Sodium glucose co-transporter inhibitors – A new class of old drugs

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Abstract

Sodium glucose co-transporter (SGLT) inhibitors are a new class of drugs which are used in the pharmacotherapy of Type-II diabetes, which happens to be a major risk factor for developing both micro as well as macro-vascular complications. These drugs inhibit the glucose reabsorption by inhibiting SGLT, which exhibits a novel and promising mechanism of action by promoting the urinary glucose excretion hence providing a basis of therapeutic intervention. Results of SGLT-II inhibitors are very encouraging as there is a significant elevation of GLP-1 level, which forms the basis of relevance in treatment of diabetes. It targets the HbA1C and keeps a check on its levels. It also exerts other positive benefits such as weight loss, reduction in blood glucose levels, reduction in blood pressure and improvement in insulin resistance and β-cell dysfunction: All contributing to effective glycemic control. SGLT inhibition will develop as effective modality as it has the capability of inhibiting reabsorption of greater percentage of filtered glucose load.

Key words: Canagliflozin, glucose reabsorption, glucosuria, HbA1C, phlorizin, proximal renal tubule, sodium-glucose co-transporter inhibitors

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Introduction

Diabetes mellitus, is a metabolic disorder caused by dysfunction of pancreatic β-cells resulting in a state of hyperglycemia and glucosuria. Defronzo while giving a fresh look to pathogenesis of Type-II diabetes mellitus in his ominous octet described that kidneys play an important role in both causing and maintaining the hyperglycemic state.

The idea was developed to lower the serum sugar levels in Type-II diabetes by inhibiting the reabsorption of sugar from the kidney generally mediated by sodium glucose co-transporter (SGLT), which has six active variants SGLT-1 to SGLT-6 [Figure 1]. SGLT-2 is responsible for 90% of glucose reabsorption, whereas SGLT-1 is responsible for remaining 10% of the reabsorption in kidneys.

Hence, the primary target of glucose reabsorption inhibition is in the early proximal tubule where this action is mediated by SGLT-2. This action is insulin independent as the elevated serum sugar levels are lowered by promoting glucosuria.

Historical Background

This new class of old drugs has a very long history. The prototype compound in this category “phlorizin” (O-glucoside phlorizin dihydrochalones, a type of flavonoid) is a bitter white glycoside isolated 179 years ago, way back in 1835 by French chemist from the apple tree bark and later on in 1886 the famous diabetologist Joseph Vas Mering first described pharmacological role of SGLT inhibitor ingestion causes glucosuria.

Phlorizin was found to improve glycemic control in diabetic animals. The key factor precluding its use in humans was the dosage. Since the majority of phlorizin gets converted into an intermediary before it can be of any use, thereby requiring an increase in dose to achieve desired hypoglycemic effect.
Beta-glycoside, phlorizin could not see the light of the day as a potent oral anti-diabetic agent as it was poorly tolerated in GIT thereby producing series of unpleasant adverse drug reactions. The renal glucose handling occurs at two main sites, proximal convoluted tubule accounts for 90% of reabsorption through SGLT-2 and remaining 10% through SGLT-1. The interpolation of this effect gave birth to new class of drugs “the SGLT inhibitors.” The search for a molecule, which has the quality of phlorizin and simultaneously eliminating the dosage issues ushered in bringing the molecules such as canagliflozin, empagliflozin, ipragliflozin and dapagliflozin [Table 1].

**Pharmacology of Sodium Glucose Co-transporter Inhibitors**

Under normal physiological conditions, 180 g of glucose is filtered in kidneys daily and 100% of it is of reabsorbed into the circulation via SGLT's. SGLT transports sodium and glucose into the cells using sodium gradient created by Na⁺/K⁺ ATPase pumps at the basolateral border of the cell membranes. Glucose is then transported passively by GLUT-2 along its concentration gradient into the interstitium [1,2] [Figure 2]. The affinity of phlorizin, the prototype drug of the group, is about 1 uM for hSGLT-1 and 20 nM for hSGLT-2. It was also found that the affinity of phlorizin congeners mirrored the stereospecific requirements for sugar translocation, supporting the view that interaction of phlorizin with the transporter occurs at the sugar binding/translocation site of transporter in microperfused rat renal tubules. [3] Thus, it was observed that phlorizin binds to the outside of SGLT at two domains one representing the sugar binding site and the other one as a glucose binding site. Hence, this double interaction describes the high affinity of phlorizin when compared to D-glucose.

