Sodium glucose transporter 2 (sGLT2) inhibitors: Current status in clinical practice

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Abstract

Sodium glucose transporter 2 (SGLT2) inhibitors including dapagliflozin, canagliflozin and empagliflozin act by a novel insulin-independent mechanism by blocking glucose reabsorption in the proximal convoluted tubules resulting in markedly increased glycosuria, a mechanism not limited by the degree of insulin resistance or beta-cell dysfunction, and which results in weight loss due to loss of 300 to 400 kcal/day. Currently dapagliflozin, canagliflozin and empagliflozin are the three primary drugs, which represent this group. They have comparable efficacy in HbA1c reduction as compared to metformin, sulfonylureas and slightly better than gliptins. They have additional beneficial effects on blood pressure and lipids. Their use is not limited by the degree of insulin resistance or beta-cell dysfunction, and hence can be used at any stage of diabetes, along with a potential for use in type-1 diabetes. Long term safety and impact on microvascular and macrovascular complications is likely to be favourable, data on which should be available in the next few years.

Keywords: Canagliflozin, Cardiovascular safety, Dapagliflozin, Empagliflozin, Genital tract infection, Glycemic efficacy, Side effects, SGLT2 inhibitors.

Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of oral antidiabetic medications that act by reducing renal glucose reabsorption in the proximal convoluted tubule, thus leading to increased glycosuria and lowering of blood glucose. This review intends to analyze SGLT-2 inhibitors with regards to their glycaemic efficacy, glycaemic durability and other non-glycaemic effects (body weight, blood pressure, lipids) and adverse effect profile in individuals with diabetes.

Mechanism of Action

It was demonstrated as early as 1951 that renal tubular resorption was increased both in type-2 diabetes (T2D) as well as type-1 diabetes (T1D). It was later discovered that the increased renal expression of SGLT2, a high-capacity, low-affinity transporter, in patients with T2D is responsible for 80% to 90% of renal glucose reabsorption. SGLT2 belongs to the family of sodium glucose co-transporters. The first protein discovered in the SGLT family, SGLT1 (by Robert K Crane, 1960), is responsible for glucose resorption in the intestinal mucosa.

Functioning of SGLTs are dependent on the Na+/K+ ATPase pump on the baso-lateral membrane which uses ATP to move 3 sodium ions outward into the blood, while bringing in 2 potassium ions. This creates a downhill sodium ion gradient inside the cell in comparison to both the blood and the tubule/ gastric lumen. The SGLT proteins use the energy from this downhill sodium ion gradient created by the ATPase pump to transport glucose across the apical membrane against an uphill glucose gradient. Therefore, these co-transporters are an example of secondary active transport. Since both sodium ions and glucose are transported in the same direction across the membrane, they are also called symporters.

Around 180 grams of glucose is filtered by the renal tubules per day. Virtually all of this is re-absorbed from the proximal tubules, and re-enters the circulation. 90% of this re-absorption is SGLT2 mediated and the remaining by SGLT1. Inhibition of these SGLT2 channels by SGLT2 inhibitors leads to persistent increased glycosuria, and lowering of blood glucose which leads to decreased glucotoxicity, decreased insulin resistance, and an improvement in insulin secretion. The advantage of this group of drugs is that their action is independent of residual beta cell function. This means that SGLT2 inhibitors may find a place in the management of T1D as well. Interestingly, in a follow-up study, it has been demonstrated that use of SGLT2 inhibitor, LX4211 (300 mg) resulted in significantly increased GLP-1 & peptide YY levels, probably by delaying SGLT1-mediated intestinal glucose absorption. Hence SGLT2 inhibitors exhibit some incretin-based effects as well.

