Drugs for diabetes: part 8
SGLT2 inhibitors

Alison MacEwen, Gerard A McKay, Miles Fisher

Authors

Alison MacEwen
Specialty Trainee in Endocrinology and Diabetes

Gerard A McKay
Consultant Physician

Miles Fisher
Consultant Physician

Wards 3, 4 & 5, Glasgow Royal Infirmary, 84 Castle Street, Glasgow, G4 0SF

Correspondence to:
Professor M Fisher
(miles.fisher@ggc.scot.nhs.uk)

Key words

canagliflozin, cardiovascular disease, dapagliflozin, SGLT2 inhibitors, type 2 diabetes

doi: 10.5837/bjc.2012.005

Br J Cardiol 2012;**19**:26–9

SGLT2 inhibitors are a new class of oral drugs for the treatment of type 2 diabetes mellitus currently in phase III studies. They inhibit glucose re-absorption in the proximal renal tubules providing an insulin independent mechanism to lower blood glucose. Their use in clinical practice is associated with improved glycaemic control, weight loss and a low risk of hypoglycaemia. Phase III cardiovascular safety studies are ongoing.

Introduction

Type 2 diabetes mellitus is a major risk factor for developing both microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary heart disease, cerebrovascular disease and peripheral vascular disease).[1] The link between maintaining good glycaemic control and prevention of these complications is well established.[2-4] Guidelines recommend a target glycosylated haemoglobin (HbA_{1c}) of 7% or less, but a large number of patients fail to meet this target and, as of yet, no ideal pharmacological blood glucose-lowering agent exists.

Existing pharmacological therapies, which have been previously described in this series, are focused on reducing insulin resistance, increasing insulin secretion, slowing carbohydrate digestion, restraining glucagon production, and supplying exogenous insulin. Treatment with traditional glucose-lowering therapies, including metformin, sulphonylureas and insulin, is commonly limited by gastrointestinal side effects, weight gain and hypoglycaemia.[2,3] Treatment with thiazolidinediones has been associated with cardiovascular safety concerns, weight gain, increased fracture risk and fluid retention.[5,6] Dipeptidylpeptidase-4 (DPP-4) inhibitors are well tolerated, but are merely weight neutral. Glucagon-like peptide-1 (GLP-1) analogues result in moderate weight loss, but they need to be injected and their use is limited by gastrointestinal side effects.[7] The increasing prevalence of type 2 diabetes, in combination with limitations of current therapies, has led to the search for newer

alternatives. SGLT2 inhibitors represent a novel 'glucuretic' therapeutic strategy for the treatment of type 2 diabetes, and are currently in phase III trials.

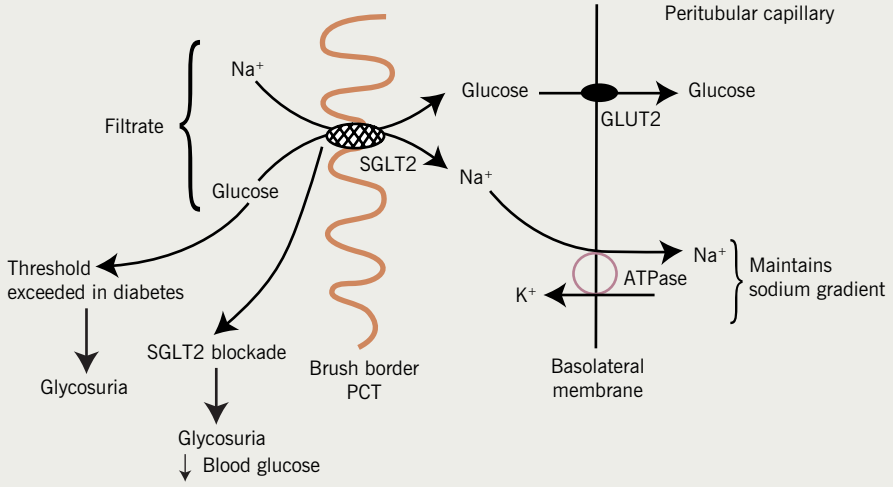
Pharmacology

Under normal physiological conditions, approximately 180 g of glucose is filtered by the kidney daily. Almost all of this is re-absorbed into the circulation via sodium glucose co-transporters (SGLTs). SGLTs transport sodium and glucose into cells using the sodium gradient created by sodium/potassium ATPase pumps at the basolateral cell membranes. Glucose is then transported passively by GLUT2 along its concentration gradient into the interstitium. Approximately 10% of renal glucose re-absorption occurs via SGLT1, and the remaining 90% occurs via SGLT2, which is found in the early proximal tubule.[8]

