Annals of Pharmacotherapy
1–4

DOI: 10.1177/1060028014529412
aop.sagepub.com
SAGE

Cerebrovascular Accident in a High-Risk Patient During the Early Initiation Phase With Canagliflozin

Jaime A. Foushee, PharmD, BCPS[1,2], Nancy H. Goodbar, PharmD, BCPS[1,2], Jason L. Kelly, MD[2], and S. Lindsey Clarke, MD, FAAFP[2]

Abstract

Objective: To report a case of cerebrovascular accident (CVA) in a high-risk patient following initiation of canagliflozin, the first-in-class sodium-glucose-co-transporter 2 inhibitor approved by the Food and Drug Administration for type 2 diabetes mellitus. **Case Summary:** We describe a 62-year-old woman, with multiple clinical risk factors for stroke, who began canagliflozin 300 mg daily in addition to basal insulin therapy for diabetes management. The patient developed expressive aphasia 15 days following initiation of canagliflozin. Neuroimaging revealed acute infarcts of the left basal ganglia and temporal and parietal lobes. The patient was diagnosed with a CVA. Canagliflozin therapy was discontinued, metformin therapy was reinitiated in addition to the patient's basal insulin, and the patient was treated with antiplatelet, statin, and speech therapies. **Discussion:** Assessment of the cardiovascular (CV) safety of canagliflozin is currently being investigated. A numerical increase in CV events, including nonfatal stroke, has been noted in preliminary data from ongoing analyses of canagliflozin in patients with preexisting CV risk factors. Although significant clinical risk factors were present in the patient described, a workup for routine causality came back negative. According to the Naranjo probability score, initiation of canagliflozin had a possible to probable association with the patient's CVA. **Conclusions:** This case suggests a potential association between the timing of canagliflozin initiation and development of stroke in patients with multiple clinical risk factors. We advise practitioners to use caution when initiating this new agent in patients at high risk for stroke while long-term CV safety surveillance is ongoing.

Keywords

diabetes mellitus type 2, adverse drug reaction, stroke, drug safety, medication safety

Introduction

Canagliflozin (Invokana) is a novel diabetes drug that was approved by the Food and Drug Administration (FDA) in April of 2013 as the first agent in a class of sodium-glucose cotransporter 2 (SGLT2) inhibitors for the management of type 2 diabetes mellitus (T2DM). Inhibition of SGLT2 reduces the reabsorption of filtered glucose, decreases the renal threshold for glucose, and ultimately enhances renal elimination of glucose.[1] Safety and efficacy evaluation of canagliflozin compared with placebo revealed a modest hemoglobin A1C reduction of 0.77% to 1.03% and significantly reduced fasting plasma glucose.[2] Canagliflozin efficacy has been compared with that of glimepiride and sitagliptin and has been studied in combination with metformin, sulfonylurea, thiazolidinedione, and insulin therapies, in which the novel SGLT2 agent has been shown to be a viable option in the management of patients with T2DM.[3,4] Other attractive observations include decreases in blood pressure, triglycerides, and body weight.[2,5,6] A dose-related increase in low-density lipoprotein (LDL) levels during canagliflozin therapy has also been observed.[3]

Increased genital mycotic infections, osmotic diuresis, and urinary tract infections are the most common adverse drug effects associated with canagliflozin.[2-4] Long-term safety is currently being assessed through ongoing trials, including the incidence of cardiovascular (CV) outcomes. During the FDA approval process, a disproportionate numerical increase in major adverse cardiac events

[1]Presbyterian College School of Pharmacy, Clinton, SC, USA
[2]Self Regional Healthcare Family Medicine Residency Program, Greenwood, SC, USA

Corresponding Author:
Jaime A. Foushee, Department of Pharmacy Practice, Presbyterian College School of Pharmacy, 307 North Broad Street, Clinton, SC 29325, USA.
Email: jafoushee@presby.edu

