SGLT2 Inhibitors: A New Generation of Antidiabetic Drugs

Kuchana Madhavi1,2, D. Samba Reddy1 and S.K. Kulkarni3*

1Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A and M University Health Science Center, Bryan, TX 77807, USA. 2Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam (Women’s University), Tirupati 517502, Andhra Pradesh, India and 3University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India.

Received February 8, 2015; accepted March 23, 2015

ABSTRACT

The incidence of type 2 diabetes is markedly increasing worldwide. Despite a plethora of therapeutic options available for the treatment of type 2 diabetes, the ability to effectively normalize blood glucose levels and prevent long-term complications of diabetes remains elusive. There is intense search for new drugs for diabetes. One novel therapeutic class of antidiabetic drugs is sodium-glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 is renal membrane transporter that plays an important role in glucose reabsorption within kidneys. Hence, inhibition of SGLT2 enhances renal glucose excretion, consequently lowers blood glucose levels in an insulin-independent manner. This article describes various SGLT2 inhibitors currently available in the market and also agents that are undergoing clinical trials for the treatment of type 2 diabetes. Currently three SGLT2 inhibitors are approved for clinical use and several others are still in development. The emerging data suggest that SGLT2 inhibitors hold great promise for the clinical management of type 2 diabetes. It remains to be seen whether this class of drugs offers additional advantages over the existing oral hypoglycemic agents.

KEYWORDS: Dapagliflozin; Canagliflozin; Empagliflozin; SGLT2; Kidney; Diabetes; Blood glucose.

Introduction

Diabetes mellitus is a metabolic disorder due primarily to insulin deficiency and it affects millions of people worldwide. The two forms of the disease, type 1 (T1DM, insulin-dependent or juvenile diabetes) and type 2 (T2DM, non-insulin dependent) diabetes mellitus are essentially caused by a decrease in plasma insulin (insulin deficiency) and/or a decrease in the response of peripheral tissues to insulin (insulin resistance). The prevalence of T2DM is alarmingly increasing across the world and is considered as one of the major non-communicable diseases affecting the humans. It is estimated that currently about 387 million people are affected by diabetes and the number is projected to reach 592 million by 2035 (International Diabetes Federation, 2013). Insulin resistance in muscle, liver and pancreatic β-cell failure secrete insulin are the core pathology of the defects in type 2 diabetes. In addition to muscle, liver and β-cell (triumvrate) the fat cell, gastrointestinal tract, pancreatic α-cell, kidney and brain all play an important role in the development of glucose intolerance in type 2 diabetic individuals. Collectively, these eight players comprise the ominous octet according to Ralph DeFronzo’s Banting Lecture (DeFronzo, 2009). Management of type 2 diabetes consists of lifestyle interventions such as diet and exercise and use of antidiabetic medications which help to reduce the plasma glucose and improving insulin resistance (Nathan et al., 2006).

There are several classes of anti-diabetic agents that are in use as monotherapy or combination therapy to treat hyperglycemia. These included biguanides, sulphonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitor, incretin mimetic and dipeptidyl dipeptidase-4 inhibitors (Tang and Zhu, 2012). The currently available drugs for the treatment of T2DM are often limited by their potential to induce significant adverse effects and moreover the glycemic control is difficult to attain at times even with combination therapy. Long-term blood glucose control becomes difficult when the treatment is accompanied by weight gain during the drug therapy (Katsuno et al., 2009). Hence, the search for newer agents with different mode or site of action in the management of T2DM continues. The key goal of therapy is to provide better glycemic control and improve quality of life in diabetes.

This article describes novel drugs targeted to kidney for treatment of diabetes. Three SGLT2 inhibitors are currently available in the market and many other similar agents are undergoing clinical trials for the treatment of type 2 diabetes.

Sodium-Glucose Cotransporter 2 (SGLT2): New target for diabetes: In 1951, it was demonstrated that renal tubular reabsorption was increased in both T2DM as well as T1DM (Farber et al., 1951; Bakris et al., 2009).
By the early 1970s, the location of active-transport system responsible for glucose reabsorption was revealed by phlorizin, a natural compound used in trials evaluating renal physiology (Vick et al., 1973). During the following decade (late 1980s and early 1990s) sodium-glucose co-transporters, (SGLTs) were characterized and realized that these SGLTs in particular, SGLT2 play contributing role in glucose reabsorption in kidney (Lee et al., 1994; Abdul Ghani and DeFronzo, 2008). Therefore, any intervention, i.e., blockade or inhibition of SGLT2 would have a significant role in the management of T2DM.

**Kidney as a target:** It is well established that the kidney plays an important role in glucose homeostasis. Normally 180 liters of plasma per day are filtered by the kidney to maintain the intravascular volume and acid-base, electrolyte and water balance by reabsorption of water, sodium chloride, bicarbonate and secretion of hydrogen ions and potassium. Similarly, glucose is also filtered and reabsorbed in order to retain energy essential for the physiological function between meals. With a glomerular filtration rate of 180 liters per day and a plasma glucose concentration of 5mmol/l, the kidney filters nearly 162 gm (900 mmol) of glucose per day to maintain normal fasting plasma glucose concentration 5.6 mmol/l (Abdul Ghani and DeFronzo, 2008; Wright et al., 2007). Reabsorption of glucose occurs mostly by 2 different sodium/glucose cotransporters SGLT1 and SGLT2. SGLT1 is a low capacity and high affinity protein principally located in the gastrointestinal tract and S-3 segment of proximal renal tubules. Only 10% of filtered glucose is reabsorbed by this protein in kidney and remaining 90% is reabsorbed by high capacity and low affinity protein SGLT2 to maintain normoglycemia.

