REVIEW

Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A Review of Their Basic and Clinical Pharmacology

Sanjay Kalra

ABSTRACT

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a newly developed class of oral anti-diabetic drugs (OADs) with a unique mechanism of action. This review describes the biochemistry and physiology underlying the use of SGLT2 inhibitors, and their clinical pharmacology, including mechanism of action and posology. The pragmatic placement of these molecules in the existing OAD arena is also discussed.

Keywords: Anti-diabetic drugs; Cardiovascular safety; Canagliflozin; Dapagliflozin; Empagliflozin; Perineal hygiene; Sodium-glucose co-transporter-2 inhibitors

S. Kalra (✉)
Bharti Hospital and B.R.I.D.E., Karnal, India
e-mail: brideknl@gmail.com

INTRODUCTION

Healthy individuals are able to maintain tight glucose homeostasis by closely regulating glucose production, reabsorption, and utilization. The importance of this homeostatic mechanism is evident from the fact that, in spite of extreme variations in glucose intake, relatively few people develop either diabetes or hypoglycemia [1].

In people without diabetes, about 180 g of glucose is filtered daily by the renal glomeruli, and is then reabsorbed in the proximal convoluted tubule (PCT). This is achieved by passive transporters, namely, facilitated glucose transporters (GLUTs), and active co-transporters, namely, sodium-glucose co-transporters (SGLTs). There are six identified SGLTs, of which two (SGLT1 and SGLT2) are considered most important [1]. These SGLTs are described in Table 1 [2].

This review describes the biochemistry and physiology underlying the use of SGLT2 inhibitors (SGLT2i), and their clinical pharmacology, including mechanism of action and posology, and discusses the pragmatic placement of these molecules in the existing oral anti-diabetic drug arena. The article is based

Table 1 Comparison of SGLT1 and SGLT2

Characteristic	SGLT1	SGLT2
Location	Small intestine; later part of PCT (segment 3)	Early PCT (segment 1, 2)
Capacity	Low	High
Affinity	High	Low
Contribution to glucose reabsorption	10%	90%
Disease state if mutation/deficiency occurs	Glucose-galactose malabsorption	Familial renal glucosuria
Physical manifestations of disease state	Diarrhea at few days age	None
Course	Fatal without glucose free/galactose free diet	Benign
Inhibitors	Phlorizin	Currently available SGLT2i

PCT proximal convoluted tubule, *SGLT* sodium-glucose co-transporter, *SGLT2i* sodium-glucose co-transporter-2 inhibitors

on previously conducted studies, and does not involve any new studies of human or animal subjects performed by the author.

HISTORY

The first SGLT2i discovered was phlorizin, a naturally occurring compound derived from apple tree bark. Because of its non-selective nature, it caused severe gastrointestinal symptoms. Due to this and to its poor oral bioavailability, work on its development could not continue [3]. Drugs which specifically inhibit SGLT2, and thereby avoid gastrointestinal effects related to SGLT1 inhibition, have now been developed, some of which are listed in Table 2.

RATIONALE

Glucosuria (i.e., the excretion of glucose through the kidneys) only occurs if the maximal capacity of various glucose transporter proteins (350 mg glucose/min) is exceeded [2, 4]. Earlier, glucosuria was thought

Table 2 Sodium glucose co-transporters in advanced development or already approved

Molecule	Approval/development status
Canagliflozin	40 countries including EU, USA, China, Russia
Dapagliflozin	40 countries including EU, USA, Japan,
Empagliflozin	Phase 3 [37]
Ipragliflozin	Japan
Luseogliflozin	Under review for approval in Japan
Tofogliflozin	Phase 3 [43, 44]

to be a pathological mechanism, or a marker of illness. However, one may approach this condition from a different view point. Persons with ambient hyperglycemia are at risk of endothelial dysfunction and resultant complications, due to the high levels of glucose in circulation. Kidneys try to prevent an excessive rise in blood glucose levels by glucuresis, thereby mitigating the adverse effects associated with high glucose levels. Theoretically, compounds which promote glucuresis should help to reduce circulating

glycemia, manage diabetes, and prevent long-term complications.

