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ORIGINAL RESEARCH

Effect of Rifampicin on the Pharmacokinetics of Evogliptin in Healthy Volunteers

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Purpose: Evogliptin (DA-1229) is a novel, potent, and selective dipeptidyl peptidase 4 (DPP-4) inhibitor for treating type 2 diabetes mellitus. This study investigates the effect of rifampicin on evogliptin pharmacokinetics.

Patients and Methods: An open-label, crossover, one-sequence study was conducted on 12 healthy subjects. Reference baseline pharmacokinetic samples were collected on day 1 after the subjects were administered a single dose of 5 mg evogliptin. After a washout period, the subjects were administered 600 mg rifampicin once daily for 10 days, from days 8 to 17, for full induction of hepatic enzyme activity. On day 17, single doses of evogliptin (5 mg) were administered along with rifampicin (600 mg). The test pharmacokinetic samples were collected with a sampling schedule identical to that used for the reference.

Results: Maximum concentration (C_{max}) and area under the plasma drug concentration-time curve ($AUC_{0\text{-}96h}$) of evogliptin with and without co-administration of rifampicin were compared. Reference and test C_{max} and $AUC_{0\text{-}96h}$ values of evogliptin were 4.70 ng/mL vs 4.86 ng/mL and 153.97 ng·h/mL vs 58.83 ng·h/mL, respectively. All adverse events were mild in intensity and considered unrelated to evogliptin administration.

Conclusion: Rifampicin decreased the $AUC_{0\text{-}96h}$ of evogliptin by 61.8% without significantly affecting C_{max}. The mechanism underlying the decrease in $AUC_{0\text{-}96h}$ is thought to be the induction of cytochrome P450 (CYP), especially 3A, by rifampicin. The adverse events, none of which were serious, were not significantly altered by the concomitant administration of evogliptin and rifampicin. Nevertheless, it would be prudent that evogliptin dosing should be carefully considered when co-administered with CYP3A inducers.

Keywords: drug–drug interaction, DPP-4 inhibitor, CYP3A inducer, evogliptin, rifampicin

Introduction

Evogliptin (DA-1229) is a newly developed dipeptidyl peptidase 4 (DPP-4) inhibitor (Figure 1). The pharmacological activity of DPP-4 inhibitors is derived from blocking the degradation of glucagon-like peptide-1 (GLP-1), which plays an important role in glucose homeostasis.[1,2] Evogliptin showed high potency (half maximal inhibitory concentration (IC_{50}): 0.98 nM) and over 6000-fold selectivity for DPP-4 compared with DPP-8 or DPP-9.[3]

Evogliptin is characterized by a long half-life (> 30 h) and is unaffected by food following a single-dose Phase 1 study.[4] In a multiple-dose phase 1 study, evogliptin showed dose proportionality within the 5–20 mg dose range.[5] In both studies, evogliptin showed rapid absorption after 5 mg oral administration and 5 h for the time to peak plasma concentration (T_{max}).[4,5] The absolute bioavailability was reported to be about 50%.[6] In a clinical trial on type 2 diabetes, administration of 5 mg of evogliptin once daily for 12 weeks reduced glycated hemoglobin (HbA1c) by 0.66% compared with a decrease of 0.09% in the control group.[7]

Patients with type 2 diabetes taking DPP-4 inhibitors commonly consume additional antidiabetic medications, such as metformin, sulfonylureas, or thiazolidinediones.[8] Moreover, antidiabetic medication regimens can become more complex and stressful for the patients.[9]

