Canagliflozin: A Novel Agent for the Treatment of Type 2 Diabetes Mellitus

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Objectives
• Describe the pathophysiological defects in Type 2 Diabetes Mellitus (T2DM) incorporated in the ominous octet
• Describe the mechanism of action of canagliflozin
• Identify the potential place in therapy of canagliflozin
• Summarize patient counseling points when dispensing canagliflozin
• Identify available strengths of canagliflozin (Pharmacy technicians***)

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Abstract: Several oral and injectable agents are available for the treatment of Type 2 Diabetes Mellitus (T2DM). A recent consensus statement published by the American Diabetes Association emphasizes a patient-centered approach. Canagliflozin belongs to a novel therapeutic class. It is the first agent in its therapeutic class approved by the Food and Drug Administration (FDA) for use adjunct to diet and exercise to improve glycemic control in adults with T2DM. Canagliflozin affords the opportunity for patients previously managed with diet, exercise, and other oral agents to achieve even further hemoglobin A1c (HbA1c) lowering. Canagliflozin is administered orally and may be a viable option for patients who refuse insulin and have not achieved optimal glycemic control. However, it is not devoid of unfavorable adverse effects. The objective of this article is to briefly discuss the pathophysiological defects of T2DM and potential role of therapy for canagliflozin in the treatment of T2DM.

Key words: canagliflozin, diabetes mellitus, sodium glucose co-transporter 2 receptor inhibitor

INTRODUCTION
T2DM is one of the four clinical classes of diabetes identified which results from a progressive insulin secretory defect on the background of insulin resistance. Signs and symptoms of T2DM include polyuria, polydipsia, and polyphagia which may not be overt. Often patients with T2DM are not diagnosed until complications appear; therefore resulting in subsequent reduction in quality of life if diabetes remains uncontrolled.

Approximately 25.8 million children and adults in the United States are living with diabetes, including 7 million who are currently undiagnosed. This equates to 8.3% of the population in the United States. In 2010, South Carolina had the fifth highest prevalence of diabetes in the nation. The prevalence of diabetes in South Carolina is presently 9.6% and has increased more rapidly than the national rate.

Previously it was thought that a triumvirate was responsible for the pathophysiological defects occurring in T2DM including muscle, liver, and beta cell involvement. Recently, five additional pathophysiological defects have been described including fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), alpha cell (hyperglucagonemia), kidney (increased glucose reabsorption) and the brain (insulin resistance). It is proposed that multiple pathophysiological defects warrant treatment with combination therapy targeting several defects (Table 1).

Since 1995, when only two medication classes were available for the treatment of T2DM, many have been approved by the FDA. Among these medication classes are dipetidyl peptidase IV inhibitors, glucagon-like-peptide (GLP)-1 agonists, and the new sodium glucose co-transporter receptor inhibitors (SGLT). Canagliflozin (Invokana™, Janssen Pharmaceuticals) is the first agent included in the therapeutic
class of sodium glucose co-transporter receptor inhibitors, approved March 2013, for use in the United States. It is indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.6

MECHANISM OF ACTION
Homeostasis in the body is maintained via multiple organ systems. One of the major contributors to homeostasis of multiple endogenous and exogenous substances is the kidneys. The kidneys are well known for the maintenance of blood pressure; however they play a substantial role in the homeostasis of blood glucose as well. The primary mechanisms in which the kidneys regulate blood glucose are through the release of glucose into blood via gluconeogenesis and glucose reabsorption in the proximal convoluted tubule (PCT).7

Glucose reabsorption is accomplished with the active transport of glucose by sodium-coupled glucose co-transporters (SGLT1 and SGLT2) found in the kidneys.8 SGLT1 is located in the heart, intestine, trachea, and kidney, whereas SGLT2 is located only in the kidney.8 SGLT1 is shown to reabsorb 10% of filtered glucose reabsorption in the S3 segment of the PCT, where the SGLT2 has been identified to conduct 90% of reabsorption in the S1 segment of the PCT.10 The mechanism in which this new class of drugs (SLGT2 inhibitors) works is through inhibition of these SGLT2 co-transporters ultimately resulting in decreased renal reabsorption of the filtered glucose.6 This inhibition of glucose reabsorption results in increased renal glucose excretion into the urine defined as glucosuria. This increased excretion of glucose may have beneficial effects of weight loss.11

