CLINICAL TRIAL REPORT

A Comparison of the Pharmacokinetics and Safety of Dapagliflozin Formate, an Ester Prodrug of Dapagliflozin, to Dapagliflozin Propanediol Monohydrate in Healthy Subjects

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Background: Dapagliflozin formate (DAP-FOR, DA-2811), an ester prodrug of dapagliflozin, was developed to improve the stability and pharmaceutical manufacturing process of dapagliflozin, a sodium-glucose cotransporter-2 inhibitor.

Purpose: This study aimed to evaluate the pharmacokinetics (PKs) and safety of dapagliflozin for DAP-FOR compared to those for dapagliflozin propanediol monohydrate (DAP-PDH, Forxiga) in healthy subjects.

Methods: This was an open-label, randomized, single-dose, two-period, two-sequence crossover study. The subjects received a single dose of DAP-FOR or DAP-PDH 10 mg in each period, with a 7-day washout. Serial blood samples for PK analysis were collected up to 48 hours after a single administration to determine plasma concentrations of DAP-FOR and dapagliflozin. PK parameters were calculated using a non-compartmental method and compared between the two drugs.

Results: In total, 28 subjects completed the study. DAP-FOR plasma concentrations were not detected in all of the blood sampling time points except for one time point in one subject, and the corresponding DAP-FOR plasma concentration in the subject was close to the lower limit of quantification. The mean plasma concentration–time profiles of dapagliflozin were comparable between the two drugs. The geometric mean ratios and its 90% confidence intervals of the maximum plasma concentration and area under the plasma concentration–time curve of dapagliflozin for DAP-FOR to DAP-PDH were within the conventional bioequivalence range of 0.80–1.25. Both drugs were well-tolerated, with a similar incidence of adverse drug reactions.

Conclusion: The rapid conversion of DAP-FOR into dapagliflozin led to the extremely low exposure of DAP-FOR and comparable PK profiles of dapagliflozin between DAP-FOR and DAP-PDH. The safety profiles were also similar between the two drugs. These results suggest that DAP-FOR can be used as an alternative to DAP-PDH.

Keywords: prodrugs, dapagliflozin, pharmacokinetics, clinical trial, phase I

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia. The aim of DM management is to maintain the recommended target range of glucose and glycosylated hemoglobin levels to avoid short-term and long-term diabetic complications and improve the quality of life of patients.[1–3] Unlike type 1 DM, which is characterized by chronic autoimmune disease of insulin-producing pancreatic β-cell destruction, type 2 DM is predominantly caused by β-cell dysfunction and insulin resistance.[4–6] Therapies for type 2 DM are considered depending on comorbidities, patient-centered treatment factors, and management needs.[7]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a class of type 2 DM treatments, excrete glucose in urine and lower plasma glucose levels by inhibiting SGLT2 proteins that are responsible for the reabsorption of sodium and glucose in the proximal convoluted tubule of the kidneys.[8–10] Dapagliflozin is a highly selective and reversible SGLT2 inhibitor, and it has been prescribed after the approval of the European Medicines Agency (Forxiga) and US Food and Drug Administration (Farxiga).

Dapagliflozin has the amorphous and amphiphilic nature of the molecule.[11] To overcome the poor solid stability and problems in the formulation process caused by its high hygroscopicity, the conventional formulation of dapagliflozin was developed as dapagliflozin propanediol monohydrate (DAP-PDH), a crystalline hydrate form of dapagliflozin with (S)-propylene glycol and water (Figure 1).[12,13] However, the crystalline hydrate form of dapagliflozin still requires management of temperature and humidity during manufacture and storage because it easily returns to its amorphous form with the loss of propanediol and water, even at slightly higher temperatures than room temperature.[12–14]

In addition to many pharmaceutical strategies (cocrystal, salt, hydrate, and solvate)[13,15,16] to overcome the physico-chemical properties of active pharmaceutical ingredients (APIs), the prodrug approach has also been used to improve the pharmaceutical, pharmacokinetic (PK), and pharmacodynamic (PD) properties of APIs.[17–20] Dapagliflozin formate (DAP-FOR, DA-2811), an ester prodrug of dapagliflozin, was developed by Dong-A ST to improve the stability and pharma-ceutical manufacturing process of dapagliflozin, which has a relatively higher melting point (approximately 104 °C) than that of DAP-PDH. DAP-FOR was designed to be rapidly converted into dapagliflozin in its active form by the hydrolysis of the ester structure in the molecule during absorption (Figure 1).

