Journal of Diabetes

Journal of Diabetes **6** (2014) 378–381

RESEARCH LETTER

Effect of canagliflozin, a sodium–glucose cotransporter 2 inhibitor, on measurement of serum 1,5-anhydroglucitol*

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Keywords: 1,5-anhydroglucitol, canagliflozin, GlycoMark®, sodium–glucose cotransporter 2 inhibitor.

Serum levels of 1,5-anhydroglucitol (1,5-AG) can be used as a measure of glycemic control in patients with diabetes.[1,2] 1,5-anhydroglucitol is a non-metabolizable glucose analog that competes with glucose for renal reabsorption. In individuals with hyperglycemia, excess plasma glucose that enters the urine prevents renal reabsorption of 1,5-AG, leading to decreased serum 1,5-AG levels. Serum levels of 1,5-AG are determined using an enzymatic assay (GlycoMark®; GlycoMark Inc., New York, NY, USA). This test provides a measure of glycemic control on a shorter time scale than measurement of HbA1c levels (1,5-AG reflects changes in plasma glucose over ~2 weeks vs 8–10 weeks for HbA1c).[3] Measurement of 1,5-AG levels has been used to evaluate the metabolic effects of several antihyperglycemic agents (AHAs); specifically, levels of serum 1,5-AG have been shown to increase when patients with type 2 diabetes mellitus (T2DM) are treated with metformin, glimepiride, or pioglitazone.[4]

Potential interference with the results of the 1,5-AG assay (GlycoMark®) has been reported for sodium–glucose cotransporter (SGLT) 2 inhibitors,[3] a new class of AHAs developed for the treatment of patients with T2DM. The SGLT2 inhibitors decrease plasma glucose in patients with hyperglycemia by inhibiting renal glucose reabsorption via SGLT2 (the primary renal transporter responsible for reabsorption of glucose from the urine), thereby increasing urinary glucose excretion.[5] 1,5-anhydroglucitol is transported by SGLT4, but there are no known interactions between 1,5-AG and SGLT2. Interference with the 1,5-AG assay by SGLT2 inhibitors may lead to falsely low serum 1,5-AG measurements in patients with improved glycemic control who are treated with this class of agent.[3]

Canagliflozin is an SGLT2 inhibitor approved in the US and by the European Union for the treatment of patients with T2DM.[6] The efficacy of canagliflozin in improving glycemic control, as measured by reductions in HbA1c and fasting and postprandial plasma glucose (FPG and PPG, respectively), and the overall safety and tolerability profile of canagliflozin in patients with T2DM have been reported previously.[7–13] Herein we report findings from a post hoc analysis of 1,5-AG levels using archived samples from a subset of patients who participated in a randomized, double-blind, placebo-controlled, Phase 3 study of canagliflozin monotherapy in patients with T2DM.[7]

Detailed methods from the Phase 3 study of canagliflozin monotherapy have been reported elsewhere.[7] Archived samples (which met manufacturer specifications for storage, namely <3 years at –70°C) from 20 patients each from the canagliflozin 300 mg and placebo treatment groups of that study were included in the present post hoc analysis; this sample size was determined based on an estimate of absolute changes in serum 1,5-AG levels. Archived samples were randomly selected from a pool of samples stored in a central laboratory (Covance, Geneva, Switzerland), from patients with matching baseline and post-baseline (Week 26) samples. In patients included in the present analysis, baseline HbA1c ranged from 6.6% to 9.1%.

All patients in the present study provided written informed consent prior to participation. The study was conducted in accordance with guidelines of Good Clinical Practices and the Declaration of Helsinki, and the protocol and amendments were approved by review boards at participating institutions.

The GlycoMark® 1,5-AG assay was performed according to manufacturer specifications.[3] Change from

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*This trial has been registered with ClinicalTrials.gov (ID NCT01081834).