**Pharmacokinetics**

The drug Canagliflozin, an oral SGLT-2 inhibitor, which is chemically a C-glucoside with a thiophene ring, can be considered as the prototype drug among the newer agents. The t½ of this group varies from 10 to 18 h, this effect is dose-dependent and peak steady state level are reached within 4–5 days. The Bioavailability of the drugs is >60% and the enzyme responsible for the metabolism is uridine diphosphate glucuronosyltransferase (UGT) 1A9 and UGT 2B4 to O-glucuronic metabolites, and also cytochrome P-450 enzymatic system causes minor metabolism. These drugs significantly improved the HbA1C especially in those who achieve a suboptimal control with lifestyle means alone and the best results are achieved, especially in those where it is used as an adjunct to metformin. The pharmacokinetic profile of the group is similar in diabetics and nondiabetics and the age, race, gender, body weight, food or mild renal dysfunction do not affect the pharmacokinetics. However, the dose adjustments are required for moderate renal dysfunction.

**Pharmacological Actions of Sodium Glucose Co-transporter Inhibitors**

**Effects on plasma glucose levels**

The effect of SGLT-Inhibitors on plasma glucose is dose-dependent[4] the effect is comparable to other anti-diabetics. In addition to improving the glycemic control it does reduce the glycated hemoglobin (HbA1C) levels; thereby preventing diabetic nephropathy in experimental animals. [5]

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**Table 1: New SGLT inhibitors and their status and selectivity**

| Name of drug | Status | Mechanism of action |
|--------------|--------|---------------------|
| Canagliflozin| Available in USA | SGLT-2 and SGLT-1 inhibitor |
| Empagliflozin| Submitted | SGLT-2 inhibitor |
| Ipragliflozin| Submitted in Japan | SGLT-2 inhibitor |
| Dapagliflozin| Available in EU, USA, Australia | Selective SGLT-2 inhibitor |
| LX 4211 | Phase-II clinical trials | Dual inhibitor |

SGLT: Sodium glucose co-transporter

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**Figure 1:** Sodium glucose co-transporter isozymes subtypes

**Figure 2:** Glucose reabsorption in kidney using proximal tubule into central compartment
On fasting hypoglycemia
Hypoglycemia is the most potential side effect of most of the oral hypoglycemic agents. It was observed that sergliflozin, an SGLT inhibitor does not cause hypoglycemia.[6] Henceforth it was postulated that these pharmacological agents be used for SGLT-2 and not SGLT-1 inhibition. As evident, the complete absence of SGLT-2 does not lead to hypoglycemia.[7] The residual glucose reabsorption in the proximal tubule is mediated by SGLT-1, which suffices to maintain the plasma glucose level to near normal.

Effect on urinary glucose excretion
Inhibition of SGLT-2 activity reduces the tubular glucose reabsorption and due to reduction in transport maximum for glucose (TmG), more and more of glucose is excreted in urine, hence reducing hyperglycemic state even after glucose loading. Since the process is selective, a residual reabsorption of about 20–25% of the filtered load of glucose remains attributable to the operation of SGLT-1 in the last part of the proximal convoluted tubule. The effect of SGLT inhibitors on urinary glucose (UG) excretion has also been associated with reduction of body weight.[7] SGLT-2 inhibitor in clinical scenario inhibits only 30–50% of the filtered glucose load. Possible explanations are: (i) Although the renal secretions may deliver sufficient drug to achieve robust UG for a longer duration, it can saturate at high dose, thus limiting SGLT-2 inhibitors from maximally inhibiting renal glucose reabsorption. (ii) Relative to the renal secretion of SGLT-2 inhibitors, the SGLT-2 transporters are located upstream, and the expression levels of SGLT-2 in the renal proximal tubule may be much higher.

Effect on total body weight
In addition to improving on the glycemic control, these agents also lead to beneficial effects like reduction in weight. Glycosuria induced by these agents is generally associated with the net calorie loss of approximately 200–300 Kcal/day.[8]

Effect on blood pressure
This group of drugs exerts a therapeutic control over the high blood pressure. SGLT-2 inhibitors when used as monotherapy additionally exerts BP lowering effect, as well possibly by acting through net sodium loss without apparently changing the heart rate.[9]

Cardiovascular Safety and Benefits
Although the long-term cardio-vascular effects remain unknown, but recent studies reveal that these drugs also decrease the systolic blood pressure when hypertension is a co-morbid condition with diabetes. These drugs also have a low intrinsic propensity to cause hypoglycemia, also do not increase the incidence of serious infections or incidence of pyelonephritis, and reduces the elevated BP without significantly changing the heart rate. Although, the decrease in uric acid and increase in hematocrit is noticed as an additional beneficial effect, there is no impact on bone mineral density or fracture of any bone, liver toxicity or elevation of liver enzymes.[10]

Summary
Sodium glucose co-transporter 2 represents promising molecular targets for developing new alternatives in treatment of diabetes since SGLT-2 is expressed exclusively in renal proximal tubules, selective SGLT-2 inhibition should not affect other tissues and UG excretion leads to negative energy balance, a beneficial effect over existing pharmacological agents.

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