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Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects

Canagliflozin, a potent, selective sodium glucose co-transporter 2 inhibitor in development for treatment of type 2 diabetes, lowers plasma glucose (PG) by lowering the renal threshold for glucose (RT_G) and increasing urinary glucose excretion (UGE). An ascending single oral-dose phase 1 study investigated safety, tolerability and pharmacodynamics of canagliflozin in healthy men (N = 63) randomized to receive canagliflozin (n = 48) or placebo (n = 15). Canagliflozin (10, 30, 100, 200, 400, 600 or 800 mg q.d. or 400 mg b.i.d.) was administered to eight cohorts (six subjects/cohort: canagliflozin; two subjects/cohort: placebo). Dose dependently, canagliflozin decreased calculated 24-h mean RT_G with maximal reduction to approximately 60 mg/dl, and increased mean 24-h UGE. At doses >200 mg administered before breakfast, canagliflozin reduced postprandial PG and serum insulin excursions at that meal. Canagliflozin was generally well tolerated; most adverse events were mild and no hypoglycaemia was reported. These results support further study of canagliflozin.

Keywords: SGLT2 inhibitor, canagliflozin, renal threshold for glucose, urinary glucose excretion

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Introduction

The plasma glucose (PG) level below which nearly all filtered glucose is reabsorbed by the kidneys, and above which glucose is excreted in urine, is designated as the renal threshold for glucose (RT_G). In healthy individuals, virtually all filtered glucose is reabsorbed up to a PG level of ~10 mmol/l (180 mg/dl), thus defining RT_G [1–3]. At PG levels $>RT_G$, the renal glucose reabsorptive capacity is saturated and the amount of glucose in urine increases proportionately to PG concentration [4]. By inhibiting the proximal renal tubule glucose transporter responsible for the majority of glucose reabsorption, sodium glucose co-transporter 2 (SGLT2) inhibitors are predicted to lower RT_G, thereby increasing urinary glucose excretion (UGE). In patients with diabetes, reduction of RT_G is expected to increase UGE and lower PG concentrations. Unlike other antidiabetic agents which often cause weight gain, the glucose-lowering effect with SGLT2 inhibitors is accompanied by urinary loss of calories, potentially resulting in weight loss. Canagliflozin is a potent, orally administered SGLT2 inhibitor in development for treatment of type 2 diabetes mellitus [5]. The safety, tolerability and pharmacodynamics (PD) of single oral doses of canagliflozin were assessed in a double-blind, randomized, placebo-controlled, ascending-dose phase 1 study in healthy subjects.

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Materials and Methods

Healthy men, aged 18–55 years, were enrolled. A liquid suspension formulation of canagliflozin at sequentially escalated doses of 10, 30, 100, 200, 400, 600 or 800 mg q.d. or 400 mg b.i.d. or matching placebo was administered in the morning (for the 400 mg b.i.d. regimen, the second dose was administered in the evening) of days 1–8 parallel cohorts (in each cohort, six subjects received canagliflozin; two received placebo). Each subject received only one dose of study medication. Three standardized meals [6] were provided at 0.5, 4.5 and 10.5 h after the day 1 morning dose (for the 400 mg b.i.d. cohort, the evening meal was given at 0.5 h after the evening dose).

Cumulative 24-h UGE (g) was assessed in each cohort on day −1 (baseline) and day 1 from pooled 24-h urine collections obtained at 0–2, 2–4, 4–7, 7–10, 10–13 and 13–24 h postdose on each day. Blood samples for measurements of PG and serum insulin were collected from intravenous cannulae at −0.5, −0.25 h (immediately prior to dosing); at 1, 1.25, 1.5, 2.0, 2.5, 3.0, 4.5 h (prior to lunch); 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.5 h (prior to dinner); 11.25, 11.5, 12.0, 12.5, 13.0, 14.0, 16.0, 19.0, 22.0 and 24 h (postdose on day 1). Plasma and urine glucose were determined using the Roche Hexokinase method, and the serum insulin was analysed by the DPC Chemiluminescence Immunoassay method.

