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REVIEW

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

Sanjay Kalra

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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

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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.

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]

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 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,

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