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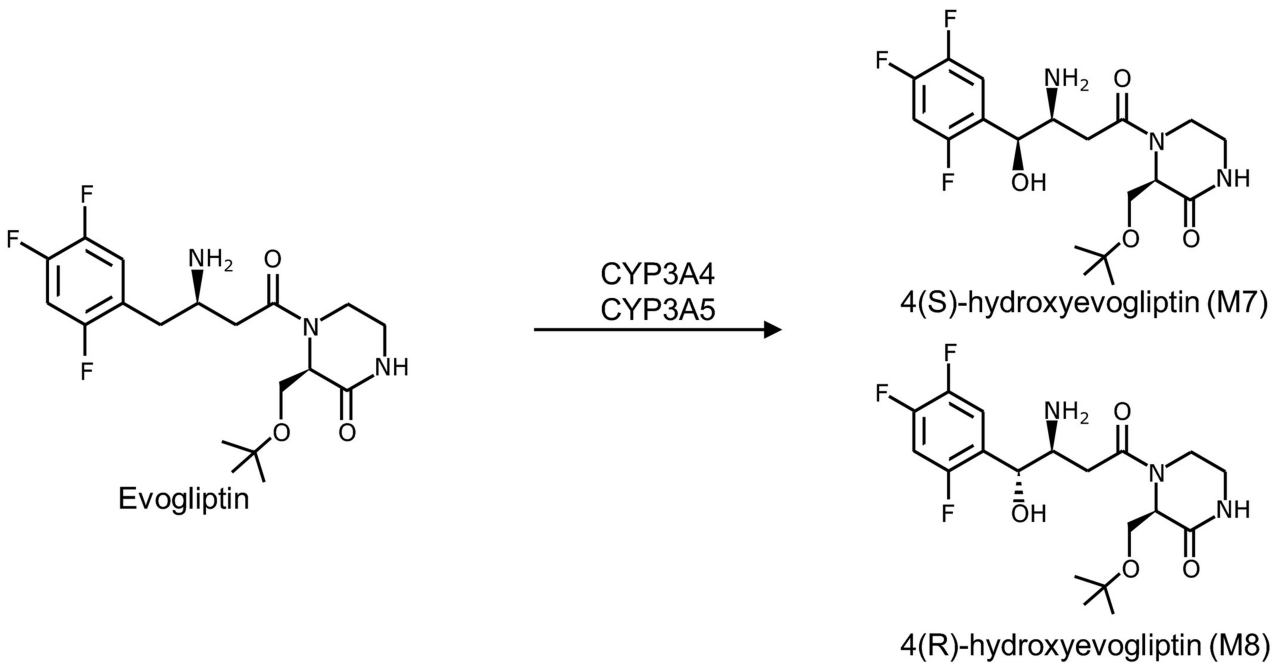

Figure 1 Structure of evogliptin and its active metabolites (M7 and M8).[37]

Enzyme induction/inhibition studies revealed that evogliptin was unlikely to induce cytochrome P450 (CYP), especially 3A, or inhibit CYP1A2, 2C9, 2C19, 2D6, or 3A4.[10] However, evogliptin exposure may be influenced by drugs that affect the pathways involved in the pharmacokinetic (PK) profile of evogliptin. In an in vitro study using human cDNA-expressed CYPs, evogliptin was mainly metabolized to hydroxy-DA-1229 (M7 or M8) by CYP3A4 in human hepatocytes, liver microsomes, and liver S9 fractions (Figure 1).[10] In healthy volunteers, the drug is excreted in a comparable amount through the hepatic and renal pathways.[11]

Several medications are known to induce CYP3A enzyme expression.[12] When CYP3A enzyme inducers are co-administered with evogliptin, CYP3A-mediated metabolic change may reduce evogliptin exposure in the body, eventually leading to treatment failure attributed to inadequate control of glucose levels.[13] Authorities recommend clinical pharmacology studies of drug interactions during drug development, especially when the potential risk of drug interactions is deemed high.[14,15] Rifampicin is an antibacterial agent that is known to be one of the most potent CYP3A inducers.[14–16] It is commonly used as a CYP3A perpetrator in in vivo drug–drug interaction studies.[14,15] To investigate the effect of CYP3A induction on the PK of evogliptin, we conducted a clinical drug–drug interaction study using rifampicin, a strong CYP inducer.

Materials and Methods

Study Design

This study used an open-label, crossover, and one-sequence design. PK assessments were performed in two periods: when a single dose of evogliptin was administered alone (reference period) and when it was co-administered with rifampicin after full induction of CYP enzyme activity by multiple doses of rifampicin (test period) in the same subjects (Figure 2). A 16-day washout period for evogliptin was allowed between the two periods. A 5 mg dose (1 tablet) of evogliptin (Dong-A ST; Seoul, Korea) and a 600 mg dose (1 tablet) of rifampicin (Rifodex, Chong Kun Dang Pharm, Seoul, Korea) were used.