**New mechanism: glucose flushing:** In humans SGLT2 is encoded by the SLC5A2 (solute carrier family 5) (sodium/glucose cotransporter) gene (Well et al., 1993). SGLT2 is mainly expressed in S-1 and S-2 segments of the proximal renal tubules where the majority of filtered glucose is absorbed. The SGLT2 is a secondary glucose transporter, which transport glucose through the membrane into the cells, against the concentration gradient of glucose (Figure 1). This is done by using sodium gradient, produced by Na+/K+ ATPase pump. More clearly Na+/K+ ATPase pump on the basolateral membrane of the proximal tubule cell uses ATP to move three sodium ions outward into the blood, while bringing in two potassium ions and creates a downhill sodium ion gradient inside the proximal tubule cell in comparison to both the blood and the tubules. From this downhill sodium ion gradient the SGLT2 protein uses the energy to transport glucose across the apical membrane against an uphill glucose gradient. In normal individuals, when plasma glucose levels exceed the maximal reabsorptive capacity of renal SGLT transport system, glycosuria occurs (DeFronzo et al., 2012). However, abnormal expression and activity of SGLT2 has been found in T2DM (Rahmone et al., 2005), a disease condition where an abnormal level of glucose is reabsorbed by the kidneys into the bloodstream contributing to the chronic hyperglycemia and glucotoxicity leading to β-cell dysfunction. Suppression of upregulated SGLT2 can reduce the plasma glucose, HbA1c levels as well as decrease bodyweight, resulting in improved β-cell function and enhanced insulin sensitivity in liver and muscle, respectively. Because the SGLT2 inhibition is independent of insulin secretion and sensitivity, this class represents a novel therapeutic approach with potential for the treatment of T2DM (Poudel, 2013).

**Current SGL T2 Inhibitors**

In 1835, French chemist isolated phlorizin, an O-β-glucoside from the bark of apple tree. Initially it was used for the treatment of fevers, infectious diseases and malaria (John and White, 2010). Later, phlorizin has been identified as a competitive inhibitor of SGLT1 and SGLT2, as it competes with D-glucose for binding to the carrier. This reduces the renal glucose transport, lowering the amount of glucose in the blood (Rossetti et al., 1987; Tatoń et al., 2010). Phlorizin was studied as a potential pharmaceutical treatment for type 2 diabetes, but it was not developed as a drug for treatment of diabetes because of its non-selectivity and low bioavailability (Oku et al., 1999). However, it has been superseded by more selective and more promising synthetic analogs, such as canagliflozin and dapagliflozin (Chao and Henry, 2010). Some of these molecules (approved by the USFDA) have been described below:

**Dapagliflozin**

Dapagliflozin is a C-glucoside developed by BMS-Astra Zeneca with trade name Farxiga in United States and Forxiga in European Union. Dapagliflozin is the first SGLT2 inhibitor approved by the European Medicines Agency for treating the type 2 diabetic patients. The US FDA approved the use of dapagliflozin on 8th January 2014 for glycemic control, along with diet.
and exercise, in adults with T2DM. Dapagliflozin was known earlier as BMS 512148 (Boldys and Okopieri, 2009), its IUPAC name is \((2S, 3R, 4R, 5S, 6R)-2-[4\text{-chloro-3-}[4\text{-ethoxy-phenyl} \text{methyl]}\text{phenyl}]\text{-6-}(\text{hydroxy-methyl})\text{oxane-3,4,5-triol}\) (Figure 2).

It was synthesized via C-arylation of 2,3,4,6-tera-O-trimethylsilyl-1-d-glucolactone with an aglycon moiety, 5-bromo-2-chloro-4-ethoxydiphenyl-methane. Commercially available glucolactone was converted to persilylated glucolactone with trimethylsilyl chloride in N-methyl morpholine and tetrahydrofuran. Lithium halogen exchange of aglycon with n-butyllithium in hexane, followed by addition of the nascent lithiated aromatic to a stirred solution of persilylated glucolactone in toluene at -78 °C gave a mixture of lactols. In situ conversion of these lactols to desilylated O-methyl lactols was performed by using methane sulphonic acid in methanol. Reduction of anomeric methoxy group with triethylsilane (Et₃SiH) and boron trifluoride-etherate (BF₃·OEt₂) followed by peracetylation, yielded tetraacetate derivative, which was recrystallized from ethanol to remove the small amount of α-anomer formed during the reduction. Deacetylation of resultant β-anomer with lithium hydroxide in aqueous THF/methanol generated dapagliflozin (Meng et al., 2008).

