Available online on www.ijtpr.com
International Journal of Toxicological and Pharmacological Research 2015; 7(2); 105-107

ISSN: 0975-5160

Research Article

Canagliflozin: A First-in-Class Medication for the Treatment of Type 2 Diabetes Mellitus

Dylan Hosein[1], Akram Ahmad[2], Muhammad Umair Khan[2] and *Sameer Dhingra[1]

[1]*School of Pharmacy, The University of the West Indies, St. Augustine, Trinidad and Tobago*
[2]*Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur, Malaysia*

Available Online:15th March, 2015

ABSTRACT
Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia and abnormalities in carbohydrate, fat, and protein metabolism. It results from defects in insulin secretion, insulin sensitivity, or both. Chronic microvascular, macrovascular, and neuropathic complications may ensue.Despite the large amount of treatment options available, Diabetes Mellitus is not well managed. Canagliflozin, a recently approved first-in-class anti-diabetic medication, employs a novel mechanism of action which is not dependent upon insulin release or improving insulin sensitivity. It is a sodium glucose co-transporter 2 (SGLT-2) inhibitor, developed to treat hyperglycemia in Type 2 Diabetes Mellitus patients. This causes more glucose to be removed from the urine, thereby lowering blood sugar levels. Canagliflozin was reported to improve glycemic control, reduce body weight and systolic BP, and was generally well tolerated in older subjects with T2DM who were on background therapy with a variety of blood glucose-lowering agents.

Keywords: canagliglozin, diabetes mellitus

INTRODUCTION

Within the last three decades, the prevalence of type-2 diabetes in the U.S. has more than tripled, accounting for 90% to 95% of the diagnosed cases[1,2]. It is projected that one in three American adults will have diabetes in 2050 if this trend continues[3]. The incidence of the disease is increased in obese patients, minority populations, and the elderly. Diabetes, which is characterized by chronic long-term hyperglycemia, is associated with serious complications, including blindness, kidney failure, amputations, and death[3].

Despite current available therapies, less than 50% of patients in the U.S. are achieving desired levels of glycosylated haemoglobin (HbA_{1c}), blood pressure, and low-density lipoprotein-cholesterol (HDL-C) levels, as recommended by the American Diabetes Association (ADA)[4]. Recent recommendations from the ADA and the European Association for the Study of Diabetes (EASD), along with the American Association of Clinical Endocrinologists (AACE), advise a patient-centred approach to management[4,5]. Preferred medications are those that carry a low risk of hypoglycemia, minimize the risk of weight gain, are easy to administer, are cost-effective, and are safe to use[5].

In March 2013, the USFDA approved canagliflozin as an adjunct to diet and exercise for adults with type-2 diabetes mellitus. This is the first oral agent in a novel class of diabetes drugs known as sodium–glucose co-transporter-2 (SGLT-2) inhibitors[6]. Current research has focused on the role of the kidney in glucose homeostasis and has identified the role of SGLT-2 in mediating the re-absorption of filtered glucose in the proximal tubule[6,7]. The inhibition of SGLT-2 provides a novel mechanism to lower elevated plasma glucose levels in diabetic patients[7,8].

INDICATIONS

Canagliflozin is approved for adults with type-2 diabetes mellitus who require improved glycemic control in addition to diet and exercise. This drug has not been studied for and is not recommend for patients with type-1 diabetes mellitus or diabetic ketoacidosis[9].

Recommended Dosage and Pre-Medication

The recommended starting dose of Canagliflozin is 100 mg once daily, taken before the first meal of the day. Assessment of renal function is recommended prior to initiation of Canagliflozin therapy and periodically thereafter[9].

In patients tolerating Canagliflozin 100 mg once daily who have an estimated Glomerular Filtration Rate of 60 mL/min/1.73 m^2 or greater and require additional glycemic control, the dose can be increased to 300 mg once daily. Canagliflozin should be discontinued when eGFR is persistently less than 45 mL/min/1.73 sq.m[10].

CLINICAL PHARMACOLOGY

Mechanism of Action

Canagliflozin is used along with diet and exercise, and sometimes with other medications, to lower blood sugar levels in patients with type 2 diabetes. Canagliflozin is in a class of medications called sodium-glucose co-transporter 2 (SGLT2) inhibitors. It lowers blood sugar by causing the kidneys to get rid of more glucose in the urine.

*Author for Correspondence

Canagliflozin is not used to treat type 1 diabetes or diabetic ketoacidosis[10].