Received: 1 November 2013; revised 8 December 2013; accepted 9 December 2013.
doi: 10.1111/1753-0407.12116

Table 1 Changes from baseline in glycemic parameters at Week 26 (last observation carried forward)

Parameter	Placebo (n = 20)	Canagliflozin 300 mg (n = 20)
HbA1c (%)		
Mean (± SD) baseline	7.70 ± 0.75	7.85 ± 0.71
Mean (± SD) Week 26	7.43 ± 0.92	6.80 ± 0.49
Mean (± SE) change	–0.28 ± 0.21	–1.05 ± 0.21
Difference versus placebo (95% CI)		–0.78 (–1.36, –0.19)
Fasting plasma glucose (mmol/L)		
Mean (± SD) baseline	9.2 ± 2.2	10.0 ± 2.1
Mean (± SD) Week 26	9.7 ± 2.6	8.0 ± 1.0
Mean (± SE) change	0.6 ± 0.4	–2.1 ± 0.4
Difference versus placebo (95% CI)		–2.7 (–3.9, –1.4)
2-h postprandial glucose (mmol/L)		
Mean (± SD) baseline	12.9 ± 2.6	14.2 ± 3.8
Mean (± SD) Week 26	13.5 ± 4.1	11.7 ± 2.1
Mean (± SE) change	0.5 ± 0.7	–2.5 ± 0.7
Difference versus placebo (95% CI)		–3.0 (–5.1, –0.9)

CI, confidence interval.

Table 2 Change from baseline in 1,5-anhydroglucitol at Week 26 (last observation carried forward)

Parameter	Placebo (n = 20)	Canagliflozin 300 mg (n = 20)
1,5-anhydroglucitol (mg/L)		
Mean (± SD) baseline	8.4 ± 4.9	7.1 ± 5.0
Mean (± SD) Week 26	9.4 ± 4.8	1.4 ± 0.7
Mean (± SE) change	1.0 ± 1.0	–5.7 ± 1.0
Difference versus placebo (95% CI)		–6.8 (–9.7, –3.8)

CI, confidence interval.

baseline in 1,5-AG was analyzed. The mean difference between groups and the associated two-sided 95% confidence intervals (CI) were calculated.

Among patients included in this analysis, mean changes from baseline in HbA1c at Week 26 were –1.05% and –0.28% for canagliflozin 300 mg and placebo, respectively; changes in FPG were –2.1 and 0.6 mmol/L, respectively; and changes in 2-h PPG were –2.5 and 0.5 mmol/L, respectively (Table 1). Baseline 1,5-AG levels in the canagliflozin 300 mg and placebo groups were 7.1 and 8.4 mg/L, respectively (Table 2). Mean change from baseline in 1,5-AG was –5.7 mg/L with canagliflozin 300 mg and 1.0 mg/L with placebo (difference [95% CI] with canagliflozin 300 mg versus placebo of –6.8 mg/L [–9.7, –3.8]). All 20 subjects treated with canagliflozin 300 mg had a decrease in serum 1,5-AG with no worsening of HbA1c.

In the present post hoc analysis, serum 1,5-AG levels were decreased with canagliflozin 300 mg compared with placebo after 26 weeks of treatment. Because reductions in 1,5-AG indicate poorer glycemic control, the findings are in contrast with improvements in HbA1c, FPG, and 2-h PPG seen with canagliflozin 300 mg compared with placebo in this analysis. In the overall population for the same study, significant reduction in HbA1c was also seen with canagliflozin 300 mg versus placebo at Week 26 (least squares mean changes from baseline of –1.03% and 0.14%, respectively; $P < 0.001$).[7] The results of this post hoc analysis are consistent with an interference with the measurement of 1,5-AG in the context of SGLT2 inhibition; thus, 1,5-AG assays may provide inaccurate results regarding glycemic control in patients with T2DM who are treated with an SGLT2 inhibitor, such as canagliflozin. These findings are consistent with the limitations acknowledged by manufacturers of the 1,5-AG assay.[3]

Acknowledgments

This study was supported by Janssen Research & Development, LLC. Editorial support was provided by Courtney St. Amour (MedErgy HealthGroup Inc., Yardley, PA, USA), and was funded by Janssen Global Services, LLC. Canagliflozin is being developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation.

Disclosures

DAB, CT, and GM are full-time employees of Janssen Research & Development, LLC.

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