---

**Fig. 2.** Chemical structures of SGLT2 inhibitors.
Dapagliflozin acts by insulin-independent mechanism, selectively inhibits the human SGLT2 (IC₅₀ 1.12 nmol/l) than SGLT1 (IC₅₀ 1919 nmol/l) such that the drug does not interfere with intestinal glucose absorption (Han et al., 2008). The clinical studies presented a significant HbA₁c reduction, an improved glycemic control and a significant decrease in bodyweight. The reduction in bodyweight during the first week of the trials represents fluid loss, whereas weight loss during the following weeks of dapagliflozin administration represents decreased fat mass (List et al., 2009). Moreover, an additional benefit of blood pressure reduction, both systolic and diastolic, has been observed with administration of dapagliflozin (Ferrannini et al., 2010). It is rapidly absorbed with maximum plasma concentrations observed within 2 hr and half-life of 17 hr (Komoroski et al., 2009). The C-aryl glucoside linkage of its structure makes dapagliflozin resistant to degradation from intestinal β-glucosidase enzymes prolonging its bioavailability. Therefore a single daily dose is sufficient to suppress both postprandial and fasting hyperglycemia (Meng et al., 2008). About 97.9%-98% of dapagliflozin is protein bound and only 2-4% is eliminated through renal excretion. Approximately 0.1% of dapagliflozin is excreted as an inactive metabolite, which has bioavailability of 84%, with a half-life of 4.6 hr (Komoroski et al., 2009). The recommended dose of dapagliflozin is 10 mg per oral, once daily for monotherapy and add-on combination therapy with other anti-diabetic medications such as metformin, sulfonylureas or insulin. The efficacy of dapagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment. Hence, it is not recommended in patients with moderate to severe renal impairment. In patients with severe hepatic impairment, low dose is recommended and no dosage adjustment is necessary for patients with mild hepatic impairment. The side effects of dapagliflozin include glycosuria (70 gm/day) which leads to weight loss and tiredness. The glucose acts as an osmotic diuretic and results into polyuria in diabetes, which can lead to dehydration. The increased renal excretion of glucose can worsen genital and urinary tract infections (Ferrannini et al., 2010). Dapagliflozin administration is also associated with hypotensive reactions. There may be considerable risk of hypoglycemia if taken with insulin or insulin secretagogue such as sulphonylurea.

**Canagliflozin**

Canagliflozin was developed by Mitsubishi Tanabe Pharma, marketed as Invokana under license by Janssen, a division of Johnson and Johnson. It is the second agent of this class that has completed phase III trials and first to be approved by USFDA in March 2013 (Clarke, 2013). This drug has been approved for a pediatric investigation plan on July 4, 2011 by European Medicines Agency. Canagliflozin is a novel thiophene derivative of C-glucoside, earlier it is known as TA-7284. The IUPAC name of canagliflozin is (2S,3R,4R,5S,6R)-2-[[S-(4-flouro-phenyl)-thiophen-2-yl]methyl]-4-methyl-phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol and its chemical structure is presented in figure 2. The synthesis of canagliflozin can be carried out by treating an aglycon, 2-(5-bromo-2-methylbenzyl)-5-(4-fluoro-phenyl)thiophene with n-butyllithium at -78 °C to generate aryli lithium followed by addition of 2,3,4,6-tetra-O-trimethylsilyl-β-D-glucolactone, then the resulting anomeric mixture of lactol was immediately converted into desilylated methyl ether and reduced sterioselectively (Nomura et al., 2010).

Canagliflozin selectively inhibits SGLT2 (160-fold more selective for SGLT2 than for SGLT1), hence this drug is prescribed for the treatment of T2DM specifically and not for the treatment of T1DM or diabetic ketoacidosis. Approximately about 50 to 80 gm of glucose per day is eliminated through urine which corresponds to loss of 200-300 kilocalories. As a result bodyweight is reduced, because the body uses fat tissue to replace the lost glucose. In placebo controlled clinical trials, canagliflozin produces a dose dependent reduction in HbA₁c from baseline, ranged from 0.3 to 1.2% when administered at different dosage as monotherapy or as combination therapy (Willson and White, 2013; Nyirjesyet al., 2012; Rosenstock et al., 2012a; Devineni et al., 2012; Stenlof et al., 2013; Yale et al., 2013). It is reported that canagliflozin present a beneficial effect on β-cell function and an increase in HOMA2-%B (Homeostasis Model Assessment) when compared with placebo (Rosenstock et al., 2012a; Stenlof et al., 2013). It also produces beneficial effects on HDL cholesterol and systolic blood pressure. However, the use of canagliflozin is associated with increased LDL cholesterol and responsible for cardiovascular problems. Canagliflozin induces changes in serum electrolytes, causes thirst, polyuria and hypotension as a result of osmotic diuresis due to increased urinary glucose excretion (Stenlof et al., 2013; Yale et al., 2013). Urinary tract infections and genital mycotic infections are other adverse events associated to the glucosuric effect of canagliflozin (Willson and White, 2013; Nyirjesyet al., 2012; Rosenstock et al., 2012a; Devineni et al., 2012; Stenlof et al., 2013; Yale et al., 2013).

The minimum dose of canagliflozin is 100 mg per oral, once a day and it may be increased to 300 mg per day in patients tolerating 100 mg/day who have an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m² and requires additional glycemic control. Following single dose oral administration of 100 mg or 300 mg of canagliflozin, it reaches peak plasma concentration within 1 to 2 hr post dose and has mean terminal plasma half-life of 10.6 and 13.1 hr with 100 and 300 mg dose, respectively (Janssen Pharmaceuticals, Inc., 2013). It is bound to the plasma proteins, mainly albumin and it undergoes O-glucuronidation as a metabolic degradation.

