Pharmacokinetic Interaction Among Telmisartan, Amlodipine, and Hydrochlorothiazide After a Single Oral Administration in Healthy Male Subjects

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ABSTRACT

Purpose: Hypertension is a major risk factor for cardiovascular diseases, necessitating hypertension control. Antihypertensive drugs are more potent when administered in combinations of 2 or 3 different classes of drugs. One such therapy includes a combination of an angiotensin receptor blocker, a calcium channel blocker, and a diuretic. The objective of this study was to evaluate the pharmacokinetic interaction among telmisartan, amlodipine, and hydrochlorothiazide.

Methods: : A randomized, open-label, 3-period, 6-sequence, 3-treatment, single-dose crossover study was conducted in healthy male subjects. Subjects were randomly assigned to 1 of 6 sequences and one of the following treatments was administered in each period: treatment A, co-administration of one tablet of telmisartan 80 mg and one tablet of amlodipine 10 mg; treatment B, one tablet of hydrochlorothiazide 25 mg alone; and treatment C, co-administration of all 3 investigational products. Serial blood samples were collected up to 144 hours postdose. Plasma drug concentrations were measured by using LC/MS−MS. Pharmacokinetic parameters, including C_{max} and AUC_{0-last}, were determined by using noncompartmental analysis. The geometric least squares mean ratios and associated 90% CIs of log-transformed C_{max} and AUC_{0-last} for separate administration or co-administration were calculated to evaluate pharmacokinetic interactions.

Findings: Twenty-seven subjects completed the study. The geometric least squares mean ratios and 90% CIs of C_{max} and AUC_{0-last} were 1.02 (0.85−1.21) and 1.04 (0.97−1.13) for telmisartan; 1.00 (0.95−1.04) and 0.95 (0.91−0.99) for amlodipine; and 0.88 (0.82−0.96) and 0.86 (0.82−0.90) for hydrochlorothiazide, respectively. No serious adverse events were recorded, and all reported adverse events were of mild intensity.

Implications: The pharmacokinetic parameters of telmisartan, amlodipine, and hydrochlorothiazide when administered separately or co-administered were compared, and all the parameters met the criteria for pharmacokinetic equivalence. Combination therapy of these 3 drugs had no significant impact on the pharmacokinetic parameters of each drug. (ClinicalTrials.gov Identifier: NCT03889145) (*Clin Ther*. 2019;41:2273−2282)

Key words: antihypertensive, drug−drug interaction, pharmacokinetics, Phase I.

INTRODUCTION

Cardiovascular diseases (CVDs) are one of the most prevalent causes of mortality worldwide, contributing to 17.9 million deaths each year (~31% of all global deaths).[1] CVDs are multifactorial disorders caused by

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multiple risk factors, including hypertension, dyslipidemia, and obesity. Among these, hypertension is responsible for fatal complications such as total ischemic heart disease and stroke.[2] Because the prevalence of hypertension is gradually increasing globally, the American College of Cardiology and the American Heart Association published a new guideline in 2017, which includes a stricter definition of hypertension to account for complications that can occur at lower numbers.[3]

According to the American College of Cardiology/American Heart Association 2017 guideline, stage 1 hypertension is now defined as systolic blood pressure (SBP) ranging from 130 to 139 mm Hg or diastolic blood pressure (DBP) ranging from 80 to 89 mm Hg.[3] In line with this new definition, blood pressure <130/80 mm Hg (SBP/DBP) is considered ideal in most patients. The guideline also recommends a detailed assessment of CVD risks, such that if the risks are high, antihypertensive medication can be initiated at earlier stages.

Further recommendations are set to guide the prescription of antihypertensive medication, such as the one announced in 2014 by the Eighth Joint National Committee.[4] Generally, the initial therapy includes the use of primary agents, such as thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) alone or in combination. Evidence supports the theory that combination therapy of 2 or more antihypertensive drugs is much more effective in lowering blood pressure,[5] and some antihypertensive medications are now marketed as a fixed-dose combination of 2 or 3 drug products that include ARBs, CCBs, and thiazide diuretics.