MECHANISM OF ACTION

Sodium-glucose co-transporter-2 inhibitors work by inhibiting SGLT2 in the PCT, to prevent reabsorption of glucose and facilitate its excretion in urine. As glucose is excreted, its plasma levels fall leading to an improvement in all glycemic parameters [4–6].

This mechanism of action is dependent on blood glucose levels and, unlike the actions of thiazolidinediones (mediated through GLUTs), is independent of the actions of insulin. Thus, there is minimal potential for hypoglycemia, and no risk of overstimulation or fatigue of the beta cells [7]. Because their mode of action relies upon normal renal glomerular-tubular function, SGLT2i efficacy is reduced in persons with renal impairment.

CLINICAL PHARMACOLOGY

Dapagliflozin is rapidly absorbed after oral administration, reaching peak plasma concentration in 2 h, and exhibiting oral bioavailability of 78% [8]. Dapagliflozin is metabolized by uridine diphosphate-glucuronosyltransferase (UGT)1A9 in both the liver and kidneys [8]. Canagliflozin achieves maximal plasma concentration 1–2 h after oral administration (oral bioavailability 65%) and steady state after 4–5 days. It is metabolized by glucuronidation by UGT1A9 and UGT2B4 [9]. Empagliflozin reaches peak plasma concentration 1.33–3.0 h after oral administration, before declining in a biphasic manner. The terminal half-life has been calculated to be 10.3–18.8 h in multiple dose studies, with steady state being achieved by day

6 [10]. No dosage adjustments are required in renal or hepatic impairment. A summary of the clinical pharmacology of SGLT2i is presented in Table 3.

Dapagliflozin and canagliflozin have proven efficacy in improving glycemic parameters, both as monotherapy and in combination [11]. A 52-week comparison between canagliflozin 100 and 300 mg showed non-inferiority, and canagliflozin 300 mg showed statistical superiority to sitagliptin in lowering glycated hemoglobin (HbA1c) [12]. Canagliflozin 100 mg and 300 mg reduced bodyweight versus placebo at week 26 and sitagliptin at week 52. The published results are summarized in Table 4. Four-year (208-week) use of dapagliflozin with metformin produced a sustained and durable reduction in blood glucose levels with significantly less frequent adverse reactions as compared to glimepiride with metformin. After 4 years, the difference in HbA1c reduction between two groups was −0.3% [95% confidence interval (CI) −0.51, −0.09]. The trend over a period of time showed further increase in the difference with more prolonged use [13].

The long-term efficacy and safety of empagliflozin have also been investigated as add-on therapy to basal insulin. Patients with type 2 diabetes mellitus (T2DM) were randomized to receive empagliflozin 10 or 25 mg once daily or placebo; the basal insulin regimen was kept constant for the first 18 weeks, after which the treating investigator could adjust the regimen at their discretion for the following 60 weeks [14]. As well as significant improvements in HbA1c, patients in both of the empagliflozin groups had significant reductions in their insulin doses at week 78, and also registered weight loss versus a small weight gain in those receiving placebo [14]. The decrease in insulin requirements in

Table 3 Clinical pharmacology of sodium-glucose co-transporter-2 inhibitors

Molecule	Dose range	Oral bioavailability (%)	Elimination pathway	Dose modifications
Dapagliflozin	5–10 mg once daily	78	Hepatic and renal UGT1A9	Should not be initiated in patients with eGFR <60 ml/mt/1.73 m^2
				No dose adjustment in patients with eGFR >60 ml/min/1.73 m^2
Canagliflozin	100–300 mg once daily	65	UGT1A9 and 2B4	Dose limited to 100 mg once daily in patients with eGFR >45 <60 ml/min/1.73 m^2
				Stopped in patients with eGFR <45 ml/min/1.73 m^2
Empagliflozin	10–25 mg once daily	N/a	UGT1A3, UGT1A8, UGT1A9, and UGT2B7	Dose adjustment in patients with creatinine clearance <60 ml/min
				Contraindicated in patients with creatinine clearance <45 ml/min
				No adjustment in hepatic failure
Ipragliflozin	100–300 mg once daily	65	UGT1A9 and UGT2B4	Dose limited to 100 mg once daily in patients with eGFR >45 <60 ml/min/1.73 m^2
				Not recommended in patients with eGFR <45 ml/min/1.73 m^2

eGFR estimated glomerular filtration rate, *N/a* not available, *UGT* uridine diphosphate-glucuronosyltransferase

patients on dapagliflozin has been evaluated in a study on insulin-mediated whole-body glucose uptake and endogenous glucose production using euglycemic hyperinsulinemic clamp technique. Dapagliflozin treatment for 2 weeks increased insulin-mediated tissue glucose disposal by 18% and resulted in an increase in endogenous glucose production (with increased fasting glucagon levels) [15].