Subjects

This study was approved by the institutional review board (IRB) of the Severance Hospital, Seoul, Korea (CR No: 4–2014-0600). The study was conducted in compliance with related regulations and guidelines, including the Declaration of

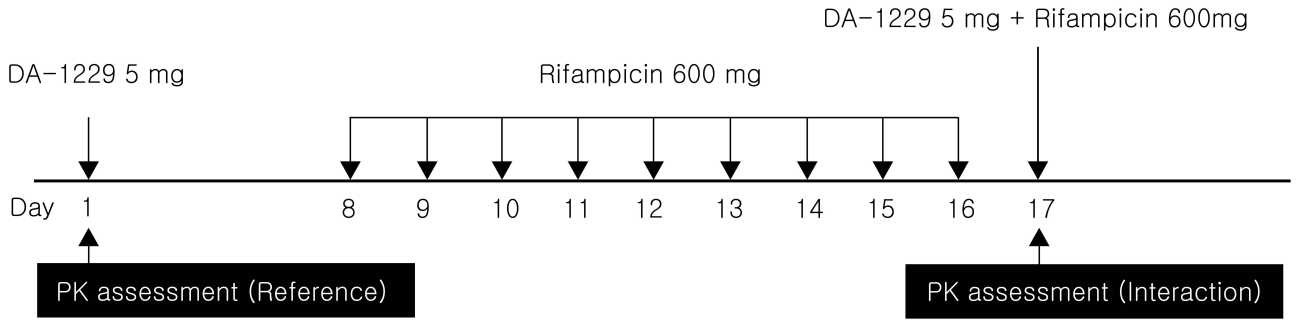

Figure 2 Schematic overview of the study design.

Helsinki. Written informed consent was obtained from healthy Korean subjects aged 20–55 years, weighing 55 kg or more, and with a body mass index of 18.5–25 kg/m^2. During the screening, vital signs (blood pressure, pulse rate, and body temperature) were measured; laboratory analyses (hematology, blood chemistry, urinalysis, urine drug screening, and serological tests) and 12-lead electrocardiography were also performed. Twelve subjects participated in this study. The participants had no significant medical conditions or history relevant to the study participated in this study. None of the patients were taking any medications. The participants were either non-smokers or casual smokers (≤ 10 cigarettes/day) and were prohibited from smoking during the study period.

Procedures

On day −1, all subjects were hospitalized at the Clinical Pharmacology Unit of the Clinical Trials Center at Severance Hospital. After overnight fasting, the subjects were administered a single dose of evogliptin (5 mg) in the morning of day 1 and were discharged after completing PK sampling. The subjects visited the site in the mornings to receive rifampicin (600 mg) once daily on days 8–16 for enzyme induction. They entered the clinical facility again in the afternoon of day 16 and received single doses of evogliptin (5 mg) and rifampicin (600 mg) in the morning of day 17.

PK blood sampling was performed on the day of evogliptin administration (days 1 and 17). An indwelling venous catheter was placed in each subject, and serial blood sampling was performed at the following time points: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h post-dose.

During the study, participants received standardized meals. Grapefruit intake was prohibited for at least 1 week before the study; caffeine, smoking, and alcohol were prohibited from day −2 until the last PK sampling.

Drug Assay

Blood samples for PK analysis were collected in heparinized tubes. Plasma was separated by centrifugation for 10 min at 3500 rpm and stored at −70 °C. The plasma concentrations of evogliptin and its metabolites (M7 and M8) were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with Prominence UFLC XR (Shimadzu; MD, USA) and API5000 (AB SCIEX; MA, USA). For analysis of evogliptin, 10 μL of internal standard (DA-1229-d_9 10 ng/mL) was added to the tube containing 200 μL of plasma sample. After precipitation with 600 μL of acetonitrile, the samples were centrifuged for 5 min at 13,000 rpm. The upper phase was evaporated under nitrogen gas and reconstituted with 100 μL of mobile phase (5 mM ammonium formate:acetonitrile, 70:30). After centrifugation, a 5-μL aliquot was injected into the analytical column. For metabolites, 15 μL of internal standard (DA-1229-M8-d_9 80 ng/mL) was added to the tube containing 300 μL of the plasma sample. After precipitation with 1 mL of acetonitrile, the samples were centrifuged for 5 min at 13,000 rpm. The upper phase was evaporated under nitrogen gas and reconstituted with 150 μL mobile phase. After centrifugation under the same conditions, 10 μL aliquots were injected into the analytical column.