Over time, people who have diabetes and high blood sugar can develop serious or life-threatening complications, including heart disease, stroke, kidney problems, nerve damage, and eye problems. Taking medication(s), making lifestyle changes (e.g., diet, exercise, quitting smoking), and regularly checking your blood sugar may help to manage your diabetes and improve your health. This therapy may also decrease your chances of having a heart attack, stroke, or other diabetes-related complications such as kidney failure, nerve damage (numb, cold legs or feet; decreased sexual ability in men and women), eye problems, including changes or loss of vision, or gum disease[10].

PHARMACOKINETICS

Canagliflozin is rapidly absorbed in the gastrointestinal (GI) tract. It has a relative oral bioavailability of 65% and reaches peak concentrations within 1 to 2 hours. It can be taken without regard to food, but it is recommended that it be taken before the first meal of the day to allow for the potential to reduce postprandial plasma glucose excursions resulting from delayed intestinal glucose absorption[11].

Canagliflozin is highly protein-bound, mostly to albumin at 99%. The half-lives of 100 mg and 300 mg are 10.6 hours and 13.1 hours, respectively. The drug is metabolized primarily into two inactive metabolites by uridine diphosphate glucuronosyl transferase (UGT) enzymes: UGT 1A9 and UGT 2B4 via glucuronidation. Approximately 7% of the drug also undergoes oxidation via cytochrome P450 (CYP) isoenzymes. Canagliflozin is eliminated largely unchanged in the faeces (41.5%) and as metabolites in the urine (30.5%). Removal by dialysis is negligible, and hepatic involvement is minimal[11].

PHARMACODYNAMICS

Following single and multiple oral doses of canagliflozin to patients with type 2 diabetes, dose-dependent decreases in the renal threshold for glucose (RTG) and increases in urinary glucose excretion were observed. From a starting value of RTG of approximately 240 mg/dL, canagliflozin at 100 mg and 300 mg once daily suppressed RTG throughout the 24-hour period. Maximal suppression of mean RTG over the 24-hour period was seen with the 300 mg daily dose to approximately 70 to 90 mg/dL in patients with type 2 diabetes in Phase 1 studies.

In patients with type 2 diabetes given 100 mg to 300 mg once daily over a 16-day dosing period, reductions in RTG and increases in urinary glucose excretion were observed over the dosing period. In this study, plasma glucose declined in a dose-dependent fashion within the first day of dosing. In single-dose studies in healthy and type 2 diabetic subjects, treatment with canagliflozin 300 mg before a mixed-meal delayed intestinal glucose absorption and reduced postprandial glucose.

Specific Populations

Age, Race and Body weight: The prevalence of the disease is increased in obese patients, minority populations, and the elderly. Canagliflozin improved glycemic control, reduced body weight and systolic BP, and was generally well tolerated in older subjects with T2DM who were on background therapy with a variety of blood glucose-lowering agents[12].

Pregnancy: It belongs to pregnancy category C [1] by the FDA, which states that studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus[11].

Lactation: There is limited available evidence and/or expert consensus that is conclusive for determining infant risk when used during breastfeeding. The potential benefits of drug treatment against potential risks must be weighed before prescribing this drug during breastfeeding[11].

Renal impairment: The use of canagliflozin is contraindicated in severe renal impairment as well as dialysis[11].

Hepatic Impairment: The use of canagliflozin is not recommended in patients with hepatic impairment[11].

CLINICAL STUDIES

In a randomized study on the efficacy and safety among older patients, seven hundred fourteen (714) subjects, aged 55 to 80 years with glycated hemoglobin (HbA1c) levels from 7.0 to 10% received canagliflozin 100 mg or 300 mg or placebo (1:1:1) daily. The prespecified primary endpoint was change from baseline in HbA1c level at week 26. These prespecified secondary endpoints included proportion of subjects achieving HbA1c levels < 7.0%, change from baseline in fasting plasma glucose (FPG) level and systolic blood pressure (BP), and percent change from baseline in body weight, triglyceride levels, and high-density lipoprotein cholesterol level. The results showed that at week 26, treatment with canagliflozin 100 mg and 300 mg significantly reduced HbA1c levels compared with placebo and that more subjects achieved HbA1c levels < 7.0% with both canagliflozin doses compared with placebo. The overall AE incidence was slightly higher with canagliflozin 300 mg than with canagliflozin 100 mg or placebo. Serious AE and AE-related discontinuation rates were low across groups. Both canagliflozin doses were associated with higher rates than placebo of genital mycotic infections, urinary tract infections, and osmotic diuresis-related AEs (ie, pollakiuria, polyuria). Documented hypoglycemia rates were modestly higher with both canagliflozin doses compared with placebo.In conclusion, canagliflozin improved glycemic control, reduced body weight and systolic BP, and was generally well tolerated in older subjects with T2DM who were on background therapy with a variety of blood glucose-lowering agents[12].

