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ORIGINAL RESEARCH

Pharmacokinetic/Pharmacodynamic Interaction Between Evogliptin and Pioglitazone in Healthy Male Subjects

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Aim: Evogliptin is a newly developed oral glucose-lowering medication of the dipeptidyl peptidase 4 (DPP-4) inhibitor class for type 2 diabetes mellitus. The combination of a DPP-4 inhibitor with pioglitazone is a promising therapeutic option. The aim of the present study was to evaluate the pharmacokinetic and pharmacodynamic interaction between evogliptin and pioglitazone.

Materials and Methods: A randomized, open-label, multiple-dose, three-treatment, three-period, six-sequence crossover study was conducted in healthy Korean male subjects. All subjects received evogliptin 5 mg once daily for 7 days (EVO), pioglitazone 30 mg once daily for 7 days (PIO) and co-administration of evogliptin 5 mg and pioglitazone 30 mg once daily for 7 days (EVO+PIO) according to the assigned sequence and period. Serial blood samples were collected for 24 hours for pharmacokinetic analysis and 3 hours after the oral glucose tolerance test for the pharmacodynamic analysis.

Results: Thirty-four subjects completed the study. EVO+PIO and EVO showed a similar maximum plasma concentration at steady state ($C_{max,ss}$) and area under the concentration-time curve during the dosing interval at the steady state ($AUC_{\tau,ss}$) of evogliptin, with geometric mean ratios (GMRs) (90% confidence interval (CI)) of 1.01 (0.97–1.05) and 1.01 (0.98–1.04), respectively. EVO+PIO and PIO showed a similar $C_{max,ss}$ and $AUC_{\tau,ss}$ of pioglitazone, with GMRs (90% CI) of 1.07 (0.99–1.17) and 1.08 (0.99–1.17), respectively. Reduction of the glucose level after EVO+PIO was larger compared to PIO and similar with EVO.

Conclusion: Concomitant administration of evogliptin and pioglitazone showed similar glucose-lowering effects with those of evogliptin alone without pharmacokinetic interactions when compared to the intake of each drug alone.

Keywords: evogliptin, pioglitazone, pharmacokinetics, pharmacodynamics, drug interaction

Introduction

Type 2 diabetes mellitus (T2DM), which accounts for more than 90% of all DM cases, is a progressive disease resulting in the gradual decline of the insulin secretory capacity.[1,2] As a result, approximately 60% of patients fail to achieve their glycemic goal with monotherapy at 6 years in Korea.[3] Current guidelines on the management of T2DM recommend metformin as a first-line medication, and glucose-lowering medications including oral agents and injectable medications as a second-line if the optimal glycemic target is not achieved.[4] Still, additional glucose-lowering medication is required in patients with inadequate glycemic control.

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Dipeptidyl peptidase 4 (DPP-4) inhibitors prevent the DPP-4 enzyme from degrading incretins including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).[5] Increased incretins subsequently lower the blood glucose level by stimulating insulin release and inhibiting glucagon production.[6] Evogliptin is an orally bioavailable, selective DPP-4 inhibitor developed for the treatment of T2DM.[7] After repeated once-daily administrations in healthy subjects in a first-in-human clinical trial (ClinicalTrials.gov Identifier: NCT00961025), evogliptin was well tolerated over time to reach a maximum plasma concentration (T_{max}) of 4–5 hours after administration and a terminal half-life ($t_{1/2}$) of 33–39 hours.[8] At steady state, evogliptin showed a dose-proportional increase in systemic exposure and sustained inhibition of DPP-4 activity above 80% in a dose range of 5–20 mg.[8] In an in vitro study, evogliptin was mainly metabolized to 4(S)-hydroxyevogliptin (M7) and 4(R)-hydroxyevogliptin (M8) by CYP3A4 and CYP3A5.[9] The pharmacological activity of the metabolites is currently unknown.[10] The recommended dosage of evogliptin for T2DM is 5 mg once daily.[11]

Pioglitazone, on the other hand, is a thiazolidinedione (TZD) that increases insulin sensitivity by acting as an agonist of peroxisome proliferator–activated receptor gamma (PPAR-γ).[12] After a once-daily oral administration, the T_{max} of pioglitazone is about 2 hours, and $t_{1/2}$ is in the range of 3–7 hours.[13] Pioglitazone is extensively metabolized, mainly by CYP2C8, CYP3A4 and CYP2C9, to form active metabolites (M3 and M4).[13,14] The recommended starting dose of pioglitazone is 15 to 30 mg once daily.[13]

The combination of DPP-4 inhibitors with pioglitazone treatment for T2DM has shown potential as an effective treatment due to their complementary mechanisms of action.[15] A recent guideline of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on T2DM suggests the addition of DPP-4 or TZD to subjects who do not achieve the target HbA_{1c} level with metformin monotherapy in case compelling need exists to reduce hypoglycemia. If dual therapy with metformin plus either DPP-4 or TZD fails to meet the target, the addition of the other one could be considered for a triple therapy according to the guideline.[1]

Because evogliptin and pioglitazone have complementary mechanisms of action, the combination of the two medications is a promising therapeutic option for T2DM treatment. However, the assessment of the drug interaction between the two drugs has not been done. The aim of the present study was to evaluate the pharmacokinetic and pharmacodynamic interaction between evogliptin and pioglitazone along with safety profiles in healthy volunteers.