The calibration curve ranges for evogliptin and its metabolites were 0.03–30 ng/mL and 0.01–10 ng/mL, respectively; all curves showed linearity ($r \geq 0.9950$). In intra/inter-validation, accuracy was within 85–115%, while precision was below 15%.

Pharmacokinetics of Evogliptin

The PK profiles of evogliptin, M7, and M8 were analyzed by a non-compartmental method using Phoenix® WinNonlin® (version 6.3, Pharsight, CA, USA). The peak plasma concentration (C_{max}) and T_{max} were obtained directly from the data. The slope of the terminal elimination phase (λ_z) was obtained based on the best-adjusted R-squared with at least three points. The terminal half-life ($t_{1/2}$) was calculated using the following equation: $t_{1/2} = \ln 2/\lambda_z$. The area under the time-concentration curve (AUC) was calculated using the linear trapezoidal rule for the rising phase and the log-linear trapezoidal rule for the descending phase. The AUC was extrapolated to infinity ($AUC_{0-\infty}$) based on the C_{last} divided by λ_z, where C_{last} is the last quantifiable concentration.

Statistical Analysis

The results are presented as mean ± standard deviation (SD) or median (range) in both the text and tables. The main PK variables (C_{max}, AUC_{0-96h}, and $AUC_{0-\infty}$) were log-transformed and analyzed. Point estimates of the geometric least-squares mean ratio and 90% confidence intervals of the parameters for the test period to the reference period were calculated. PK data were analyzed using Phoenix® WinNonlin® (version 6.3, Pharsight, CA, USA). T_{max} data for the two periods were compared using the Wilcoxon signed-rank test; for the Wilcoxon test, the "wilcox.test" package in R (version 3.2.2, R Foundation for Statistical Computing, Vienna) was used.[17,18]

Results

Participant demographics are presented in Table 1. Following the inclusion and exclusion criteria for the subjects, 12 subjects were enrolled; 11 subjects completed the study, and their data were analyzed. The subjects included in this analysis were 29.3 ± 5.1 years old (mean ± SD) and weighed 70.1 ± 7.6 kg. In total, 41.6% were smokers, 66.6% were alcohol consumers, and 50% were caffeine consumers. The plasma evogliptin concentration-time curve and those of its metabolites (M7 and M8) are presented in Figure 3. The PK properties of evogliptin and the individual changes between the periods are provided in Table 2 and Figure 4, respectively.

There was no significant change in the C_{max} of evogliptin between the groups treated with and without rifampicin, 4.70 ng/mL and 4.86 ng/mL, respectively (Table 2). However, the AUC_{0-96h} of evogliptin decreased from 153.97 to 58.83 ng·h/mL. Individual fluctuations in PK parameters are presented in Figure 4. The median T_{max} of evogliptin decreased from 5.0 to 1.0 h in the presence of rifampicin.

As for the metabolites, the mean C_{max} of both M7 and M8 increased in the presence of rifampicin; M7, from 0.42 to 1.41 ng/mL; M8, from 0.37 to 0.85 ng/mL. The AUC_{0-96h} result was mixed for the two metabolites; for M7, AUC_{0-96h} increased from 8.38 to 9.42 ng·h/mL; for M8, AUC_{0-96h} decreased from 9.76 to 5.70 ng·h/mL.

No difference in safety could be found as the baseline conditions of the subjects before and after the washout time were similar. In the reference and test periods, one subject in each period experienced an adverse event (8.3% and 9.1%, respectively). In the induction phase (administration of rifampin alone), four subjects (36.4%) experienced adverse events (Table 3). Among these, one adverse event (hyperhidrosis) was considered related to rifampicin. All the adverse events were mild and resolved without treatment.