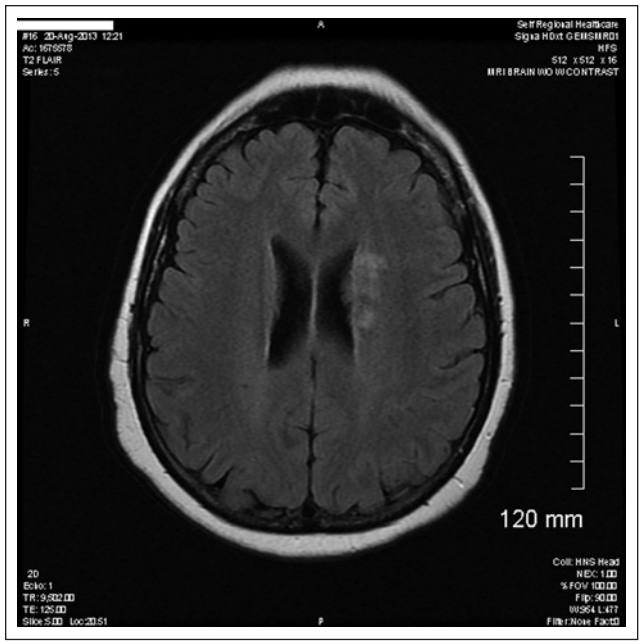

Figure 1. Magnetic resonance imaging on patient presentation, revealing acute left basal ganglia and posterior temporoparietal infarctions.

(MACE-plus) associated with canagliflozin was noted in preliminary data from the ongoing CV outcomes study[7] during the first 30 days of therapy. The FDA concluded that this finding was of concern but potentially because of low overall event rates in the control group. To our knowledge, we report the first postmarketing case of nonfatal stroke during the first 30 days following canagliflozin initiation in a patient at high risk for ischemic stroke with multiple clinical risk factors.

Case Report

A 62-year-old Caucasian woman presented to the emergency care center with a chief complaint of word finding difficulty for the past 5 days. The patient's past medical history was significant for hypertension, T2DM, hypothyroidism, and obesity (BMI = 32 kg/m^2), with no prior cerebrovascular accident (CVA). Home medications included lisinopril 20 mg orally daily, albuterol inhaler 1 to 2 puffs every 6 hours as needed, and levothyroxine 137 µg orally daily. Her diabetes was being treated with 110 units of insulin detemir daily, with the recent initiation of canagliflozin 300 mg orally daily 20 days earlier (15 days prior to the onset of CVA symptoms). Further investigation of medication history revealed prior metformin therapy, which was recently replaced by canagliflozin by the primary care physician because of "poor control." Family history was significant for paternal CVA and coronary artery disease. The patient's father had his first stroke at the age of 42 years and died of a subsequent stroke at the age of 52. The patient quit smoking 12 years ago following 12 years of use and did not consume alcohol.

Physical examination revealed both expressive and receptive aphasia and a slight left-sided facial droop. Mental status and motor, sensory, and cerebellar function were intact. Blood pressure on presentation was initially elevated at 226/92 mm Hg but improved to 154/72 mm Hg without pharmacological intervention by the time of admission. Recorded blood pressure readings from outpatient medical documentation over the 3 months immediately prior to the event were 142/70, 144/74, and 140/80 mm Hg. The patient was in sinus rhythm, and peripheral circulation appeared adequate. A 2/6 systolic murmur was noted at the base of the heart, which was documented in previous physician progress notes and followed by cardiology.

Laboratory assessment revealed complete blood count, electrolytes, renal and hepatic function, and coagulation factors to be within normal limits. A urine drug screen was negative. Her glucose level was 186 mg/dL, with an elevated hemoglobin A1C of 11.8%, suggesting significantly uncontrolled diabetes. Urinalysis revealed glycosuria and trace proteinuria. A fasting lipid profile included an elevated LDL of 125 mg/dL and a decreased high-density lipoprotein of 35 mg/dL. Thyroid-stimulating hormone was decreased at 0.22 mIU/mL (normal = 0.36 to 3.74).