Telmisartan is a highly selective ARB for the angiotensin II type 1 receptor, which is known to mediate most of the physiological actions related to blood pressure regulation.[6] It reduces blood pressure independently from the angiotensin II synthesis pathway by blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Telmisartan reaches peak concentrations ~0.5−1 h after oral administration and is mainly eliminated by feces via biliary excretion with an elimination $t_{1/2}$ of ~24 h.

Amlodipine is one of the most widely marketed CCBs that works by disrupting calcium movement, thereby relaxing smooth muscles located in heart and blood vessels. This action leads to lowering afterload, increasing glomerular filtration and the subsequent diuretic effect, resulting in lowered blood pressure. Amlodipine is slowly absorbed after administration, with a $t_{1/2}$ of 35−40 h, and its antihypertensive effect is gradual with a low possibility of adverse events (AEs) such as orthostatic hypotension.[7]

Telmisartan and amlodipine, as well as telmisartan and hydrochlorothiazide, have already been marketed as fixed-dose combinations after the lack of pharmacokinetic interactions between the components was reported.[8,9] However, for patients with hypertension who need strict blood pressure control, a combination therapy of all 3 drugs may help improve therapeutic outcomes. Hence, a fixed-dose combination of these 3 drugs (telmisartan, amlodipine, and hydrochlorothiazide) may improve patient compliance by reducing pill burden, while maintaining the antihypertensive effect. The objective of the present study was to evaluate the pharmacokinetic interaction among telmisartan, amlodipine, and hydrochlorothiazide after single oral administration in healthy volunteers.

PATIENTS AND METHODS

Study Population

Healthy male volunteers, defined as individuals with no clinically significant abnormalities in medical history, physical examination, 12-lead ECG, and clinical laboratory tests, were enrolled after providing written informed consent. The eligible subjects were aged between 20 and 55 years, weighed at least 55 kg, with a body mass index of at least 17.5 kg/m^2 and no greater than 30.5 kg/m^2. Specific exclusion criteria included a history or current evidence of acute or chronic illness, including hypersensitivity to any of the investigational products or any other clinically relevant hypersensitivity. Individuals with clinically significant abnormalities in blood chemistry, hematology, serology, urinalysis, and urine drug screening tests were excluded. Individuals with SBP $\leq$100 mm Hg, or $\geq$150 mm Hg, or whose DBP was $\leq$60 mm Hg, or $\geq$100 mm Hg, were also excluded. Subjects who participated in other clinical trials within 2 months, who donated whole blood within 2 months, or who received a blood transfusion or donated blood components within 1 month of the first day of the study were excluded. Subjects who could not refrain from consuming alcohol during hospitalization or who smoked >20 cigarettes a day were also excluded from the study.

Study Design

This study was a randomized, open-label, 3-period, 6-sequence, 3-treatment, single-dose crossover trial. Eligible subjects were randomly assigned to 1 of the 6 sequences and were admitted to Chonbuk National University Hospital a day before investigational product administration in each period; a 21-day washout period was set between each period. Fasting subjects received one of the following treatments, with 240 mL of water, once in each period: treatment A, co-administration of one tablet of telmisartan 80 mg and one tablet of amlodipine 10 mg; treatment B, one tablet of hydrochlorothiazide 25 mg alone; and treatment C, co-administration of all 3 investigational products. Serial blood samples were collected up to 144 hours postdose. Pharmacokinetic blood samples were collected in EDTA tubes and were centrifuged within 1 h of collection at 4 °C for 10 min, and 4 aliquots of 1 mL plasma were collected and stored at −70 °C until further analysis.

The study protocol was approved by the Institutional Review Board of Chonbuk National University Hospital and conducted in accordance with the principles of the Declaration of Helsinki and Korean Good Clinical Practice (ClinicalTrials.gov identifier, NCT03889145).

