CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1036510

Available online at: http://www.iajps.com *Review Article*

REVIEW ON SODIUM GLUCOSE CO-TRANSPORTER-2 (SGLT2) INHIBITORS: A NEW CLASS OF ANTI-DIABETIC DRUG

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Abstract:

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 II diabetes. When untreated, type II 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 I diabetes, and FDA has not approved them for use in these patients. Reabsorption occurs in the proximal convoluted tubule (PCT) and is carried out by two isoforms of SGLT. SGLT-2 is located in the S1 and S2 segments of the PCT and has a high capacity but low affinity for glucose transport. In healthy individuals, it reabsorbs ~ 90% of filtered glucose. SGLT-1 governs glucose transport in the S3 segment and is a low-capacity, high-affinity glucose transporter that reabsorbs the remaining 10% of the filtered glucose.SGLT-2 inhibitors have a novel mechanism of action that is independent of insulin secretion and action. These agents block glucose reabsorption, leading to urinary glucose excretion. The advantages of this approach are reduced hyperglycemia without hypoglycemia, along with weight loss and blood pressure reduction. [2]

Keywords: *SGLT2 inhibitors, Canagliflozin, Dapagliflozin, Empagliflozin, Type II diabetes.*

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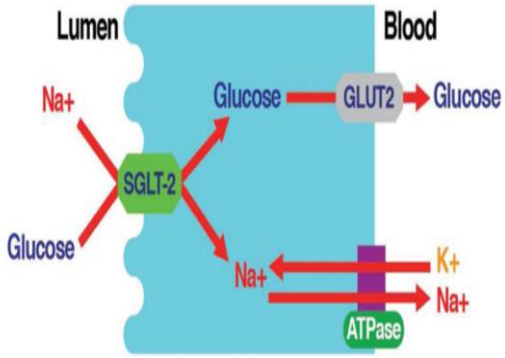
Please cite this article in press as Renuka R et al ***Review on Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A New Class of Anti-Diabetic Drug****, Indo Am. J. P. Sci, 2017; 4(10).*

INTRODUCTION:

Selective sodium glucose co-transporter 2 (SGLT2) inhibitors, represent the latest development in pharmacologic treatment options for type II diabetes. This class offers some unique advantages, when compared with other classes available, including low risks of hypoglycemia and weight gain, once-daily dosing, and a minimal side effect profile.



Fig;1: SGLT2 mediates glucose reabsorption in the kidney[6]

SGLT-2 catalyzes the active transport of glucose (against a concentration gradient) across the luminal membrane by coupling it with the downhill transport of Na+. The inward Na+ gradient across the luminal epithelium is maintained by active extrusion of Na+ across the basolateral surface into the intracellular fluid.

MECHANISM OF ACTION OF SGLT2 INHIBITORS:

SGLT-2 is a low affinity, high capacity glucose transporter protein in humans which is primarily expressed in the kidney, on the epithelial cells lining the first segment of the proximal convoluted tubule. It is the major transport protein that promotes the reabsorption of glucose from the glomerular filtration back into circulation. It is responsible for approximately 90% of the kidney's glucose reabsorption. By inhibiting SGLT-2, medications of the gliflozin class prevent the kidneys' reuptake of glucose from the glomerular filtrate and subsequently lower the glucose level in the blood and promote the excretion of glucose in the urine (glucosuria). Thus they lower renal threshold for glucose excretion. Sodium glucose co transporter 2 (SGLT2) inhibitors are a new class of diabetic medication indicated only for the treatment of type II diabetes. The mechanism of action of this new class of drugs also offers further glucose control by allowing increased insulin sensitivity and uptake of glucose in the muscle cells, decreased gluconeogenesis and improved first phase insulin release from the beta cells.[1]