THERAPEUTIC EFFICACY
Since the discovery of canagliflozin in the late 2000s, its safety and effectiveness was evaluated in nine clinical trials involving over 10,000 patients with T2DM, including patients with chronic kidney disease.12-21 As monotherapy at week 26, a statistically significant reduction in HbA1c was achieved from baseline with canagliflozin 100 and 300 mg compared with placebo (−0.77, −1.03 and 0.14%, respectively).6 Canagliflozin has also been studied in combination with metformin showing a reduction in HbA1c from baseline with 100 mg and 300 mg dose versus placebo (−0.79, −0.94, −0.17%, respectively), with glimepiride vs. placebo (−0.85, −1.06, −0.13%, respectively), with metformin and a sulfonylurea vs. sitagliptin (−1.03, 0.66%, respectively), with metformin and a thiazolidinedione (−0.89, −1.03, −0.26, respectively), and in combination with insulin (−0.63, −0.72, 0.01%, respectively). Associated mean reductions in HbA1c (absolute reductions of 0.45–0.92%), fasting plasma glucose (decreases ranged from 16.2% to 42.4%) and weight loss ranging from 0.7 to 3.5 kg were also observed in clinical trials.12-21

Dapagliflozin, an agent in the same therapeutic class, has been approved for use in Europe since 2012. The body of literature supporting its efficacy is also available. Decreased risk in macrovascular complications has not been established. In July 2011, an FDA Advisory Committee voted against the approval of dapagliflozin as they cited higher rates of breast and bladder cancer in the treatment arms of trials analyzed.22 Further clinical trials with an extended duration are necessary.

PHARMACOKINETICS
In regards to absorption, canagliflozin is found to reach peak plasma concentrations within 1-2 hours postdose.6 The 100 mg oral tablet has an apparent half-life of 10.6 hours as compared to the 300 mg tablet which possesses a 13.1 hour half-life. Steady-state plasma concentration was reached after 4-5 days of administration.6

Canagliflozin can be administered without regards to meals, but improved glycemic control may occur when dosed before the first meal of the day due to delayed gastrointestinal absorption of glucose. The oral bioavailability of canagliflozin is nearly 65%.6

Canagliflozin is 99% plasma protein bound, mainly

Table 1. Ominous Octet and Medications to Target Defects

<table>
<thead>
<tr>
<th>Origin of Defect</th>
<th>Pathophysiologic Defect</th>
<th>Medication Class</th>
<th>Targeting Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>Insulin resistance</td>
<td>TZDs</td>
<td>GLP-1 (exenatide, saxagliptin, linagliptin, alogliptin) and amylin</td>
</tr>
<tr>
<td>Liver</td>
<td>Insulin resistance</td>
<td>Biguanides (metformin) and TZDs</td>
<td></td>
</tr>
<tr>
<td>β-cell</td>
<td>Insulin resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat cell</td>
<td>Accelerated lipolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Incretin deficiency/resistance</td>
<td>GLP-1 (exenatide, saxagliptin, linagliptin, alogliptin) and amylin</td>
<td></td>
</tr>
<tr>
<td>β-cell</td>
<td>Hyperglucagonemia</td>
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</tr>
</tbody>
</table>

TZDs = Thiazolidinediones; DPP = dipetidyl peptidase; GLP = glucagon like peptide
to albumin. The mean apparent volume of distribution was 119 L after single intravenous (IV) administration. Metabolism is mainly through O-glucuronidation by UGT1A9 and UGT2B4, producing two inactive metabolites. In humans, small amounts (7%) are metabolized through CYP3A4.6

The average clearance of canagliflozin was 192 ml/min when administered by IV route to healthy individuals. Approximately 33% and 41.5% of the administered dose was excreted in the urine and feces, respectively. The renal clearance of canagliflozin ranged from 1.30 to 1.55 mL/min.6