This study aimed to evaluate the PKs and safety of dapagliflozin for DAP-FOR, the ester prodrug of dapagliflozin, compared to those for DAP-PDH, the crystalline hydrate form of dapagliflozin, in healthy subjects. Additionally, the PKs and safety of DAP-FOR itself were explored according to the guidelines of general bioequivalence studies.[21–23]

Materials and Methods

The study protocol and informed consent form were reviewed and approved by the Ministry of Food and Drug Safety of Korea and the Institutional Review Board at Seoul National University Bundang Hospital (IRB number: B-2104-676-002). This study was registered at ClinicalTrials.gov (NCT04938752) and performed in accordance with the tenets of the Declaration of Helsinki and the Korean Good Clinical Practice guidelines. Written informed consent was obtained from all subjects prior to the study procedures.
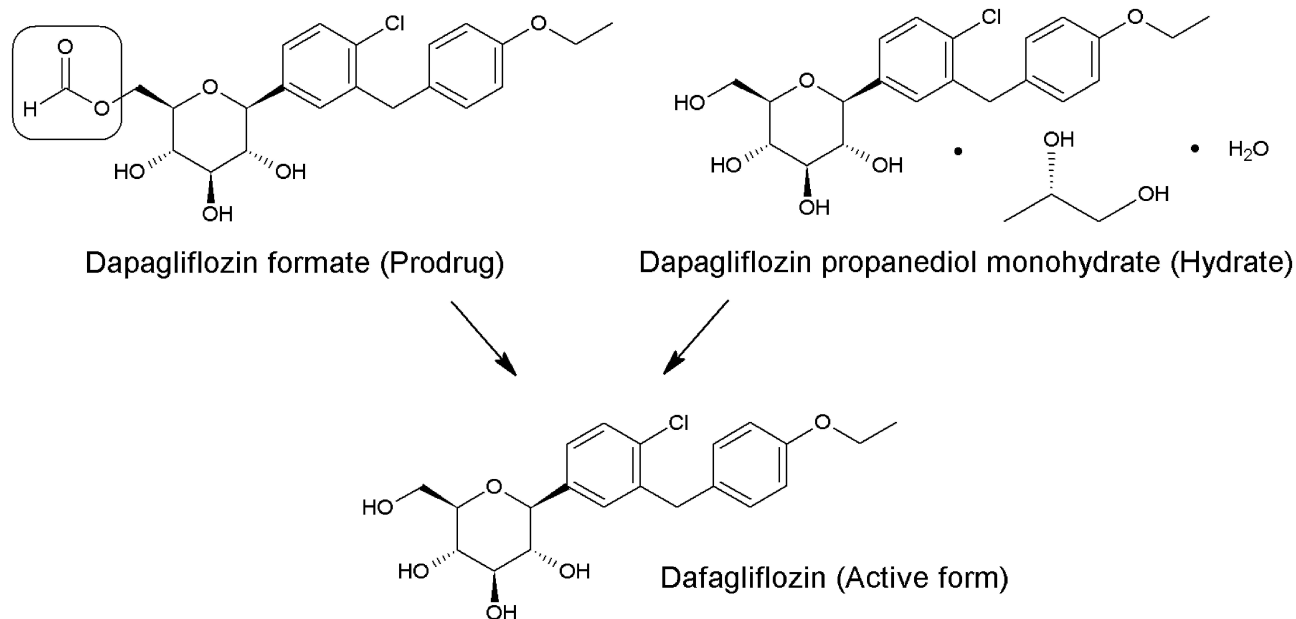
Figure 1 Chemical structure comparison of dapagliflozin formate (DAP-FOR, DA-2811) and dapagliflozin propanediol monohydrate (DAP-PDH, Forxiga).