Plasma Drug Concentration Analysis

Plasma telmisartan concentrations were determined according to a validated LC/MS−MS (Agilent 1200 series LC system coupled with Agilent 6460 Triple Quad LC/MS; Agilent Technologies, Palo Alto, California) by using telmisartan-d_3 as the internal standard. Chromatographic separation was performed by using a Hypersil GOLD C_{18} column (2.1 mm internal diameter [ID] × 100 mm L, 5 μm; Thermo Fisher Scientific, Waltham, Massachusetts) at a flow rate of 0.3 mL/min. The mobile phase used was 10 mM ammonium acetate:acetonitrile (60:40, v/v). Electrospray ionization in positive ion mode was used for detection and quantification. The multiple reaction monitoring (MRM) transitions were m/z 515.3 → 276.2 for telmisartan and 518.3 → 279.2 for the internal standard. A calibration curve covering the range of 2−2000 ng/mL was constructed. The intraday accuracy was 95.31%−105.08% (with a precision of 0.41%−1.03%), and the interday accuracy was 95.49%−104.40% (with a precision of 0.29%−1.08%).

For amlodipine, LC-MS/MS (Thermo Dionex UltiMate 3000 [Thermo-Dionex, Sunnyvale, California]; Thermo TSQ Vantage [Thermo Fisher Scientific, San Jose, California]) was used to determine plasma concentrations using amlodipine-d_4 as the internal standard. Chromatographic separation was performed by using a Hypersil GOLD C_{18} column (2.1 mm ID × 50 mm L, 1.9 μm) at a flow rate of 0.25 mL/min. The mobile phase used was 0.1% formic acid:acetonitrile (50:50, v/v). The MRM transitions were m/z 409.2 → 238.2 for amlodipine and 413.3 → 238.2 for the internal standard. A calibration curve covering the range of 0.2−20 ng/mL was constructed. The intraday accuracy was 96.83%−103.60% (with a precision of 2.30%−6.21%), and the interday accuracy was 97.19%−100.36% (with a precision of 4.53%−7.32%).

For hydrochlorothiazide, LC-MS/MS (Agilent 1260 Infinity [Agilent Technologies]; API 3200 [AB Sciex, Foster City, California]) was used to determine plasma concentrations by using topiramate as the internal standard. Chromatographic separation was performed by using a Luna Phenyl-Hexyl column (2.0 mm ID × 100 mm L, 3 μm; Phenomenex, Torrance, California) at a flow rate of 0.2 mL/min, and the mobile phase used was Milli-Q water:methanol (15:85, v/v). The MRM transitions were m/z 295.8 → 268.8 for hydrochlorothiazide and 337.9 → 78.0 for the internal standard. A calibration curve covering the range of 1−300 ng/mL was constructed. The intraday accuracy was 98.35%−105.55% (with a precision of 2.31%−4.68%), and the interday accuracy was 98.21%−110.58% (with a precision of 0.75%−4.49%).

All the assays were validated according to the Guideline on Bioanalytical Method Validation published by Korean Ministry of Food and Drug Safety (2013).[10] Details regarding all assays were previously published.[11−13]

Pharmacokinetic Analysis

The pharmacokinetic analysis included all subjects who had completed the study according to the protocol. The pharmacokinetic parameters were assessed by using a noncompartmental method provided by Phoenix WinNonlin software version 6.3 (Certara L.P [Pharsight], Princeton, New Jersey). C_{max} and T_{max} were directly obtained from the plasma concentration−time profiles. The terminal

elimination $t_{1/2}$ was calculated as ln $2/\lambda_z$, where λ_z was the slope of the apparent elimination phase of the natural logarithmic (ln) transformation of the plasma drug concentration–time profiles. AUC_{0-last} was calculated according to the linear trapezoidal method. $AUC_{0-\infty}$ was estimated as $AUC_{0-last} + C_{last}/\lambda_z$, where C_{last} is the plasma concentration of the last measurable sample. CL/F was calculated as dose/$AUC_{0-\infty}$.