Computed tomography and magnetic resonance imaging (Figure 1) revealed acute, multifocal infarctions of the left basal ganglia and the left temporal and parietal lobes. An electrocardiogram showed normal sinus rhythm with no cardiac tachyarrythmias. An echocardiogram showed normal valves, ventricular function, and wall motion, with no evidence of interatrial communication by agitated saline study. Carotid duplex scan revealed clinically nonsignificant plaque formation bilaterally. A hypercoagulability workup, including protein C and S activity, antithrombin III activity, and a lupus anticoagulant profile, was negative.

The patient was diagnosed with a CVA and admitted to a telemetry unit. Aspirin, pravastatin, and speech therapy were initiated. Once blood pressure had stabilized, lisinopril was restarted. Glycemic control (blood glucose levels between 146 and 177 mg/dL) was maintained with a diabetic diet and insulin. Canagliflozin was discontinued on hospital admission, and metformin was reinitiated at discharge. Other medication changes included a dose reduction of levothyroxine. Follow-up care was coordinated with primary care, neurology, and speech therapy. At the time of hospital discharge, the patient's aphasia was improving, but it was not apparent whether she would be able to resume employment as an elementary school teacher.

Discussion

Diabetic patients are at risk for macrovascular complications, including MI, stroke, and CV death. The association between glycemic control and CV complications is controversial.[8]

Metformin is currently recommended as the first-line treatment for pharmacological management of T2DM in position statements from both the American Diabetes Association[9] and the American Association of Clinical Endocrinologists[10] because of experience and evidence regarding its safety and efficacy as well as a potential for decreased macrovascular complications.[11] Conversely, poor CV outcomes have also been associated with certain diabetes medications over the past decade. Thiazolidinediones, notably rosiglitazone, were once an appealing option for add-on therapy to metformin because of the lower incidence of hypoglycemia associated with it in comparison to sulfonylurea therapy; however, an increased risk of nonfatal MI as well as a potential increased risk of CV death was noted in postmarketing analyses of rosiglitazone.[8,12] Based on these findings, this once popular new medication has been removed from clinical practice guidelines and is available to patients only through a restricted access program. In 2008, the FDA began requiring CV outcome data for all new oral diabetes medications.

One novel oral hypoglycemic agent is canagliflozin, a SGLT2 inhibitor. During the approval process for canagliflozin, the FDA Briefing Document[7] prepared for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting on January 10, 2013 included a CV safety statistical review. A meta-analysis of pooled data from 9 studies assessing MACE-plus events (CV death, nonfatal MI, and nonfatal stroke plus hospitalization for unstable angina) presented from the sponsor did not show an increase in MACE-plus events, with a hazard ratio (HR) of 0.91 (95% CI = 0.68-1.22), but did show a nonsignificant numerical increased risk of stroke: canagliflozin 47/6876 (6.8%) and comparators 16/3470 (4.6%); HR = 1.46 (95% CI = 0.83-2.58). The initial analysis contained interim data from a phase 3 study specifically designed to assess the effect of canagliflozin on macrovascular complications in high-risk patients—the Canagliflozin Cardiovascular Assessment Study (CANVAS).[13]

A disproportionate numerical imbalance in MACE-plus events was noted in the interim data from this study during the first 30 days of treatment in patients receiving canagliflozin (13/2886, 0.45%) compared with placebo (1/1441, 0.07%); HR = 6.50 (95% CI 0.85-49.66). Of these 13 MACE-plus events on canagliflozin, 5 were nonfatal stroke. Although this HR crosses 1 and does not meet statistical significance requirements, these findings are subject to significant changes to the HR should additional events occur during the remaining duration of the trial as a result of the small sample size. Of note, there was no difference in MACE-plus events after day 30 between canagliflozin (95/3175, 29.9%) and placebo-treated patients (52/1546, 33.6%); HR = 0.89 (95% CI = 0.64-1.25). In addition, subsequent analyses of trials excluding CANVAS found no difference in MACE-plus events. The FDA concluded that although there did not appear to be an overall increased risk of MACE-plus CV events with canagliflozin compared with controls, a concern exists secondary to the disproportionately high incidence during the first 30 days. They further commented that it is unclear if this finding is a true increase or falsely elevated because of a lower-than-expected event rate in the control groups for patients at high risk for a CV event. The panel voted to recommend approval of canagliflozin but also cited concerns over the drug's CV safety. The sponsor will continue to assess CV outcomes through the completion of the CANVAS study.