A second study had the purpose of evaluating the safety and efficacy of canagliflozin compared to glimepiride (study A) and placebo and sitagliptin (study B) in adults with type 2 diabetes with inadequate glycemic control on metformin monotherapy.The results showed that as an add-on therapy to metformin, canagliflozin 100 mg is noninferior and canagliflozin 300 mg is superior to

glimepiride and sitagliptin over 52 weeks. The incidence of hypoglycemia with canagliflozin was significantly lower than with glimepiride and similar to sitagliptin. AEs more commonly reported with canagliflozin were associated with its mechanism of action (i.e., increased urinary glucose excretion and osmotic diuresis) and included genital mycotic infection, pollakiuria, and polyuria.)[13]

ADVERSE EFFECTS

The most common adverse effects include frequent micturition, polyuria, Urinary tract infectious disease and Female genital mycosis. Some of the serious adverse effects include pancreatitis, severe hypoglycemia, hypovolemia, hyperkalemia, moderate to severe renal impairment and angioedema[11].

CONTRAINDICATIONS, CAUTIONS AND PRECAUTIONS

The drug is contraindicated in Severe renal impairment; such as eGFR <30mL/min/1.73m^2), End-stage renal disease or patients on dialysis. Alternate methods of glycemic control must be taken into consideration as GLT-2 inhibitors can increase urinary glucose excretion and will lead to positive urine glucose tests. Hypoglycemia has been reported; concomitant use with insulin or insulin secretagogues (eg, sulfonylureas) may increase risk; dose reduction of insulin or sulfonylurea may be required.

Hyperkalemia is reported in patients with moderate renal impairment who take potassium sparing diuretics or drugs that alter RAS are more likely to develop hyperkalemia. The drug increases serum creatinine and decreases eGFR, patients with hypovolemia are more susceptible to renal function impairment.For elderly patients; symptomatic hypotension may occur; monitoring recommended; correct hypovolemia prior to initiating therapy. Use is not recommended if patient has a hepatic impairment. Genital mycotic infections have been reported; uncircumcised men or patients with prior genital mycotic infections are at increased risk. Hence, it is important to monitor these patients[11].

REFERENCES

1. Number (in millions) of civilian, non-institutionalized persons with diagnosed diabetes, United States, 1980–2011. CDC Data Sheet. Available at: www.cdc.gov. (Accessed January 26, 2015)
2. Centers for Disease Control and Prevention (CDC) National Diabetes Fact Sheet. 2011. Available at: www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. (Accessed January 26, 2015)
3. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the U.S. adult population: Dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr. 2010;8:29.
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: Patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35:1364–1379.
5. Garber AJ, Abrahamson MJ, Barzilay JI. AACE Comprehensive diabetes management algorithm. Endocr Pract. 2013;19(2):327–336.
6. Nomura S, Sakamaki S, Hongu M, Kawanishi E, Koga Y, Sakamoto T, Tsuda-Tsukimoto M, Discovery of canagliflozin, a novel c-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus. J Med Chem. 2010;53:6355–6360.
7. Valentine V. The role of the kidney and sodium-glucose co-transporter-2 inhibition in diabetes management. Clin Diabetes. 2012;30:151-155.
8. FDA approves Invokana to treat type 2 diabetes: First in a new class of diabetes drugs. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/Ucm345848.htm. (Accessed May 20, 2014)
9. Brocavich SS, Hilas O. Canagliflozin (Invokana), a Novel Oral Agent For Type-2 Diabetes. P T. 2013;38(11):656-666.
10. Nisly SA, Kolanczyk DM, Walton AM, Canagliflozin, a new sodium–glucose cotransporter 2 inhibitor, in the treatment of diabetes. Am J Health-Syst Pharm.2013;70:311-319
11. Ruven Health Analytics. Micromedex Solutions. http://www.micromedexsolutions.com.ezproxy.sastudents.uwi.tt:2048/micromedex2/librarian/ (Accessed 22 nd January 2014).
12. Bode B, Stenlöf K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract (1995). 2013;41(2):72-84.
13. Battise DM. Efficacy and Safety of Canagliflozin as Add-On Therapy to Metformin in Type 2 Diabetes. Clinical Diabetes. 2014;32(2):81-86.