**Empagliflozin**

Empagliflozin is a new drug for the treatment of T2DM in adults, earlier mentioned as BI 10773 marketed under the trade name Jardiance, a tablet
formulation of dose 10mg or 25mg. It was developed by Boehringer Ingelheim and Eli Lilly Company, approved in May 2014 by European Medicines Agency and in August 2014 by USFDA (Grempler et al., 2012; Miriam, 2013; Elizabeth Mechatie, 2014). The IUPAC nomenclature of Empagliflozin is (2S, 3R, 4R, 5S, 6R)-2-[(4-chloro-3-[(4-(3S)-oxolan-3yl)oxyphenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol and the structure is presented in figure 2. It is structurally related to dapagliflozin, possess a tetrahydrofuran moiety in place of ethyl group of ethyl phenyl ether. The synthesis of empagliflozin can be carried out by C-arylation of persilylated glucolactone with (S)-3-(4-chloro-5-iodobenzyl) phenoxy/tetrahydrofuran in presence of Knochel’s isopropylmagnesium chloride lithium chloride (PrMgCl-LiCl) complex to give an intermediate lactol. Subsequent in situ treatment of the resulting lactol with hydrochloric acid (HCl) and methanol produces β-anomeric methyl glycol-pyranoside, which is directly reduced with Et3SiH mediated by AlCl3 as a Lewis acid in dichloro-methane and acetonitrile to afford empagliflozin (Wang et al., 2014).

Empagliflozin is a potent inhibitor of hSGLT2, with an IC₅₀ value of 3.1 nM and has >2,500-fold selectivity for inhibition of SGLT2 versus SGLT1 (Grempler et al., 2012). In phase III clinical trials, the efficacy and safety of empagliflozin has been investigated in a randomized, placebo controlled study of T2DM patients with HbA₁c levels of 7 to 10% and found significant reduction not only HbA₁c levels but also fasting plasma glucose (FPG) and bodyweight compared with placebo. Reduction in systolic blood pressure on administration of empagliflozin has also been observed. In addition, compared with placebo HDL cholesterol increased significantly from baseline in patients treated with empagliflozin, but levels of total cholesterol, LDL-cholesterol or triglycerides did not change (Roden et al., 2013). The important identified risks with administration of empagliflozin are urinary tract infections, genital infections, dehydration and hypoglycemia. Other potential risks with empagliflozin are renal impairment, hepatic impairment, cancer of kidney and bladder.

The pharmacokinetic and pharmacodynamics studies revealed that after oral administration of empagliflozin in T2DM patients, it reaches maximum plasma concentration after 1.33 - 3.0 hr and then decline in a biphasic fashion, with a mean t½ ranging from 10.3 to 18.8 hr (Heise et al., 2013a; Heise et al., 2013b). The urinary glucose excretion rose from baseline to 74 and 90 gm with single dose of 10mg and 25mg respectively.

**New SGLT2 Inhibitors in Development**

**Ipragliflozin**

Ipragliflozin is an orally active, next generation SGLT2 inhibitor, has been developed by Astellas Pharma and Kotobuki Pharmaceutical for the treatment of T2DM. Ipragliflozin has received its first approval in Japan and marketed under the trade name Suglat®, as use as monotherapy. It is also useful in combination with other antihyperglycemic agents such as metformin, pioglitazone, a sulphonylurea, α-glycosidase inhibitor, a DPP-4 inhibitor and nateglinide (Poole and Dungo, 2014a). Ipragliflozin is a novel C-glucoside with benzothiophene ring and it is commonly represented as ASP 1941. IUPAC nomenclature of ipragliflozin is (2S, 3R, 4R, 5S, 6R)-2-[3-(1-benzothiophen-2-ylmethyl)-4-fluorophe-nyl]-6-(hydroxyethyl)oxane-3,4,5-triol and its chemical structure is presented in figure 2. The synthesis can be carried out by lithiation of benzothiophene followed by the addition of lithiated aromatic to (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-(3-formylphenyl)-D-glucitol, to produce lactol. The resultant lactol on reduction with Et3SiH and boron trifluoride ether ethyl complex (BF3-OEt2) followed by treatment with boron trichloride (BCl3) gave ipragliflozin (Imamura et al., 2009; Imamura et al., 2012).

The mechanism of action of ipragliflozin is similar to other novel SGLT2 inhibitor drugs, increases the urinary excretion of glucose by selective inhibition of SGLT2. In a recent multi center, double-blind, randomized study with T2DM patients, it is found that a significant dose dependent decrease in HbA₁c and FPG with ipragliflozin when compared with placebo. Additionally reduction in bodyweight and waist circumference has been observed among patients with ipragliflozin treatment (Fonseca et al., 2013; Kashiwagi et al., 2014).

The recommended dose of ipragliflozin is 50 mg once daily in the morning. If the effects are not satisfactory, the dosage may be increased up to 100 mg once a day, while carefully monitoring disease progress. Clinical pharmacokinetic and pharmacodynamics of single and multiple doses of ipragliflozin showed an increase in maximum plasma concentration and area under the plasma concentration time curve (AUC) in a dose dependent manner. No clinically relevant effects of age, gender or food on the exposure of ipragliflozin were observed. Further, it is mentioned that 20-30% enhancement in AUC for ipragliflozin in patients with moderate renal or hepatic impairment than in patients with normal renal and hepatic function. Urinary glucose excretion also increased in a dose-dependent manner, approaching a maximum effect at 50-100 mg dosages in Japanese healthy volunteers and patients with type 2 diabetes (Kadokura et al., 2014).