Phlorizin, a bitter white glycoside isolated from apple tree bark by French chemists in 1835, is a naturally occurring inhibitor of both SGLT1 and SGLT2 and was used for the treatment of diabetes in the pre-insulin era. Its use was limited by poor oral bioavailability and side effect profile. SGLT1 is expressed in the intestinal mucosa as well as the kidney. Its use as a therapeutic target is limited by side effects from malabsorption of glucose and galactose in the small intestine.[8]

Several specific SGLT2 inhibitors are currently under development including dapagliflozin,

Figure 1. SGLT2, a high-capacity, low-affinity transporter of glucose and sodium is found in high concentration at the brush border membrane of the S1 and S2 segment of the proximal convoluted tubule (PCT). SGLT2 binds to sodium and glucose in the filtrate and these compounds are translocated across the apical cell membrane, an active process driven by the electrochemical sodium gradient between tubular filtrate and the cell. The second stage of re-absorption is the transport of glucose through the utilisation of GLUT2 transporters in the basolateral membrane. In poorly controlled diabetes, the threshold for re-absorption is exceeded resulting in glycosuria. By blocking the SGLT2 transporter, re-absorption of glucose is reduced resulting in glycosuria and a reduction in blood glucose levels



Key: ATP = adenosine triphosphate; GLUT2 = glucose transporter 2

canagliflozin, empagliflozin, ipragliflozin and tofogliflozin. These work independently of insulin to prevent glucose re-absorption from the glomerular filtrate resulting in a reduced renal threshold for glucose, glycosuria and net calorie loss (**figure 1**).[8]

Of the SGLT2 inhibitors under development, dapagliflozin is furthest along in development. Phase I clinical data indicate that dapagliflozin has a pharmacokinetic profile of a once-daily drug with good oral bioavailability. It produces glycosuria in a dose-dependent fashion with a maximum plasma concentration within two hours and a mean half-life ranging from 11 to 17 hours.[9]

In phase IIa studies, dapagliflozin administered at 5 mg, 25 mg and 100 mg doses inhibits approximately 40% of renal glucose re-absorption when compared with baseline resulting in excretion of up to 70 g of glucose per day.[10] Overall, dapagliflozin was well tolerated. Reported side effects include a higher incidence of genital fungal infections, particularly at higher doses.

Less published data are currently available on canagliflozin. A phase I study has recently reported that canagliflozin also produces glycosuria in a dose-dependent fashion and is well tolerated in healthy euglycaemic subjects.[11]

Trials of safety and efficacy

Evidence for improved glycaemic control/microvascular benefit

Monotherapy

Two published studies have evaluated the use of dapagliflozin as monotherapy for type 2 diabetes. In a phase IIb study, List *et al.* randomised 389 drug-naïve obese patients with poorly controlled type 2 diabetes to treatment with one of five doses of dapagliflozin, extended-release metformin or placebo for 12 weeks. At week 12, the dapagliflozin group achieved a mean reduction in HbA_{1c} ranging from 0.55 to 0.90%. This was compared with patients in the metformin group who had a mean reduction in HbA_{1c} of 0.73% and the placebo group who had a mean reduction in HbA_{1c} of 0.18%.[12]

Ferrannini *et al.* randomised 485 drug-naïve obese patients with poorly controlled type 2 diabetes to 24 weeks' treatment with either placebo or dapagliflozin 2.5 mg, 5 mg or 10 mg once daily. Metformin was added in at 12 weeks to the maximum tolerated dose in those patients who remained poorly controlled at that stage. Overall, a mean reduction in HbA_{1c} ranging from 0.58 to 0.89% was observed in the dapagliflozin group compared with 0.23% in the placebo group. The reduction was statistically significant in the 5 and 10 mg dapagliflozin arms ($p=0.0005$ and $p<0.0001$, respectively). No major episodes of hypoglycaemia were observed. Signs and symptoms of urinary and genital tract infection were more frequent in the dapagliflozin arms. All resolved with standard treatment and rarely led to discontinuation.[13] Further phase III trials of dapagliflozin and canagliflozin monotherapy are ongoing.