Statistical Analysis

Pharmacokinetic drug interactions were assessed for the principal parameters of systemic exposure (AUC_{0-last} and C_{max}). The log-transformed AUC_{0-last} and C_{max} were analyzed by using a mixed effects ANOVA with sequence, period, and treatment as fixed effect, and subject within sequence as random effect in SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina). The results for AUC_{0-last} and C_{max} were reported as 90% CIs surrounding the ratio of the geometric least squares means (GLSMs) of the pharmacokinetic parameters.

Safety Analysis

The safety analysis included all subjects who received at least 1 dose of any of the investigational drugs. Safety measurements included physical examination, clinical laboratory test results (including hematology, serum chemistry, and urinalysis), vital signs, 12-lead ECGs, and assessment of AEs. Descriptive statistics were used to summarize any clinically significant findings from thephysical examination, clinical laboratory test results, vital signs, and ECGs in each treatment arm.

RESULTS

Disposition of Subjects and Demographic Characteristics

Thirty subjects were randomized to treatment and received investigational products at least once. Three subjects dropped out after randomization due to withdrawal of consent, and 27 subjects completed the study. Descriptive statistics were used to analyze demographic characteristics for 30 subjects who were administered investigational products at least once. Subjects' age, height, weight, and BMI (mean [SD]) were 24.6 (2.3) years, 174.33 (4.52) cm, 69.80 (6.27) kg, and 22.96 (1.75) kg/m^2, respectively.

Pharmacokinetic Parameters of Telmisartan

The geometric mean plasma concentration–time profiles of telmisartan when administered with amlodipine only or in combination with all other investigational products are shown in Figure 1. The GLSM ratios and 90% CIs of telmisartan (when treatment C was administered compared with treatment A) were 1.02 (0.85–1.21) for C_{max} and 1.04 (0.97–1.13) for AUC_{0-last} (Table).

Pharmacokinetic Parameters of Amlodipine

The geometric mean plasma concentration–time profiles of amlodipine when administered with telmisartan only or in combination with all other investigational products are shown in Figure 2. The GLSM ratios and 90% CIs of amlodipine (when treatment C was administered compared with treatment A) were 1.00 (0.95–1.04) for C_{max} and 0.95 (0.91–0.99) for AUC_{0-last} (Table).

Pharmacokinetic Parameters of Hydrochlorothiazide

The geometric mean plasma concentration–time profiles of hydrochlorothiazide when administered separately or in combination with all other investigational products are shown in Figure 3. The GLSM ratios and 90% CIs of hydrochlorothiazide (when treatment C was administered compared with treatment B) were 0.88 (0.82–0.96) for C_{max} and 0.86 (0.82–0.90) for AUC_{0-last} (Table).

Safety and Tolerability of Telmisartan, Amlodipine, and Hydrochlorothiazide

In total, 3 AEs were reported from 2 subjects who were administered the investigational products at least once. Two cases of dizziness and one case of headache were reported, all of which were of mild severity and were expected. All AEs were considered to be related to the investigational products, and subjects recovered spontaneously, without sequelae. No clinically significant changes in the laboratory test results, vital signs, 12-lead ECGs, or physical examination were reported.

DISCUSSION

The pharmacokinetic parameters, when telmisartan, amlodipine, and hydrochlorothiazide were administered separately or co-administered, were