Materials and Methods

Subjects

Healthy Korean male volunteers aged between 19 and 45 years with a body mass index (BMI) between 18.0 and 27.0 kg/m^2 were eligible for inclusion in this study. Volunteers with a fasting plasma glucose (FPG) <70 mg/dL or >125 mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >60 IU/mL, creatinine clearance (MDRD equation) <80 mL/min, corrected QT interval (Bazett correction) >450 ms, known allergy or hypersensitivity to components of the investigational drug (evogliptin and pioglitazone) were excluded. Other major reasons for exclusion were as follows: clinically significant abnormalities in the medical history, vital sign measurements, physical examination, clinical laboratory tests (hematology, biochemistry and urinalysis) and 12-lead electrocardiogram. According to the results from previous studies, the largest intra-subject variability of the selected pharmacokinetic parameters (C_{max} and $AUC_{\tau,ss}$) of evogliptin, pioglitazone and their major metabolites was assumed to be 29%.[8,16] A sample size of 30 was required to detect a 20% difference in those pharmacokinetic parameters with a power of 80% and a significance level of 0.05. The actual sample size was determined as 36 considering drop-out. The study was conducted in accordance with the Declaration of Helsinki and the Korean Good Clinical Practice. The study protocol was approved by Institutional Review Board (IRB) of Seoul National University Hospital (ClinicalTrials.gov identifier: NCT02753803, IRB number: 1604-135-757) and the Ministry of Food and Drug Safety, Republic of Korea. All volunteers provided written informed consent prior to the study procedure.

Study Design

This randomized, open-label, multiple-dose, three-treatment, three-period, six-sequence crossover study was conducted at the Clinical Trials Center of Seoul National University Hospital (Seoul, Republic of Korea). Eligible subjects were randomly assigned to one of six treatment sequence groups (Figure 1). Subjects received either evogliptin 5 mg once daily for 7 days (EVO), pioglitazone 30 mg once daily for 7 days

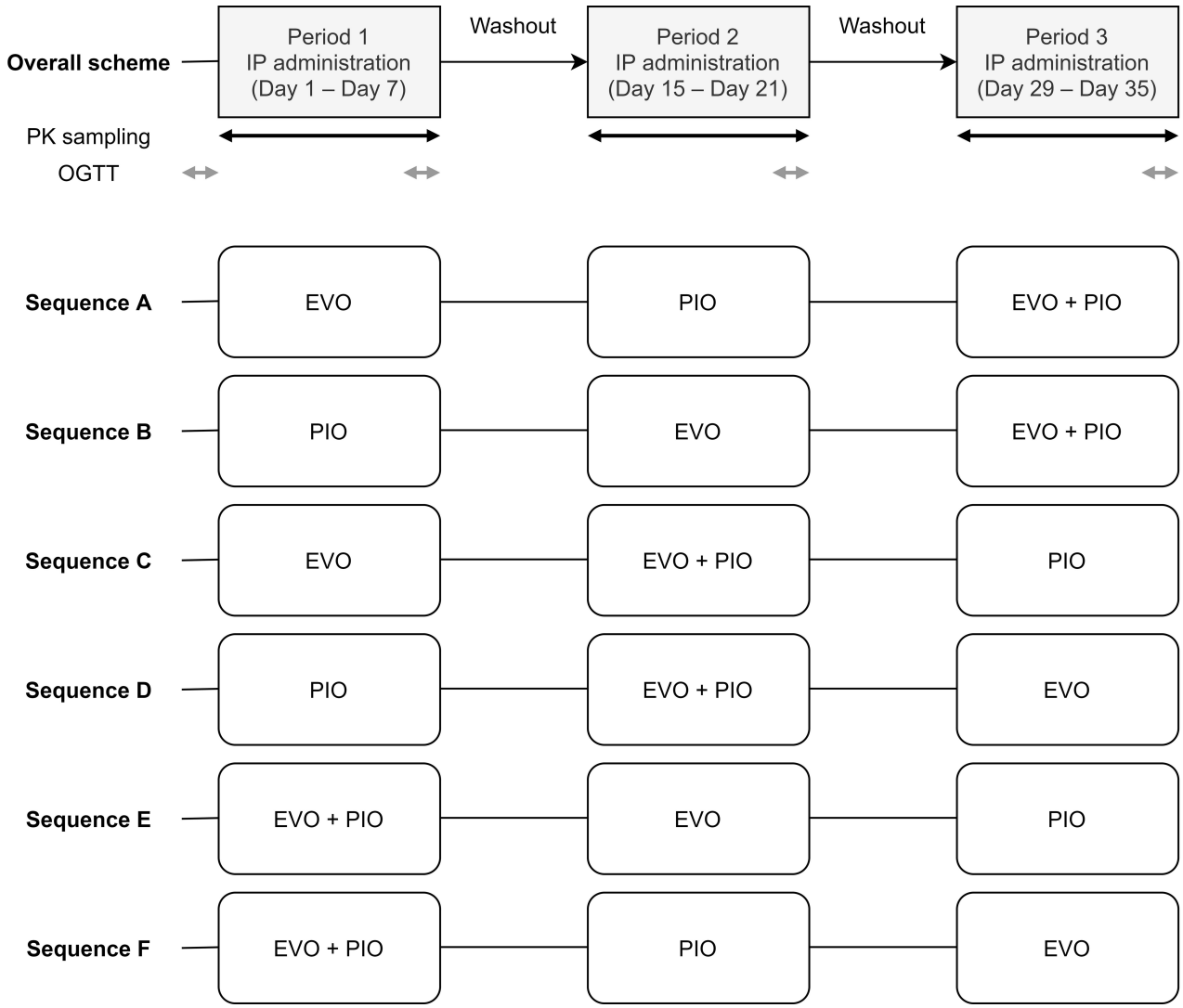

Figure 1 Study design.
Abbreviations: PK, pharmacokinetics; OGTT, oral glucose tolerance test; EVO, evogliptin 5 mg once daily; PIO, pioglitazone 30 mg once daily; EVO+PIO, evogliptin 5 mg + pioglitazone30 mg once daily.