Combination therapy

In a phase III multi-centre, double-blind, parallel-group, placebo-controlled trial, Bailey *et al.* randomised 546 adults with type 2 diabetes mellitus already receiving metformin (≥1,500 mg/day) with inadequate glycaemic control (HbA_{1c} 7–10%) to treatment with one of three doses of dapagliflozin (2.5, 5 or 10 mg) or placebo. At 24 weeks, mean HbA_{1c} decreased by 0.30% in the placebo group compared with 0.67% ($p=0.0002$) in the dapagliflozin 2.5 mg group, 0.70% ($p<0.0001$) in the dapagliflozin 5 mg group and 0.84% ($p<0.0001$) in the dapagliflozin 10 mg group. Rates of hypoglycaemia were similar between the dapagliflozin and placebo groups (2–4% *vs.* 3%). A higher incidence of genital infection was recorded in the dapagliflozin groups (8–13%) compared with the placebo group (5%). Seventeen patients had serious adverse events (four in each of the dapagliflozin groups and five in the placebo group).[14]

In a phase IIb multi-centre, double-blind, three-arm, parallel-group, placebo-controlled

study, Wilding *et al.* randomised 71 patients receiving high-dose insulin plus insulin sensitisers to treatment with either placebo, 10 mg dapagliflozin or 20 mg dapagliflozin. All oral antidiabetic agents were continued, but baseline insulin doses were reduced by 50%. At week 12, HbA_{1c} levels in the dapagliflozin 10 mg and 20 mg groups fell by 0.70% and 0.78%, respectively, when compared with placebo.[15] Further phase III trials of combination therapy for both dapagliflozin and canagliflozin are ongoing.

Effects on weight

In addition to improvements in glycaemic control, dapagliflozin therapy is also associated with beneficial reductions in total body weight. The glycosuria induced by dapagliflozin monotherapy is associated with a net calorie loss of approximately 200–300 kilocalories per day. List *et al.* noted that 12 weeks' monotherapy with dapagliflozin was associated with weight loss of 2.5–3.4 kg compared with weight loss of 1.2 kg and 1.7 kg in the placebo and metformin arms.[12] Bailey *et al.* observed a 2.2–2.9 kg weight loss over 24 weeks in the dapagliflozin group compared with 0.9 kg weight loss in the placebo arm.[14] Wilding *et al.* also noted a mean weight loss of 4.5 kg and 4.3 kg in the dapagliflozin 10 mg and 20 mg groups versus 1.9 kg in the placebo group.[15] Ferrannini *et al.*, however, did not find a statistically significant difference in weight at 24 weeks between the dapagliflozin group and placebo. The authors attributed this to a large placebo effect due to greater impact of diet and exercise counselling on motivated, newly diagnosed patients in a clinical trial setting. Glycosuria consistent with a loss of 200–300 kilocalories was observed in the treatment group, consistent with other studies.[13]

Effects on blood pressure

The long-term benefit of tight blood pressure control in patients with type 2 diabetes is well established. In the UK Prospective Diabetes Study (UKPDS) patients assigned to the tight blood pressure arm had a relative risk reduction of 24% for any diabetes-related end point, 32% for diabetes-related death, 44% for stroke and 37% for microvascular disease.[16] Dapagliflozin, as monotherapy or as an addition to metformin therapy over periods of 12–24 weeks in doses of 2.5–10 mg per day, has been noted to reduce blood pressure. This is possibly mediated through net sodium loss. Doses of 10 mg/day reduced mean systolic blood pressure in the groups studied by 3–5 mmHg and diastolic blood pressure by approximately 2 mmHg with no apparent change in heart rate or increase in syncopal episodes.[12-14] This small decrease in blood pressure may convey additional cardiovascular benefit in addition to the effects of improvement in glycaemic control and reduced weight.

