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Canagliflozin, a sodium glucose co-transporter 2 inhibitor, reduces post-meal glucose excursion in patients with type 2 diabetes by a non-renal mechanism: results of a randomized trial☆,☆☆

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ABSTRACT

Objective. Canagliflozin is a sodium glucose co-transporter 2 inhibitor approved for treating patients with type 2 diabetes. This study evaluated renal and non-renal effects of canagliflozin on postprandial plasma glucose (PG) excursion in patients with type 2 diabetes inadequately controlled with metformin.

Materials/Methods. Patients (N = 37) were randomized to a four-period crossover study with 3-day inpatient stays in each period and 2-week wash-outs between periods. Patients received Treatments (A) placebo/placebo, (B) canagliflozin 300 mg/placebo, (C) canagliflozin 300 mg/canagliflozin 300 mg, or (D) canagliflozin 300 mg/canagliflozin 150 mg on Day 2/Day 3 in one of four treatment sequences (similar urinary glucose excretion [UGE] expected for Treatments B–D). A mixed-meal tolerance test (MMTT) was given 20 minutes post-dose on Day 3 of each period.

Results. A single dose of canagliflozin 300 mg reduced both fasting and postprandial PG compared with placebo, with generally similar effects on fasting PG and UGE observed for Treatments B–D. An additional dose of canagliflozin 300 mg (Treatment C), but not 150 mg

Abbreviations: AE, adverse event; AUC, area under the concentration-time curve; BMI, body mass index; C150, canagliflozin 150 mg; C300, canagliflozin 300 mg; CI, confidence interval; CRC, clinical research center; CV, coefficient of variation; FPG, fasting plasma glucose; LS, least squares; MET, metformin; MMTT, mixed-meal tolerance test; NA, not applicable; PBO, placebo; PG, plasma glucose; ΔPG, incremental plasma glucose; SD, standard deviation; SE, standard error; SGLT1, sodium glucose co-transporter 1; SGLT2, sodium glucose co-transporter 2; SU, sulfonylurea; UGE, urinary glucose excretion.

☆ Disclosure statement: PS was a full-time employee of Janssen Research & Development, LLC, at the time the study was conducted. DP, EA, SR, NV, and DD are full-time employees of Janssen Research & Development, LLC. JKB has no relevant conflicts of interest to report. LM is an employee and shareholder of the Profil Institute for Clinical Research, which has received research support from the pharmaceutical industry.

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(Treatment D), prior to the MMTT on Day 3 provided greater postprandial PG reduction versus placebo (difference in incremental glucose AUC_{0-2h}, −7.5% for B vs A; −18.5% for C vs A; −12.0% [P = 0.012] for C vs B), leading to modestly greater reductions in total glucose AUC_{0-2h} with Treatment C versus Treatment B or D. Canagliflozin was generally well tolerated.

Conclusions. These findings suggest that a non-renal mechanism (ie, beyond UGE) contributes to glucose lowering for canagliflozin 300 mg, but not 150 mg.

1. Introduction

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor approved in over 30 countries, including the United States and the European Union, as an adjunct to diet and exercise for the treatment of adults with type 2 diabetes [1–8]. Clinical studies in patients with inadequately controlled type 2 diabetes have shown that canagliflozin lowers fasting and post-meal glucose, reduces HbA_{1c}, and is also associated with reductions in body weight and blood pressure [1–8]. The decreases from baseline in the total glucose area under the time-concentration curve (AUC) after a standard meal reflect decreases in the pre-meal glucose concentration as well as a decrease in the glucose excursion above the pre-meal glucose level. The primary mechanism by which canagliflozin treatment provides glucose lowering in patients with type 2 diabetes is by reducing renal tubular reabsorption of glucose, leading to increased urinary glucose excretion (UGE), and thereby directly reducing elevated plasma glucose (PG) concentrations. A previous single-dose study of this agent, conducted in healthy volunteers, showed that higher doses of canagliflozin (>200 mg) administered prior to a standard meal challenge reduced the post-meal glucose excursion to a greater extent than did lower doses, despite similar UGE [9]. Although it is a selective SGLT2 inhibitor, canagliflozin is a low-potency inhibitor of sodium glucose co-transporter 1 (SGLT1); it has ~160-fold greater potency against SGLT2 relative to SGLT1 [10]. SGLT1 is an important glucose transporter in the small intestine [11]. The observation that higher doses of canagliflozin further reduced the increase in glucose level after a meal raises the possibility that higher concentrations of canagliflozin in the intestinal lumen after dose administration, but prior to systemic drug absorption, might transiently inhibit SGLT1-mediated glucose absorption in the gut, and thereby delay the rate of glucose rise after a meal. Further evidence for this hypothesis was provided by a dual-tracer study in healthy participants demonstrating that a single dose of canagliflozin 300 mg delayed intestinal glucose absorption [12].