(PIO), or coadministration of evogliptin 5 mg and pioglitazone 30 mg once daily for 7 days (EVO+PIO) according to the assigned sequence and period. Each treatment period was separated by 7 days of washout period. Study drugs were administered with 150 mL of water in the fasted state.

Pharmacokinetic Assessment

For the pharmacokinetic evaluation, serial blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours after the last dose for evogliptin and its metabolites (M7, M8), and at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours after the last dose for pioglitazone and its metabolites (M3, M4). Urine samples for evogliptin, pioglitazone and their metabolites were collected up to 24 hours after the last dose.

Individual steady-state pharmacokinetic parameters of each period were calculated by non-compartmental methods using the Phoenix WinNonlin® software version 8.0 (Certara, Princeton, NJ, USA). The maximum plasma concentration of each analyte at steady-state ($C_{max,ss}$) and the time to reach $C_{max,ss}$ ($T_{max,ss}$) were directly derived from the observed data. Area under the plasma concentration-time curve during a dosing interval at steady-state ($AUC_{\tau,ss}$) was calculated by the linear trapezoidal method when the concentrations were increasing in the interval, and by the log trapezoidal method when the concentrations were decreasing in the interval. Apparent clearance at

steady-state (CL_{ss}/F) was calculated as the administered dose/$AUC_{\tau,ss}$. Renal clearance at steady-state ($CL_{R,ss}$) was calculated as the amount of unchanged drug excreted into the urine during a dosing interval at steady state ($Ae_{\tau,ss}$)/$AUC_{\tau,ss}$. Metabolic ratio at steady state was calculated as the $AUC_{\tau,ss}$ of the metabolite/$AUC_{\tau,ss}$ of the parent drug.

The plasma and urine concentrations of evogliptin, pioglitazone and their metabolites (M7, M8 of evogliptin and M3, M4 of pioglitazone) were analyzed with a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (LC: Shimadzu UFLC, Shimadzu, Japan. MS: TQ5500(3)/5500QTRAP, SCIEX, USA). Internal standards (ISs) for evogliptin, M7 and M8 were evogliptin-d_9, M8-d_9 and M8-d_9, respectively, and the ISs for pioglitazone, M3 and M4 were pioglitazone-d_4, M3-d_4 and M4-d_5, respectively.

For the plasma sample analysis, the mobile phase consisted of 5 mM ammonium formate with 0.1% formic acid and acetonitrile for evogliptin and deionized water with 0.1% formic acid and methanol for M7 and M8. For pioglitazone, M3 and M4, the mobile phase consisted of 10 mM ammonium formate with 0.1% formic acid and acetonitrile. All plasma analytes and their ISs were separated in a C_{18} column (evogliptin: 100 × 2.1 mm, 1.7 μm, M7/M8: 100 × 2.1 mm, 5 μm, pioglitazone/M3/M4: 50 × 2.1 mm, 3 μm). Positive electrospray ionization (ESI) mode with multiple reaction monitoring (MRM) was used to detect the transition (*m/z*) of evogliptin (402.2 → 346.2), evogliptin-d_9 (411.2 → 347.2), M7 (418.2 → 362.2), M8 (418.2 → 362.2), M8-d_9 (427.2 → 363.2), pioglitazone (357.2 → 134.1), pioglitzone-d_4 (361.2 → 138.2), M3 (371.2 → 148.1), M3-d_4 (375.3 → 152.3), M4 (373.2 → 150.2) and M4-d_5 (378.3 → 154.4). The calibration curves of the plasma analytes were linear within the range of 0.1–60 ng/mL for evogliptin, 10–10,000 pg/mL for M7 and M8, 10–10,000 ng/mL for pioglitazone and 10–5000 ng/mL for M3 and M4 ($r \geq 0.9950$). The accuracy and precision of the intra-batch quality control (QC) were 98.0–106.3% and <8.3% for evogliptin, 96.0–107.8% and <6.7% for M7, 93.9–-105.9% and <6.5% for M8, 89.4–108.2% and <6.7% for pioglitazone, 95.6–106.9% and <7.3% for M3, and 92.-6–111.2% and <6.2% for M4.

For the urine sample analysis, the mobile phase consisted of 5 mM ammonium formate with 0.1% formic acid and acetonitrile for evogliptin, and it consisted of 5 mM ammonium formate with 0.1% formic acid and methanol for M7 and M8. For pioglitazone, M3 and M4, the mobile phase consisted of 10 mM ammonium formate with formic acid and acetonitrile. The other LC and MS/MS conditions were the same as in the plasma sample analysis. Calibration curves of the plasma analytes were linear within the range of 5–5000 ng/mL for evogliptin, 0.5–500 ng/mL for M7 and M8, 30–10,000 ng/mL for pioglitazone and 30–10,000 ng/mL for M3 and M4 ($r \geq 0.9950$). Accuracy and precision of the intra-batch quality control (QC) were 100.4–107.1% and <3.6% for evogliptin, 95.3–99.4% and <5.2% for M7, 97.4–110.8% and <6.2% for M8, 92.4–105.4% and <9.9% for pioglitazone, 103.3–109.1% and <4.3% for M3, and 99.2–107.8% and <8.2% for M4.