DOING
Canagliflozin is available as 100 mg and 300 mg tablets. The initial recommended dose for canagliflozin is 100mg by mouth prior to the first meal of the day. Maximum adult daily doses of 300 mg may be warranted in patients needing additional glycemic control with normal renal function, defined as an estimated glomerular filtration rate (eGFR) greater than or equal to 60mL/min/1.73m2. Canagliflozin is associated with increases in serum creatinine (SCr) and decreased eGFR. It is important to note the need for baseline renal function tests before initiation of therapy as well as regular renal function monitoring throughout the course of treatment in these patients.6

Patients with moderate renal impairment, eGFR 45-60 mL/min/1.73m2, are recommended to maintain maximum daily doses of 100mg, and careful monitoring of SCr and eGFR. Patients with severe renal impairment, eGFR less than 45 mL/min/1.73m2 should avoid the use of canagliflozin. Hypovolemic patients should avoid use of canagliflozin, until euvoeemia is restored, due to the increased risk of symptomatic hypotension. No dosage adjustments are needed in patients with hepatic impairment.6

DRUG INTERACTIONS
Co-administration of canagliflozin with UDP-glucuronosyltransferase (UGT) inducers poses a drug interaction and a dose increase may be warranted. Canagliflozin administered with nonselective inducers of UGT enzymes, such as rifampin, decrease canagliflozin efficacy by a 51% reduction in the area under the curve (AUC).6 Clinicians choosing to initiate concomitant administration of UGT inducers with canagliflozin should consider increasing the dose to 300 mg once daily under the following conditions: patient is currently tolerating canagliflozin100 mg once daily, has an eGFR greater than 60 mL/min/1.73 m2, and requires additional glycemic control.6 Other antidiabetic agents should be considered for use in patients who require additional glycemic control and do not meet this criteria.

Conversely, an increase in the area AUC and mean peak drug concentration (Cmax) of digoxin (20% and 36%, respectively) is expected when co-administered with canagliflozin 300 mg. Patients taking canagliflozin with concomitant digoxin should be monitored appropriately.6

SIDE EFFECTS
Four placebo-controlled pooled studies revealed the five most common adverse effects as female genital mycotic infections, urinary tract infections, increased urination, male genital mycotic infections and vulvovaginal pruritus. Evidence supports that patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. This subset of patients should be monitored and treat appropriately. Lab parameters and associated symptomology should be monitored to coincide with precautions including hyperkalemia, hypoglycemia, increase in low density lipoprotein, and impairment in renal function.6 Hypoglycemia was more likely to occur in patients taking canagliflozin and insulin or a secretagogue. Hyperkalemia was more likely to occur in patients taking other medications also known to increase potassium including angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEI), or aldosterone antagonists.

The FDA is necessitating five postmarketing studies be conducted by the manufacturer, three of which target the adult population: a cardiovascular outcomes trial; an enhanced pharmacovigilance program to monitor for malignancies, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes; and a bone safety study.23

SPECIAL POPULATIONS
Pediatrics and Geriatrics
The prevalence of T2DM in children is increasing. Use of canagliflozin has not been established in patients under the age of 18, due to insufficient evidence of safety and efficacy. Of the five aforemen-
tioned postmarketing studies to be conducted by the manufacturer, two are pediatric studies including a pharmacokinetic and pharmacodynamic study and a safety and efficacy study.23 Recently published recommendations regarding the management of T2DM favor the use of metformin as first-line therapy for children and adolescents at the time of diagnosis.24

A study found that canagliflozin use in geriatric patients was associated with increased risk of hypovolemic related adverse events such as hypotension, syncope, dehydration, and dizziness. These effects were reported at higher levels in geriatric patients taking daily doses of 300 mg or patients 75 years of age or older.6

**Pregnancy and Lactation**

Canagliflozin is categorized as pregnancy level C. There is no human data available for teratogenic effects from use during pregnancy and lactation. In studies using rats, it was observed that canagliflozin may affect renal development and maturation. It was reported that doses of 300 mg resulted in a greater than or equal to 0.5 fold increased kidney weights and renal pelvic and tubular dilation. This exposure in rats was comparable to the second and third trimester of pregnancy in humans, concluding that canagliflozin use during pregnancy may result in fetal malformations. Careful consideration must be made if initiation during pregnancy is desired, and should only be used if the potential benefit outweighs potential risk to fetus.6