**Tofogliflozin**

Tofogliflozin is an orally active small molecule SGLT2 inhibitor, developed by Chugai Pharmaceutical for the treatment of T2DM. A marketing authorization application was filed in Japan in 2013 by licensees Sanofi K.K. and Kowa. Tofogliflozin has received its first global approval for this indication in Japan under the trade name Apleway®Deberza®. It is prescribed as either monotherapy or in combination with other Antihyperglycemic agents (Poole and Prossler, 2014b). Tofogliflozin is a novel C-aryl glucoside with an O-spiroketal ring system. It has a code name CSG452 and its IUPAC nomenclature is (1S,3'R,4'S,5'S,6'R)-6'-(4-ethylphenyl)methyl]-6'-[(hydroxymethyl) spiro [1H-2-
benzofuran-1,2′,3′,4′,5′-triol]. Figure 2 shows the chemical structure of tofogliflozin. The synthesis of tofogliflozin can be performed by using (1S,3′R,4′S,5′R, 6′R)-3′,4′,5′-tris(benzyloxy)-6′-((benzoyloxy)methyl)-3′,4′,5′- 6′-tetrahydro-3H-spiro[2-benzo[3,4]-furan-1,2′-pyran]-3′,4′,5′-triol. Figure 2 shows the chemical structure of tofogliflozin. The synthesis of tofogliflozin can be performed by using (1S,3′R,4′S,5′R, 6′R)-3′,4′,5′-tris(benzyloxy)-6′-((benzoyloxy)methyl)-3′,4′,5′- 6′-tetrahydro-3H-spiro[2-benzo[3,4]-furan-1,2′-pyran]-3′,4′,5′-triol. Its chemical structure is represented in figure 2. Ertugliflozin can be synthesized in an analog friendly fashion starting from advanced intermediate Weinreb amide (Mascitti and Collman, 2010), chemically (2R,3S,4S)-2,3,4-tris (benzoyloxy)-5-hydroxy-6-[(4-methoxybenzyl)oxy]-5-[(4-methoxy- benzyl) oxy] methyl hexanoic acid methoxy-methyl- amide, which is obtained by a multistep synthesis starting from D-glucose. Nucleophilic addition of appropriate organolithium to the above Weinreb amide produces the corresponding cyclic lactol. Then acid promoted one-pot removal of p-methoxy benzyl groups from cyclic lactol followed by stereo selective intra- molecular trapping of oxonium ion intermediate gave a compound containing the desired dioxa-bicyclo [3.2.1] octane ring system. This on hydrolysis deproteins the benzyl groups to yield ertugliflozin (Mascitti et al., 2011). Recently a new commercial route has been developed for the synthesis of ertugliflozin, a highly telescopied process involves only three intermediate isolations over a 12-step sequence. The dioxa-bicyclo [3.2.1] octane motif is prepared from commercially available 2,3,4,6-tetra-O-benzyl-D-glucose, with nucleophilic hydroxymethylation of a 5-ketoglucosamine intermediate as a key step. Further, a co-crystalline complex of amorphous ertugliflozin with L-pyroglutamic acid has been prepared in order to improve the physical properties for manufacture and to ensure robust API (Active Principal Ingredient) quality (Bowles et al., 2014).

Ertugliflozin is potent and selective SGLT2 inhibitor incorporating a structurally novel dioxa-bicyclo [3.2.1] octane ring system. It is hypothesized that the bridged ketal system confers rigidity and reduces the rate of human phase 2 metabolism and further improves the potency. Ertugliflozin has been evaluated for its potential to induce urinary glucose excretion in vivo. Compared to vehicle, the compound caused a dose responsive increase in urinary glucose excretion in rats for the doses ranged from 0.1mg - 60mg/kg bodyweight. The maximal urinary glucose excretion over 24 hr was reached at a single oral dose of 30mg/kg corresponding to a free average plasma concentration of 408 nM. It is reported that free in vivo IC50 was 1.8 nM which is in agreement with rat SGLT2 in vitro IC50 of 1.15 nM (Mascitti et al., 2011).

The pharmacokinetics of ertugliflozin was evaluated in healthy human volunteers in a randomized placebo controlled ascending single oral dose, cross over study over the dose range of 0.5 to 300 mg. The study revealed that ertugliflozin was rapidly absorbed with mean plasma concentration occurring at 0.5 to 1.5 hr post dose and the terminal half-life was 11 to 17 hr (Kalugutkar et al., 2011). In another study of pharmacokinetics, metabolism and excretion, using a single dose of [14C] ertugliflozin in healthy human subjects, mass balance was observed approximately 91% of administered dose recovered in urine and feces. The total administered radioactivity excreted in urine and feces was 40.9 and 50.2% respectively. The total radioactivity excreted in feces and urine, unchanged ertugliflozin collectively accounted for ~35.3% of the dose, suggestive of moderate metabolic elimination in humans. A total of eight
metabolites were identified in human excreta by LC-MS/MS with primary biotransformation pathway involving glucuronidation of the glycoside hydroxyl groups in ertugliflozin to afford three regioisomeric metabolites (~39.3% of administered dose in urine), of which Ertugliflozin-3-O-glucuronide was the major regioisomer (Miao et al., 2013).

