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ORIGINAL ARTICLE

Lack of pharmacokinetic interaction between dapagliflozin, a novel sodium–glucose transporter 2 inhibitor, and metformin, pioglitazone, glimepiride or sitagliptin in healthy subjects

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Aims: Dapagliflozin increases urinary glucose excretion by selectively inhibiting renal sodium–glucose transporter 2, an insulin-independent mechanism of action that may be complementary to that of other oral antidiabetes drugs. The current studies assessed the potential for pharmacokinetic (PK) interaction between dapagliflozin and pioglitazone, metformin, glimepiride or sitagliptin in healthy subjects following single-dose administration.

Methods: In open-label, randomized, three-period, three-treatment crossover studies, 24 subjects received 50 mg dapagliflozin, 45 mg pioglitazone or the combination, while 18 subjects received 20 mg dapagliflozin, 1000 mg metformin or the combination. In an open-label, randomized, five-period, five-treatment, unbalanced crossover study, 18 subjects first received 20 mg dapagliflozin, 4 mg glimepiride or the combination, and afterward 100 mg sitagliptin or sitagliptin plus 20 mg dapagliflozin. Blood samples were taken over 72 h of each treatment period. Lack of PK interaction was defined as the ratio of geometric means and 90% confidence interval (CI) for combination:monotherapy being within the range of 0.80–1.25.

Results: Co-administration of dapagliflozin with pioglitazone, metformin, glimepiride or sitagliptin had no effect on dapagliflozin maximum plasma concentration (C_{max}) or area under the plasma concentration-time curve (AUC). Similarly, dapagliflozin did not affect the C_{max} or AUC for the co-administered drug, except for slight extensions of the 90% CI for the ratio of geometric means for glimepiride AUC (upper limit 1.29) and pioglitazone C_{max} (lower limit 0.75). All monotherapies and combination therapies were well tolerated.

Conclusion: Dapagliflozin can be co-administered with pioglitazone, metformin, glimepiride or sitagliptin without dose adjustment of either drug.

Keywords: antidiabetic drug, clinical trial, pharmacokinetics, SGLT2 inhibitor, type 2 diabetes

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Introduction

Current guidelines from the American Diabetes Association and the European Association of the Study of Diabetes recommend the use of metformin along with lifestyle management as first-line treatment for the management of hyperglycaemia in newly diagnosed patients with type 2 diabetes mellitus (T2DM) [1]. However, most patients require combination therapy to maintain adequate glycaemic control as the disease progresses over time [2].

Dapagliflozin is an orally active, potent and highly selective inhibitor of the renal sodium–glucose transporter 2 (SGLT2) that is currently under development for the treatment of T2DM [3,4]. Plasma glucose is filtered by the renal glomerulus into the tubule and SGLT2 is responsible for the majority of the glucose reabsorbed by the kidney [5]. Inhibition of SGLT2 by dapagliflozin increases urinary glucose excretion in healthy subjects [6] and patients with T2DM [7–9]. The increase in urinary glucose excretion improves glycaemic control in patients with T2DM [8,9] (figure 1).

Metformin acts primarily by reducing hepatic glucose production and improving insulin resistance [10,11]. Thus, the insulin-independent mechanism of action of dapagliflozin does not overlap with that of metformin, and the two drugs represent a potentially attractive oral combination therapy for patients with T2DM. In addition to metformin, other oral antidiabetic drugs (OADs), with insulin-dependent mechanisms of action may also be candidates for combination therapy

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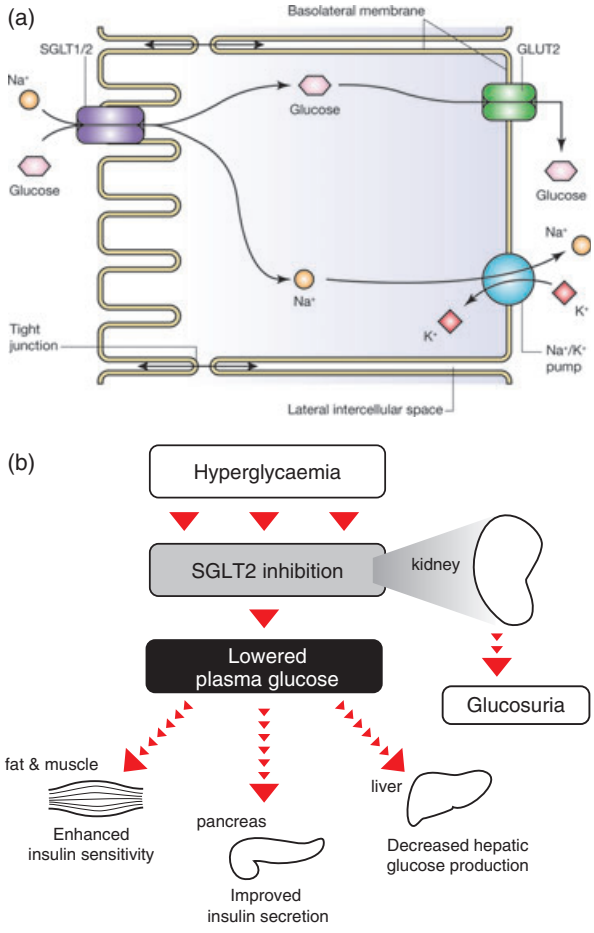