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Subjects

Healthy subjects aged 19–45 years with body weight ≥ 50 kg and body mass index of 18.5–29.9 kg/m^2 were eligible to participate in the study. The major exclusion criteria were as follows: fasting blood glucose < 70 mg/dL or > 110 mg/dL; estimated glomerular filtration rate calculated using the MDRD equation ≤ 80 mL/min/1.73 m^2; aspartate aminotransferase or alanine aminotransferase > upper limit of normal (ULN) range × 2; total bilirubin > ULN range × 2.5; creatine phosphokinase > ULN range × 3; Bazett's corrected QT interval > 460 msec; systolic blood pressure < 100 mmHg or > 150 mmHg; and diastolic blood pressure < 60 mmHg or > 100 mmHg.

Study Design

This was an open-label, randomized, single-dose, two-period, two-sequence crossover study. The enrolled subjects were randomly assigned to one of two sequences in a ratio of 1:1, in which the subjects received a single dose of DAP-FOR 10 mg as a test drug or DAP-PDH 10 mg as a reference drug in the first period, and an alternate drug in the second period. Between the treatment periods, there was a 7-day washout period, which was 10 times longer than the elimination half-life ($t_{1/2}$) of dapagliflozin reported in previous clinical trials.[24–27]

The number of study subjects was calculated based on the intra-subject coefficient of variation (CV) of 21% for maximum plasma concentration (C_{max}) and 10% for the area under the plasma concentration–time curve (AUC) from time 0 to infinity (AUC_{inf}) as the major PK parameters of dapagliflozin.[26] Assuming a maximum intra-subject CV of 21%, an expected DAP-FOR/DAP-PDH ratio of 1.0, and a dropout rate of 25%, a total sample size of 30 subjects was estimated to determine whether 90% confidence intervals (CIs) for the comparison of dapagliflozin PK parameters for DAP-FOR to DAP-PDH were within the conventional bioequivalence range of 0.8–1.25 with 90% power at a significance level of 0.05.

Blood samples for PK assessment were collected at 0 (pre-dose), 5, 10, 15, 30, and 45 minutes and at 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 hours post-dose. The blood sampling time points were established considering the rapid conversion of DAP-FOR into dapagliflozin and the reported $t_{1/2}$ of dapagliflozin.[24–27] Approximately 7 mL of blood at each time point was collected in K_2-ethylenediaminetetraacetic acid tubes and centrifuged at 1 °C and 3000 × g for 5 minutes. The supernatants were mixed well in tubes containing 1% formic acid solution and stored at −70 °C or lower until sample analysis.

Determination of Plasma Concentrations of Dapagliflozin Formate and Dapagliflozin

The plasma concentrations of DAP-FOR and dapagliflozin were determined separately by validated liquid chromatography (LC; Shimadzu UFLC, Shimadzu, Japan) with tandem mass spectrometry (MS/MS; TQ5500 for DAP-FOR, API5000 for dapagliflozin, SCIEX, USA) using dapagliflozin-d_5 as an internal standard. All data were processed using Analyst version 1.6.3 (SCIEX, USA).

DAP-FOR and dapagliflozin-d_5 were separated under the LC conditions of a C18 column (2.0 mm, I.D. × 75 mm, L; particle size, 3 μm) at 30 °C with a mobile phase of 0.001% acetic acid in 1 mM ammonium acetate and methanol (35:65 [vol/vol]), at a flow rate of 0.4 mL/min, and detected under the MS/MS conditions of negative ion electrospray ionization with multiple reaction monitoring at the m/z transition of 495.2 → 407.3 for DAP-FOR and 472.3 → 334.2 for dapagliflozin-d_5. For sample preparation, plasma was mixed with the same volume of 1% formic acid solution as a stabilizer. An aliquot of mixed plasma (200 μL) was transferred into a tube, to which 10 μL of the internal standard solution and 200 μL of acetonitrile were added and vortex-mixed for 1 min. After vortexing, the mixture was centrifuged at 13,000 rpm for 5 min. Next, 3 mL of methyl *tert*-butyl ether was added to the supernatant, followed by vortexing for 5 min and centrifugation at 3000 rpm for 1 min. The organic phase was dried under nitrogen gas at 45 °C and the residue was completely dissolved in 100 μL of acetonitrile. The supernatant was injected into the LC-MS/MS system. For calibration curve and quality control samples of DAP-FOR, the accuracy ranges were 96.5–105.4% and 99.1–100.4%, and the CVs were ≤ 3.0% and ≤ 3.8%, respectively. The calibration curve for DAP-FOR ranged from 1 to 2000 μg/L.