Pharmacodynamic Assessment

For the pharmacodynamic analysis, serial blood samples were collected during the oral glucose tolerance test (OGTT): 0 (pre-OGTT), 0.25, 0.5, 1, 1.5, 2 and 3 hours after the administration of glucose (75 g) to measure the serum glucose and plasma insulin levels. OGTT was conducted the day before the first study drug administration at period 1 (baseline) and 2 hours after the study drug administration at the sixth day of each period.

Individual steady-state serum glucose and plasma insulin parameters of each period were calculated by non-compartmental methods using the Phoenix WinNonlin® software. Maximum concentration of the serum glucose and plasma insulin at steady-state ($G_{max,ss}$, $E_{max,ss}$) were directly derived from the observed data. Area under the serum glucose and plasma insulin concentration-time curve during a dosing interval at steady-state ($AUGC_{\tau,ss}$, $AUEC_{\tau,ss}$) were calculated by the linear trapezoidal method.

The plasma concentrations of insulin were analyzed with the immunoradiometric assay (IRMA) method (gamma counter: Dream Gamma-10, Shin Jin, Republic of Korea). Serum concentrations of glucose were analyzed with the glucose hexokinase assay method (automatic chemical analyzer: TBA-FX8, Toshiba, Japan).

Safety Assessment

Safety and tolerability were assessed through vital signs, physical examination, clinical laboratory test, 12-lead electrocardiogram (ECG) and adverse event (AE) monitoring. All AEs that occurred during the study were recorded, coded using MedDRA® (Version 19.0), and evaluated by investigators.

Statistical Analysis

Descriptive statistics were used to summarize the demographic characteristics and the pharmacokinetic and pharmacodynamic parameters. To assess pharmacokinetic interaction between evogliptin and pioglitazone, geometric mean ratios (GMR) and 90% confidence intervals (CI) of the log-transformed pharmacokinetic parameters ($C_{max,ss}$, $AUC_{\tau,ss}$) of EVO+PIO and EVO or PIO alone were calculated using the linear mixed effect model which assumed the treatment, period and sequence as fixed effects.

Results

Demographics

A total of 36 healthy male subjects were enrolled in this study. Age, height, weight, and BMI were 33.0 ± 6.0 years (mean ± standard deviation), 173.7 ± 5.3 cm, 68.8 ± 7.7 kg, and 22.8 ± 2.0 kg/m^2, respectively. The baseline demographic characteristics were similar across the sequence groups. During this study, one subject discontinued before drug administration due to non-treatment emergent adverse events (lethargy, dizziness and cold sweat) which occurred after baseline OGTT, and one subject withdrew consent in the first period of the study. Therefore, 35 subjects who received the study drug at least once were included in the safety assessment, and 34 subjects who completed the whole study were included in the pharmacokinetic and pharmacodynamic assessments.

Pharmacokinetics

The pharmacokinetic profiles of evogliptin and pioglitazone after EVO+PIO were similar with those after evogliptin or pioglitazone alone, respectively. The mean plasma concentration-time profiles of evogliptin with its metabolites (M6, M7) after EVO and EVO+PIO and pioglitazone with its metabolites (M3, M4) after PIO and EVO+PIO were comparable (Figure 2 and Supplementary Figure 1).

GMR (90% CI) of EVO+PIO to EVO and for the $C_{max,ss}$ and $AUC_{\tau,ss}$ of evogliptin were 1.01 (0.97–1.05) and 1.01 (0.98–1.04), which were within the conventional bioequivalence range[17] of 0.80–1.25 (Table 1). The corresponding values of EVO+PIO to PIO and its 90% CI for the $C_{max,ss}$ and $AUC_{\tau,ss}$ of pioglitazone were 1.07 (0.99–1.17) and 1.08 (0.99–1.17), which were within the conventional bioequivalence range as well (Table 2).

Pharmacodynamics

The reduction of the serum glucose level during OGTT for EVO+PIO was greater than PIO and similar to EVO (Figure 3). The $G_{max,ss}$ and $AUGC_{\tau,ss}$ for EVO+PIO compared to baseline also showed a similar trend (Table 3). On the other hand, the reduction of the plasma insulin level during OGTT for all treatments were similar (Figure 3), as well as the $E_{max,ss}$ and $AUEC_{\tau,ss}$ (Table 3).

Safety

A total of 35 subjects received the study drug at least once, and 10 of them reported 20 AEs. A total of 13 AEs (muscle twitching, oropharyngeal pain, diarrhea, vomiting, blister of lip, two cases of headache, rhinorrhea, two cases of oropharyngeal swelling, pharyngeal erythema, dyspepsia, and neck stiffness), 3 AEs (muscle twitching, amylase increased, and rhinorrhea) and 4 AEs (urticaria, headache, sore throat, and anemia) were reported after EVO, PIO, and EVO+PIO, respectively. Among the reported AEs, 12 AEs were evaluated as drug-related by the investigators (Table 4). One AE reported after PIO (amylase increased) was considered an Adverse Event of Special Interest (AESI) according to the study protocol. All AEs were spontaneously recovered during the study period, except for one case of lip blister which recovered during the follow-up period. No serious AEs or clinically significant findings in the vital signs, physical examinations, clinical laboratory tests and ECGs were reported.