PLEIOTROPIC EFFECTS

Sodium-glucose co-transporter-2 inhibitors use leads to a reduction in body weight, ranging from about 1 to 5 kg [16]. A greater fall is seen in patients with long-standing diabetes and in those with a higher baseline weight. This weight loss is sustained after up to 2 years of use of dapagliflozin, and may be linked to a reduction in insulin dose requirements of patients with long-standing diabetes [16]. Analysis of 208-week data comparing dapagliflozin in combination with metformin versus glimepiride in combination with metformin showed 4.38 kg (95% CI −5.31, −3.46) difference between two groups. Patients in the glimepiride group gained a mean of 0.73 kg while those in dapagliflozin group lost 3.65 kg [13].

While it may be argued that weight loss is because of volume depletion, it has been shown that two-thirds of the decreased weight is lost from fat mass (especially visceral abnormal fat), as compared to lean mass [14]. An initially rapid

Table 4 Glucose-lowering efficacy of sodium-glucose co-transporter-2 inhibitors

Molecule (duration of study)	Parameter	Monotherapy	Combination with other oral anti-diabetic drugs					As add-on to insulin
			Initial combination with Met	With Met	With SU	With Met + SU	With Met + TZD	
Canagliflozin 300 mg (26-week study)	HbA1c (%)	−1.03	–	−0.94	−0.79	−1.06	−1.03	−0.72
	FPG (mg/dl)	−35	–	−27	–	−31	−33	−25
	PPG (mg/dl)	−59	–	−48	–	–	–	–
Dapagliflozin 10 mg (24-week study)	HbA1c (%)	−0.9	−2.0	−0.8	−0.8	−1.0	−0.4	−0.9
	FPG (mg/dl)	−28.8	−60.4	−23.5	−28.5	−29.6	−24.1	−21.7
	PPG (mg/dl)	–	–	–	−60.6	−67.5	–	–
Ipragliflozin 300 mg (24 week study)	HbA1c (%)	−1.29	–	−0.48	−1.14	−0.88	–	–
	FPG (mg/dl)	−39.4	–	–	−38	−41	–	–

FPG fasting plasma glucose, *HbA1c* glycated hemoglobin, *Met* metformin, *MetXR* metformin extended release, *PPG* post-prandial plasma glucose, *SU* sulfonylurea, *TZD* thiazolidinedione

decline in weight is followed by a slower rate of weight loss, and is also marked by a reduction in weight circumference. Concomitant use of SGLT2i can attenuate or neutralize weight gain due to insulin, if given in combination with insulin [16].

Sodium-glucose co-transporter-2 inhibitors also cause significant reductions in both systolic and diastolic blood pressure (BP). These changes are relatively more prominent for systolic BP, are not dose dependent, and are not characterized by concomitant tachycardia or symptoms of hypotension/syncope in most of the cases. The effects on BP seem to be independent of glycemic or body weight reduction, and are greater in patients with high baseline systolic BP [17]. BP reduction with SGLT2i occurs due to osmotic diuresis initially, and to local rennin-angiotensin system inhibition later on [18]. Some studies have reported reduction of up to 13.4–17 mmHg in systolic BP with empagliflozin, a magnitude similar to that observed with many anti-hypersensitive drugs [19, 20]. A recently published 104-week outcome study of canagliflozin showed that the 100 and 300 mg dose reduced systolic and diastolic BP compared with glimepiride, with no notable changes in pulse rate [20]. Analysis of 208-week data comparing dapagliflozin in combination with metformin versus glimepiride with metformin showed an increase of 0.2 mmHg (95% CI −1.66, 1.61) in the glimepiride group while those on dapagliflozin showed a reduction of 3.69 mmHg (95% CI −5.24, −2.14) [13].