Dapagliflozin and dapagliflozin-d_5 were separated under the LC conditions of the C18 column at 40°C, with a mobile phase of 1 mM ammonium acetate and acetonitrile (55:45 [vol/vol]), at a flow rate of 0.2 mL/min, and detected under the MS/MS conditions of negative ion electrospray ionization with multiple reaction monitoring at the m/z transition of 467.2 → 329.2 for dapagliflozin and 472.3 → 334.2 for dapagliflozin-d_5. For sample preparation, 200 μL of plasma was

transferred into a tube, to which 10 μL of internal standard solution and 1 mL of methyl *tert*-butyl ether were added and vortex-mixed for 3 min. After vortexing, the mixture was centrifuged at 13,000 rpm for 3 min. Thereafter, the organic phase was dried under nitrogen gas at 45 °C and the residue was completely dissolved in 200 μL of 50% acetonitrile. The supernatant was injected into the LC-MS/MS system. For the calibration curve and quality control samples of dapagliflozin, the accuracy ranges were 98.2–101.6% and 98.5–98.7%, and the CVs were ≤ 2.4% and ≤ 3.0%, respectively. The calibration curve for dapagliflozin ranged from 0.5 to 500 μg/L.

Pharmacokinetic and Statistical Assessment

PK parameters were derived from plasma concentration–time curves by a non-compartmental method using Phoenix WinNonlin version 8.3 (Certara, USA). The primary PK parameters were C_{max} and AUC from time 0 to the last measurable time point (AUC_{last}) of dapagliflozin, and the secondary PK parameters were AUC_{inf}, time to reach the C_{max} (T_{max}), $t_{1/2}$, apparent total clearance (CL/F), and apparent volume of distribution (V_d/F) of dapagliflozin. The exploratory PK parameters were the corresponding parameters of DAP-FOR.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., USA). The geometric mean ratios (GMRs) and its 90% CIs of C_{max}, AUC_{last}, and AUC_{inf} of dapagliflozin for DAP-FOR to DAP-PDH were estimated using a linear mixed–effects model. The model included sequence, period, and treatment as fixed effects and subjects nested within the sequence as a random effect. We concluded that the two drugs were bioequivalent if the GMRs and its 90% CIs of the primary PK parameters were within the conventional bioequivalence criteria of 0.8–1.25. The intra-subject CV of dapagliflozin was calculated using the residual of the linear mixed–effects model as follows: intra-subject CV (%) = $100 \times \sqrt{exp(Residual) - 1}$

Safety Assessment

Safety was assessed via monitoring of adverse events (AEs), physical examination, evaluation of vital signs, clinical laboratory tests, and 12-lead electrocardiograms. Additional blood glucose tests were performed using blood glucose meters to monitor hypoglycemia at 2 and 4 hours after dosing. Hypoglycemia was defined by a plasma glucose concentration below 70 mg/dL with clinically significant signs or symptoms. Whipple's triad was used to prove that hypoglycemia was the cause of the suspected symptoms.[28,29]

Results
Study Population

In this study, 30 healthy Korean male subjects were enrolled and randomized; however, two subjects withdrew their consent before the first and second periods, respectively. Thus, 28 participants completed the study. The mean ± standard deviation values of the 30 randomized subjects were 24.20 ± 5.50 years for age, 175.91 ± 4.79 cm for height, 71.49 ± 8.09 kg for weight, and 23.10 ± 2.43 kg/m² for body mass index. In terms of demographics, there were no statistically significant differences between the two sequences when calculated using the Mann–Whitney *U*-test or Student's *t*-test, depending on the normality of the variables.