Discussion

According to in vitro studies, evogliptin does not induce or inhibit CYP enzymes, while its metabolism is primarily mediated by CYP3A4 to form metabolites with unknown activity (M7 and M8).[10,18] On the other hand, pioglitazone is extensively metabolized, mainly by CYP2C8, CYP3A4 and CYP2C9 to form active metabolites (M3 and M4).[13,14] No clinically significant CYP enzyme induction or inhibition by pioglitazone has been identified in vivo.[13,14] Because the elimination pathways of evogliptin and pioglitazone show little possibility to affect each other, the pharmacokinetic interaction of the two drugs is unlikely to occur, as the result of the current study suggests.

For pioglitazone, the total pioglitazone (pioglitazone, M3 and M4) concentration was also similar between the treatment groups. GMR (90% CI) of EVO+PIO to PIO for the $C_{max,ss}$ and $AUC_{\tau,ss}$ were 106.95 (102.16–111.97) and 106.38 (101.76–111.22), respectively, which were within the conventional limits of bioequivalence.

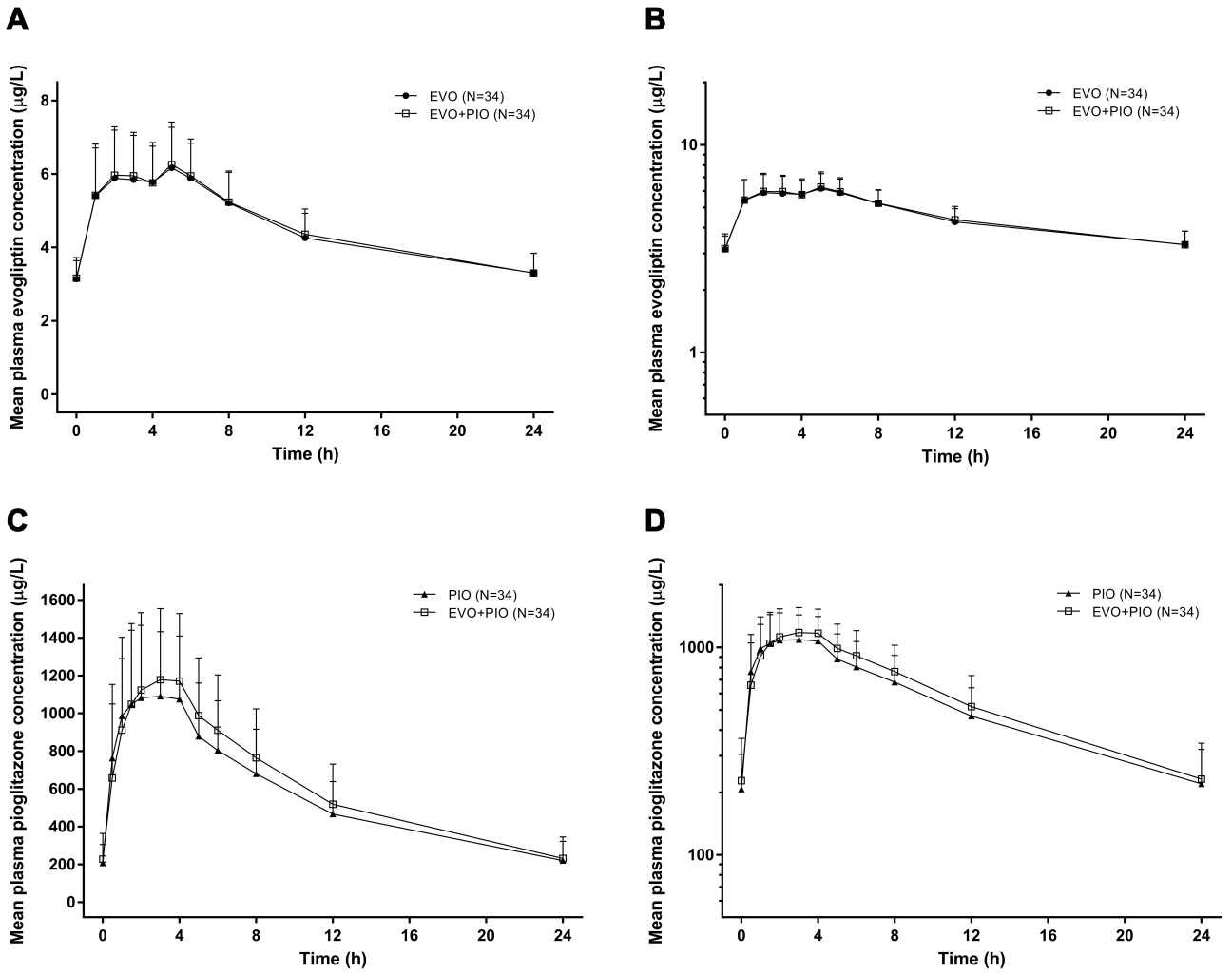

Figure 2 Mean plasma evogliptin and pioglitazone concentration-time profiles at steady-state for (**A**) evogliptin, linear scale, (**B**) evogliptin, semi-log scale, (**C**) pioglitazone, linear scale, and (**D**) pioglitazone, semi-log scale after EVO, PIO, and EVO+PIO.
Note: Error bars represent standard deviations.