Figure 1. Sodium–glucose co-transport in the renal proximal tubule (a) and clinical effects of SGLT2 inhibition (b).

with dapagliflozin. Pioglitazone is a perixosome proliferator-activated receptor (PPAR-γ) activator that improves insulin sensitivity [12]. Glimepiride stimulates the release of insulin from pancreatic beta cells [13]. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that increases plasma levels of GLP-1 in a glucose-dependent manner, which in turn stimulates insulin secretion and inhibits glucagon secretion [14].

The aim of the three studies reported here was to determine the effect of co-administration of dapagliflozin with the OADs pioglitazone, metformin, glimepiride or sitagliptin on the pharmacokinetics (PK) of dapagliflozin and each OAD following single-dose administration and to assess the safety and tolerability of the combined therapies in healthy subjects.

Materials and Methods

The protocol, protocol amendments and informed consents were approved by the New England Institutional Review Board for the dapagliflozin/pioglitazone drug–drug interaction (DDI) study and by the Integreview, Ltd Review Board for the dapagliflozin/metformin and dapagliflozin/glimepiride or sitagliptin DDI studies. Written informed consent was obtained from all study participants prior to study enrolment. The studies were carried out in accordance with the Guidelines for Good Clinical Practice and adhered to the principles of the Declaration of Helsinki and the US Food and Drug Administration Code of Federal Regulations.

Subjects

Healthy men and women (not nursing or pregnant and using an acceptable method of contraception) aged 18–45 years with body mass index (BMI) of 18–30 kg/m^2 inclusive (study 1) and 18–32 kg/m^2 inclusive (studies 2 and 3) were eligible. Medical history was disclosed and physical examination, electrocardiogram (ECG) and clinical laboratory determinations, including routine haematological, biochemical and urine tests, were conducted to determine eligibility for enrolment.

Exclusion criteria included history of significant drug allergies, previous exposure to dapagliflozin, use of prescription medications or over-the-counter (OTC) acid controllers within 4 weeks prior to enrolment, and use of any other drugs, including OTC medication and herbal preparations.

Study Designs

Study 1: Dapagliflozin/Pioglitazone DDI

An open-label, randomized, three-period, three-treatment, crossover, single-dose study design was employed to investigate the interaction of dapagliflozin and pioglitazone (figure 2A). Twenty-four subjects were randomized to one of the six treatment sequences and to receive the following three treatments: treatment A, 50 mg dapagliflozin; treatment B, 45 mg pioglitazone; treatment C, 50 mg dapagliflozin + 45 mg pioglitazone. There was at least a 6-day washout period between dosing periods. Blood samples were collected at predose (0), 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 32, 40, 48, 60 and 72 h following administration of dapagliflozin, pioglitazone or dapagliflozin + pioglitazone.

Study 2: Dapagliflozin/Metformin DDI

The same study design was employed to investigate the interaction of dapagliflozin and metformin (figure 2A). Eighteen subjects were randomized to one of the six treatment sequences and to receive the following three treatments: treatment A, 20 mg dapagliflozin; treatment B, 1000 mg metformin; treatment C, 20 mg dapagliflozin + 1000 mg metformin. There was at least a 4-day washout period between dosing periods.

Blood samples were collected at predose (0), 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 32, 40, 48, 60 and 72 h following administration of dapagliflozin, metformin or dapagliflozin + metformin.

Study 3: Dapagliflozin/Glimepiride or Sitagliptin DDI

An open-label, randomized, five-period, five-treatment, unbalanced crossover single-dose study design was employed to investigate the interaction of dapagliflozin and glimepiride or sitagliptin (figure 2B). In phase A, 18 subjects were randomized