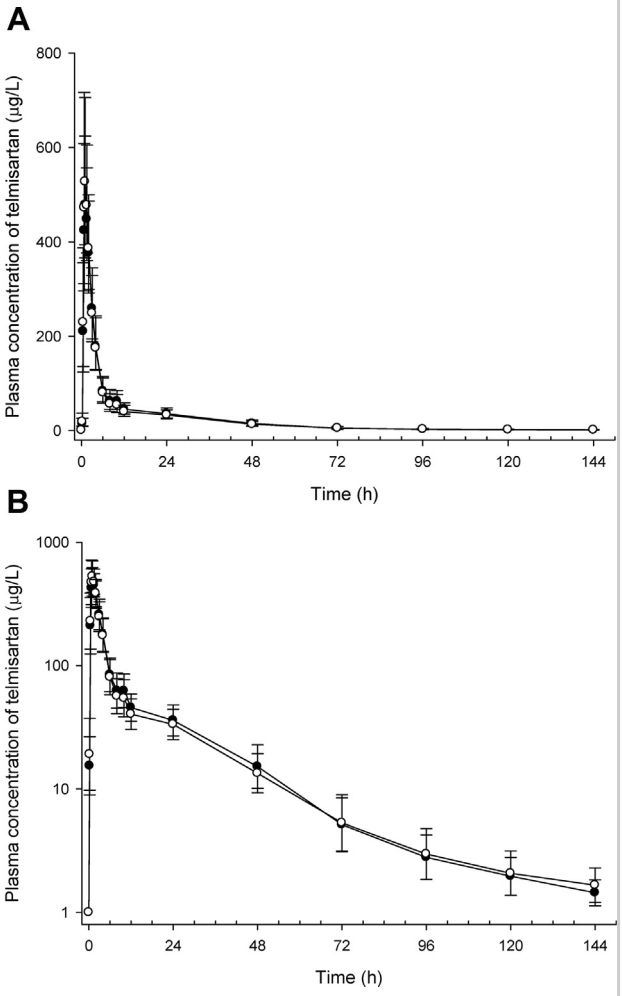

Figure 1. Geometric mean plasma concentration−time profiles of telmisartan when administered in treatment A (co-administration of telmisartan 80 mg and amlodipine 10 mg; open circle) or in treatment C (co-administration of telmisartan 80 mg, amlodipine 10 mg, and hydrochlorothiazide 25 mg; closed circle), in linear (A) and semi-logarithmic (B) scale. Each point represents the geometric mean (± 95% CIs).

compared. All the calculated values of AUC_{0-last} and C_{max} upon co-administration of telmisartan, amlodipine, and hydrochlorothiazide were similar to the results of individual administration.

Although 2 or 3 antihypertensive agents are often prescribed to patients in clinical practice, many times they have been used in incorrect or controversial ways,[14] and in some cases the pharmacokinetic interactions between each antihypertensive agent are not well evaluated. After the completion of this present study, lack of pharmacokinetic interaction among telmisartan, amlodipine and hydrochlorothiazide was also reported in a Japanese study,[15] the results of which were consistent with our results. Apart from the pharmacokinetic parameters, the effectiveness of triple-drug therapy with these 3 drugs was evaluated in a separate Phase III study[16] and was found to be highly effective. A study that compared the pharmacokinetic variables of the fixed-dose combination versus the concurrent administration of individual components also showed bioequivalence.[17] Along with the results from the present study, it can be concluded that the combination therapy using telmisartan, amlodipine, and hydrochlorothiazide does not require dose adjustment and could be used to produce better antihypertensive effects.

According to the literature, the longest $t_{1/2}$ of the investigational products was observed for amlodipine (30−50 h), whereas telmisartan and hydrochlorothiazide exhibited $t_{1/2}$ values of 24 h and 14.8 h, respectively.[6,7,18] Based on the longest $t_{1/2}$ of amlodipine, the final pharmacokinetic sampling time was set at 144 h' postdose, and the washout period was set at 21 days, which was >5 times the $t_{1/2}$ of amlodipine. In this study, the $t_{1/2}$ of amlodipine was found to be 41.59−43.17 h; the washout period was therefore deemed adequate.