ADVANTAGES OF SGLT2 INHIBITORS

SGLT-2 inhibition offers several putative advantages. Acting independently of insulin, these agents should not confer a risk of hypoglycemia and could be employed as monotherapy or in combination with other agents. Given their mechanism of action, these agents should be effective in patients with any degree of insulin resistance or β-cell function. They should also be associated with weight loss resulting from the loss of glucose (calories) in urine and glucose-induced osmotic diuresis.[6]

Table 1: List of SGLT2 Inhibitors

Compound	Latest Stage	Sponser
Dapagliflozin	Approved by European Medicines Agency	Bristol-Myers Squibb, AstraZeneca
Canagliflozin	Approved by U.S. Food and Drug Administration	Johnson & Johnson, Mitsubishi Tanabe
Empagliflozin	Phase 3	BoehringerIngelheim, Eli Lilly
Ipragliflozin	Phase 3	Astellus, Kotobuki
Tofogliflozin	Phase 3	Chugai
Luseogliflozin	Phase 3	Taisho
Ertugliflozin	Phase 2	Pfizer
LX 4211	Phase 2	Lexicon
EGT 0001442	Phase 2	Theracos
GW 369682	Phase 2	GlaxoSmithKline
ISIS 388626	Phase 1	Isis

DAPAGLIFLOZIN

Dapagliflozin is an example of an SGLT-2 inhibitor, it is a competitive, highly selective inhibitor of SGLT. It acts via selective and potent inhibition of SGLT-2, and its activity is based on each patient's underlying blood sugar control and kidney function. Therefore, dapagliflozin reduces the blood glucose concentration with a mechanism that is independent of insulin secretion and sensitivity, unlike many other antidiabetic drugs.[3]

DOSAGE AND ADMINISTRATION

•The recommended starting dose is 5 mg once daily, taken in the morning, with or without food.

•Dose can be increased to 10 mg once daily in patients tolerating the drug who require additional glycemic control.

•Assess renal function before initiating dose. Do not initiate, if eGFR is below 60 ml/min/1.73 m2.

DOSAGE FORMS AND STRENGTHS:

Tablets: 5 mg and 10 mg[4]

CONTRAINDICATIONS

History of serious hypersensitivity reaction.

ADVERSE REACTIONS

The most common adverse reactions associated with dapagliflozin (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections. [6]

PHARMACOKINETICS

With dose-dependent concentrations the half-life is about 12–13 hours, tmax 1–2 hours and it is protein-bound, so the medication has a rapid absorption and minimal excretion by the kidney renal disease.

Table 2: Pharmacokinetic And Pharmacodynamic Characteristics of SGLT2 Inhibitors

Drug	Bioavailability (%)	t_{max} (hours)	Protein Binding (%)	$t_{1/2}$
Canagliflozin	65	1-2	99	100 mg = 10.6 hours, 300 mg = 13.1 hours
Dapagliflozin	78	1-2	91	10 mg = 12.9 hours
Empagliflozin	85	1.5	86.2	10 mg = 12.4