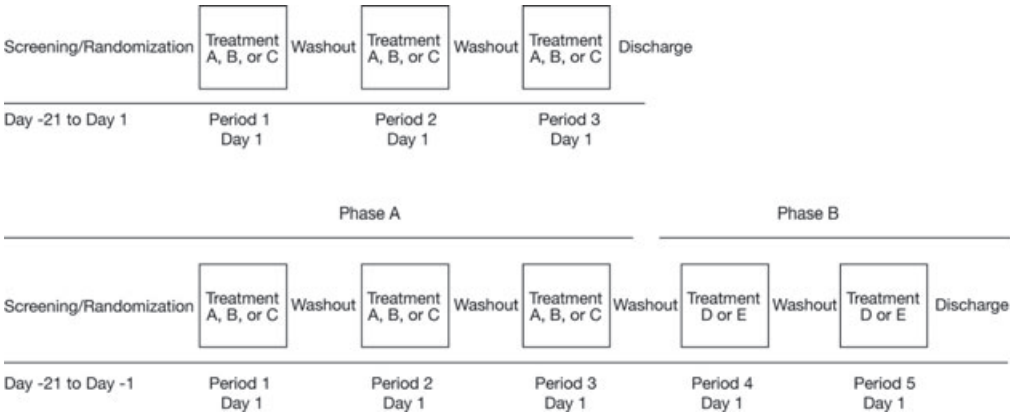

Figure 2. Study designs. The top diagram depicts the three-period, three-treatment study in which subjects received 50 mg dapagliflozin, 45 mg pioglitazone, or the combination or 20 mg dapagliflozin, 1000 mg metformin, or the combination (treatments represented as A, B or C). The bottom diagram depicts the five-period, five-treatment study in which subjects first received 20 mg dapagliflozin, 4 mg glimepiride or the combination (treatments represented as A, B or C) and afterward 100 mg sitagliptin or sitagliptin plus 20 mg dapagliflozin (treatments represented as D or E).

to one of the six treatment sequences and to receive the following three treatments: treatment A, 20 mg dapagliflozin; treatment B, 4 mg glimepiride; treatment C, 20 mg dapagliflozin + 4 mg glimepiride. In phase B, the same subjects were randomized to one of two sequences and to receive the following two treatments: treatment D, 100 mg sitagliptin; treatment E, 20 mg dapagliflozin + 100 mg sitagliptin. At the time of dosing, 240 ml of a 20% glucose solution in water was administered along with study medication. Thereafter, 60 ml of the glucose solution was administered every 15 min for 4 h postdose to prevent hypoglycaemia. There was at least a 4-day washout period between dosing periods. Blood samples were collected at predose (0), 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 32, 40, 48, 60 and 72 h following administration of dapagliflozin, glimepiride, dapagliflozin + glimepiride, sitagliptin or dapagliflozin + sitagliptin.

Vital signs were measured at screening, during each treatment period and prior to discharge from the study. Routine clinical laboratory determinations were made at screening, prior to treatment with any study medications and prior to discharge. Safety monitoring for serious and non-serious adverse events (AEs) was conducted during each period of study drug administration. Study drugs were administered after a fast of at least 10 h, with a 4-h fast postdosing on PK sampling days. Serial blood samples were collected for 72 h postdose for PK assessments.

The dose of dapagliflozin for each study was chosen to produce a higher maximum observed plasma concentration (C_{max}) and greater area under the plasma concentration-time curve (AUC) than those produced at steady state from the currently anticipated clinical dose of 10 mg. The mean steady state C_{max} for dapagliflozin 10 mg is 119 ng/ml and the mean steady state AUC of 506 ng·h/ml, in healthy subjects at day 14 [6]. The dose used of each OAD is a recommended clinical dose.

Drug Analyses

The plasma concentration of dapagliflozin was assayed by a validated LC-MS/MS method as described previously [6]. In study 1, the between- and within-run variability for the quality controls of dapagliflozin was 6.2 and 7.3%, respectively, of the coefficient of variation, with deviation from nominal concentration of no more than ±1.0%. The lower and upper limits of quantification in plasma were 1–1000 ng/ml. In study 2, the respective numbers were ≤1.8%, ≤7.9%, ±4.0% and 1–500 ng/ml, while in study 3 they were ≤2.4%, ≤6.9%, ±1.9% and 1–200 ng/ml. Assays for pioglitazone, metformin, glimepiride and sitagliptin were also performed using LC-MS/MS. The between- and within-run variability for the quality controls of pioglitazone was 2.4 and 4.1%, respectively, with deviation from nominal concentration of no more than ±6.8%. The lower and upper limits of quantification in plasma were 1–1000 ng/ml. For metformin the respective numbers were ≤4.8% and ≤8.4%, ±3.2% and 2–2000 ng/ml. For glimepiride they were ≤6.0% and ≤9.8%, ±1.5% and 2–1000 ng/ml, respectively, while for sitagliptin they were ≤4.1% and ≤3.6%, ±5.7% and 1–1000 ng/ml, respectively. The determination of plasma drug concentration was performed by Atlanbio (Saint-Nazaire Cedex, France) for studies 1 and 2. For study 3, plasma concentrations of dapagliflozin were analysed by CEDRA Corporation (Austin, TX, USA), while those of glimepiride and sitagliptin were analysed by PPD Lab (Richmond, VA, USA) and Tandem Labs (West Trenton, NJ, USA), respectively.

