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Effect of a high-fat meal on the pharmacokinetics of dapagliflozin, a selective SGLT2 inhibitor, in healthy subjects

Dapagliflozin is a potent and selective inhibitor of sodium–glucose co-transporter type 2 that is being developed for the treatment of type 2 diabetes mellitus. This open-label, randomized, two-period, two-treatment (single doses of 10-mg dapagliflozin fasted or fed), crossover study was conducted to evaluate the effect of a high-fat meal on the pharmacokinetics of dapagliflozin in 14 healthy subjects. Compared to the fasted state, a high-fat meal decreased mean dapagliflozin maximum plasma concentrations (C_{max}) by 31%, increased the time to C_{max} (T_{max}) by 1 h, but did not affect overall dapagliflozin systemic exposure [area under the plasma concentration-time curve (AUC)]. As the cumulative (daily) amount of glucose excreted in the urine induced by dapagliflozin is dependent upon dapagliflozin AUC, the effect of food on dapagliflozin C_{max} is unlikely to have a clinically meaningful effect on dapagliflozin's efficacy. On the basis of these findings, dapagliflozin can be administered without regard to meals.

Keywords: dapagliflozin, diabetes mellitus, fat, food effect, high-fat meal, inhibitors, pharmacodynamics, pharmacokinetics, SGLT2

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Background

Dapagliflozin, a competitive, reversible and selective renal sodium–glucose co-transporter type 2 (SGLT2) inhibitor is being developed as a treatment for type 2 diabetes mellitus [1,2]. The transport of glucose from the renal tubule into the tubular epithelial cells is facilitated by SGLT2 which is expressed primarily in the kidney in the early proximal tubule of the nephron [1]. By inhibiting SGLT2, dapagliflozin blocks the reabsorption of filtered glucose, in turn promoting urinary glucose excretion and thereby reducing plasma glucose [3]. Currently, dapagliflozin is in Phase 3 clinical development, with doses of 2.5–10 mg administered once daily representing the most common dose range tested in long-term safety and efficacy studies [2].

Clinical pharmacokinetic studies have shown that dapagliflozin is rapidly absorbed following oral administration and it is cleared predominantly by metabolism to an inactive metabolite, dapagliflozin 3-O-glucuronide by uridine diphosphate glucuronosyltransferase isoform 1A9 (UGT1A9) pathway [4]. The impact of food on the pharmacokinetics of any new medicine needs to be characterized in order to guide prescribers and patients as to how to use the medicine with respect to the timing of dosing relative to meals. The effect of food on the pharmacokinetics of medicines is variable and the impact of food often depends on physiochemical and gastrointestinal permeability characteristics of the molecule [5,6]. Dapagliflozin has a high aqueous solubility at physiological pHs (>1 mg/ml), and a high permeability in *in vitro* models of intestinal absorption [4]. These characteristics are predictive of a modest impact of food on dapagliflozin absorption [5,6]. This communication describes the effect of a high-fat meal on the pharmacokinetics of dapagliflozin in order to inform the clinical use with regard to dosing relative to meals.

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Materials and Methods

Subjects

The protocol and informed consent were approved by an Institutional Review Board and written, signed, informed consent was obtained from all study participants prior to enrollment. Male and female subjects determined to be healthy by medical history, physical examination, clinical laboratory testing and ECG aged 18–45 years, with body mass index 18–32 kg/m^2 not taking any medicines that might influence the results were enrolled. Female subjects could not be nursing, pregnant or of childbearing potential.

Statistical Considerations

Fourteen subjects provided at least 90% confidence interval (CI) that the estimate of the fed-to-fasted ratio of geometric means for dapagliflozin C_{max} and the area under the plasma concentration-time curve extrapolated to infinity [AUC (INF)] were within 15–3%, respectively. Data from 12 subjects would provide at least 99% power to conclude absence of effect of food if food had no effect on dapagliflozin AUC (INF). Absence of a food effect was to be concluded if 90% CIs for the fed : fasted ratios of geometric means were entirely contained within (0.80, 1.25) for both dapagliflozin maximum observed plasma concentration (C_{max}) and area under the dapagliflozin plasma concentration-time curve extrapolated to infinity (AUC_{∞}).