**Sergliflozin etabonate**

Sergliflozin etabonate (active form of sergliflozin) is an investigational antiabetic drug developed by GlaxoSmithKline. It has a code name GW869681X and its IUPAC nomenclature is ethyl [(2R, 3S, 4S, 5R, 6S)-3, 4,5-trihydroxy-6-[2-[(4-methoxyphenyl)methyl]phenoxy] oxan-2-yl]methyl carbonate. The chemical structure of Sergliflozin etabonate has been represented in figure 2. Usually etabonate refers to ethyl carbonate, hence it has been syntehsized by treating the sergliflozin with ethyl-chloroformate in presence of 2,4,6-trimethylpyridine. Actually, sergliflozin was synthesized from 2-(4-methoxybenzyl)phenol, and 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetimidoyl-o-D-glucopyranosyl in the presence of boron trifluoride diethyl ether complex and dichloromethane as solvent to give O-tetra acetyl derivative of sergliflozin as an intermediate. This intermediate on subsequent hydrolysis with sodium methoxide resulted in sergliflozin (Iyobe et al., 2004).

Sergliflozin etabonate, active form of sergliflozin, is potent and selective SGLT2 inhibitor. Sergliflozin etabonate was approximately 7 times more active against SGLT2, but only one-fifth as active against SGLT1 when compared with phlorizin (Katsuno et al., 2007). Sergliflozin etabonate encouraged excretion of glucose depending on blood glucose levels. Upon chronic administration of sergliflozin etabonate to Zucker fatty rats there is no alteration in bodyweight as well as food intake but it reduces both the glycated heamoglobin and fasting plasma glucose (Fujimori et al., 2009). In a study which validates the critical role of SGLT2 in renal glucose reabsorption and modulates plasma glucose level using sergliflozin, it is mentionted that the transport maximum for glucose in the kidney was reduced by sergliflozin etabonate in normal rats. As a result of this effect sergliflozin, a prodrug increased urinary glucose excretion in mice, rats and dogs in dose dependent manner. Sergliflozin exhibited glucose lowering effects independently of insulin secretion as evident from oral glucose tolerance test in diabetic rats. The study also mentioned that, any glucose excretion induced by sergliflozin did not affect normoglycemia or electrolyte balance (Katsuno et al., 2007). In another study, long-term treatment with sergliflozin etabonate improved hyperglycemia and prevented bodyweight gain dose dependently. In addition to the improvement in glycemic control, fatty liver and pancreatic β-cell abnormalities were ameliorated in mice treated with sergliflozin etabonate (Katsuno et al., 2009).

Single dose pharmacokinetics and pharmacodynamics study of sergliflozin etabonate in healthy volunteers and patients with T2DM was reported (Hussey et al., 2010a).

It was mentioned that sergliflozin etabonate was rapidly and extensively converted to sergliflozin, the later displayed linear kinetics, reached maximum plasma concentrations at approximately 30 to 45 minutes post dose and had a plasma elimination half-life of approximately 0.5 to 1 hr. Both prodrug and active entity exhibited low glomerular filtration and/or extensive renal tubular reabsorption, with <0.5% of the administered dose being recovered in the urine. In both populations, a dose-related glucosuria under fasting conditions and following glucose loading was observed with sergliflozin etabonate, but no appreciable effect on urinary electrolyte excretion or fluid balance. Further, it is mentioned that single doses of sergliflozin etabonate 5 to 500 mg were well tolerated and there were no clinically significant adverse laboratory findings.

Multiple-dose pharmacokinetics and pharmacodynamics of sergliflozin etabonate (500 or 1000mg, 3times daily for 14 days) in healthy overweight human volunteers revealed that the test compound produced rapid and sustained suppression of renal glucose reabsorption, resulting in a dose-related glucosuria and a transient increase in urinary electrolyte and fluid loss. The test compound also produced a rapid, dose-related reduction in bodyweight, apparently through increased urinary calorie loss rather than through osmotic diuresis. The study also reported that sergliflozin etabonate was generally well tolerated with no clinically significant adverse effects (Hussey et al., 2010b).

However, sergliflozin has been discontinued due to various unfavorable effects such as non-desired pharmaceautical properties, non-selectivity and development of other new SGLT2 inhibitors (Hussey et al., 2007).

**Remogliflozin etabonate**

Remogliflozin etabonate (GSK189075; KGT-1681) is a prodrug based on benzylpyrazole glucoside and metabolized to its active form, remogliflozin (GSK 189074; KGT-1650). It is a proposed drug for the treatment of T2DM being investigated by GlaxoSmithKline. Its IUPAC Nomenclature is ethyl [(1R, 2R, 3S, 4R, 5R)-2,3,4,6-tetra-O-acetyl-1-O-trichloroacetimidoyl-o-D-glucopyranosyl in presence of silver carbonate and 4A molecular sieves in tetrahydrofuran, which resulted in tetra-O-acetylated intermediate. This intermediate on hydrolysis with sodium methoxide resulted in remogliflozin (Shiohara et al., 2007).
Remogliflozin, the active form of remogliflozin etabonate, is a potent and selective SGLT2 inhibitor. The inhibitory effect of remogliflozin for hSGLT2 was approximately 3 times greater than that of phlorizin, but for SGLT1, it was only one twentieth of that of phlorizin. The ratio of selectivity (Kᵩ value of hSGLT1/Kᵩ value of hSGLT2) of remogliflozin and phlorizin was 365 and 7. In the literature it is reported that oral administration of remogliflozin etabonate increased urinary glucose excretion in a dose dependent manner in both mice and rats. Remogliflozin etabonate also exhibited antihyperglycemic effects in both streptozotocin-induced diabetic rats in oral glucose tolerance and db/db mice in the fed condition. In db/db mice, chronic treatment with remogliflozin etabonate reduced the levels of fasting plasma glucose and glycated hemoglobin and it ameliorated glucosuria. Remogliflozin etabonate also improved hyperglycemia, hyperinsulinemia, hypertriglyceridemia and insulin resistance (Fujimori et al., 2008).