PK Analyses

The single-dose PK parameters were derived from plasma concentration versus time data. They included the C_{max}, the time of maximum observed plasma concentration (T_{max}), the AUC from time zero to the last time of the last quantifiable concentration ($AUC_{(0\text{-}T)}$), the AUC from time zero extrapolated to infinite time ($AUC_{(INF)}$), and plasma half-life ($T_{1/2}$). Individual subject PK parameters were derived by non-compartmental methods by a validated PK analysis programme. C_{max} and T_{max} were recorded directly from experimental observations. The AUC was calculated by a

combination of log and linear trapezoidal summations. The elimination $T_{1/2}$ was determined by the equation of $T_{1/2} = \ln 2/\lambda$, where λ, the first-order elimination rate constant, was determined from the terminal phase of concentration profiles using at least three time points.

Statistical Analyses

To assess the effect of co-administration of an OAD and dapagliflozin on the PK of dapagliflozin and the OAD, analyses of variance were performed on C_{max}, $AUC_{(0\text{-}T)}$ and $AUC_{(INF)}$ of each analyte. In the analysis of variance, sequence, period and treatment were considered as fixed effects and subject within sequence as a random effect. *A priori*, the variables C_{max}, $AUC_{(0\text{-}T)}$ and $AUC_{(INF)}$ were log-transformed. Point estimates and 90% confidence intervals (CIs) for treatment differences on the log scale were exponentiated to obtain point estimates and 90% CIs for the ratios of geometric means on the original scale of measurement. Lack of an effect of an OAD on the PK of dapagliflozin would be concluded if the 90% CIs for the dapagliflozin + OAD to dapagliflozin alone ratios of population geometric means were contained within 80 and 125% for the C_{max}, $AUC_{(0\text{-}T)}$ and $AUC_{(INF)}$ of dapagliflozin. Lack of an effect of dapagliflozin on the PK of the OAD would be concluded if the 90% CIs for the dapagliflozin + OAD to OAD alone ratios of population geometric means were contained within 80 and 125% for the C_{max}, $AUC_{(0\text{-}T)}$ and $AUC_{(INF)}$ of the OAD.

For all studies, frequency distributions of gender and race were tabulated. Summary statistics for age, body weight, height and BMI were tabulated. Summary statistics were tabulated for C_{max}, T_{max}, $AUC_{(INF)}$, $AUC_{(0\text{-}T)}$ and terminal half-life ($T_{1/2}$) by treatment, for each analyte. Geometric means and coefficients of variation were presented for C_{max}, $AUC_{(INF)}$ and $AUC_{(0\text{-}T)}$. Medians and ranges were presented for T_{max}. Means and standard deviations were presented for $T_{1/2}$.

Results

Patient Disposition and Demographics

A total of 24 subjects were randomized and treated with study drugs in Study 1, and 22 subjects completed the study. One subject discontinued as a result of an AE (dysuria); the other had a positive drug screen on readmittance. In study 2, 18 subjects were randomized and treated with study drugs; 17 completed the study and 1 discontinued because of elevated creatinine phosphokinase. Eighteen subjects were randomized and treated with study drugs in study 3 and all completed the study.

Demographic characteristics of the subjects are shown in Table 1. Most subjects were male and either African American or Caucasian. Study 1 comprised only male subjects, and study 3 only Caucasians. The mean age of the subjects across studies ranged from 32 to 33 years and their mean BMI ranged from 25.6 to 26.7 kg/m^2.

Effect of Co-administered OADs on Dapagliflozin PK

Mean dapagliflozin plasma concentration versus time profile with and without co-administration of metformin, pioglitazone, glimepiride or sitagliptin is shown in figure 3. The PK for dapagliflozin with and without co-administration of each OAD is summarized in Table 2. The prespecified criteria to conclude a lack of interaction between dapagliflozin and pioglitazone, metformin, glimepiride or sitagliptin were met for C_{max} and AUC in all cases, as the 90% CIs were within the no-effect interval of 0.8–1.25.

Table 1. Subject demographics.