RT_G was calculated using a new method based on measured UGE, PG and glomerular filtration rate (GFR; estimated using 24-h creatinine clearance), extending a previously described

method used for calculating phosphate renal threshold [7]. By accounting for changes in PG and GFR, the calculated RT_G values provide a more refined measure of SGLT2 inhibition than simply measuring 24-h UGE. In this study, RT_G was calculated (over specific time intervals where UGE was measured) using an iterative method (fminbnd in MATLAB software version 7.9. Mathworks, Natick, MA, USA, 2009) that finds the unique value of RT_G satisfying the threshold equation (Equation 1), integrated over time intervals where UGE was measured.

$$\text{Rate of UGE} = \begin{cases} \text{GFR} \times (\text{PG} - \text{RT}_G) & \text{if PG} > \text{RT}_G \\ 0 & \text{if PG} \leq \text{RT}_G \end{cases} \quad (1)$$

where rate of UGE is in mg/min, GFR is in dl/min, and PG and RT_G are in mg/dl.

Safety was evaluated through adverse events (AEs) and clinical laboratory tests including renal function, electrocardiograms, vital sign measurements and physical examinations.

PD parameters were analysed using summary statistics [mean, standard deviation and standard error of the mean (SEM)]. Mixed-effect analysis of variance (ANOVA) modelling was used to investigate PD effects of canagliflozin. Because the postprandial PG and serum insulin excursions for the canagliflozin 100 and 200 mg dose groups were similar and were different from all groups treated with canagliflozin >200 mg doses (data not shown), the postprandial PG and serum insulin concentration data were pooled for cohorts receiving the 100 and 200 mg doses (n = 12) and for all cohorts treated with doses >200 mg (n = 24). Incremental area under the curve (AUC), defined as the AUC above the baseline (prebreakfast) value, was calculated for the first 2 h after breakfast, lunch and dinner for PG and serum insulin in the pooled groups.

Results

Of the 63 subjects randomized, 48 received canagliflozin and 15 received placebo. All randomized subjects completed the study. Baseline demographics were comparable among the eight cohorts. Mean values for age, body mass index and GFR (estimated using 24-h creatinine clearance) were 37.1 years (range: 19–55 years), 24 kg/m^2 (range: 20.4–29.8 kg/m^2) and 97.1 ml/min/1.73 m^2 (range: 69.7–138.0 ml/min/1.73 m^2), respectively.

At baseline (day −1), mean 24-h urine volume was ~2–4 l in all treatment groups. Mean change from baseline in 24-h urine volume on day 1 was −0.5 l in placebo group compared to −0.6, +0.2, +0.2, −0.3, +0.4, −0.7, +0.2 and −0.1 l in the canagliflozin 10, 30, 100, 200, 400, 600, 800 mg q.d. and 400 mg b.i.d. groups, respectively.

Canagliflozin dose dependently decreased 24-h mean RT_G; maximally effective doses lowered the calculated RT_G to ~60 mg/dl (figure 1a). Canagliflozin increased UGE dose dependently on day 1 vs. day −1 with a maximum mean 24-h UGE of ~70 g at doses >200 mg (figure 1b). The canagliflozin 400 mg b.i.d. dose regimen had similar effects to that of 800 mg q.d. dose regimen on both 24-h UGE and the calculated RT_G.

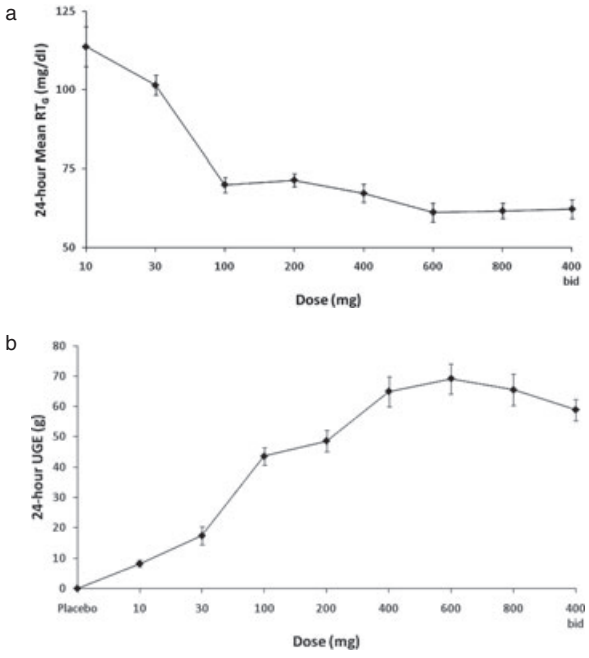

Figure 1. Calculated 24-h mean RT_G (a) and mean 24-h urinary glucose excretion (UGE) (b) on day 1 after dosing. Results are mean ± SEM (N = 15/placebo; N = 6/canagliflozin).