Discussion

To investigate the interaction between rifampicin and evogliptin, a single-group crossover study was conducted. The design was regarded as appropriate considering the known absorption, distribution, metabolism, and excretion properties of evogliptin and rifampicin, especially CYP3A induction/recovery for rifampicin. Evogliptin is a known substrate of CYP3A and is more rapidly metabolized by the induced CYP3A enzyme. Rifampicin reportedly induces CYP enzyme expression.[19,20] Multiple reports have shown that 600 mg of rifampicin administration for 10 days is sufficient to induce CYP enzyme expression.[21,22] It has been documented that propranolol concentration reaches a new steady state after daily administration of 600 mg rifampicin for 10 days.[21] Another study showed that administrating 600 mg rifampicin doses daily for 7–14 days could increase the clearance of antipyrine up to a maximum.[22] In this study, a daily dose of 600 mg of rifampicin was administered for 10 days for maximum induction of the CYP enzyme, aiming to study the full

Table 1 Demographics and Baseline Characteristics of Study Subjects

Demographic Variable		Total (N=12)
Age (years)	N	12
	Mean	29.3
	SD	5.1
	Median	28
	Min	22
	Max	42
Weight (kg)	N	12
	Mean	70.1
	SD	7.6
	Median	69.3
	Min	60.2
	Max	83.6
Height (cm)	N	12
	Mean	173.9
	SD	7.1
	Median	175.8
	Min	159.7
	Max	183.7
BMI (kg/m^2)	N	12
	Mean	23.1
	SD	1.6
	Median	23.1
	Min	19.9
	Max	24.7
Gender		
Male	N	12
	(%)	100
Smoking		
Yes	N	5
	(%)	41.6
Alcohol		
Yes	N	8
	(%)	66.6
Caffeine		
Yes	N	6
	(%)	50

Abbreviation: BMI, body mass index.

interaction of rifampicin with the study drug. After the last dose of rifampicin was administered together with evogliptin for PK analysis, no additional dose was administered as induced enzyme activity persisted after rifampicin discontinuation, and complete recovery from enzyme induction took up to 3–4 weeks.[23]

To prevent a carry-over effect, the washout period for evogliptin was set to 16 days, which is five times longer than the $t_{1/2}$ of evogliptin (32.5–39.8 h).[4] The washout period was adequate because none of the subjects had detectable plasma evogliptin levels at pre-dose sampling in the rifampicin period. To minimize the period effect, this study was conducted on healthy volunteers in the same environment, providing the same diet, and found no significant differences in the pre-dose baseline conditions of the individuals. Although the period effect cannot be ruled out, it was negligible.

The presence of rifampicin altered the PK properties of evogliptin. Although rifampicin is well-known as a CYP3A inducer, it also exerts inhibitory effects on certain transporters, including organic anion-transporting polypeptide (OATP),[24,25] P-glycoprotein (P-gp),[26] and multidrug resistance-associated protein 2 (MRP2).[27] P-gp and MRP2 are expressed on the membrane of enterocytes and are involved in the excretion of specific exogenous substances.[28,29] The

