Sodium glucose co-transporter-2 inhibitors: A novel drug class

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Recent developments in pharmacotherapy for the management of type 2 diabetes have identified a diversity of pathophysiological targets for drug action to improve blood glucose lowering. Sodium glucose co-transporter type-2 inhibitors are a new class of blood glucose-lowering agent in an advanced state of development that may soon be available for routine clinical practice. This article discusses their discovery, mode of action and development, focusing on one drug in phase 3 trials, dapagliflozin.

Article points

1. Sodium glucose co-transporter type-2 (SGLT-2) inhibitors are a new class of blood glucose-lowering agent in an advanced state of development that may soon be available for routine clinical practice.
2. The promotion of glycosuria for managing hyperglycaemia and achieving weight loss, while theoretically counterintuitive, is proving an effective mechanism without provoking hypoglycaemia.
3. SGLT-2 inhibitors can significantly improve glycaemic control and cause weight loss with a low risk of hypoglycaemia in people with type 2 diabetes.

Key words

- Dapagliflozin
- Sodium glucose co-transporter-2 inhibitor
- Renal glycosuria

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A natural sodium glucose co-transporter (SGLT) inhibitor, phlorizin, was isolated from the root bark of the apple tree, and other fruit trees, in the early part of the 19th century. Its ability to lower glucose in animals was first recognised in 1903 and confirmed in humans in 1933 (Chasis et al, 1933). As a dihydrochalcone compound with glucose-lowering properties, it has only recently been investigated for commercial purposes.

Phlorizin's main action is to produce renal glycosuria and block intestinal glucose absorption through inhibition of the sodium glucose transporters located in the proximal renal tubule and mucosa of the small intestine. However, its utility as a therapeutic agent is limited because it is hydrolysed within the intestine and poorly absorbed as a result. Diarrhoea can be a troublesome result of its non-selective SGLT blockade. A number of compounds have been developed that are glycosides of the original phlorizin molecule, which originally consisted of a glucose moiety and two aromatic carbocycles (Ehrenkranz et al, 2005).

Role of SGLT-2 in glucose absorption

Glucose enters cells via either the facilitative glucose transporters (GLUTs) or the sodium-coupled glucose co-transporters (SGLTs) (Wood and Trayhurn, 2003). GLUT-4 promotes insulin-dependent glucose uptake in adipose tissue and muscle, while GLUT-1, expressed on endothelial cells and erythrocytes, supports glucose transport independent of insulin action (Idris and Donnelly, 2009). SGLTs enable the transport of glucose against a concentration gradient at the same time as sodium ions are transported down a concentration gradient (Mackenzie et al, 1996).

The SGLT-2 belongs to the solute carrier 5A gene family, which consists of 12 genes widely expressed in human tissue (Jabbour and Goldstein, 2008). Half of the gene products act as facilitative-diffusion glucose transporters that promote glucose uptake across membranes into fat and muscle, while the others actively drive the transport of glucose in association with sodium ions. Two members of the solute carrier gene family have been extensively investigated for their therapeutic potential.

SGLT-2 is expressed in the S1 segment of the proximal renal tubule and is responsible for 90% of glucose reabsorption via the renal tract (Kanai et al, 1994). It is an amino acid with low affinity and high capacity transporter characteristics. By contrast, SGLT-1 is a high affinity, low capacity glucose transporter that is expressed in the small intestine, heart and, to a much lesser extent than SGLT-2, in the S3 segment of renal tubule. It also acts as a transporter for galactose.

Glucose absorption from the intestine is mediated by SGLT-1, acting at the epithelial surface of the bowel. Glucose filtered in the renal glomeruli is then reabsorbed predominantly via the physiological action of SGLT-2, with SGLT-1 playing a minor role. The potential benefit of blocking the action of these co-transporters has long been recognised with SGLT-2 inhibition being extensively reported. By inhibiting SGLT-2 renal reabsorption of glucose, loss of glucose in the urine is significantly increased. The promotion of glycosuria for managing hyperglycaemia and achieving weight loss, while theoretically counterintuitive, is proving an effective mechanism without provoking hypoglycaemia.