Pharmacokinetics

DAP-FOR plasma concentrations were not detected in all of the blood sampling time points except for one time point (15 minutes after administration of DAP-FOR) in one subject, and the corresponding DAP-FOR plasma concentration in the subject was 1.04 μg/L which was close to the lower limits of quantification of DAP-FOR (1 μg/L). The mean plasma concentration–time profiles and PK parameters of dapagliflozin for DAP-FOR were comparable to those for DAP-PDH (Figure 2, Table 1). The GMRs (90% CIs) of dapagliflozin for DAP-FOR to DAP-PDH were 0.9766 (0.8635–1.1044), 0.9797 (0.9427–1.0182), 0.9844 (0.9553–1.0145) for C_{max}, AUC_{last}, and AUC_{inf}, respectively, which are within the conventional bioequivalence range of 0.80–1.25. The highest intra-subject CV for dapagliflozin was 27.41%, observed in C_{max} (Table 2).
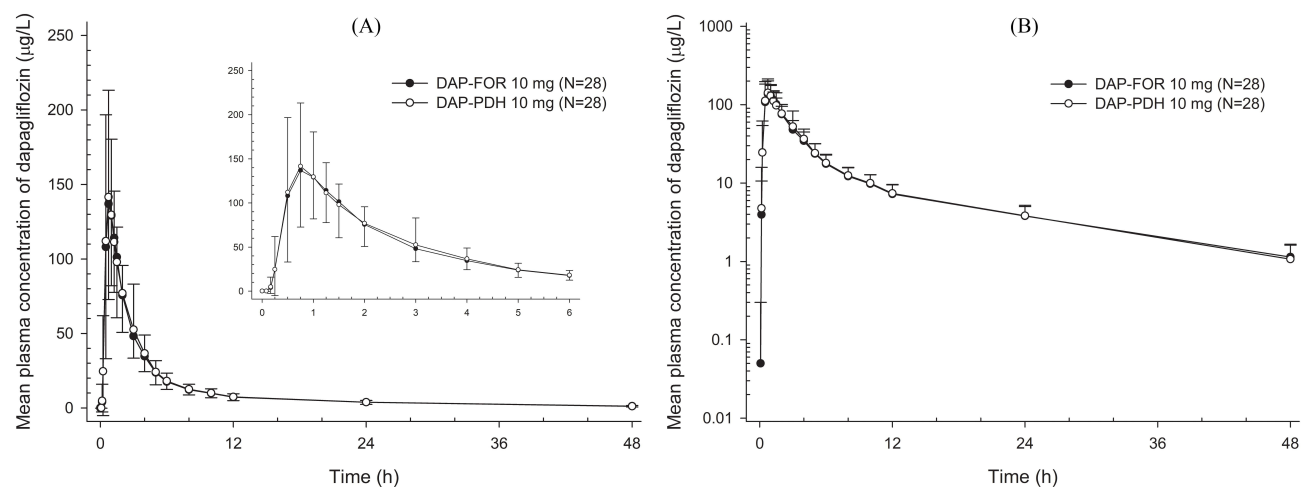
Figure 2 Mean plasma concentration–time profiles of dapagliflozin after a single administration of DAP-FOR 10 mg as a test drug or DAP-PDH 10 mg as a reference drug in **(A)** linear scale and **(B)** log scale.
Note: The vertical bars represent standard deviation.
Abbreviations: DAP-FOR, dapagliflozin formate; DAP-PDH, dapagliflozin propanediol monohydrate.

Safety

All AEs were mild, and no serious AEs were reported throughout the study. Seven adverse drug reactions (ADRs) were reported in 5 of the 29 subjects. There were no statistically significant differences in the incidence of ADRs between the two drugs when calculated using Fisher's exact test (*P*-value = 0.67). Five ADRs (one case of diarrhea, headache, and proteinuria; two cases of dizziness) occurred in three subjects after the administration of DAP-FOR, and two ADRs (one case of epigastric discomfort and nausea) occurred in two subjects after the administration of DAP-PDH.