The lack of pharmacokinetic interaction among the antihypertensive drugs observed in this study suggests that the enzymes and transporters involved in absorption, disposition, and elimination of the drugs do not overlap, or do not interact significantly despite a possible overlap. This is partly predictable because the target proteins and metabolic pathways are well known for the 3 drugs; telmisartan, amlodipine, and hydrochlorothiazide all target different proteins, such as angiotensin receptor, calcium channel, and sodium/chloride transporter.[6,7,18] The same explanation can be applied to elimination pathways. Telmisartan is mostly eliminated unchanged in feces (>97%) via biliary excretion; only a small amount is conjugated

Table. Summary of pharmacokinetic parameters when telmisartan, amlodipine, and hydrochlorothiazide were administered separately (S: co-administration of telmisartan 80 mg and amlodipine 10 mg, or separate administration of hydrochlorothiazide 25 mg), or co-administered (C). The pharmacokinetic parameters (AUC_{0-last} and C_{max}) when co-administered were compared versus those parameters when administered separately (C/S) by using geometric least squares mean (GLSM) ratios and 90% CIs.

Variable	T_{max} (h)	$t_{1/2}$ (h)	C_{max} (μg/L)	AUC_{0-last} (μg·h/L)	$AUC_{0-\infty}$ (μg·h/L)	CL/F (L/h)
Telmisartan						
S (N = 27)	0.75 (0.50–2.00)	25.73 (15.52)	857.62 (491.66)	4470.48 (3331.89)	4683.87 (3415.55)	26.95 (18.05)
C (N = 27)	1.00 (0.50–3.00)	20.99 (6.14)	795.97 (362.16)	4612.14 (3554.54)	4735.85 (3565.20)	25.36 (14.40)
GLSM ratio (90% CI)	N/A	N/A	1.02 (0.85–1.21)	1.04 (0.97–1.13)	N/A	N/A
Amlodipine						
S (N = 27)	6.00 (4.00–12.00)	43.17 (8.40)	6.89 (1.61)	346.67 (104.47)	388.80 (129.43)	28.34 (8.77)
C (N = 27)	6.00 (4.00–10.00)	41.59 (6.85)	6.90 (1.54)	328.34 (86.82)	363.40 (103.29)	29.78 (8.76)
GLSM ratio (90% CI)	N/A	N/A	1.00 (0.95–1.04)	0.95 (0.91–0.99)	N/A	N/A
Hydrochlorothiazide						
S (N = 27)	2.00 (1.00–4.00)	8.91 (1.01)	169.69 (41.41)	1096.67 (197.88)	1143.22 (182.47)	22.41 (3.57)
C (N = 27)	1.50 (1.00–4.00)	8.68 (1.43)	148.29 (34.21)	960.35 (252.21)	1021.41 (240.03)	25.81 (6.12)
GLSM ratio (90% CI)	N/A	N/A	0.88 (0.82–0.96)	0.86 (0.82–0.90)	N/A	N/A

Note: Pharmacokinetic parameters are represented as arithmetic mean (SD), except $T_{max,}$ where the values are represented as the median (minimum–maximum). N/A represents Not Applicable.