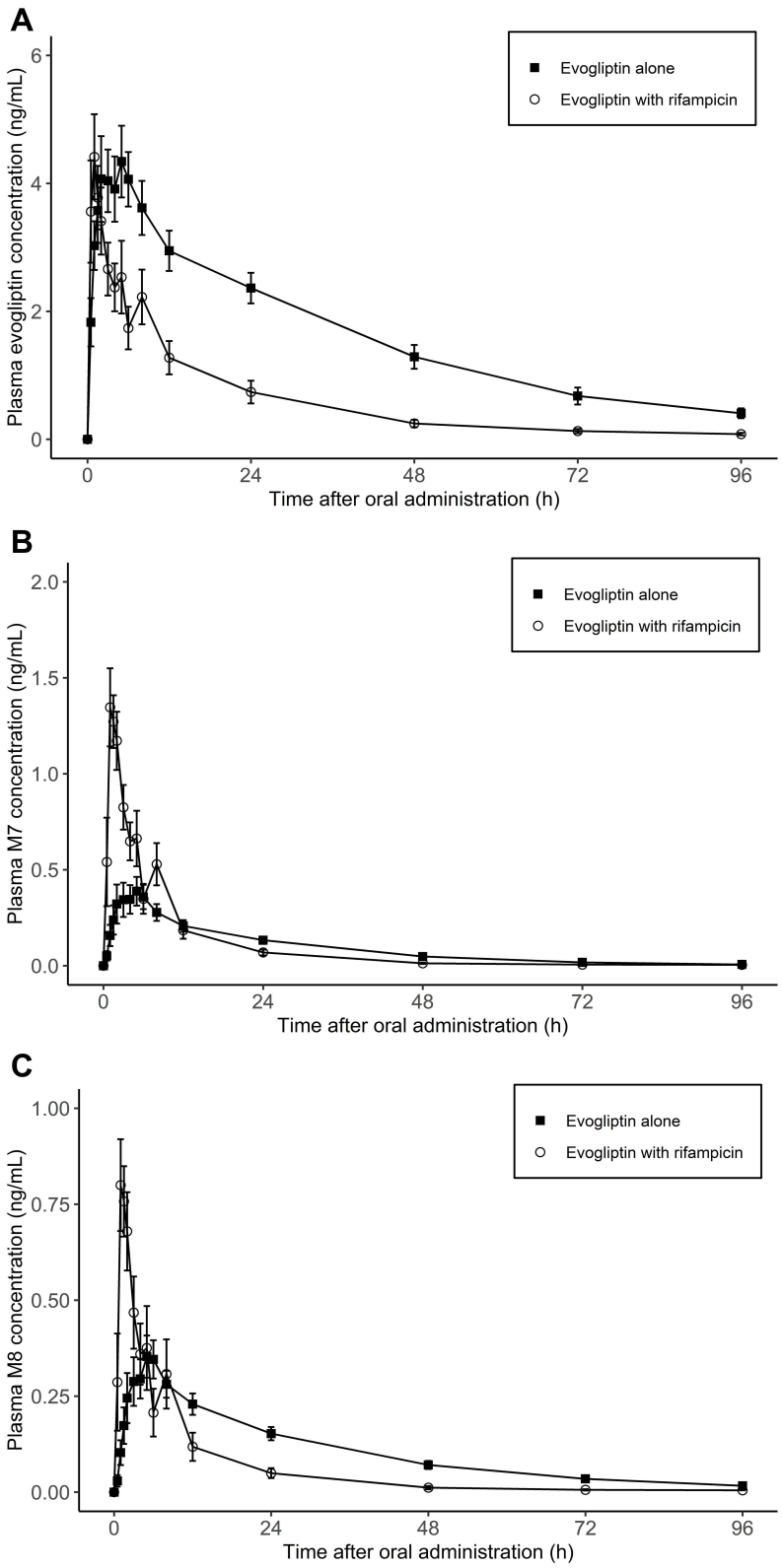

Figure 3 Arithmetic mean ± SD values for (**A**) plasma concentrations of evogliptin and its metabolites (**B**) M7 and (**C**) M8 following administration of a single 5 mg dose with or without 600 mg rifampicin.

Table 2 Pharmacokinetic Parameters and Statistical results of Evogliptin Following Single-Dose Administration of Evogliptin 5 Mg with or Without Rifampicin

Parameter	Evogliptin Alone (N=11)	Evogliptin With Rifampicin (N=11)	Geometric Mean Ratio (90% CI)
C_{max} (ng/mL)	4.70 ± 1.28	4.86 ± 1.52	1.027 (0.897, 1.176)
$AUC_{0\text{-}96h}$ (ng·h/mL)	153.97 ± 35.92	58.83 ± 23.19	0.371 (0.335, 0.411)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	170.84 ± 43.45	61.86 ± 25.17	0.352 (0.316, 0.392)
T_{max} (h)	5.0 (2.0, 6.0)	1.0 (0.5, 1.5)	-
$t_{1/2}$ (h)	27.7 ± 3.3	24.5 ± 5.8	-

Notes: Data are presented as mean ± SD; T_{max} data are given median (range).
Abbreviation: CI, confidence interval.

co-administration of rifampicin and evogliptin may result in evogliptin exhibiting T_{max} reduction with a constant C_{max}; this was likely due to the relationship between absorption and elimination rates. Following the strong induction of CYP3A by rifampicin, the total clearance of evogliptin may be increased, thereby suspected to influence a reduction in exposure ($AUC_{0\text{-}96h}$ decreased by 61.8%) and T_{max}. Since C_{max} is stable, rapid absorption may occur during the absorption period, which is rate-limiting.

