ratio (test/reference) of the C_{max}, AUC_{last}, AUC_{inf} values were 0.959, 0.924, and 0.923, and the 90% CI values were 0.820–1.120, 0.805–1.060, and 0.801–1.061, respectively. Therefore, all PK parameters were within the range of 0.8–1.25, which is the criterion for bioequivalence (Table 3).

Safety and tolerability analysis

In total, 273 AEs were reported throughout the study, and 258 AEs developed after administering the study drug. In terms of maximum intensity, 212 mild, 39 moderate, and 7 severe AEs developed after administration. Among these, 248 AEs were considered adverse drug reactions (ADRs) (i.e., possibly related to the drug). The most common AEs were gastrointestinal (GI) (90 cases), followed by musculoskeletal (66 cases) and general disorders (55 cases). Common GI symptoms included diarrhea (43 cases), abdominal pain (32 cases), abdominal discomfort (6 cases), and dyspepsia (5 cases), while myalgia (49 cases), bone pain (8 cases), and arthralgia (5 cases) were common musculoskeletal symptoms. Influenza-like symptoms (23 cases), pyrexia (16 cases), febrile sensation (6 cases), and chills (7 cases) were commonly reported general disorders. In addition, 23 cases of headache were reported, of which 22 cases were considered probably or possibly drug-related. To treat or prevent the high incidence of AEs (like pyrexia, bone pain, myalgia, influenza-like symptoms, and headache), 92 participants received ≥ 1 administration of acetaminophen.

Table 3. Geometric mean ratio and 90% confidence interval limits of the primary ibandronate PK parameters (DP-R206*:150 mg tablet ibandronate)

PK parameter	Geometric mean ratio	90% Confidence interval
C_{max}	0.959	0.820–1.120
AUC_{last}	0.924	0.805–1.060
AUC_{inf}	0.923	0.801–1.062

*DP-R206: fixed-dose 150 mg ibandronate/24,000 IU vitamin D_3

Two serious AEs were reported. One subject's admission was extended by 1 day after ibandronate (reference drug) administration due to influenza-like symptoms with fever. After symptomatic treatment, including acetaminophen, symptoms abated and the subject was discharged. This AE was assessed and considered probably drug-related. The other subject developed anaphylactic shock 10 minutes after orally receiving preventive acetaminophen at 14 hours after ibandronate (reference drug) dosing. The subject developed generalized urticaria with hypotension and nausea, but no mental changes developed. Hydration with pheniramine, metoclopramide, and intravenous methylprednisolone was provided, and ECG, laboratory tests (including arterial blood gas analysis), and the continuous monitoring of vital signs were conducted. The subject completely recovered and was discharged without extending the admission period. This AE was considered possibly drug-related.

AEs were categorized by treatment group, and 56% and 69%

Table 4. Adverse events

Treatment		Ibandronate 150 mg (n=85)				DP-R206* (n=90)				Total
System organ class	Severity	Probably related	Possibly related	Unlikely related	Definitely not related	Probably related	Possibly related	Unlikely related	Definitely not related	
Gastrointestinal disorders	Mild	27	6	0	0	35	7	0	0	75
	Moderate	2	1	0	0	6	2	0	0	11
	Severe	1	0	0	0	3	0	0	0	4
General disorders and administration site conditions	Mild	19	1	0	0	20	1	0	0	41
	Moderate	7	0	0	0	6	0	0	0	13
	Severe	0	0	0	0	1	0	0	0	1
Immune system disorders	Mild	0	0	0	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0	0	0
	Severe	0	1	0	0	0	0	0	0	1
Infections and infestations	Mild	0	1	0	0	0	0	1	0	2
	Moderate	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0
Injury, poisoning, and procedural complications	Mild	0	0	0	0	0	0	0	1	1
	Moderate	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0
Investigations	Mild	0	1	2	0	0	0	0	0	3
	Moderate	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0
Metabolic and nutritional disorders	Mild	0	0	0	0	0	1	0	0	1
	Moderate	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	Mild	25	0	0	0	26	1	0	0	52
	Moderate	8	0	0	0	6	0	0	0	14
	Severe	0	0	0	0	0	0	0	0	0
Nervous system disorders	Mild	9	7	0	0	9	3	0	1	29
	Moderate	0	0	0	0	0	1	0	0	1
	Severe	0	0	0	0	0	0	0	0	0
Renal and urinary disorders	Mild	0	2	0	0	0	0	0	0	2
	Moderate	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	Mild	0	0	1	0	0	0	1	3	5
	Moderate	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0
Dermal and subcutaneous tissue disorders	Mild	1	0	0	0	0	0	0	0	1
	Moderate	0	0	0	0	0	0	0	0	0
	Severe	0	1	0	0	0	0	0	0	1
Total		99	21	3	0	112	16	2	5	258

*DP-R206: fixed-dose 150 mg ibandronate/24,000 IU vitamin D_3

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of participants in the ibandronate group (85 subjects) and DP-R206 groups (90 subjects) reported ADRs, respectively. Three severe AEs were reported after administering ibandronate, while 4 severe AEs developed after administering DP-R206. The percentages of AEs considered above moderate intensity among all AEs were 17% and 19% in the ibandronate and DP-R206 groups, respectively. The number of subjects who reported AE above moderate intensity were not statistically significant different between treatment groups (p=0.230; McNemar test). Also, the number of subjects who reported AEs and ADRs were not statistically significant different between treatment groups (p=0.112; McNemar test). GI symptoms (the most common AE) developed in 37 and 53 cases after ibandronate and DP-R206 administration; musculoskeletal symptoms developed in 33 cases in each treatment group; and influenza-like symptoms developed in 11 and 12 cases in the reference and test groups, respectively.