The mechanism behind this potential increased incidence of stroke within the first 30 days of canagliflozin therapy is not understood; however, a concern exists regarding the association between these early CV events and volume changes from canagliflozin, including hemoconcentration and acute kidney injury.[7] Our patient did not present with either of these findings. The association between increased LDL values secondary to canagliflozin therapy and CV risk has not yet been determined. To our knowledge, this is the first postmarketing case report of a stroke during the first 30 days of canagliflozin therapy in a patient at high risk for ischemic stroke, with multiple risk factors. Our patient had been initiated on canagliflozin 300 mg daily approximately 20 days prior to presentation. The stroke was diagnosed by clinical presentation and confirmed by MRI. Although additional workup for causality was likely noncontributory, the patient had significant clinical risk factors for stroke, including uncontrolled diabetes, hypertension, obesity, dyslipidemia, and family history of CVA. It is possible that intracranial and extracranial vessel disease secondary to atherosclerosis exists that was not visualized.

Using the Naranjo adverse drug reaction probability scale,[14] the association between initiation of canagliflozin in a high-risk patient and the CVA event could be classified as probable; the outcome appeared following initiation of the drug; no "definitive" alternative causes of the stroke were identified; the outcome was confirmed by objective evidence; and previous reports of this phenomenon exist from the preliminary data. However, a possible association could also be obtained using the Naranjo scale, depending on how one views the answer to whether "definitive" causes of stroke were identified. Although no specific cause for the stroke was identified, practitioners could perceive the multiple risk factors to weigh heavily in the development of stroke for this patient, which would lower the causality score to possible. In examining the CANVAS study inclusion and exclusion criteria, patients with multiple clinical risk factors for stroke were targeted for inclusion in this study to determine CV safety in a high-risk population. Although the authors do not suggest canagliflozin to be the sole cause of stroke in this case, it is important for practitioners to be cognizant of the possible to probable association of CVA timing within the first 30 days of canagliflozin therapy in patients already at high risk for stroke.

SGLT2 inhibitors are novel oral hypoglycemics. Their unique mechanism may make them an attractive option for certain patients. Reporting cases of adverse outcomes occurring on initiation of newer therapies is crucial to alert practitioners to this unknown but potentially devastating association during the early initiation phase in high-risk patients. The authors would caution practitioners against utilizing recently approved medications without long-term CV outcomes over therapies with well-established safety profiles. The practitioner must assess the risk-benefit profile of utilizing newer agents for improved glycemic control versus the potentially negative CV outcomes that may occur on initiation of such therapies in patients with preexisting risk factors for CV morbidity.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Invokana (canagliflozin) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013.
2. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15:372-382.
3. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimiperide in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet*. 2013;382:941-950.
4. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36:2508-2515.
5. Devineni D, Morrow L, Hompesch M, et al. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. *Diabetes Obes Metab*. 2012;14:539-545.
6. Rosenstock J, Aggarwal N, Polidori D, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care*. 2012;35:1232-1238.
7. Food and Drug Administration. FDA Briefing Document NDA 204042: Invokana (canagliflozin) tablets. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM334550.pdf. Accessed August 21, 2013.
8. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published correction appears in *N Engl J Med*. 2007;357:100]. *N Engl J Med*. 2007;356:2457-2471.
9. American Diabetes Association. Standards of medical care in diabetes: 2013. *Diabetes Care*. 2013;36(suppl 1):S11-S66.
10. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American association of clinical endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement: executive summary. *Endocr Pract*. 2013;19:536-557.
11. UK Prospective Diabetes Study Group (UKPDS). Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. *Lancet*. 1998;352:854-865.
12. Singh S, Loke YK, Furberg CD. Long term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007;298:1189-1195.
13. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS): a randomized placebo-controlled trial. *Am Heart J*. 2013;166:217-223.e11.
14. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.