Changes in the glucose and insulin levels during OGTT were measured as pharmacodynamic parameters at baseline and each treatment period. The reduction of the glucose level after the combination therapy compared to the baseline, expressed as the maximum concentrations ($G_{max,ss}$, $E_{max,ss}$) and area under-curves ($AUGC_{\tau,ss}$, $AUEC_{\tau,ss}$), was not superior compared to the administration of each drug alone. Because the combination of other DPP-4s (alogliptin, vildagliptin, and linagliptin) with pioglitazone have led to a greater efficacy (HbA1C reduction) than each medication alone in T2DM patients, a greater reduction of the glucose level was expected.[19–21] This discrepancy could be attributable to the study design which includes healthy subjects with unimpaired glucose homeostasis. We hypothesized that the endocrine system of healthy people whose basal blood glucose level is within normal range could have attenuated the synergistic antidiabetic effect of the combination of evogliptin and pioglitazone. Therefore, to verify the pharmacodynamic interaction and clinical implication of the combination of evogliptin and pioglitazone for T2DM patients, further studies with a larger sample size of T2DM patients should be considered.

Despite the insulinotropic effect of the DPP-4 inhibitor, the postprandial insulin level at all three treatment periods were lower than the baseline. Similar insulin profiles were obtained from previous studies which administered evogliptin and other drugs of the same class including sitagliptin to healthy subjects.[8] In the case of sitagliptin, the insulinotropic effect was observed in DM patients after administration of the same dose that did not produce a significant change of

Table 1 Pharmacokinetic Parameters of Evogliptin, Evogliptin M7 and Evogliptin M8 at Steady-State After EVO and EVO+PIO

Parameters		Treatment		GMR (90% CI)[b]
		EVO[a] (N=34)	EVO + PIO[a] (N=34)	
Evogliptin	$T_{max,ss}$ (h)	4.5 (1.0–6.0)	5.0 (1.0–6.0)	
	$C_{max,ss}$ (μg/L)	6.5 ± 1.2 (4.5–9.7)	6.6 ± 1.3 (3.6–9.3)	1.01 (0.97–1.05)
	$AUC_{\tau,ss}$ (μg·h/L)	108.5 ± 16.7 (68.0–147.3)	109.7 ± 17.1 (58.1–150.9)	1.01 (0.98–1.04)
	$t_{1/2,ss}$ (h)	26.1 ± 7.2 (15.5–49.6)	25.5 ± 4.9 (16.1–37.3)	
	CL_{ss}/F (L/h)	47.1 ± 7.7 (33.9–73.4)	46.8 ± 9.1 (33.0–86.0)	
	$Ae_{\tau,ss}$ (mg)	1.2 ± 0.3 (0.5–1.7)	1.1 ± 0.3 (0.4–2.0)	
	$CL_{R,ss}$ (L/h)	11.0 ± 2.4 (5.0–15.9)	10.4 ± 2.6 (4.3–15.8)	
Evogliptin M7	$C_{max,ss}$ (μg/L)	0.6 ± 0.2 (0.3–1.2)	0.7 ± 0.2 (0.2–1.2)	1.12 (1.06–1.19)
	$AUC_{\tau,ss}$ (μg·h/L)	9.2 ± 3.0 (4.0–18.4)	10.5 ± 3.3 (3.5–17.4)	1.14 (1.08–1.19)
	MR[c]	0.08 ± 0.02 (0.04–0.13)	0.09 ± 0.02 (0.05–0.14)	
Evogliptin M8	$C_{max,ss}$ (μg/L)	0.7 ± 0.2 (0.3–1.0)	0.8 ± 0.2 (0.2–1.1)	1.10 (1.03–1.16)
	$AUC_{\tau,ss}$ (μg·h/L)	11.4 ± 3.0 (4.4–17.0)	12.6 ± 3.3 (3.5–17.8)	1.10 (1.05–1.15)
	MR[c]	0.10 ± 0.02 (0.06–0.14)	0.11 ± 0.02 (0.06–0.15)	

Notes: [a]Data are presented as mean ± standard deviation (minimum – maximum), except for $T_{max,ss}$ where data are presented as median (minimum – maximum); [b]Geometric mean ratio and 90% confidence interval of EVO+PIO to EVO; [c]MR (metabolic ratio) = $AUC_{\tau,ss}$ of metabolite/$AUC_{\tau,ss}$ of parent.

Abbreviations: $T_{max,ss}$, time to reach maximum plasma concentration at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $AUC_{\tau,ss}$, area under the concentration time curve during a dosing interval at steady state; $t_{1/2,ss}$, elimination half-life at steady state; CL_{ss}/F, apparent clearance at steady-state; $Ae_{\tau,ss}$, amount of unchanged drug excreted into the urine during a dosing interval at steady state; $CL_{R,ss}$, renal clearance at steady-state; Evogliptin M7, 4(S)-hydroxyevogliptin; Evogliptin M8, 4(R)-hydroxyevogliptin.