	Study 1	Study 2	Study 3
Gender			
Male, n (%)	24 (100)	15 (83)	12 (67)
Female, n (%)	0 (0)	3 (17)	6 (33)
Race, n (%)			
African American	11 (46)	12 (67)	
Caucasian	11 (46)	6 (33)	18 (100)
Asian	2 (8)		
Age, year, mean (range)	32 (23–45)	33 (22–45)	33 (25–42)
BMI, kg/m^2, mean (range)	25.6 (18.6–29.4)	26.1 (19.6–31.6)	26.7 (19.2–31.2)

The T_{max} and $T_{1/2}$ for dapagliflozin were also unaffected by co-administration of OADs. The median (range) T_{max} for dapagliflozin was 1.5 (1.0–3.0) h without and 1.5 (1.0–2.0) h with co-administration of metformin, 1.0 (0.5–2.0) h with or without pioglitazone, 1.5 (1.0–4.0) h without and 1.5 (1.0–6.0) h with glimepiride and 1.7 (1.0–6.0) h with sitagliptin co-administration. The mean $T_{1/2}$ value (s.d.) for dapagliflozin was 17.8 (14.0) h without and 18.5 (16.8) h with pioglitazone (mean R^2 values were 0.969 and 0.958, respectively). 16.5 (8.9) h without and 14.0 (8.0) h with metformin (mean R^2 values were 0.983 and 0.985, respectively), 14.3 (10.1) h without and 12.4 (3.4) h with glimepiride (mean R^2 values were 0.987 and 0.983) and 15.9 (7.1) h with sitagliptin co-administration (mean R^2 value was 0.981). Mean R^2 for the regression of the points used in the $T_{1/2}$ determination ranged from 0.956 to 0.994.

Effect of Dapagliflozin on PK of Co-administered OAD

Figure 4 shows the mean plasma concentration versus time profile for each OAD with or without dapagliflozin, and Table 3 summarizes their PK. The PK profiles for the OADs when administered alone are generally comparable with values previously reported, although in some cases direct comparisons were not possible because of differences in sampling interval and dosage [15–19].

There were no meaningful differences in C_{max} or AUC for any OAD in the presence of dapagliflozin, as the 90% CIs were within the no-effect interval, with two exceptions. The lower boundary of the 90% CI for the C_{max} ratio for pioglitazone + dapagliflozin and pioglitazone alone was 0.75, slightly outside the prespecified no-effect interval, and the upper limit of the 90% CIs for glimepiride $AUC_{(INF)}$ and $AUC_{(0\text{-}T)}$ ratios (1.29) was slightly extended above the usual 1.25 no-effect interval (Table 3).

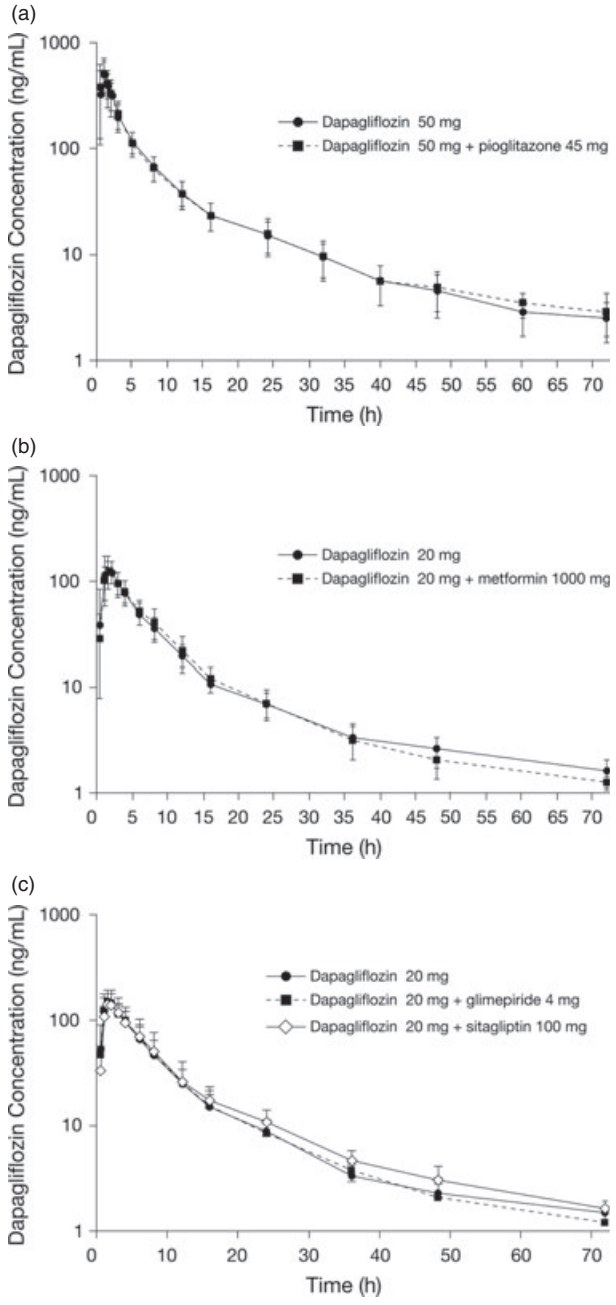

Figure 3. Mean plasma concentration versus time profile for dapagliflozin with and without co-administration of pioglitazone (a), metformin (b) and glimepiride or sitagliptin (c).