Sodium-glucose co-transporter-2 inhibitors are either lipid-friendly or lipid-neutral drugs. Canagliflozin, for example, increases high-density lipoprotein (HDL) by 7.1–10.6%, low-density lipoprotein (LDL) by 7.1%, and reduces triglycerides by 2.3% [21, 22]. Treatment with canagliflozin for 104 weeks was also associated with increases in HDL-C and LDL-C, which is consistent with findings at week 52. However, the proportion of patients who started or modified therapy with lipid-modifying agents were 13%, 11.5%, and 13.3% in the canagliflozin 100 mg, canagliflozin 300 mg,

and glimepiride groups, respectively [23]. After 4 years of use, sustained and stable weight loss was observed with dapagliflozin versus weight gain with glimepiride (−3.95 vs. +1.12 kg). Mean systolic BP was reduced with dapagliflozin but not with glimepiride [24].

Data from 21 clinical studies, including 2 that exclusively enrolled patients with a history of cardiovascular disease (CVD), were included in a prespecified meta-analysis ($n = 9,339$) to assess the cardiovascular (CV) safety of dapagliflozin (2.5 mg to >10 mg/day; $n = 5,936$) versus comparators (placebo or active $n = 3,403$) [25]. The prespecified primary end point was a composite of time to CV death, myocardial infarction (MI), stroke, or hospitalization for unstable angina. The secondary end point included the primary end point plus unplanned coronary revascularization and hospitalization for heart failure. The estimated hazard ratio (HR) using a Cox proportional hazards method was 0.787 (95% CI 0.579, 1.070). Analyses of the secondary end point (HR 0.758; 95% CI 0.581, 0.988) and of an ad-hoc major adverse CV events composite end point of CV death, MI, and stroke (HR 0.772; 95% CI 0.543, 1.097) were consistent with the primary end point results. These findings suggest that there is no increase in CV risk associated with dapagliflozin in an updated CV risk analysis that includes more patients and a substantial proportion of older patients (>20%) and patients with established CVD (>30%). Although these results are encouraging, presently the evidence is lacking regarding macro and micro-vascular complications of T2DM in patients managed with this class of drugs. A randomized-controlled clinical trial is already underway to explore the long-term CV outcomes in patients on treatment with SGLT2i as primary end point [26].

Uric acid levels, a marker of metabolic dysfunction, are markedly reduced (5.9–17.8%) by SGLT2i, with the effect sustained for 2 years [27]. The drugs may affect uric acid excretion directly, by acting on its transport system, or indirectly, but reducing sodium reabsorption in the PCT. The beneficial impact of SGLT2i on uric acid is attenuated if insulin is co-prescribed.

Renal hyperfiltration has been found to be closely associated with the development of diabetic nephropathy (DN) [28]. Pooled data from 2 randomized clinical trials including 600 patients with normo- or microalbuminuria followed up for 4 years which demonstrated that hyperfiltration has central role in pathogenesis of DN [28]. SGLT2 is one of the main determinants of glomerular hyperfiltration and blockade of SGLT2 has potential nephroprotective action.

POSOLOGY

Dapagliflozin is approved as 10 mg once-daily drug, as monotherapy, or as add-on to metformin, sulfonylurea (SU), dipeptidyl peptidase-4 (DPP-4) inhibitors, and/or insulin. It can be prescribed alone to persons who do not tolerate or cannot take metformin safely. A 5-mg dose is available for persons with hepatic insufficiency. In mild to moderate hepatic impairment, no dosage adjustment is required. However, in severe hepatic impairment, 5 mg starting dose is recommended [29].

Canagliflozin has a two-stage dosage regime. The starting dose approved is 100 mg once daily, before the first meal of the day. In those who do not respond adequately, the dose can be increased to 300 mg, provided renal function is normal [10].

Empagliflozin is being studied in daily doses of 10 and 25 mg. Trials have revealed dose-dependent HbA1c reductions with

empagliflozin monotherapy, which are greater as compared to those observed with sitagliptin, but similar to those experienced with metformin. Empagliflozin can be administered without relation to meal timings, in a once-daily frequency [30].