Table 2 Pharmacokinetic Parameters for Pioglitazone, Pioglitazone M3 and Pioglitazone M4 at Steady-State After PIO and EVO+PIO

Parameters		Treatment		GMR (90% CI)[b]
		PIO[a] (N=34)	EVO + PIO[a] (N=34)	
Pioglitazone	$T_{max,ss}$ (h)	2.0 (1.0–5.0)	3.0 (0.5–4.0)	
	$C_{max,ss}$ (μg/L)	1174.7 ± 372.8 (356.1–1841.0)	1255.2 ± 397.1 (307.1–2400.9)	1.07 (0.99–1.17)
	$AUC_{\tau,ss}$ (μg·h/L)	13360.6 ± 4450.7 (4652.5–23277.9)	14456.0 ± 4903.7 (3368.0–30527.8)	1.08 (0.99–1.17)
	$t_{1/2,ss}$ (h)	10.5 ± 4.3 (6.3–31.0)	9.3 ± 2.0 (6.1–14.4)	
	CL_{ss}/F (L/h)	2.6 ± 1.2 (1.3–6.4)	2.4 ± 1.3 (1.0–8.9)	
Pioglitazone M3	$C_{max,ss}$ (μg/L)	541.4 ± 190.9 (247.7–897.5)	588.8 ± 189.2 (275.5–1117.6)	1.11 (1.05–1.17)
	$AUC_{\tau,ss}$ (μg·h/L)	11102.0 ± 3777.5 (5388.7–19051.1)	11695.7 ± 3888.0 (5746.3–21275.6)	1.06 (1.01–1.11)
	MR[c]	0.91 ± 0.36 (0.34–1.67)	0.87 ± 0.30 (0.30–1.71)	
Pioglitazone M4	$C_{max,ss}$ (μg/L)	1206.1 ± 321.1 (481.9–1829.4)	1293.3 ± 314.1 (497.3–1841.5)	1.08 (1.03–1.12)
	$AUC_{\tau,ss}$ (μg·h/L)	25757.1 ± 6820.6 (10172.5–38756.1)	27351.6 ± 6802.4 (10047.7–38951.1)	1.07 (1.02–1.11)
	MR[c]	2.05 ± 0.56 (0.90–3.18)	1.99 ± 0.45 (1.16–3.03)	

Notes: [a]Data are presented as mean ± standard deviation (minimum – maximum), except for $T_{max,ss}$ where data are presented as median (minimum – maximum); [b]Geometric mean ratio and 90% confidence interval of EVO+PIO to PIO; [c]MR (metabolic ratio) = $AUC_{\tau,ss}$ of metabolite/$AUC_{\tau,ss}$ of parent.

Abbreviations: $T_{max,ss}$, time to reach maximum plasma concentration at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $AUC_{\tau,ss}$, area under the concentration time curve during a dosing interval at steady state; $t_{1/2,ss}$, elimination half-life at steady state; CL_{ss}/F, apparent clearance at steady-state; Pioglitazone M3, 5-[[4-[2-(5-acetyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione; Pioglitazone M4, 5-[[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione.

the insulin level in healthy subjects.[22,23] Therefore, these pharmacodynamic results in healthy volunteers should not be used alone to determine the efficacy of evogliptin. Synergism at the molecular level could also take place in the combination of evogliptin and pioglitazone. Because recent studies have revealed oxidative stress as a key player in the pathogenesis of T2DM and its complications, redox regulation is under extensive investigation for potential antidiabetic therapy.[24] Thiazolidinediones increase antioxidant enzymes through the activation of PPAR- γ and inhibit overproduction of free-radicals.[25] In terms of DPP-4s, their antioxidant activity has been proven in vivo (linagliptin, sitagliptin, and alogliptin) and in vitro (teneligliptin).[25] Comparison of the oxidative stress level between treatment groups could be made in further studies on

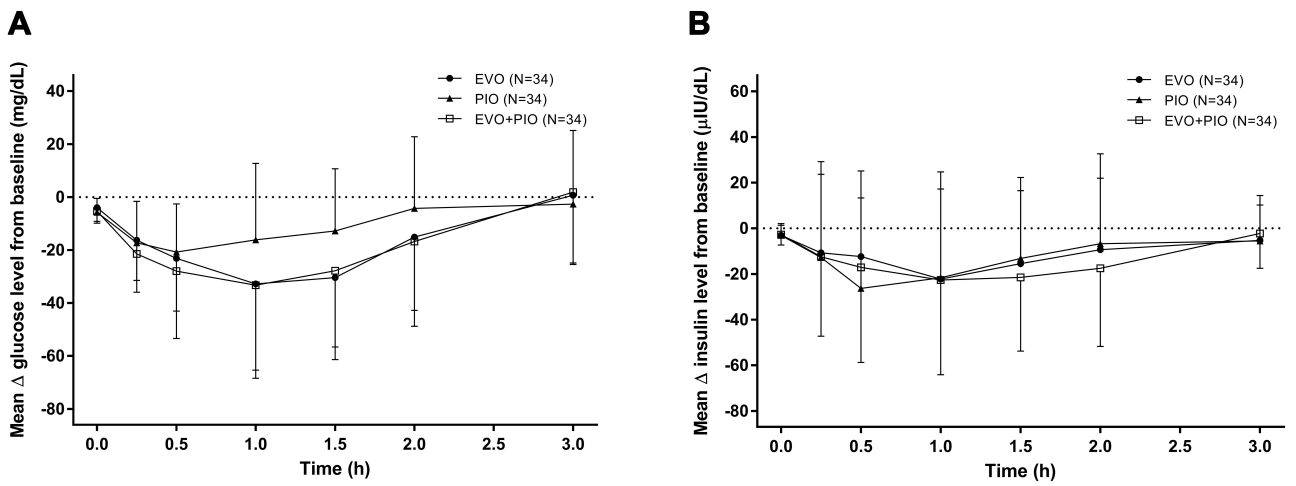

Figure 3 Mean (**A**) Δ serum glucose and (**B**) Δ plasma insulin level-time profiles at steady-state after EVO, PIO, and EVO+PIO.
Note: Error bars represent standard deviations.

evogliptin and pioglitazone, using FORT and FORD assays which are suggested by recent studies.[26]

Because most T2DM patients suffer from comorbidities, polypharmacy poses a major threat to the management of the disease.[27] To minimize the accompanied risks of drug–drug interactions, sufficient evidence is needed especially for certain combinations of drugs which are commonly prescribed together. Results of the current study may help physicians in prescribing multiple oral antidiabetics with evidence on safety and efficacy.