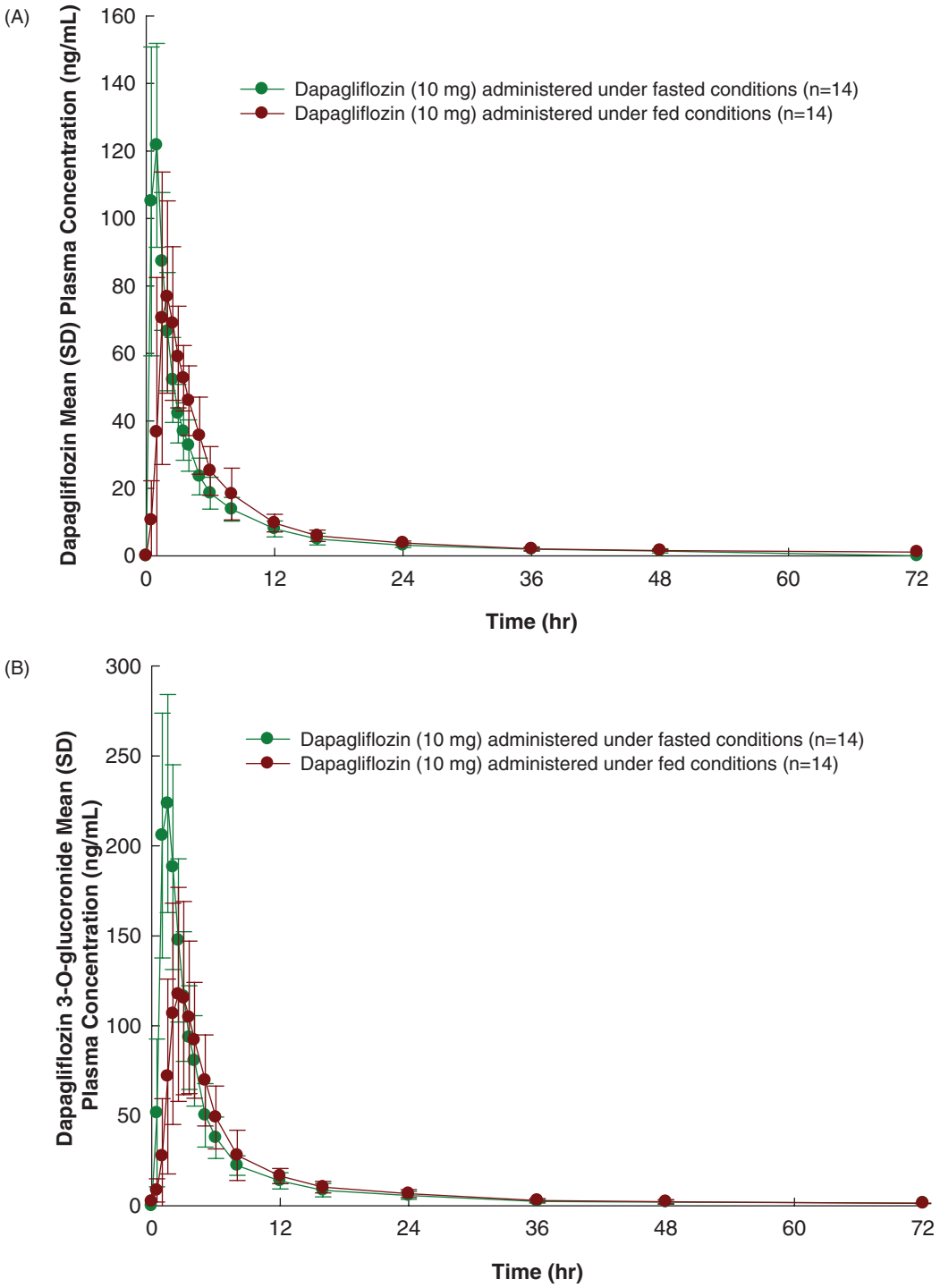

Figure 1. Plot of mean (±s.d.) plasma concentration-time profiles of (A) dapagliflozin and (B) dapagliflozin 3-O-glucuronide following administration of 10-mg dapagliflozin in the fasted state or following a high-fat meal (n = 14 healthy subjects for both fed and fasted states).

Study Design, Procedures and Data Analysis

Following a ≥10-h overnight fast, subjects were randomized to receive a single oral dose of 10 mg of dapagliflozin, either in the fasted state or 5 min after finishing a high-fat meal (52% calorie content from fat) [7]. A washout period of at least 4 days was used between treatment periods, after which subjects received 10-mg dapagliflozin in the fasted or fed state, whichever state they did not receive it previously. Vital signs were measured at screening, during each treatment and prior to discharge. Routine clinical laboratory determinations were made at screening, prior to dosing and prior to discharge.

Table 1. Summary statistics and statistical analyses of the pharmacokinetic parameters of dapagliflozin and dapagliflozin 3-O-glucuronide for 10-mg dapagliflozin administered in the fasted state or following a high-fat meal.

	Dapagliflozin (n = 14)			Dapagliflozin 3-O-glucuronide (n = 14)		
Pharmacokinetic parameters	Dapagliflozin (fasted state)	Dapagliflozin (following a high-fat meal)	Point estimates (90% CI) (fed/fasted)	Dapagliflozin 3-O-glucuronide (fasted state)	Dapagliflozin 3-O-glucuronide (following a high-fat meal)	Point estimates (90% CI) (fed/fasted)
C_{max} (ng/ml) geometric mean (% CV)	136 (22)	94 (33)	0.694 (0.580–0.830)	224 (26)	128 (36)	0.571 (0.502–0.649)