PG and serum insulin concentration profiles over 24 h postdose on day 1 were generally comparable among treatment groups with the exception of postbreakfast excursions. Administered 30 min before breakfast, canagliflozin doses >200 mg reduced postprandial PG (figure 2a) and serum insulin excursions (figure 2b). Incremental PG (figure 2c) and serum insulin AUCs (figure 2d) for the first 2 h after breakfast were lower in the canagliflozin >200 mg dose groups pooled, relative to the canagliflozin 100 and 200 mg dose groups pooled. Notably, the UGE from 0 to 2 h was comparable between these two pooled-dose groups (5.4 g in 100 and 200 mg dose groups pooled, and 5.9 g in >200 mg dose groups pooled). Postprandial PG excursions at lunch and dinner were not affected by canagliflozin treatment (data not shown).

There were no serious or severe treatment-emergent AEs (TEAEs) or discontinuations because of TEAEs. The majority of TEAEs were mild in severity. Transient postural dizziness and headache were the most frequent TEAEs, but were not dose dependent; each was reported in four canagliflozin subjects (8%) and none were treated with placebo. Postural dizziness reported in two subjects (one received canagliflozin 10 mg and one canagliflozin 600 mg) was accompanied by transient postural hypotension. No hypoglycaemia was observed. There were no clinically meaningful changes from baseline in plasma or urine electrolytes or 24-h creatinine clearance. Vital signs and electrocardiograms also showed no clinically meaningful changes.

Conclusions

In this study, canagliflozin was generally well tolerated in healthy men across the range of single doses studied up to