The safety, tolerability, pharmacokinetic and pharmacodynamics study was conducted in both healthy human volunteers and in patient with T2DM. In this study, it is mentioned that single oral doses of remogliflozin etabonate (20 mg to 1000 mg for healthy subjects; 50 mg to 500 mg for subjects with T2DM) were generally safe and well tolerated. Remogliflozin etabonate was rapidly absorbed and converted to remogliflozin, reached maximum plasma concentration approximately 1 hr. Remogliflozin undergoes further transformation to GSK279782, an active metabolite. Remogliflozin-Tabonate was rapidly eliminated with a mean t½ of ~25 min and the plasma t½ for remogliflozin was 120 min. All subjects showed dose-dependent increase in 24 hour urinary glucose excretion. In patients with T2DM, increased plasma glucose following oral glucose tolerance test was attenuated by remogliflozin etabonate in a dose dependent manner, but there were no clear trend in plasma insulin (Kapur et al., 2013). In another study, oral administration of remogliflozin etabonate reduced postprandial glucose excursions without inducing hypoglycemia, improved plasma glucose concentration in subjects with diabetes and reduced HbA1c levels (Dobbins et al., 2012).

**Therapeutic Status of SGLT2 Inhibitors**

**Clinical uses:** Currently available therapies to rationalize the hyperglycemia in T2DM patients generally involve insulin-dependent mechanisms and lose their effectiveness as pancreatic β-cell function decreases to a greater extent. Recently, inhibition of SGLT2 has emerged as a new potential therapeutic option for the treatment of T2DM, as kidney play a crucial role in reabsorption of glucose through SGLTs, a novel pathophysiological mechanism responsible for T2DM. The newly approved SGLT2 inhibitors acts by insulin-independent mechanism, reduces plasma glucose and HbA1c levels by inducing glucosuria. They also decrease bodyweight, resulting in improved pancreatic β-cell function and enhanced insulin sensitivity in lever and muscle. In addition to reduction of blood glucose levels and bodyweight, SGLT2 inhibitors have a potential in amelioration of metabolic and cardiovascular risk factors, blood pressure, lipid profile (HDL cholesterol). The mechanism of action of SGLT2 inhibitors suggests that they are not only suitable for monotherapy but also used in combination with other oral antidiabetic agents as well as insulin to exert synergic effect.

**Risk Vs. benefits:** Although SGLT2 inhibitors exhibit inherent potential benefits, there may be negative effects of glucosuria such as polyuria, polydipsia which results in hypovolemia particularly in dehydrated patients and also urinary tract and genital infections. A systematic review and meta-analysis of SGLT2 inhibitors showed that urinary tract and genital infections are more common among the patients treated with SGLT2 inhibitors (odd ratios, 1.42 [CI, 1.06 to 1.90] and 5.06 [CI, 3.44 to 7.45], respectively), than among those receiving placebo (Vasilakou et al., 2013). However, these urinary tract and genital infections may be circumvented by rigorous hygiene.

Other adverse events reported with SGLT2 inhibitors include hypoglycemia, cardiovascular risks and cancer. As SGLT2 inhibitors act by a novel insulin-independent mechanism, hypoglycemia is a rare adverse event in treatment groups, except among the patients receiving sulfonylureas and insulin along with SGLT2 inhibitors as combination therapy (Vasilakou et al., 2013; Rosenstock et al., 2012b; Riser and Harris, 2013). Several large clinical trials assessing cardiovascular safety of SGLT2 inhibitors are ongoing (Oliveros et al., 2014). The meta-analysis of cardiovascular outcomes for dapagliflozin based on 14 trials involving 6,300 patients yielded an odds ratio of 0.73 compared to controls (Vasilakou et al., 2013). The primary end point was a composite of time to first event of cardiovascular death, myocardial infraction, stroke or hospitalization for unstable angina. The reduced HbA₁c levels achieved with SGLT2 inhibitor treatments are clinically meaningful in terms of cardiovascular risk. It is mentioned that a 0.8% reduction in HbA₁c causes 8% reduction in terms of cardiovascular risk (Control et al., 2009). Furthermore SGLT2 inhibitors have demonstrated benefits in terms of other cardiovascular risk factors, particularly in terms of reductions in blood pressure and bodyweight (Oliveros et al., 2014). Pooled analyses to determine the potential increased risk of cancer were performed. Among 5,478 diabetic patients who received dapagliflozin, there were nine cases of bladder cancer compared with one case in 3,136 controls (Riser and Harris, 2013; Bhartia et al., 2011). There were nine cases of breast cancer in 2,223 diabetic patients treated with dapagliflozin compared with one case in 1,053 controls (Bhartia et al., 2011). A pooled analysis of nine canagliflozin trials, no difference in incidence of bladder cancer has been observed between canagliflozin (5 of 6,648 patients) and control (4 of 3,640 patients) groups (Vasilakou et al., 2013). Similarly, no difference in incidence of breast cancer has been observed with patients who received canagliflozin (12 of 2,827 patients) and comparators (6 of 1,501 patients). However, a careful monitoring of diabetic patients...
treated with SGLT2 inhibitors is required to establish incidence of cancer risk in long term therapy.