Ipragliflozin has Japanese approval for the treatment of T2DM, either alone or in combination with metformin, pioglitazone, SU, α-glucosidase inhibitor, DPP-4 inhibitor, or with nateglinide [30].

ADVERSE EVENTS

The incidence of adverse events in clinical trials of SGLT2i is similar to that observed with other anti-diabetic drugs. The overall incidence of adverse events has ranged from 57.3 to 83.0%, while that of serious adverse events have varied between 1.0% and 12.6% [31].

Uro-genital tract infections are the most frequently noticed adverse events in subjects on SGLT2i [32], especially in women and in uncircumcised men. Pooled data from 12 placebo-controlled clinical trials of dapagliflozin reveal that when used in dose 2.5, 5, and 10 mg per day, the incidence of clinically diagnosed uro-genital tract infection was 4.1%, 5.7% and 4.8%, respectively, while it was 0.9% in the placebo group [33]. Common infections include vulvitis and vulvo-vaginitis in women, as well as balanitis and balanoposthitis in men. These can be prevented by maintaining adequate perineal hygiene, and through treatment with antifungal therapy. Genital infections are thought to be caused by an increased glucose load in the urinary tract, which encourages fungal growth. The incidence of urinary tract infections does not increase with SGLT2i therapy [34].

The osmotic diuresis associated with SGLT2i use also has the potential to cause volume depletion and orthostatic hypotension. In randomized-controlled trials, however, the incidence of these adverse events has been minimal (<3%) [25]. All such events have been mild to moderate in severity. The extra diuresis experienced per day is 350–450 ml (one extra void per day) [34], and does not cause nocturia. The diuresis seen with SGLT2i may result in slight transient increase in serum creatinine and blood urea, with a corresponding fall in glomerular filtration rate (GFR).

The risk of hypoglycemia is minimal with SGLT2i, as they have a non-insulin-based mechanism of action. However, hypoglycemia may occur when these molecules are used in complication with other anti-diabetic drugs, including metformin. Four-year comparison between dapagliflozin plus metformin and glipizide plus metformin showed a tenfold decrease in the incidence of hypoglycemic episodes (5.4% and 51.5%, respectively) [13]. In this 208-week study, patients treated with dapagliflozin plus metformin had 35 hypoglycemic events as compared to 1,191 events in glipizide plus metformin group. Dose-down titration during first year was required in 2.7% patients in the dapagliflozin-treated group compared with 15.8% in the glipizide-treated group. This finding is very significant in light of the long-term consequences of hypoglycemic episodes on the physiology of patients and their compliance to treatment.

Sodium-glucose co-transporter-2 inhibitors use leads to a slight reduction in bone formation, and a rise in bone resorption markers, although there are no major changes on bone mineral density. A 102-week study with dapagliflozin did not identify any changes in markers of bone turnover as compared to

placebo when added to metformin [27]. Other long-term studies have not demonstrated any significant increase in adverse drug reactions related with skeletal system with any of the SGLT2i [35, 36].

USE IN RENAL IMPAIRMENT

In patients with reduced GFR, the amount of glucose reaching the PCT falls and the efficacy of SGLT2 may be suboptimal. Canagliflozin is prescribed in a full dose of 300 mg daily if GFR is above 60 ml/min and as 100 mg once daily if GFR is 45–60 ml/min [10]. Dapagliflozin can be prescribed as 5 or 10 mg once daily, depending upon the regulatory label in the country concerned [29]. A pooled analysis of 13 clinical trials exploring the long-term renal safety of dapagliflozin 10 mg as compared to placebo or other oral hypoglycemic agents showed no change in renal functions over a period varying from 12 to 104 weeks [25]. Similarly, empagliflozin is being studied in doses of 10 and 25 mg per day [37].