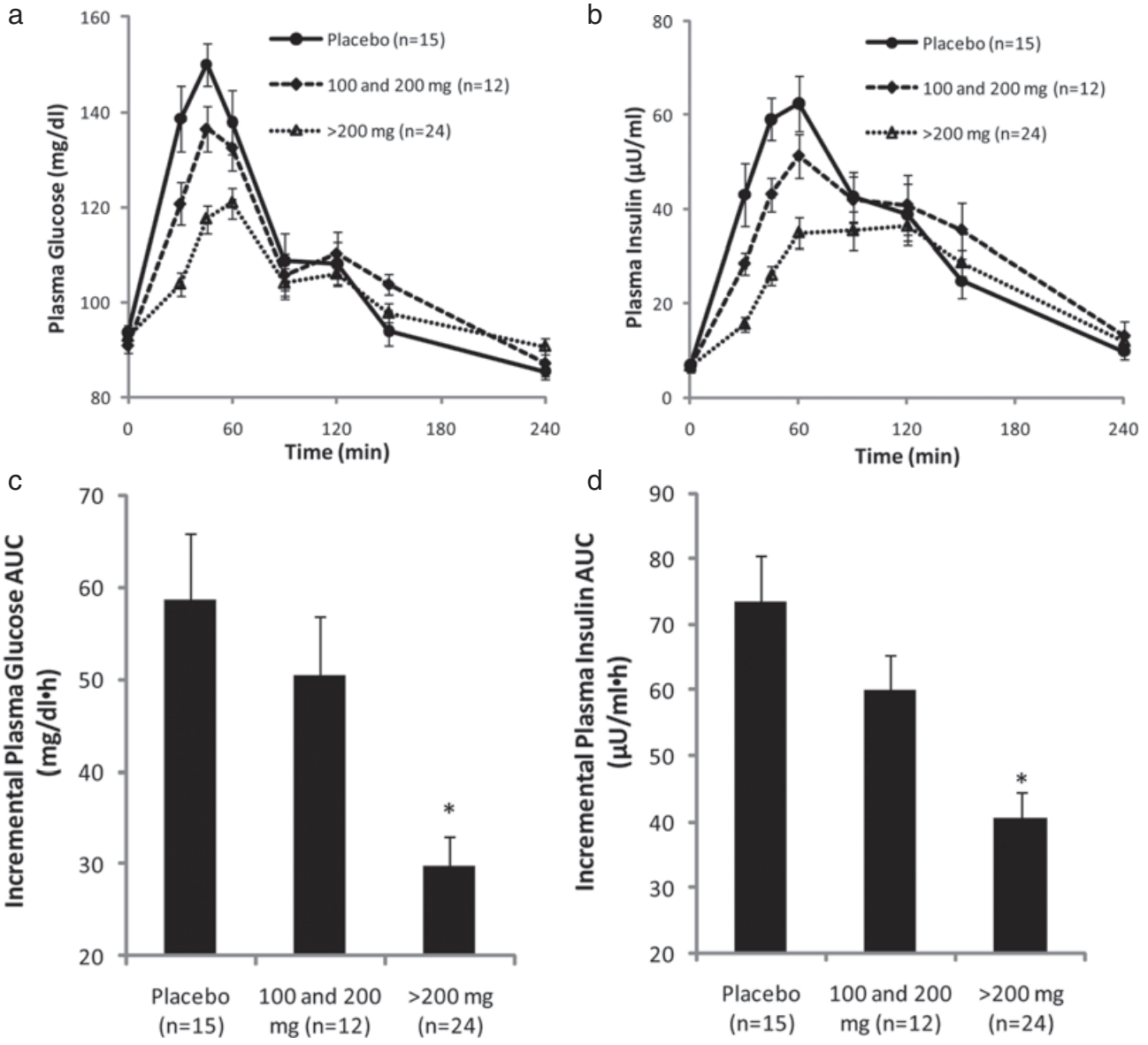

Figure 2. Plasma glucose (PG) and insulin excursions after breakfast. Results have been pooled for the cohorts receiving 100 and 200 mg of canagliflozin (n = 12) and for all cohorts treated with higher than 200 mg of canagliflozin (n = 24). Postbreakfast PG (a) and serum insulin (b) concentrations. Incremental area under the curves (AUCs) above baseline (prebreakfast) for the first 2 h after the meal for PG (c) and serum insulin (d). In all graphs and analyses, the prebreakfast concentrations used were the average of the three samples taken prior to the meal. The meal was consumed in 15–20 min. Results shown are mean ± SEM and are plotted with $t = 0$ corresponding to start of breakfast, which was 30 min after drug administration. In (c) and (d), *$p < 0.05$ compared to both placebo and the pooled 100 and 200 mg cohorts by one-way analysis of variance (ANOVA).

800 mg. The long-term safety and tolerability of repeated administration of canagliflozin is under investigation in larger clinical trials of longer duration.

By inhibiting SGLT2, canagliflozin treatment dose dependently decreased RT_G, leading to a dose-dependent increase in UGE. The maximal reduction in the calculated 24-h mean RT_G with canagliflozin was ~60 mg/dl.

Mean 24-h PG and serum insulin concentrations postdose on day 1 were not affected by canagliflozin treatment in these euglycaemic healthy subjects. This is expected as normal homeostatic regulation, with modulation of glucose production and disposal, probably maintains stable PG concentrations, despite urinary glucose loss.

Postprandial glucose and serum insulin excursions at breakfast 30 min postcanagliflozin administration—but not at lunch or dinner—appeared to decrease in subjects treated with canagliflozin doses >200 mg, when compared with excursions in subjects treated with canagliflozin 100 or 200 mg. The reduced glucose excursions were not accounted for by a difference in UGE, which was minimally different in subjects receiving 100 or 200 mg compared with those receiving higher

doses, thus raising the possibility that canagliflozin has a direct effect on intestinal glucose absorption.

While the dose-dependent increase in UGE shown in this study is similar to that in a dapagliflozin study [8], the effects on the RT_G and early postprandial glucose excursions have not been reported in previous studies with SGLT2 inhibitors in healthy subjects. Further studies are ongoing to compare the calculated RT_G values with values obtained using traditional glucose clamp approaches for determining RT_G [3,4], and also to assess mechanisms underlying the observed postprandial reduction in PG and insulin excursions.

In summary, canagliflozin, a potent SGLT2 inhibitor, provided dose-dependent reduction in RT_G and increases in UGE, and was well tolerated in these healthy euglycaemic subjects.

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Conflict of Interest

All authors are employees of Johnson & Johnson Pharmaceutical Research & Development, LLC.

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