AUC_{∞} (ng×h/ml) geometric mean (% CV)	497 (19)	507 (16)	1.020 (0.985–1.057)	941 (28)	812 (27)	0.862 (0.819–0.908)
AUC_{0-t} (ng×h/ml) geometric mean (% CV)	470 (20)	478 (16)	—	906 (28)	780 (28)	—
T_{max} (h) median (min, max)	0.98 (0.48, 1.50)	1.98 (0.98, 3.98)	—	1.48 (0.98, 2.00)	2.50 (1.50, 5.00)	—
$t_{1/2}$ (h) mean (s.d.)	12.0 (4.62)	14.0 (4.38)	—	13.0 (4.88)	12.6 (3.36)	—

AUC_{∞}, area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to the time of last quantifiable plasma concentration; CI, confidence interval; C_{max}, maximum (peak) plasma drug concentration; CV, coefficient of variation; max, maximum; min, minimum; T_{max}, time to reach maximum (peak) plasma concentration following drug administration; $t_{1/2}$, elimination half-life.

To characterize the plasma concentration-time profiles of dapagliflozin and dapagliflozin 3-O-glucuronide, serial blood samples were collected up to 72-h post-dose following each dose. Plasma concentrations of dapagliflozin and dapagliflozin 3-O-glucuronide were determined by a validated liquid chromatography-tandem mass spectrometry assay. The pharmacokinetic parameters of dapagliflozin and dapagliflozin 3-O-glucuronide were determined by non-compartmental analysis using validated software.

Results

All 14 subjects completed the study as designed. There were no unexpected safety or tolerability findings in this study and single 10-mg dapagliflozin was well tolerated by the healthy subjects in both the fed and fasted states. There were no serious adverse events, or discontinuations because of events, nor were there any clinically relevant effects on the subjects' vital signs or ECG parameters.