The T_{max} and $T_{1/2}$ for each OAD were also unaffected by co-administration of dapagliflozin. The median T_{max} (range) for pioglitazone was 2.0 (0.5–24.0) h without dapagliflozin and 3.0 (1.0–3.0) h with dapagliflozin. The respective T_{max} values were 3.0 (1.0–4.0) h and 3.0 (1.0–6.0) h for metformin, 8.0 (1.5–8.0) h and 8.0 (1.5–12.0) h for glimepiride and 3.0 (0.5–5.8) h and 4.0 (1.5–8.0) h for sitagliptin. The mean $T_{1/2}$ (s.d.) for pioglitazone was 11.7 (5.9) h and 16.7 (14.1) h in the absence and presence of dapagliflozin, respectively (mean R^2 values were 0.990 and 0.981). The respective $T_{1/2}$ values were 13.6 (11.5) h and 15.4 (10.9) h for metformin (mean R^2 values were 0.960 and 0.964), 5.1 (2.1) h and 6.0 (3.3) h for glimepiride (mean R^2 values were 0.960 and 0.956) and 14.2 (2.0) h and 14.4 (2.0) h for sitagliptin (mean R^2 values were 0.993 and 0.994).

Safety and Tolerability

Each drug and drug combination was well tolerated by the healthy subjects in these studies. There were no serious AEs, deaths or significant change in vital signs or ECG parameters. One subject had severely elevated creatinine phosphokinase (26,147 U/l) on day 8 after receiving dapagliflozin + metformin on day 1 and dapagliflozin on day 4. The subject discontinued on day 12 and the AE resolved without treatment by day 19.

Consistent with the pharmacodynamic effect of dapagliflozin, positive urine glucose at discharge was a common laboratory finding. The most frequently reported treatment-emergent AEs for each study are summarized in Table 4.

Discussion

Inhibition of SGLT2 with dapagliflozin represents an attractive therapeutic option for patients with T2DM whose blood glucose levels are inadequately controlled by metformin and/or other OADs, as dapagliflozin offers a complementary insulin-independent mechanism of action to the other drugs. This study assessed the effects of co-administration of dapagliflozin with pioglitazone, metformin, glimepiride or sitagliptin on the PK of dapagliflozin and each OAD following single-dose administration in healthy subjects. The results show that there are no clinically significant PK interactions that would complicate any of these combinations and each combination was well tolerated.

The PK of dapagliflozin following administration as monotherapy was consistent with those previously reported in healthy volunteers [6]. Co-administration of pioglitazone, metformin, glimepiride or sitagliptin with dapagliflozin had no significant effect on either the C_{max} or AUC for dapagliflozin, as the 90% CIs for the geometric mean ratios with and without those OADs were within the predefined bioequivalence limits of 0.8–1.25. The median T_{max} and mean $T_{1/2}$ for dapagliflozin were also unaffected by co-administration. Likewise, dapagliflozin had no clinically relevant effect on the C_{max}, AUC, T_{max} or $T_{1/2}$ for metformin, sitagliptin, pioglitazone or glimepiride. While the lower limit of the 90% CI of the ratio of geometric means for the C_{max} for pioglitazone with or without dapagliflozin was slightly outside the no-effect interval, the 90% CIs for the AUCs were wholly contained within that interval, indicating that the overall exposure of pioglitazone was unaffected by the presence of dapagliflozin. The 13% increase in glimepiride AUC is not likely to be clinically significant and will not require dose adjustment.

The lack of effect on the PK of the various combinations is consistent with what might be predicted from the metabolism of each entity. Dapagliflozin is primarily metabolized via UGT1A9 to form the inactive glucuronidated metabolite, dapagliflozin 3-O-glucuronide (BMS-801576),

Table 2. Pharmacokinetic parameters and statistical analysis for dapagliflozin with and without co-administration of pioglitazone, metformin, glimepiride or sitagliptin.