Familial renal glycosuria: A genetic link

It has been recognised that mutations of the SGLT-2 gene lead to familial renal glycosuria, classified as type A, B or O depending on the

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1. Dapagliflozin is a C-aryl glucoside highly selective inhibitor of sodium glucose co-transporter-2. It is not degraded by glucosidase and, therefore, does not need to be administered as a prodrug.
2. Dapagliflozin was initially assessed in healthy adults between the age of 18 and 45 with a BMI of 18–30 kg/m^2.
3. In the second safety study, no serious adverse events were reported and there were no study withdrawals due to adverse events. No hypoglycaemia was reported.

severity of the glycosuria. Type O is the most severe form with complete absence of renal tubular glucose reabsorption arising from non-functioning SGLT-2 gene mutations. Most people have no symptoms or clinical consequences as a result of familial renal glycosuria and the condition is often termed "benign glycosuria".

Those affected by milder type A or B forms have either reduced affinity for glucose or diminished SGLT-2 expression (Santer et al, 2003; Magen et al, 2005), and have normal blood glucose levels. Reassuringly, these people have normal kidney function, no hypoglycaemia, no electrolyte imbalance, no hypovolaemia or increased frequency of urinary tract infections – all theoretical risks associated with inducing significant glycosuria.

In addition, the condition does not impact significantly on life expectancy. Even extreme glycosuria found in type O variant has been associated with a favourable outlook (Scholl-Bürgi et al, 2004). This safety signal has promoted research into SGLT-2 inhibitors as potential agents for managing hyperglycaemia in humans.

Drugs in development

Several pharmaceutical companies have SGLT-2 inhibitors in development, including dapagliflozin (Astrazeneca, Bedfordshire; Bristol-Myers Squibb, Uxbridge), BI 10773 and BI 44847 (Boehringer Ingelheim, Bracknell), TA-7284 (Mitsubishi Tanabe Pharmaceutical Corporation, Japan), YM-543 (Astellas Pharmaceutical, Staines) and KGA-3235 (Kissei Pharmaceutical, Japan: Glaxo Smith Kline [GSK], Brentford). Remogliflozin (GSK), sergliflozin (GSK) and AVE-2268 (sanofi-aventis, Guildford) were discontinued in either phase 1 or 2. Dapagliflozin is probably closest to licence application with phase 3 trials in progress.

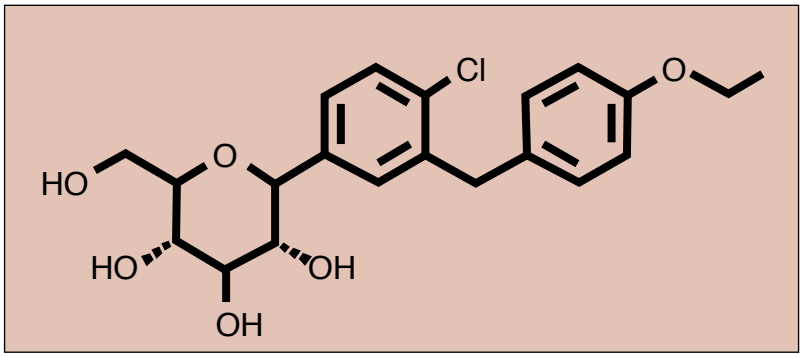

Figure 1. Chemical structure of dapagliflozin. ($C_{21}H_{25}ClO_6$; H=Hydrogen; O=Oxygen; Cl=Chlorine).

Dapagliflozin

Dapagliflozin is a C-aryl glucoside highly selective inhibitor of SGLT-2 (*Figure 1*). It is not degraded by glucosidase and, therefore, does not need to be administered as a prodrug (Meng et al, 2008). In vitro studies have demonstrated a 30-fold increase in inhibition of human SGLT-2 and 4-fold reduction in inhibition of human SGLT-1 compared with the naturally derived phlorizin (Bakris et al, 2009).

Dapagliflozin has a 1200-fold specificity for SGLT-2 over SGLT-1 (Han et al, 2008). It has a maximum observed concentration of 1–2 hours and a half-life of 16–17 hours allowing a once-daily dosing regimen. It is metabolised to an inactive metabolite. As a highly protein-bound molecule (97%), renal excretion is very limited. Higher drug doses do not increase glucose excretion but do prolong duration of action.

Phase 1 studies

Safety and dose–response studies

Two studies have been reported. Dapagliflozin was initially assessed in healthy adults between the age of 18 and 45 with a BMI of 18–30 kg/m^2. In the first study, 64 people were randomised to receive placebo or one of a range of dapagliflozin doses using a sequential ascending dosing regimen (2.5 mg, increasing to 5, 10, 20, 50, 100, 250 and 500 mg). There was a low incidence of adverse events reported (21% [*n*=10] of dapagliflozin-treated vs. 35% [*n*=9] of placebo-treated group) and no relationship between the dose of dapagliflozin and adverse event incidence (Komoroski et al, 2009a).