The analysis of the two active major metabolites showed that the C_{max} of M7 and M8 increased 3.6-fold and 2.3-fold, respectively. However, $AUC_{0\text{-}96h}$ values thereof only slightly increased (M7: from 8.38 to 9.42 ng·h/mL) or decreased (M8: from 9.76 to 5.70 ng·h/mL). Given the function of the transporters and their potential rifampicin inhibition, an acute dose of rifampicin may have increased the early absorption of evogliptin by blocking P-gp or MRP2, thereby resulting in a significantly increased C_{max} of the metabolites in the absorption phase. Considering the nearly 2-fold decrease in the $t_{1/2}$ of both M7 and M8 in the presence of rifampicin, the disposition of the metabolites could be affected by the induction of enzymes or transporters. An internal qualitative analysis using samples from in vivo studies suggested that the main metabolites, M7 and M8, are glucuronidated to form M14 and transferred by another Phase I metabolism process to form M5, respectively. Therefore, M8 may undergo CYP-mediated metabolism. However, the increased clearance of M7 could

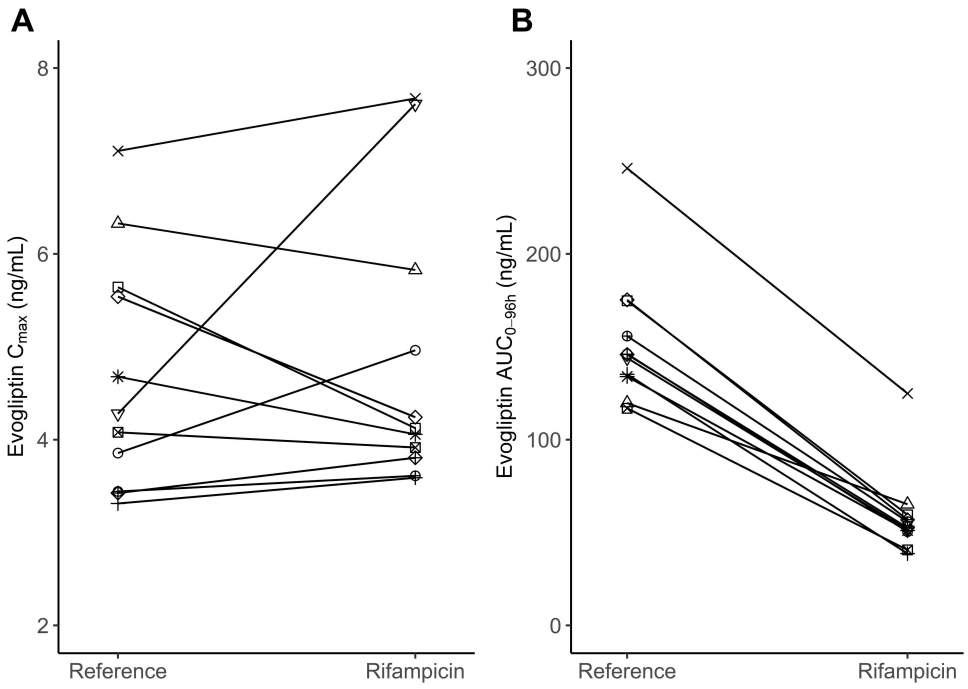

Figure 4 Individual evogliptin (**A**) C_{max} and (**B**) $AUC_{0\text{-}96h}$ changes from the period when evogliptin 5 mg was administered alone (Reference) to the period when evogliptin 5 mg was administered with rifampicin 600 mg (Rifampicin).