	Adjusted geometric means			Ratio of adjusted geometric means point estimate (90% CI)	
Drug/PK parameter	A	B	C	B/A	C/A
Dapagliflozin 50 mg PK	Dapagliflozin	Dapagliflozin + pioglitazone			
C_{max}, ng/ml	551	599	—	1.09 (1.00–1.18)	—
$AUC_{(INF)}$, ng·h/ml	2303	2373	—	1.03 (0.98–1.08)	—
$AUC_{(0\text{-}T)}$, ng·h/ml	2236	2292	—	1.03 (0.98–1.07)	—
Dapagliflozin 20 mg PK	Dapagliflozin	Dapagliflozin + metformin			
C_{max}, ng/ml	134	125	—	0.93 (0.85–1.02)	—
$AUC_{(INF)}$, ng·h/ml	947	943	—	1.00 (0.94–1.05)	—
$AUC_{(0\text{-}T)}$, ng·h/ml	903	908	—	1.01 (0.95–1.06)	—
Dapagliflozin 20 mg PK	Dapagliflozin	Dapagliflozin + glimepiride	Dapagliflozin + sitagliptin		
C_{max}, ng/ml	151	152	147	1.01 (0.92–1.10)	0.96 (0.88–1.05)
$AUC_{(INF)}$, ng·h/ml	1139	1126	1235	0.99 (0.96–1.02)	1.08 (1.03–1.13)
$AUC_{(0\text{-}T)}$, ng·h/ml	1101	1095	1185	1.00 (0.97–1.02)	1.08 (1.03–1.13)

which is excreted in the urine [6]. Metformin and sitagliptin are excreted unchanged in urine via tubular secretion and glomerular filtration [20,21], whereas glimepiride and pioglitazone are oxidatively metabolized by CYP2C9 and CYP2C8, respectively, and excreted in the urine [22,23]. In addition, dapagliflozin does not inhibit or induce cytochrome P450 enzymes nor is it a strong inhibitor of or substrate for drug transporters (AstraZeneca and Bristol-Myers Squibb, unpublished data). Given this and the different mechanisms of metabolism and elimination, significant DDI between dapagliflozin and the other OADs would not have been expected.

The clinical benefits of adding dapagliflozin to metformin were investigated in a double-blind, parallel-group

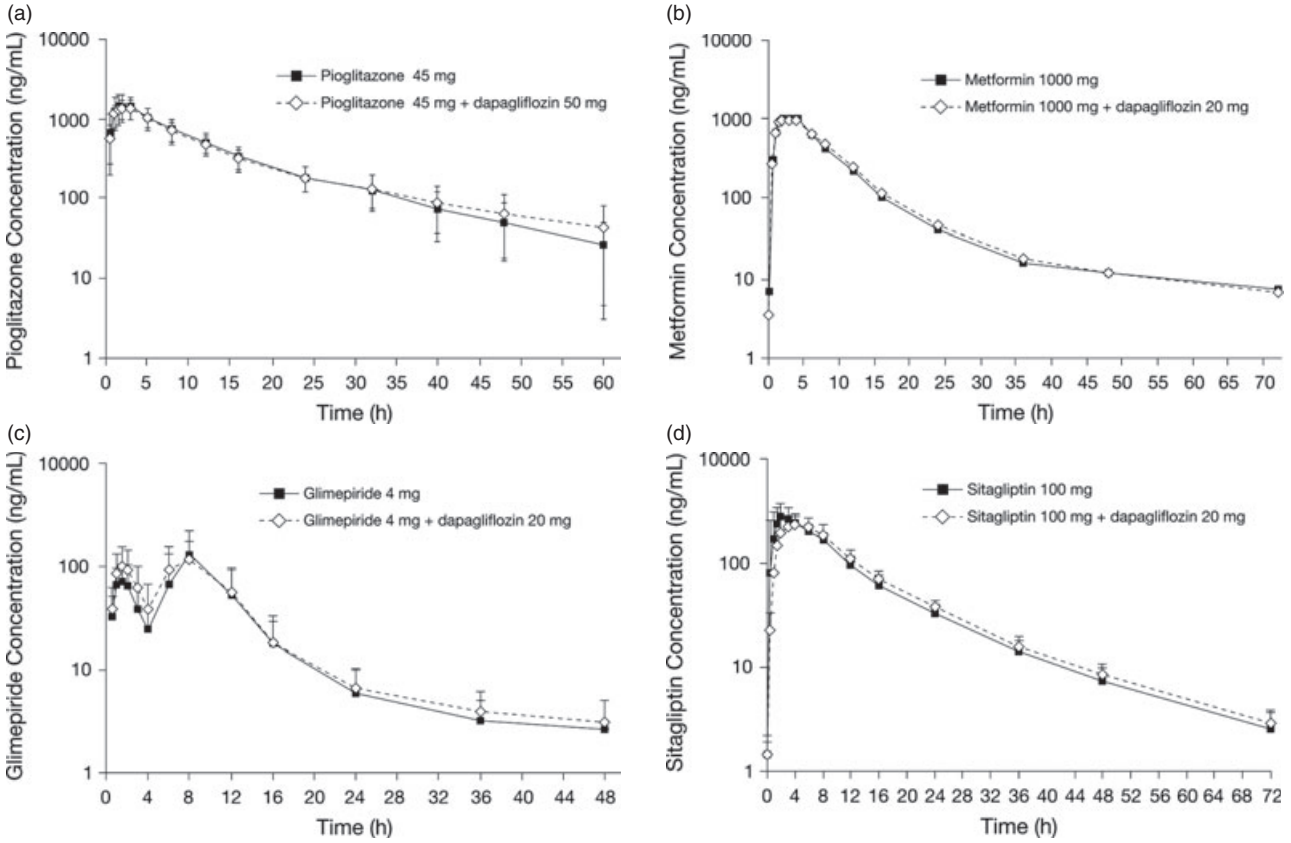

Figure 4. Mean plasma concentration versus time profile for pioglitazone (a), metformin (b), glimepiride (c) and sitagliptin (d) with or without co-administration of dapagliflozin.