There were no clinically significant changes in physical examinations, vital signs, clinical laboratory tests, blood glucose tests, or 12-lead electrocardiograms, except for the occurrence of proteinuria and stomatitis. The continuous proteinuria from the administration of DAP-FOR in the first period to the post-study visit was reported as an ADR; the study was terminated without confirming complete recovery of the proteinuria because of the subject's refusal for the additional follow-ups. Although stomatitis was reported after DAP-FOR administration, there was no temporal correlation between drug administration and AE onset.

Table 1 Summary of Pharmacokinetic Parameters of Dapagliflozin After a Single Administration of DAP-FOR 10 Mg as a Test Drug or DAP-PDH 10 Mg as a Reference Drug

Pharmacokinetic Parameter	DAP-FOR 10 mg (N=28)	DAP-PDH 10 mg (N=28)	*P*-value*
T_{max} (h)	0.75 [0.50–3.00]	0.75 [0.50–3.00]	0.37
C_{max} (µg/L)	164.50 ± 53.47	167.93 ± 54.24	0.75
AUC_{last} (h·µg/L)	503.29 ± 133.13	509.41 ± 117.13	0.56
AUC_{inf} (h·µg/L)	534.53 ± 126.88	540.09 ± 115.61	0.54
$t_{1/2}$ (h)	12.42 ± 3.50	11.46 ± 3.44	0.12
CL/F (L/h)	19.66 ± 4.33	19.31 ± 4.02	0.35
V_d/F (L)	353.03 ± 132.17	316.90 ± 114.19	0.08

Notes: Data are presented as the mean ± standard deviation, except for T_{max} presented as median [minimum–maximum]. *Differences in each pharmacokinetic parameter between DAP-FOR 10 mg and DAP-PDH 10 mg were analyzed by paired *t*-test, except for T_{max} analyzed by Wilcoxon signed rank test.
Abbreviations: AUC_{inf}, area under the plasma concentration–time curve (AUC) from time 0 to infinity; AUC_{last}, AUC from time 0 to the last measurable time point; CL/F, apparent total clearance; C_{max}, maximum plasma concentration; DAP-FOR, dapagliflozin formate; DAP-PDH, dapagliflozin propanediol monohydrate; $t_{1/2}$, elimination half-life; T_{max}, time to reach the maximum plasma concentration; V_d/F, apparent volume of distribution.

Table 2 Comparison of Pharmacokinetic Parameters of Dapagliflozin Between DAP-FOR 10 Mg as a Test Drug and DAP-PDH 10 Mg as a Reference Drug

| Pharmacokinetic Parameter	Geometric Mean		Geometric Mean Ratio [90% CI] (DAP-FOR 10 mg/DAP-PDH 10 mg)	Intra-Subject CV (%)
	DAP-FOR 10 mg (N=28)	DAP-PDH 10 mg (N=28)		
C_{max} (μg/L)	155.07	158.79	0.9766 [0.8635–1.1044]	27.41
AUC_{last} (h·μg/L)	484.72	494.75	0.9797 [0.9427–1.0182]	8.45
AUC_{inf} (h·μg/L)	518.61	526.81	0.9844 [0.9553–1.0145]	6.58

Abbreviations: CI, confidence interval; CV, coefficient of variation; DAP-FOR, dapagliflozin formate; DAP-PDH, dapagliflozin propanediol monohydrate.

Discussion

This study was conducted to evaluate the PKs and safety of dapagliflozin for DAP-FOR (dapagliflozin formate), the ester prodrug of dapagliflozin, compared to those for DAP-PDH (dapagliflozin propanediol monohydrate), the crystalline hydrate form of dapagliflozin, in healthy subjects. The mean plasma concentration–time profiles of dapagliflozin for DAP-FOR were similar to those for DAP-PDH, and the 90% CIs of C_{max} and AUC_{last} of dapagliflozin for DAP-FOR to DAP-PDH satisfied the conventional bioequivalence criteria of 0.80–1.25. This suggests that DAP-FOR can be used as an alternative to DAP-PDH.