DRUG–DRUG INTERACTIONS

Sodium-glucose co-transporter-2 inhibitors do not exhibit any clinically relevant drug–drug interactions, including with other anti-diabetic drugs and diuretics. They can be combined with metformin, SU, pioglitazone, sitagliptin, and voglibose. Concomitant prescription of loop diuretics and SGLT2i should be avoided because of the potential risk for volume depletion. Co-administration of canagliflozin with UGT-inducer drugs, for example, rifampicin, phenytoin, phenobarbitone, and ritonavir, should prompt an increase in dose from 100 to 300 mg, if otherwise tolerated [10]. UGT enzyme-inducing agents increase the metabolism of canagliflozin thus leading to a decrease in peak plasma levels and reduced efficacy [32].

CLINICAL USE

Current management of diabetes is characterized by opportunities, options, and obstacles. In spite of the availability of a wide array of oral and injectable options, it remains difficult to achieve good glycemic control, while avoiding hypoglycemia and weight gain, and ensuring CV safety. These adverse effects are obstacles to the optimal use of pharmaceuticals options currently available.

Sodium-glucose co-transporter-2 inhibitors are a novel class of drugs with a novel mechanism of action, which can be useful in almost every stage of the natural history of diabetes, and represent a means of achieving better and safer glycemic control.

Sodium-glucose co-transporter-2 inhibitors can be used as initial monotherapy in persons in whom metformin is not indicated, or not tolerated. Examples include those with hepatic impairment and gastrointestinal intolerance. SGLT2i can also be used as second-line drugs, and third-line drugs, in persons inadequately controlled on a single or dual glucose-lowering therapy. Their glucose-lowering effect may help some people with diabetes delay insulin injections. Additionally, a significantly low risk of hypoglycemia with these agents can improve outcomes and compliance considerably.

The pleiotropic effects of SGLT2i—weight loss, BP reduction, and uricosuria—make them especially attractive for use in persons with metabolic syndrome, and in those with mild fluid overload. Their oral mode of administration may favor their use over the injectable glucagon-like peptide-1 receptor agonists.

This class of drugs can also be used in combination with insulin, and its insulin-sparing effect allows for more effective, well-tolerated glycemic control, without weight gain. A 24-week clinical trial comparing dapagliflozin versus placebo in patients taking a high dose of insulin demonstrated a decrease in insulin requirement of 0.79% and 0.39%, respectively [38]. Additionally, there was a significant decrease in insulin dose required by patients treated with dapagliflozin as compared to an increase in placebo group. A statistically significant decrease in body weight of up to 2.4 kg in the dapagliflozin 10 mg group as compared to an increase of 0.43 kg in the placebo group was also seen [38].

The ability to prescribe SGLT2i to persons with renal [39] and hepatic impairment, an easy two-step or one-step dose titration, a lack of relevant drug–drug interactions, and safety in combination with all routinely used CV and anti-diabetic drugs, are all points which will encourage their use.

Counseling regarding potential side effects and ways to prevent them, for example, perineal hygiene and avoidance of volume depletion, must accompany SGLT2i prescription.

A recent pilot study explored the potential role of SGLT2i in managing hyperglycemia associated with type 1 diabetes mellitus (T1DM) [40]. This 2-week exploratory study of dapagliflozin in doses ranging from 1 to 10 mg per day in addition to insulin, established its safety and pharmacokinetics, and explored the pharmacodynamics of a new class of drug for managing T1DM. Glucosuria increased by 88 mg/day in the dapagliflozin group while it decreased by 21.5 mg/day in the placebo group. Additionally, a fall of 16.2% in the dapagliflozin group and an increase of 1.7% in the placebo group for total daily insulin dose were seen

during this period [40]. More proof-of-concept studies are available documenting reno-protection provided by these agents in T1DM. Renal hyperfiltration which is an early hemodynamic abnormality preceding frank nephropathy in T1DM was improved with short-term use of these agents [41, 42]. Newer SGLT2i, still in pre-clinical and clinical phases of development, are expected to have a safer profile in view of their highly selective action [43, 44].

CONCLUSION

The SGLT2i represent a novel class of drugs which will certainly help a large number of people with diabetes achieve target control in a safe and well-tolerated manner. Their unique mechanism of action, coupled with pleiotropic benefits on weight and blood pressure, should make them attractive choices for add-on therapy to persons not controlled on other medications.

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human or animal subjects performed by the author.

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