The present study was designed to assess the renal and non-renal (ie, gut glucose absorption) effects of canagliflozin on PG excursion after a meal in patients with type 2 diabetes with inadequate glycemic control on metformin. To examine this, the effect of canagliflozin in lowering post-meal glucose through SGLT2 inhibition of renal glucose reabsorption was separated from the potential gastrointestinal effect of this agent. Prior studies have shown that maximal effects on UGE are sustained for 24 hours after treatment with canagliflozin doses of ≥300 mg [4,9,13]. Based upon this, administration of canagliflozin 300 mg 24 hours prior to a meal would be expected to provide the full renal tubular (SGLT2 inhibition) effect on glucose excursion post-meal. If canagliflozin does delay intestinal glucose absorption due to transiently high intraluminal drug concentrations, administering an additional dose of canagliflozin 300 mg just prior to the meal would further lower the glucose excursion, relative to administration only 24 hours prior to the meal. To evaluate the dose response for a non-renal mechanism, which would be expected to be different from the dose response for renal SGLT2 inhibition, the present study included doses of 150 and 300 mg based on the previous observation suggesting effects of canagliflozin on gut glucose absorption at doses >200 mg, but not at lower doses [9].

2. Methods

2.1. Patients and study design

This double-blind, placebo-controlled, randomized-sequence, four-period crossover study (ClinicalTrials.gov NCT01381887) was conducted from July 2011 to November 2011 at five clinical centers in the United States and consisted of the following three phases: pre-treatment, double-blind treatment, and post-treatment. During the pre-treatment phase, patients on metformin monotherapy (≥1,500 mg/day) directly entered the 2-week run-in period while patients on metformin dual therapy or metformin monotherapy at a dose <1,500 mg/day first entered a metformin dose-adjustment and dose-stable period during which sulfonylurea (SU), meglitinide, or dipeptidyl peptidase-4 (DPP-4) inhibitor therapy was discontinued (if applicable) and/or metformin dose was up-titrated to 1,500 mg/day (Fig. 1).

Eligible patients included men and women 25–70 years of age with a diagnosis of type 2 diabetes for ≥3 months who met one of the following criteria: (1) on metformin monotherapy at a stable dose of ≥1,500 mg/day for ≥8 weeks prior to screening with HbA_{1c} ≥7.0% (53 mmol/mol) and ≤9.0% (75 mmol/mol) at screening; (2) on metformin monotherapy at a stable dose of <1,500 mg/day for ≥8 weeks prior to screening with HbA_{1c} ≥7.5% (58 mmol/mol) and ≤9.5% (80 mmol/mol) at screening; or (3) on dual combination of metformin (stable dose of ≥1,000 mg/day for ≥8 weeks prior to screening) and an SU, meglitinide, or DPP-4 inhibitor with HbA_{1c} ≥6.5% (48 mmol/mol) and ≤8.5% (69 mmol/mol) at screening. Patients were also required to have a fasting fingerstick glucose of ≥7.2 mmol/L and ≤13.9 mmol/L at the investigational site on Day 1. Patients were excluded if they had a history of type 1 diabetes; repeated fasting PG (FPG) measurements ≥13.9 mmol/L during the pre-treatment phase; history of at least one severe hypoglycemic episode within 6 months before