Carboxylesterase (CES) is the main esterase involved in the hydrolysis of endogenous esters, ester-containing drugs, and environmental toxicants.[30–34] In the CES families, CES1 and CES2 play major roles in the metabolism of ester xenobiotics and are abundantly expressed in the liver and the small intestine, respectively.[30–32] In general, based on ester substrate specificity, CES1 prefers to hydrolyze esters to a small alcohol group and a bulky acyl group; however, CES2 prefers to metabolize them to a relatively large alcohol group and a small acyl group.[30,31] In this study, almost all the plasma concentrations of DAP-FOR were not detected; however, the mean plasma concentration profile of dapagliflozin for DAP-FOR was similar to that of DAP-PDH, specifically during absorption. Expectedly, these results showed that DAP-FOR was rapidly converted into dapagliflozin by hydrolysis of the intramolecular ester structure. In addition, many esterases, especially CES2, were expected to be involved in the rapid and complete first-pass bioconversion of DAP-FOR into dapagliflozin.

According to the classification of prodrugs in regulatory perspectives,[35] we suggest that DAP-FOR be classified as a Type IIA prodrug that is rapidly converted in gastrointestinal fluids. It is recommended that Type II prodrugs should be evaluated for the comparative toxicity profiles of prodrugs and active drugs, including their time-dependent expression.[35,36] The subject with one measured concentration of DAP-FOR after the administration of DAP-FOR had no ADR throughout the study.
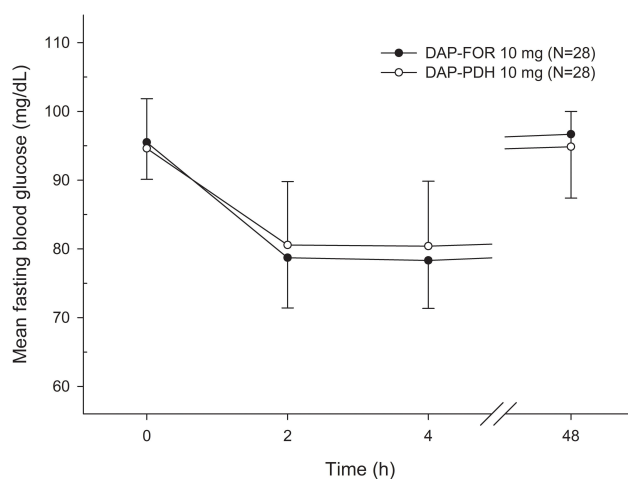
Figure 3 Mean fasting blood glucose–time profiles after a single administration of DAP-FOR 10 mg as a test drug or DAP-PDH 10 mg as a reference drug in healthy subjects.
Note: The vertical bars represent standard deviation.
Abbreviations: DAP-FOR, dapagliflozin formate; DAP-PDH, dapagliflozin propanediol monohydrate.

Therefore, it was concluded that the extremely low exposure of DAP-FOR would be clinically insignificant. The overall safety profiles of the two drugs were comparable, with no statistically significant differences in the incidence of ADRs.

Despite the normal range of fasting blood glucose during enrollment, the fasting blood glucose level was monitored for post-dose hypoglycemia. The mean fasting blood glucose–time profiles of the two drugs were comparable (Figure 3). The maximum decreases in the mean fasting blood glucose from baseline measured at 0 hour (pre-dose) were 17.18 mg/dL for DAP-FOR and 14.22 mg/dL for DAP-PDH 4 hours after administration; however, the values were recovered two days post-dose. The evaluation of fasting blood glucose was not the aim of this study; however, these results show that DAP-FOR would have similar blood glucose lowering effect to DAP-PDH.

Conclusion

The rapid conversion of DAP-FOR into dapagliflozin led to the extremely low exposure of DAP-FOR and comparable PK profiles of dapagliflozin between DAP-FOR and DAP-PDH. The safety profiles were also similar between the two drugs. These results suggest that DAP-FOR can be used as an alternative to DAP-PDH.

Data Sharing Statement

The authors do not intend to share substantial data of this study, but they are ready to share deidentified data in excel format and all other study-related documents (in Korean), at any specific time for any period, if the editorial board requires.

Disclosure

Siyoung Sung and Eunjin Kim are employees of Dong-A ST. The other authors have no conflicts of interest to report in this study.

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