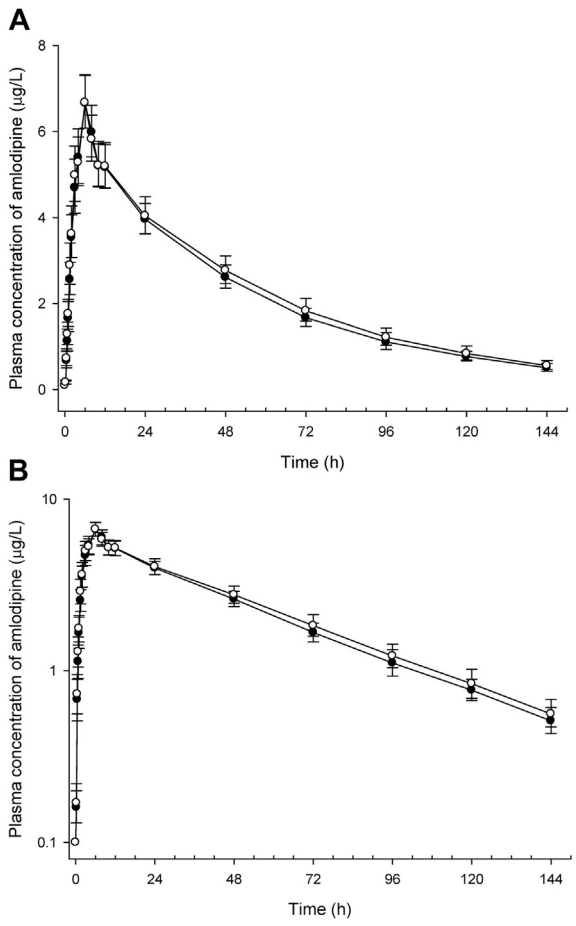

Figure 2. Geometric mean plasma concentration–time profiles of amlodipine when administered in treatment A (co-administration of telmisartan 80 mg and amlodipine 10 mg; open circle) or in treatment C (co-administration of telmisartan 80 mg, amlodipine 10 mg, and hydrochlorothiazide 25 mg; closed circle), in linear (A) and semi-logarithmic (B) scale. Each point represents the geometric mean (± 95% CIs).

to form an inactive acyl glucuronide, and cytochrome P450 (CYP) enzymes are not involved in telmisartan metabolism.[6] Conversely, amlodipine mainly undergoes hepatic metabolism (~90% converted to inactive metabolites, with 10% of the parent compound and 60% of the metabolites excreted in the urine) through CYP3A4 and CYP3A5, in which CYP3A4 is more likely to be involved in amlodipine metabolism.[7,19] Because hydrochlorothiazide is mostly excreted in urine unchanged (>95%),[18] it can be inferred that the 3 investigational products in this study do not interfere with each other in absorption or elimination.

Changes in enzyme activity and transporter induction were not evaluated in the present study, however, and as a result, only speculations can be made about enzyme and/or transporter induction potentials of the 3 investigational products. There are references that transporters such as organic anion transporter 1 could be inhibited by thiazide diuretics,[20] and multidrug resistance protein 1 could be inhibited by telmisartan and amlodipine[21,22]; telmisartan also reportedly activates peroxisome proliferator-activated receptor gamma.[23] Possible interactions that involve such transporters could be determined if further studies are conducted.

Several fixed-dose combinations that included 2 or more antihypertensive drugs have been approved and are currently in development. The combinations approved by the US Food and Drug Administration include amlodipine/valsartan/hydrochlorothiazide, losartan/hydrochlorothiazide, amlodipine/telmisartan, and telmisartan/hydrochlorothiazide. The US Food and Drug Administration has also issued a new Guidance for Industry, named "Hypertension: Developing Fixed-Combination Drug Products for Treatment," to assist the clinical development of fixed-dose combination drug products for treatment of hypertension.[24] Although the effect of fixed-dose combinations on lowering drug costs is disputable, fixed-dose combinations in hypertensive therapy reportedly improve patient persistence and adherence by reducing the pill burden.[25,26] Because a Phase III clinical trial has already shown significantly increased efficacy for triple therapy with telmisartan, amlodipine, and hydrochlorothiazide compared with telmisartan and amlodipine double therapy,[16] the fixed-dose combination of the 3 investigational products would be beneficial to patients in terms of compliance and efficacy.

In this study, the pharmacokinetic interaction between telmisartan and amlodipine was not evaluated because these 2 drugs were known to have no such interaction.[8] Also, a study design that included separate administrations of telmisartan and