Table 3. Pharmacokinetic parameters and statistical analysis for pioglitazone, metformin, glimepiride and sitagliptin in the absence and presence of dapagliflozin.

	Adjusted geometric means		Ratio of adjusted geometric means (B/A)	
Drug/PK parameter	A	B	Point estimate	90% CI
Pioglitazone 45 mg PK	Pioglitazone	Pioglitazone + dapagliflozin		
C_{max}, ng/ml	1398	1294	0.93	0.75–1.15
$AUC_{(INF)}$, ng·h/ml	17 347	17 433	1.00	0.90–1.13
$AUC_{(0\text{-}T)}$, ng·h/ml	17 054	16 504	0.97	0.87–1.08
Metformin 1000 mg PK	Metformin	Metformin + dapagliflozin		
C_{max}, ng/ml	1084	1033	0.95	0.87–1.05
$AUC_{(INF)}$, ng·h/ml	8910	8922	1.00	0.93–1.08
$AUC_{(0\text{-}T)}$, ng·h/ml	8753	8761	1.00	0.94–1.07
Glimepiride 4 mg PK	Glimepiride	Glimepiride + dapagliflozin		
C_{max}, ng/ml	145	151	1.04	0.91–1.20
$AUC_{(INF)}$, ng·h/ml	994	1125	1.13	1.00–1.29
$AUC_{(0\text{-}T)}$, ng·h/ml	970	1094	1.13	0.99–1.29
Sitagliptin 100 mg PK	Sitagliptin	Sitagliptin + dapagliflozin		
C_{max}, ng/ml	288	255	0.89	0.81–0.97
$AUC_{(INF)}$, ng·h/ml	3388	3429	1.01	0.99–1.04
$AUC_{(0\text{-}T)}$, ng·h/ml	3335	3369	1.01	0.98–1.04

Table 4. Most common treatment-emergent adverse events (n ≥ 2).

Drug combination/adverse event	n (%)
Dapagliflozin/pioglitazone	
Headache	3 (12.5)
Dapagliflozin/metformin	
Nausea	6 (33.3)
Fatigue	3 (16.7)
Headache	2 (11.1)
Anxiety	2 (11.1)
Dapagliflozin/glimepiride/sitagliptin	
Nausea	6 (33.3)
Hypoglycaemia	2 (11.1)

placebo-controlled trial involving 546 patients with T2DM inadequately controlled on daily metformin ≥1500 mg. At 24 weeks, dapagliflozin significantly improved glycaemic control and induced clinically significant weight loss compared with placebo [24]. Co-administration of dapagliflozin and metformin was well tolerated in that study, as it was in the current study. Similar benefits of dapagliflozin on glycaemic control and body weight were observed after 12 weeks in 71 patients with T2DM who were inadequately controlled on metformin and/or a thiazolidinedione plus insulin [9].

A unique feature of one of the DDI studies was the use of an open-label, randomized, five-period, five-treatment, unbalanced crossover single-dose study design to investigate the interaction of dapagliflozin and glimepiride or sitagliptin versus the traditional three-period, three-treatment design employed with pioglitazone or metformin. The advantage of this design is that it resulted in saving of resources by reducing the total number of studies and by streamlining processes. Fewer subjects were required and it reduced costs associated with development and execution of protocols by decreasing study-site start-up and bioanalytical costs.

In summary, the lack of PK interaction between dapagliflozin and pioglitazone, metformin, glimepiride or sitagliptin and the good tolerability of each combination indicates that dapagliflozin can be safely co-administered with each of these OADs without a dose adjustment of either drug. With its insulin-independent mechanism of action and low potential for PK drug interactions, dapagliflozin may prove to be a useful and versatile therapeutic option for T2DM.

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Conflict of Interest

The authors were shareholders and/or employees of Bristol-Myers Squibb at the time the studies were conducted.

SK, DWB, WCS and XL designed the study. SK, XL and WZ conducted the study and did data collection. Analysis was performed by SK, XL, WZ, SCG, TL, MP and DWB. SK, DWB and FPL wrote the manuscript.

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