Table 3: Side Effects of FDA Approved Drugs

	Canagliflozin	Dapagliflozin	Empagliflozin
Genitourinary	Female genital mycotic infections (10-11%) Male genital mycotic infections (4%) Urinary tract infections (4-6%) Polyuria (5%) Vulvovaginal ,pruritis (2-3%)	Female genital mycotic infections (7-8%) Male genital mycotic infections (3%) Urinary tract infections (4- 6%) Polyuria (3-4%) Dysuria (2%)	Female genital mycotic infections/ urinary tract infections (5-6%) Male genital mycotic infections (2-3%) Polyuria/nocturia (3%)
Neuromuscular and Skeletal	Bone fracture (<1%)	Bone fracture Back pain (3-4%) Limb pain (2%)	Not reported
Endocrine and metabolic	Hypoglycemia (3-4%, monotherapy) Increased thirst (2-3%) Dehydration Increased LDL-C Increased serum potassium (12-24%, >5.4 mEq/mL) Increased serum phosphate Pancreatitis (<1%)	Increased LDL- C Increased serum phosphate	Severe hypoglycemia (28%, with insulin; 1-2% with metformin) Increased LDL-C (5-7%) Dyslipidemia (4%)
Gastrointestinal	Abdominal pain (2%) Constipation (2%)	Not reported	Nausea (2%)
Cardiovascular	Hypotension Orthostatic hypotension Syncope	Not reported	Hypotension Hypovolemia
Central Nervous system	Fatigue (2%) Dizziness	Not reported	Not reported
Renal	Renal insufficiency (2-4%; 18-23% in patients with baseline eGFR 30-50 mL/min/1.73m2) Acute renal failure	Decreased estimated GFR Increased serum creatinine	Decreased estimated GFR Increased serum creatinine
Hematological and oncological	Increased hematocrit Increased hemoglobin	Increased hematocrit (1%) Bladder neoplasm	Increased hematocrit (3-4%)
Infection	Not reported	Influenza (2-3%)	Not reported
Respiratory	Not reported	Nasopharyngitis (6-7%)	Not reported

Table 4: Drug Interaction with SGLT2 Inhibitors

Medication	Interaction Description
Digoxin	Inhibition of P glycoprotein by canagliflozin can significantly increase digoxin exposure
Insulin & Sulfonylureas	SGLT2 Inhibitors may enhance the hypoglycemic effect of Insulin and Sulfonylureas. Consider a decrease in insulin dose when initiating therapy with a sodium glucose co-transporter 2 inhibitor and monitor patients for hypoglycemia
Loop diuretics	SGLT2 Inhibitors may enhance the hypotension risk of loop diuretics due to enhanced volume depletion by combined diuretic effects.
-UGT1A9 inhibitors (rifampicin, phenytoin, phenobarbital, ritonavir)	UGT1A9 inhibitors can reduce serum concentrations of SGLT2 inhibitors resulting in lack of clinical effect of the SGLT2 inhibitors.

CONCLUSION:

SGLT-2 inhibitors have a novel mechanism of action that is independent of insulin secretion and action. These agents block glucose reabsorption, leading to urinary glucose excretion. The advantages of this approach are reduced hyperglycemia without hypoglycemia, along with weight loss and blood pressure reduction. Data from multiple phase 3 studies of > 5,000 subjects demonstrate these findings. The safety and efficacy of SGLT2 inhibitors (including dapagliflozin, canagliflozin, empagliflozin) for the treatment of hyperglycemia in Type II DM has been well documented. For now, these drugs have proven to be a useful addition to the diabetes treatment, given their beneficial effects on CV risk factors. Looking to the future, the results of planned and ongoing trials to investigate long term safety and efficacy of SGLT2 inhibitors, especially in term of CV outcomes, will be of enormous interest. These results may provide additional motivation for investigating the use of SGLT2 inhibitors in the treatment of a boarder range of CV related conditions.[6]

ACKNOWLEDGEMENT

We would like to thank **God Almighty** who gave us strength to complete the work.

We would like to express our heartfelt thanks to our **Beloved Parents** who supported us throughout this work.

It gives us great pleasure to express our deep sense of gratitude and immense respect to our esteemed guide, **Mrs. Renuka R,** Assistant Professor, Dept. of Pharmacy Practice, Nazareth College of Pharmacy, Othera for her inspiring guidance, sound advice, timely help, encouragement and kind support throughout this review article.

I am indebted to **Dr. Elessy Abraham**, Principal, Nazareth College of Pharmacy, Othera, for her keen interest, timely help, valuable suggestions and constant encouragement throughout this work.

We would like to thank all **staff members** of Pharmacy Practice department, Nazareth College of Pharmacy for their kind co-operation for the successful completion of the work

It's a pleasure to thank all our **batchmates, juniors and seniors** of Nazareth College of Pharmacy for being so good and friendly to us throughout the article.

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