In a second safety study, participants were randomly allocated to receive dapagliflozin or placebo in a 3:1 ratio. Dosages of dapagliflozin were sequentially escalated over 14 days (2.5 mg, increasing to 10, 20, 50 and

100 mg), with matched capsules for the placebo group. Study participants were observed for 27 days. No serious adverse events were reported and there were no study withdrawals due to adverse events. No hypoglycaemia was reported (Komoroski et al, 2009a).

Phase 2 studies

Studies in people with type 2 diabetes

Two phase 2 studies with dapagliflozin have been reported. A randomised, placebo-controlled, parallel-group, multidose study was conducted to determine the safety and tolerability of dapagliflozin. A total of 47 participants with type 2 diabetes who were either treated with metformin or drug-naïve, were given a placebo or dapagliflozin 5 mg, 25 mg or 100 mg daily for 14 days. Dose-dependent, and clinically significant reductions in fasting glucose and oral glucose tolerance test excursions were observed (Brooks and Thacker, 2009). Two cases of hypoglycaemia were reported in the study. Both were mild and resolved spontaneously. In addition, two people reported candidal vulvovaginitis, which resolved with antifungal treatment (Komoroski et al, 2009b).

It remains to be established whether added glucose excretion increases bacterial growth in clinical practice (Abdul-Ghani and DeFronzo, 2008).

In a 12-week, randomised, parallel-group, double-blind, placebo-controlled study, 389 treatment-naïve people with type 2 diabetes were randomised to either once-daily dapagliflozin (2.5, 5, 10, 20 or 50 mg), metformin extended release 750 mg (force titrated at week 2 to 1500 mg) or placebo. The primary endpoint was mean HbA_{1c} change from baseline for each dapagliflozin group versus placebo at 12 weeks.

Compared with placebo, significant HbA_{1c} reductions were recorded in the dapagliflozin group (–0.55 to –0.90 percentage points) with weight reduction of between 1.3 kg and 2 kg. Both fasting blood glucose and postprandial glucose levels were reduced throughout the dosage range. Urinary glucose loss equated to 200–300 kcal per day.

Treatment-related adverse events were similar across all groups and there were no clinically significant changes in renal status, urinary volume or urine osmolarity. Between 2% and 7% of the dapagliflozin group reported genital infections compared with none in the placebo group and 2% in those treated with metformin. Urinary tract infections occurred in 5–12% of those treated with dapagliflozin, 6% in those on placebo and 9% in the metformin group (List et al, 2009).

Phase 3 studies

Several studies are currently investigating dapagliflozin use, either alone or in combination with other blood glucose-lowering agents, in the treatment of type 2 diabetes. The studies involve three doses: 2.5 mg, 5 mg or 10 mg daily.

A three-arm, parallel-group, placebo-controlled, multicentre study has reported the efficacy of dapagliflozin in people with type 2 diabetes with poor glycaemic control on high insulin doses plus oral antidiabetes drugs. Seventy-one people on oral antidiabetes drugs plus >50 units of insulin daily were randomised to either placebo, dapagliflozin 10 mg or dapagliflozin 20 mg, plus 50% of their daily insulin dosage. By 12 weeks, placebo-adjusted HbA_{1c} reductions were 0.7% for the 10 mg group and 0.78% for those taking 20 mg. Placebo-adjusted weight losses were 2.6 kg and 2.4 kg, respectively. Adverse events were similar in all three arms, although more genital infections were reported in the 20 mg dapagliflozin group. This group of people with type 2

diabetes and poor glycaemic control on high insulin dosing regimens exhibited the potential for weight loss, insulin dose reduction and improved glycaemic control when treated with dapagliflozin (Wilding et al, 2009).

Conclusion

SGLT-2 inhibitors have the potential to significantly improve glycaemic control and cause weight loss with a low risk of hypoglycaemia in people with type 2 diabetes. Their mode of action does not interfere with glucose counter-regulatory mechanisms. The further understanding of the role of this glucose-modulating factor from the genetic phenotype underscores the potential utility of this new drug class.

With the early clinical drug studies demonstrating few adverse effects or symptoms, other than candidiasis in a small number of trial participants, the longer-term studies that are currently being undertaken will be key to assessing the efficacy, tolerability and utility of this class of drugs in the management of people with type 2 diabetes. ■

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