Compared with baseline, body temperature tended to increase in both treatment groups: subjects with body temperatures >37.5°C increased 24 hours after drug administration, but tended to decrease within 48 hours. On the other hand, blood pressure and heart rate did not demonstrate any tendencies between pre- and post-dose. During the study period, parathyroid hormone tended to increase about 2-fold from baseline regardless of treatment. Except for the reported AEs, no clinically significant findings were observed on physical examinations, laboratory tests, or ECG.

Discussion

Osteoporosis and bone fracture continuously increase in rapidly aging societies.[17] This is especially true in Korea: according to a recent 2008 report, about 2.9 million patients are receiving treatment of osteoporosis and >80% of patients are women >50 years of age. In addition, 33.3% of women >50 years might suffer from osteoporosis.[18] Until recently, bisphosphonate comprised the main treatment of osteoporosis regimen. Many efforts have been approved to increase dosing intervals, notably once-a-month 150 mg ibandronate.[19] Recent trials have also confirmed the non-inferiority of once-a-month ibandronate vs repeated daily doses of 2.5 mg ibandronate.[20,21] Also, considering that ibandronate and vitamin D combination therapy has been recommended for the treatment of osteoporosis, the DP-R206 (150 mg ibandronate/24,000 IU vitamin D3) once per month is expected to increase adherence by decreasing the number of required daily doses, as well as to obtain the treatment efficacy.

This study was conducted to compare the PK characteristics of DP-R206 and ibandronate. As a result, the 90% CI values of the geometric mean ratios for the primary PK parameters range between 0.8–1.25. Ibandronate demonstrates very low bioavailability (0.63%) when administered as part of an oral dosing regimen, as well as large inter- and intra-individual variability (approximately 70% and 46%, respectively).[22] Therefore, ≥68 participants are needed to obtain statistical power >80% and level of significance <0.05 after considering intra-individual variability (46% assumption). After considering dropouts, our goal was to recruit 84 participants.[23] Although total 72 subjects completed this study, that was satisfied with the minimum required number of subjects. In addition, this study was designed to administer drugs during fasting in order to reduce variability. To minimize esophageal irritation, drug dosing was administered in an upright position, and this position was maintained for 1 hour.[19]

According to this study, DP-R206 and ibandronate was bioequivalent in the aspect of ibandronate pharmacokinetics. Also, the T_{max} of ibandronate is about 2 hours after dosing and the half-life is about 30 hours and these results are similar to the previous studies on 2.5 mg ibandronate.[19] Another study reported the bioequivalence of vitamin D when administered as DP-R206 or vitamin D_3.[24] Therefore, ibandronate and vitamin D-both ingredients in DP-R206-are bioequivalent, and it is expected that DP-R206 administration would be shown similar pharmacokinetic characteristics compared to the each component of drug administration. But this study is conducted in only healthy male volunteers with single dose administration, further long-term studies in osteoporosis patients might be helpful to evaluate clinical efficacy of DP-R206.

Throughout this study, similar AEs were reported regardless of DP-R206 or ibandronate administration. Most AEs were previously known events, including GI symptoms, influenza-like symptoms, musculoskeletal symptoms, and headache.[19] The development of influenza-like symptoms after ibandronate administration is a kind of acute reaction, and mostly occurred after the first dosing (rarely after repeated administration).[19] This mechanism is associated with inflammation-mediated cytokines (e.g., interlukin-6), and symptoms generally spontaneously recover or antifebrile agents can control symptoms.[25] Musculoskeletal pain is commonly associated with influenza-like symptoms. Although the mechanism is unclear, secondary hyperparathyroidism affects cytokines and synergistically increases drug concentration in bone, which is followed by local pain.[25] Here, all AEs, including influenza-like symptoms and musculoskeletal pain, spontaneously recovered or lessened following the administration of intermittent acetaminophen, and no sequelae were reported. The overall characteristics of AEs and ADRs following DP-R206 administration were not significantly different than following ibandronate administration, and no clinically significant findings were reported.

In conclusion, the PK characteristics of ibandronate are similar when administered as single-dose ibandronate or DP-R206 to healthy volunteers, and both drugs are generally tolerable.

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final decision regarding its submission. Authors contributed this paper to conduct the clinical trial in this paper and we all read and approved of the contents.

Conflict of Interest

We authors have not any conflicts of interest regarding the content of the article.

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