Table 3 Summary of Adverse Events

Adverse Events System Organ Class Preferred Term (MedDRA 17.1)	Period			Total (N=12)
	Evogliptin (N=12)	Rifampicin (N=11)	Evogliptin + Rifampicin (N=11)	
Total	**1 (8.3)**	**4 (36.4)**	**1 (9.1)**	**5 (41.7)**
Gastrointestinal disorders	–	1 (9.1)	–	1 (8.3)
Lip dry	–	1 (9.1)	–	1 (8.3)
Respiratory, thoracic, and mediastinal disorders	–	2 (18.2)	–	2 (16.7)
Pharyngitis	–	1 (9.1)	–	1 (8.3)
Rhinorrhea	–	1 (9.1)	–	1 (8.3)
General disorders and administration site conditions	–	–	1 (9.1)	1 (8.3)
Administration site paresthesia	–	–	1 (9.1)	1 (8.3)
Musculoskeletal and connective tissue disorders	–	1 (9.1)	–	1 (8.3)
Myalgia intercostal	–	1 (9.1)	–	1 (8.3)
Nervous system disorders	1 (8.3)	–	–	1 (8.3)
Headache	1 (8.3)	–	–	1 (8.3)
Skin and subcutaneous tissue disorders	–	1 (9.1)	–	1 (8.3)
Hyperhidrosis	–	1 (9.1)	–	1 (8.3)

Note: Unit: number of subjects (%).

not be sufficiently explained by the induction of oxidation/reduction reactions. It has been reported that rifampicin is not only capable of inducing CYP enzymes but is also capable of inducing non-CYP enzymes, including uridine diphosphate glucuronyltransferases (UGTs), by binding to the pregnane X receptor.[20] Collectively, the UGT activity induced by rifampicin may have contributed to the increased clearance of M7.

This mechanism also explains the shortened T_{max} of evogliptin in the presence of rifampicin. The median (min, max) T_{max} values of evogliptin with or without rifampicin were 1.0 h (0.5, 1.5) and 5.0 h (2.0, 6.0), respectively. During the period of rifampicin and evogliptin co-administration, the T_{max} of evogliptin significantly decreased (p = 0.0037, Wilcoxon signed-rank test), indicating an increase in the absorption rate. The PK of evogliptin observed during the absorption phase may be mediated by intestinal transporters. Benet et al reported that food could reduce the T_{max} of drugs depending on the Biopharmaceutics Drug Disposition Classification System, among which one mechanism could be the inhibition of the efflux cycling in the intestine, thereby decreasing T_{max} and increasing drug bioavailability.[30] Similarly, blocking intestinal transporters by rifampicin may interfere with efflux cycling, decreasing the T_{max} of the affected drugs. Other than P-gp or MRP2, certain transporters are known to cause the efflux of xenobiotics from intestinal enterocytes, such as MRP3 or breast cancer resistance protein.[31] Although their interactions with rifampicin are unclear and not clinically proven, they cannot be ruled out. Further studies, including in vitro transporter assays, are needed to investigate the factors contributing to the absorption profile. The decreased $t_{1/2}$ of evogliptin from 27.7 to 24.5 h is also indicative of enzyme induction. Additionally, the individual differences of $t_{1/2}$ were increased after rifampicin induction. As a strong PXR agonist, rifampicin has large inter-individual variability inducing CYP3A4 expression in humans.[32,33] CYP3A4 mutations are substantially more common across east Asians than in other ethnic groups.[34]

Similar PK interactions that result in decreased AUC without significant changes in the C_{max} of drugs in the presence of rifampicin have been reported. Rifampicin decreased the $AUC_{0\text{-}96h}$ of both pioglitazone and moxifloxacin without significantly affecting the C_{max} of each drug being observed.[35,36] Moreover, the formation of pioglitazone metabolites during the absorption phase was more rapid, with a shorter T_{max}.

Although this study involved only a small number of participants and clinical experience in larger populations would yield a more conclusive result, all adverse events observed in the study were mild and were not altered by co-administration of evogliptin with rifampicin. Additionally, enzyme induction by rifampicin is likely to be modest, as there was only a slight change observed in the total amount of the parent drug and its metabolites.

Conclusion

In conclusion, rifampicin moderately decreased the plasma AUC of evogliptin, most likely via CYP3A induction. However, no significant change in plasma C_{max} of evogliptin was observed. The adverse events, none of which were serious, were not significantly altered by the concomitant administration of evogliptin and rifampicin. Nevertheless, evogliptin dosing should be carefully considered when co-administered with CYP3A inducers.

Data Sharing Statement

The data that support the findings of this study are not available due to confidentiality.

Funding

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Disclosure

None of the authors have any conflicts of interest to declare for this work.

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