Use in Diabetes

SGLT2 inhibitors have been reported to have an impressive
Combination Therapy

SGL T2 Inhibitors as a Part of Oral

non-fatal stroke, non-fatal myocardial infarction and cardiovascular end points consisting of vascular death, term outcomes with dapagliflozin show a hazard ratio of 0.5-0.92% in different studies. This is comparable to the efficacy shown by other oral anti-diabetic medications (sulfonylureas, metformin, gliptins) available in the market. SGLT2 inhibitors cause comparable HbA1c reduction, with a greater weight loss, as compared to metformin. The advantage of SGLT-2 inhibitors over sulfonylureas is that they are not associated with hypoglycaemia. The weight loss associated with SGLT2 is a distinct benefit in contrast to the weight gain associated with sulfonylureas and pioglitazone, and weight neutral effects of gliptins. Head to head data comparing SGLT2 inhibitors with glitazones and alpha-glucosidase inhibitors are lacking as of now. Currently published studies comparing SGLT2 inhibitors and gliptins, a commonly used second line oral anti-diabetic agent after metformin, are short to medium term, predominantly of 12-102 weeks. These studies have shown a greater reduction of HbA1c with canagliflozin and empagliflozin as compared to sitagliptin. SGLT2 inhibitors resulted in a weight loss of 2-3 kgs in contrast to no change with gliptins.

An additional beneficial effect of SGLT2 inhibitors is the reduction in the blood pressure. SGLT2 inhibitors have been associated with 5-6 mm Hg reduction in systolic blood pressure, comparable to many anti-hypertensive medications. This is in contrast to sulfonylureas, which are associated with a mild increase in blood pressure at 1 year of therapy, primarily believed to be mediated by their enhancing effect on body mass index. Metformin, in general, is believed to be blood pressure neutral, while pioglitazone is associated with mild reduction in systolic blood pressure in T2D. SGLT2 inhibitors have been reported to be associated with mild increase in high density lipoprotein-cholesterol (HDL-C) (+1.8-4.4% with dapagliflozin vs. 0.4% with placebo) and small reduction in triglycerides (-2.4-6.2% vs. -2.1%) with placebo. This is in contrast with sulfonylureas and metformin, which are believed to be associated with a mild decrease in HDL-C with little or no effects on LDL-C, triglycerides and total cholesterol. Although long term data on cardiovascular safety of SGLT2 inhibitors is currently not available, short term outcomes with dapagliflozin show a hazard ratio of 0.67 (95% confidence interval 0.42-1.08) for composite cardiovascular end points consisting of vascular death, non-fatal stroke, non-fatal myocardial infarction and hospitalized angina. Because of their beta cell independent action, SGLT2 inhibitors may also have some role in the management of T1D, where they may help in reducing the total daily dose of insulin.

**SGLT2 Inhibitors as a Part of Oral Combination Therapy**

SGLT2 inhibitors have been evaluated in combination with metformin, sulfonylureas and pioglitazone in different doses. Combination with metformin has been associated with a greater reduction of HbA1c along with a greater weight reduction. Although SGLT2 inhibitor dapagliflozin use is associated with decreased insulin resistance and increased insulin mediated glucose disposal into the muscles, it is also associated with substantial increase in plasma glucagon concentration, leading to increased endogenous glucose production, and hence decreasing the efficacy of SGLT2 inhibitors. The amount of glucose produced is around 47 grams, which is almost half the amount of glucose excreted into urine (91 grams) secondary to SGLT2 inhibition. Incretin based therapies like DPP-4 inhibitors and GLP-1 analogues inhibit glucagon production, which would lead to a decrease in endogenous glucose production. Hence a combination of SGLT2 inhibitors with incretin-based therapies would likely to have a synergistic effect in lowering plasma glucose and HbA1c. Dapagliflozin has been reported to be efficacious in controlling blood glucose as an add-on therapy in patients with inadequately controlled with metformin and sitagliptin. Hence, SGLT2 inhibitors can be used not only as monotherapy, but also as part of dual and triple combinations.

**SGLT2 Inhibitors as a Part of Combination Therapy with Insulin**

Add on therapy of dapagliflozin in patients on insulin as well as insulin with 2 other oral anti-diabetic agents, resulted in significant reduction in HbA1c, reduction in total daily dose of insulin, along with a statistically significant reduction in body weight, as compared to placebo, at 12 and 24 weeks of follow-up. Similar results were obtained with canagliflozin, when added to patients taking 2 or more oral anti-diabetic agents along with daily insulin requirement of >30 units. At 18 weeks of follow-up, not only a greater proportion of patients achieved HbA1c target of <7%, there was a significant reduction in body weight as well as blood pressure, when compared to those receiving placebo.