Indian scenario: diabetic capital

Diabetes usually referred as “Madhumeha” in the ancient texts Charaka Samhita and Susruta Samhita, suggesting that diabetes must have been present in India even before 2500BC (Anjana et al., 2011). Although, there is no exact number known, a recent epidemiological data suggested that more than 66 million people suffer from the disease and equal number if not more, are estimated to be pre-diabetic in India, an alarming number (International Diabetes Federation, 2013). India leads the world with largest number of diabetic subjects earning the dubious distinction of being the “diabetes capital of the world” (Mohan et al., 2007). In 2000, India (31.7 millions) scored top for the highest number of people with diabetes mellitus among the world diabetic population (Wild et al., 2004). According to the IDF Diabetes Atlas 2014, diabetes related deaths in India were high among the South East Asia and the expenditure per person with diabetes is low (International Diabetes Federation, 2013).

The demographic and economic changes, particularly urban migration of population, growing stress and lifestyle changes have been the cause of Non-Communicable Diseases especially T2DM in India (Kaveeshwar and Cornwall, 2014). The disease is also seen amongst the rural population which was not afflicted until recently causing disease burden to the economy (Anjana et al., 2011; Deepa et al., 2014). The pharmaceutical companies ever ready to introduce new molecules into the market considering the population size of the country, it is expected that early 2015 SGLT2 inhibitors are likely to be made available for consumers. The cost and affordability would be a cause for concern to general public (Venkataramanet al., 2009; Tharkar et al., 2010).

Given the ever-expanding incidence of diabetes in Indian population and sub optimal glycemic control with currently available agents, there is now great demand for the intensive research to discover new compounds from natural and/or synthetic origin with new mechanism of action, particularly inhibition of SGLT2 protein to attain the associated benefits.

Conclusions

Inhibition of SGLT2 represents a novel approach for the treatment of diabetes. Several SGLT2 inhibitors have been developed as a result of modification of phlorizin, a prototype of non-specific inhibitor of SGLT1 and SGLT2. The clinical use of phlorizin for the treatment of T2DM was not feasible due to non-selectivity and limited oral bioavailability. Some of the newer SGLT2 inhibitors such as sergliiflozin and remogliflozin etabonate were discontinued because of non-selectivity and unfavorable pharmaceutical properties. The reason for withdrawal of these drugs and other phlorizin analogs was mainly due to O-glucoside linkage in their chemical structure which caused quick degradation by gastrointestinal β-glucosidase. As far as the pharmacokinetic profile concerned C-glucosides are longer acting than the O-glucosides.

The current SGLT2 inhibitors approved by US FDA and European Medical Agency as well as drugs approved in Japan were C-glucosides with different glycone and aglycon moieties. Thus all the clinically available SGLT2 inhibitors have different selectivity, pharmacokinetic profiles, potency and efficacy. The selective SGLT2 inhibitors offer potential therapeutic benefits in attaining better glycemic control by lowering fasting and post prandial serum glucose levels and causes reduction in blood pressure and bodyweight with minimum risk of hypoglycemia. Due to such remarkable benefits, SGLT2 inhibitors can also be used to treat comorbidities like hypertension, obesity and dyslipidemia, which are major adverse events with other oral anti-diabetic agents. Additionally the efficacy of SGLT2 inhibitors was not affected by insulin resistance and β-cell function and hence they can be used at any stage of T2DM. Moreover the novel insulin independent mechanism of action of SGLT2 inhibitors might provide better treatment for T2DM patients either as monotherapy or in combination with other oral anti-diabetic agents or insulin. Further, long term studies are needed to outline the safety and efficacy as well as to add this class of drugs in the standard treatment of T2DM.

References


Elizabeth Mechatie for Clinical Endocrinology News Digital Network August 1, 2014 FDA approves Empagliflozin for Adults with Type 2 Diabetes.


Riser TS and Harris KB (2013). The Clinical Efficacy and Safety of Sodium Glucose Cotransporter-2 Inhibitors in Adults with Type 2 Diabetes Mellitus. Pharmacotherapy. 33(9): 894-909.


FDA Drug Safety Communication

FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first talking to your prescriber. Health care professionals should evaluate for the presence of acidosis, including ketoacidosis, in patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels.

SGLT2 inhibitors are a class of prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine. These medicines are available as single-ingredient products and also in combination with other diabetes medicines such as metformin. The safety and efficacy of SGLT2 inhibitors have not been established in patients with type 1 diabetes, and FDA has not approved them for use in these patients.

A search of the FDA Adverse Event Reporting System (FAERS) database identified 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014 (see Data Summary). All patients required emergency room visits or hospitalization to treat the ketoacidosis. Since June 2014, we have continued to receive additional FAERS reports for DKA and ketoacidosis in patients treated with SGLT2 inhibitors.

DKA, a subset of ketoacidosis or ketosis in diabetic patients, is a type of acidosis that usually develops when insulin levels are too low or during prolonged fasting. DKA most commonly occurs in patients with type 1 diabetes and is usually accompanied by high blood sugar levels. The FAERS cases were not typical for DKA because most of the patients had type 2 diabetes and their blood sugar levels, when reported, were only slightly increased compared to typical cases of DKA. Factors identified in some reports as having potentially triggered the ketoacidosis included major illness, reduced food and fluid intake, and reduced insulin dose.