Restriction of the study subjects to Korean ethnicity could be recognized as a limitation of this study. DPP-4s are known to be more effective in Asians compared to other ethnic groups, due to the different insulin secretory capacity among ethnic groups.[28] For pioglitazone, the ethnic difference in the polymorphism of the drug-metabolizing enzyme (CYP2C8) and target receptor (PPAR-γ) could be a source of pharmacokinetic/pharmacodynamic variation across ethnic groups.[29] Therefore, further studies on T2DM patients should include subjects from various ethnic groups to generalize the result across ethnic groups.

Conclusion

In conclusion, concomitant administration of evogliptin and pioglitazone showed similar glucose-lowering effects with those of evogliptin alone and no clinically significant pharmacokinetic interactions. The safety and tolerability of the concomitant administration were comparable to those of the administration of each drug alone. Further studies with a large number of T2DM patients are required to determine the synergistic antihyperglycemic effect of the combination of evogliptin and pioglitazone.

Table 3 Pharmacodynamic Parameters of Serum Glucose and Plasma Insulin at Steady-State After EVO, PIO and EVO+PIO

Parameters		Treatment			
		Baseline (N=34)	EVO (N=34)	PIO (N=34)	EVO + PIO (N=34)
Serum glucose	G_{max} (mg/dL)	174.8 ± 34.2 (126.0–274.0)	144.2 ± 22.4 (108.0–202.0)	156.3 ± 30.3 (99.0–244.0)	140.2 ± 23.3 (102.0–201.0)
	ΔG_{max} (mg/dL)	–	−50.1 ± 31.2 (−128.0 – −8.0)	−38.9 ± 20.4 (−98.0–1.0)	−53.1 ± 26.5 (−111.0 – −13.0)
	$AUGC_{\tau}$ (h·mg/dL)	392.9 ± 66.7 (288.1–561.3)	337.2 ± 41.7 (247.9–428.9)	361.1 ± 65.1 (228.6–572.1)	334.3 ± 49.8 (256.5–486.1)
	$\Delta AUGC_{\tau}$ (h·mg/dL)	–	−55.8 ± 49.5 (−170.1–33.8)	−31.9 ± 42.7 (−161.5–46.8)	−58.8 ± 46.8 (−185.6–16.0)
Plasma insulin	E_{max} (μIU/mL)	106.9 ± 55.5 (36.1–266.3)	80.3 ± 40.4 (28.6–204.8)	74.2 ± 46.1 (32.8–247.2)	77.3 ± 39.5 (28.1–251.8)
	ΔE_{max} (μIU/mL)	–	−50.1 ± 43.2 (−189.2–1.8)	−54.2 ± 43.4 (−196.1 – −0.7)	−56.7 ± 41.7 (−163.9–1.3)
	$AUEC_{\tau}$ (h·μIU/mL)	175.1 ± 76.9 (67.6–393.1)	138.9 ± 74.5 (54.8–452.8)	136.4 ± 77.3 (57.0–412.9)	129.0 ± 48.0 (57.3–288.3)
	$\Delta AUEC_{\tau}$ (h·μIU/mL)	–	−36.2 ± 55.1 (−170.7–84.8)	−38.6 ± 52.9 (−144.8–102.3)	−46.2 ± 53.7 (−200.0–36.7)

Note: Data are presented as mean ± standard deviation (minimum – maximum).
Abbreviations: G_{max}, maximum serum glucose concentration; ΔG_{max}, maximum change of serum glucose concentration from baseline; $AUGC_{\tau}$, area under the serum glucose concentration curve during a dosing interval; $\Delta AUGC_{\tau}$, change of area under the serum glucose concentration curve during a dosing interval; E_{max}, maximum plasma insulin concentration; ΔE_{max}, maximum change of plasma insulin concentration from baseline; $AUEC_{\tau}$, area under the plasma insulin concentration curve during a dosing interval; $\Delta AUEC_{\tau}$, change of area under the plasma insulin concentration curve during a dosing interval from baseline.

Table 4 Adverse Drug Reactions (ADRs) Following EVO, PIO or EVO+PIO

	Treatment		
	EVO (N=35)	PIO (N=35)	EVO+PIO (N=35)
Anaemia			1 (1)
Diarrhoea	1 (1)		
Dyspepsia	1 (1)		
Lip blister	1 (1)		
Vomiting	1 (1)		
Amylase increased		1 (1)	
Muscle twitching	1 (1)		
Musculoskeletal stiffness	1 (1)		
Headache	1 (1)		1 (1)
Oropharyngeal swelling	1 (1)		
Urticaria			1 (1)

Note: Data are presented as the number of subjects who reported ADRs (the number of ADRs).

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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