Evidence is lacking on use during lactation in humans, though a study in rats found that canagliflozin is secreted in milk of rats at levels up to 1.4 times that of maternal plasma levels. These levels in rats have shown malformation of the developing kidney, leading to the conclusion that canagliflozin use should be avoided in nursing mothers.6

**CONCLUSIONS**

Canagliflozin represents the first of many agents in its class. It holds promise to a unique mechanism to treat T2DM. The place of therapy for canagliflozin has yet to be elucidated. Expected HbA1c lowering observed was comparable to other oral agents currently marketed to treat T2DM including alpha glucosidase inhibitors, meglitinides, and dipeptidyl peptidase inhibitors. Conversely, distinguishing adverse effects may limit its use. Perhaps it is a viable option for adults with T2DM who cannot achieve glycemic control with multiple agents but refuse injectable medications. Extensive patient counseling is warranted due to drug interactions, administration, and side effects (Table 2).

**RESOURCES FOR HEALTH CARE PROFESSIONALS IN SOUTH CAROLINA**

**Useful Websites**

- Endocrinology-Diabetes Initiative of South Carolina: [http://clinicaldepartments.musc.edu/medicine/divisions/endocrinology/dsc](http://clinicaldepartments.musc.edu/medicine/divisions/endocrinology/dsc)
- American Association of Clinical Endocrinologists: [https://www.aace.com/](https://www.aace.com/)

**Table 2. Patient Counseling Take Home Points**

<table>
<thead>
<tr>
<th><strong>Side effects</strong></th>
<th>This medication may affect how your immune system works and may cause a yeast infection or urinary tract infection.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A change in electrolytes has occurred in patients taking canagliflozin.</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>Some medications interact with canagliflozin.</td>
</tr>
<tr>
<td></td>
<td>Inform your doctor, pharmacist, or other healthcare professionals if you have started a new medication or stopped any medications since your last visit including rifampin or digoxin.</td>
</tr>
<tr>
<td></td>
<td>Dose adjustments may be made if you are taking medications that interact with canagliflozin.</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>For optimal results, canagliflozin should be taken with the first meal of each day.</td>
</tr>
<tr>
<td><strong>Laboratory Test</strong></td>
<td>Canagliflozin will cause you to test positive for glucose in your urine.</td>
</tr>
</tbody>
</table>
REFERENCES


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Learning Assessment Questions:

1. The pathophysiologic defect in Type 2 Diabetes Mellitus at the level of the kidney is:
   A. Hyperglucagonemia
   B. Increased glucose reabsorption
   C. Incretin deficiency
   D. Insulin resistance

2. Canagliflozin works to inhibit:
   A. Glucagon-like-peptide 1
   B. Insulin growth factor 1
   C. Sodium glucose co-transporter 2

3. Canagliflozin is indicated for use in adult patients with:
   A. Diabetic Ketoacidosis
   B. Hyperglycemic Hyperosmolar State
   C. Type 2 Diabetes Mellitus
   D. Type 1 Diabetes Mellitus

4. Canagliflozin is supplied as a tablet in which of the following doses?
   A. 50 and 100 mg
   B. 100 and 300 mg
   C. 200 and 300 mg
   D. 200 and 400 mg

5. Canagliflozin has been studied in combination with all the following EXCEPT:
   A. Insulin
   B. Insulin + Sitagliptin
   C. Metformin + Pioglitazone
   D. Metformin + Glimepiride

6. Which of the following is NOT a common side effect experienced in patients on canagliflozin therapy?
   A. Changes in urination
   B. Upper respiratory tract infection
   C. Urinary tract infection
   D. Yeast infection of the penis

7. Inhibition of sodium glucose transport 2 results in:
   A. Higher renal threshold for glucose
   B. Decrease in sodium reabsorption
   C. Decrease in urinary glucose excretion
   D. Reduction of reabsorption of filtered glucose

8. When administered concomitantly with an angiotensin receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACEI), or aldosterone antagonist, canagliflozin may cause:
   A. Hyperkalemia
   B. Hypernatremia
   C. Hypomagnesemia
   D. Hyponatremia