**Posology**

SGLT2 inhibitors have minimal to no interaction with food intake and can be taken before, with or after food. Because of their long half lives, all these agents are generally recommended once a day before meals in the morning. The recommended dosages of dapagliflozin, canagliflozin and empagliflozin have been elaborated in table.

**Use in Special Populations**

Although this use sounds promising, because of the unique mechanism of action, no data is currently available...
regarding the use of SGLT2 inhibitors in the prevention of diabetes in individuals with prediabetes. SGLT2 inhibitors are not recommended for use in pregnancy at present, primarily due to lack of data. SGLT2 inhibitors should preferably be avoided in patients with advanced renal disease (stage 4 chronic kidney disease and higher). Although data is not available, it is likely that SGLT2 inhibitors will be less efficacious in glucose elimination in patients with advanced kidney disease. They should also be used with caution in elderly who are at risk for dehydration, and in patients with recurrent history of infections, especially genital tract infections.

SGLT2 inhibitors are generally considered to be safe in mild to moderate hepatic insufficiency (Table-1). Canagliflozin has not been studied in severe hepatic insufficiency and hence not recommended.

### Adverse Events

These drugs in general are considered to be safe with minimal side effects. SGLT2 inhibitors use has been associated with a mild increase in the incidence of lower urinary tract infections. The cause of this increased occurrence of infection is not well known. In a study of dapagliflozin (10mg) added to metformin in the management of T2D, the incidence of urinary tract infections and genital infection in the treatment group was 8.1% and 8.9% respectively, where as in the placebo group was 8% and 5.1% respectively. Diabetes itself is associated with some degree of immune dysfunction, which may also contribute to the increased risk of infections. Because of the osmotic diuresis effect of SGLT2 inhibitors, few patients may complain of orthostatic hypotension, increased thirst, and hypotension.

There have been some reports suggestive of increased risk of cancer with dapagliflozin. However on close analysis of the data, 9 cases of bladder cancer were observed in 5478 dapagliflozin recipients (0.16%) versus 1 case in 3156 (0.03%) control individuals. Of these 10 cases of bladder cancer, 6 were associated with haematuria at the time of recruitment in the study and the remaining cases were identified within the first year. Since bladder cancer is an indolent disease, it is most likely the patient had occult disease previously and this is representative of ascertainment bias. There were 9 reported cases of breast cancer in 2223 (0.4%) dapagliflozin recipients versus 1 case in 1053 (0.1%) individuals in the control. All breast cancer cases were identified in the first year of treatment. Breast cancer is also an indolent disease, which remains occult for decades before it is diagnosed, and hence was unlikely due to dapagliflozin. No carcinogenic or genotoxic activity of SGLT2 inhibitors have been reported in preclinical studies.

### Current Status

USA FDA approved the use of dapagliflozin on 8th January 2014. Dapagliflozin had already received approval for use in Europe. Canagliflozin was approved for use in USA and Europe in 2013. As of today, empagliflozin approval is pending with FDA, not because of the efficacy or safety issues with the drug, but due to manufacturing issues at the plant under evaluation. Ipragliflozin is currently approved for use in Japan only. These drugs are not currently available in Pakistan, but are likely to be introduced in the market after necessary approval.

### Conclusion

In managing diabetes, SGLT2 inhibitors act by a novel insulin-independent mechanism by blocking glucose reabsorption in the proximal convoluted tubules resulting in markedly increased glycosuria, a mechanism not limited by the degree of insulin resistance or beta-cell dysfunction. Hence SGLT2 inhibitors can be used at any stage in the natural history of diabetes, with a potential
for use in T1D. SGLT2 inhibitors are attractive agents in managing diabetes cause of their additional beneficial effects on blood pressure and lipids. They are likely to have a beneficial effect against microvascular and macrovascular, long term data for which are likely to be available in the next few years.

References

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