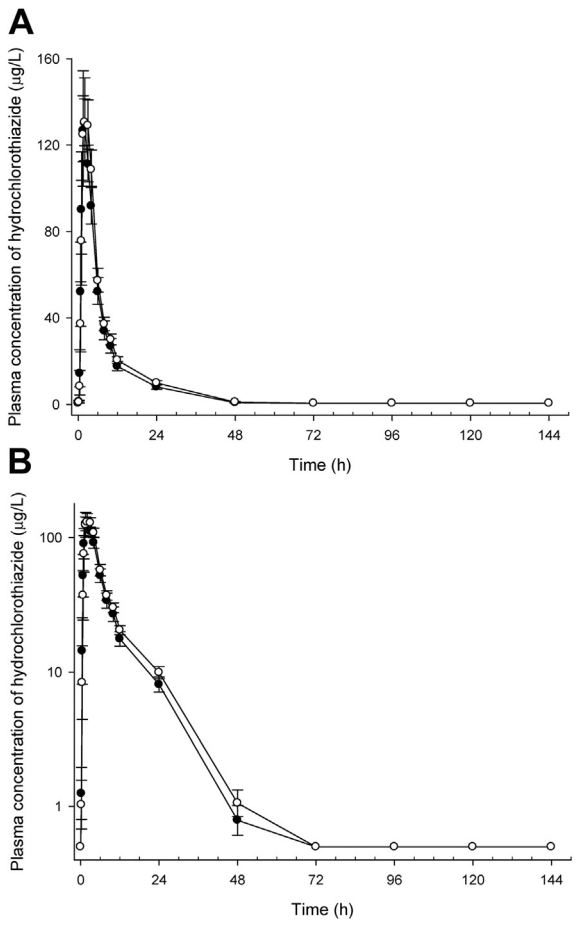

Figure 3. Geometric mean plasma concentration–time profiles of hydrochlorothiazide when administered in treatment B (administration of hydrochlorothiazide 25 mg; open circle) or in treatment C (co-administration of telmisartan 80 mg, amlodipine 10 mg, and hydrochlorothiazide 25 mg; closed circle), in linear (A) and semi-logarithmic (B) scale. Each point represents the geometric mean (± 95% CIs).

amlodipine would have required more extensive blood sampling and longer study duration, which could burden the study participants. Because there is evidence that these 2 components do not interact significantly with each other, interpretation of the study results would not be affected by the present study design.

Only male subjects were recruited in this study because of practical reasons, mainly that assigning separate hospital wards for female participants was difficult in the current research site. Smokers who consumed <20 cigarettes per day were included due to a similar reason: recruiting nonsmoking male participants was difficult in the current research site. The study participants were asked to refrain from smoking during hospitalization, but their smoking habits were kept uniform during outpatient visits, which were confirmed by interviewing the subjects. Smoking is related to induced enzymes such as CYP1A1, CYP1A2, CYP2E1, and CYP2B6[27]; among these, CYP1A2 activity is known to be significantly induced in heavy smokers who smoke >20 cigarettes per day.[28] Because our study recruited subjects who smoked <20 cigarettes per day, and because the 3 investigational products are not metabolized by CYP1A2, it is assumed that smoking would not limit the interpretation of the study results.

This study was explorative in nature, and the sample size was determined empirically. Previous studies have included 12 to 18 subjects to detect pharmacokinetic interactions[29–31]; considering dropout rates, it was determined that 5 subjects per sequence group would be adequate. No power calculations were conducted a priori.

CONCLUSIONS

All the pharmacokinetic parameters of telmisartan, amlodipine, and hydrochlorothiazide met the pharmacokinetic equivalent criteria. Combination therapy of these 3 drugs does not have a significant impact on the pharmacokinetic parameters of each drug.

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Dr. Moon was responsible for the formal analysis and the writing of the original draft. Dr. Jeon was responsible for project administration; investigation; formal analysis; and writing, review, and editing. Dr. Yu was responsible for formal analysis; and writing, review, and editing. Dr. Kim was responsible for conceptualization; funding

acquisition; investigation; and writing, review, and editing. All authors contributed toward data analysis, and drafting and critically revising the paper; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

IlDong Pharmaceutical Co, Ltd was responsible for the monitoring and reviewing the analyses and the report of this study, and also provided protocol-specific training for all investigators and responsible study site staff. Study protocol procedures, study requirements, and Korean Good Clinical Practice responsibilities were reviewed by IlDong Pharmaceutical Co, Ltd. IlDong Pharmaceutical Co, Ltd did not fund medical writing support for this article, and the authors made the final decision to submit the article for publication.

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