The mean (±s.d.) plasma concentration-time profiles for dapagliflozin and dapagliflozin 3-O-glucuronide are presented in figure 1A, B, respectively. Summary statistics and statistical analyses of the pharmacokinetic parameters for dapagliflozin and dapagliflozin 3-O-glucuronide are presented in Table 1. The 90% CIs for the ratios of the population geometric means of the fed versus fasted state were within the prespecified (0.80–1.25) no-effect interval for dapagliflozin and dapagliflozin 3-O-glucuronide AUC_{∞} values, whereas the intervals fell outside these limits for the C_{max} of both analytes (the point estimates were 30.6 and 42.9% lower, respectively). The median T_{max} values for dapagliflozin and dapagliflozin 3-O-glucuronide were both ~1-h longer in the fed state. No meaningful change in the half-life of either analyte was observed.

Discussion

As indicated by the lack of a meaningful effect of food on dapagliflozin and dapagliflozin 3-O-glucuronide AUC_{∞}, food did not affect the overall extent of oral absorption of dapagliflozin, nor on the extent of its metabolism. These findings are consistent with dapagliflozin's high aqueous solubility and high degree of intestinal permeability. The administration of dapagliflozin with food resulted in decreased C_{max} and increased T_{max} values for both dapagliflozin and dapagliflozin 3-O-glucuronide, indicating a decrease in the rate of absorption of dapagliflozin with food consistent with a delay the rate of gastric emptying following ingestion of a meal [8,9]. Food did not have any meaningful effect on the half-life of either dapagliflozin or dapagliflozin 3-O-glucuronide, indicating that a change in systemic clearance was not probably to be a mechanism for the C_{max} findings.

The clinical impact of a reduced and delayed C_{max} for dapagliflozin as a result of its administration with food can be made by examining the urinary excretion of glucose over the range of individual T_{max} values for dapagliflozin administered with and without food (i.e. up to 8-h post-dose). In a previous study, the cumulative amount of glucose excreted in the urine from 0 to 8 h at steady state (i.e. encompassing the range of dapgliflozin T_{max} values when administered with food) following 2.5-mg dapagliflozin once daily (7.34 g of glucose) was comparable to 10-mg dapagliflozin once daily (8.78 g of glucose) [3]. Thus, dapagliflozin C_{max} from a 10-mg dose could decrease by a greater extent than was observed with food, that is, at least 75% to the dapagliflozin C_{max} values observed at 2.5 mg and still have little effect on urinary glucose excretion over the range of time of C_{max} when dapagliflozin is administered with food. Additionally, in dapagliflozin Phase 3 trials, patients with type 2 diabetes were instructed to take dapagliflozin tablets irrespective of their meal times [2,10]. Results from these studies showed a significant improvement in the markers of glycaemic control after 24 weeks of dapagliflozin. Collectively, these data indicate the effect of decrease in dapagliflozin C_{max} under fed conditions is not probably to be clinically meaningful.

As the daily amount of glucose excreted in the urine is dependent upon dapagliflozin AUC and not the peak concentration, changes in dapagliflozin C_{max} will not influence dapagliflozin's

safety, tolerability and efficacy hence dapagliflozin may be taken without regard to meals.

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Conflict of Interest

This study was sponsored by Bristol-Myers Squibb Company and AstraZeneca. All of the authors, except Dr. S. B. R., were shareholders and/or employees of Bristol-Myers Squibb at the time this study was conducted. Dr. S. B. R. is a consultant to AstraZeneca. Dr. W. Z. is now an employee of Hoffman La-Roche (Nutley, NJ). S. K., W. Z., X. L. and D. W. B. designed this study. W. Z. and A.-F. A. conducted the data collection. S. K., W. Z., F. P. L., D. W. B. and X. L. performed the analysis of the study. S. K., D. W. B., F. P. L. and A.-F. A. wrote the manuscript.

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