Evidence for cardiovascular safety and benefit

The cardiovascular effects of long-term SGLT2 inhibition remain unknown. The Food and Drugs Administration (FDA) requires evidence that new treatments for diabetes do not increase cardiovascular risk. For dapagliflozin these data are being obtained from the study programme, which includes two ongoing phase III studies evaluating the safety and efficacy of dapagliflozin therapy in patients with type 2 diabetes and established cardiovascular disease and/or hypertension. Both of these are expected to complete in December 2011. Cardiovascular safety data for canagliflozin is being obtained from a large, dedicated phase III study: CANagliflozin cardiovascular Assessment Study (CANVAS). This will evaluate the use of canagliflozin or placebo in the treatment of around 5,000 patients with type 2 diabetes with a history of, or high risk for, cardiovascular disease. The primary end point for this study will be the incidence of major cardiovascular events including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. The study is expected to run for four years and to complete in April 2013. If the safety parameters are met and the drug obtains a licence it is the intention to expand this into a study of possible cardiovascular benefits in 20,000 patients.

Other considerations

Extrapolation from the mechanism of action of SGLT2 inhibitors raises the possibility of side effects such as dehydration and electrolyte loss, although this is generally not supported by the results of the studies discussed above. Familial renal glycosuria (FRG) is a rare condition caused by a mutation in the SGTL2 gene. Subjects with FRG exhibit varying degrees of glycosuria, however, remain asymptomatic, do not become dehydrated or become hypoglycaemic.[8] This disease model of SGLT2 inhibition is reassuring in terms of adverse long-term outcomes.

12 weeks' treatment with 20 mg/day of dapagliflozin resulted in a mean increase in daily urine output of 107–375 ml/day secondary to a mild osmotic diuresis.[12] Study populations were counselled about symptoms of dehydration and their avoidance with adequate fluid consumption, and this generally seemed effective. One patient in a phase II study with dapagliflozin developed dehydration and renal impairment. This resolved with oral rehydration and withholding their angiotensin-converting enzyme (ACE) inhibitor and diuretic treatment.[15] In contrast to individuals with FRG, a relatively high proportion of patients with diabetes are likely to be treated with ACE inhibitors and diuretic therapy, and are likely to have an increased prevalence of comorbidities, such as renal impairment, cardiovascular disease and autonomic neuropathy, and, thus, further evidence from phase III studies is still required to evaluate the safety and efficacy of SGLT2 inhibition in the long term, including possible effects on cancer.

Summary

SGLT2 inhibitors offer a novel insulin-independent approach for the control of hyperglycaemia without incurring hypoglycaemia. Their efficacy is not affected by the extent of insulin resistance or beta-cell dysfunction and, therefore, in principle, they can be used at any stage in the natural history of type 2 diabetes. Initial studies suggest they can be used as monotherapy or in combination with insulin or metformin. Treatment is associated with mean weight loss and a small reduction in blood pressure, which may also be beneficial to patients with co-existing cardiovascular disease. Further trials regarding long-term cardiovascular outcomes are ongoing

Conflict of interest

AM: None declared. MF has served on advisory boards for Astra Zeneca/Bristol Myers Squibb, Johnson and Johnson, and Boehringer Ingelheim. GM has served on advisory boards for Astra Zeneca, Bristol Myers Squibb, and Boehringer Ingelheim.

Key messages

- SGLT2 inhibitors are a new class of oral drugs in phase III development for the treatment of type 2 diabetes
- In addition to reductions in HbA_{1c}, SGLT2 inhibitors reduce weight and blood pressure
- SGLT2 inhibitors are being studied for cardiovascular safety and possible cardiovascular benefits in accordance with the demands of the licensing authorities

References

1. Turner R, Cull C, Holman R. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996;**124**:136–45.

2. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854–65. http://dx.doi.org/10.1016/S0140-6736(98)07037-8

3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–52. http://dx.doi.org/10.1016/S0140-6736(98)07019-6

4. Holman RR, Paul SK, Angelyn Bethel M *et al*. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;**359**:1577–89. http://dx.doi.org/10.1056/NEJMoa0806470

5. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;**356**:2457–71. http://dx.doi.org/10.1056/NEJMoa072761

6. Schwartz AV. Diabetes, TZDs, and bone: a review of the clinical evidence. *PPAR Res* 2006;**2006**:24502.

7. Barnett AH. Treatment options for type 2 diabetes: introducing the incretin-based therapies. *Pract Diabetes Int* 2009;**26**:179–83. http://dx.doi.org/10.1002/pdi.1367

8. Nair S, Joseph F, Ewins D, Wilding J, Goenka N. From history to reality: sodium glucose co-transporter 2 inhibitors – a novel therapy for type 2 diabetes mellitus. *Pract Diabetes Int* 2010;**27**:311–16. http://dx.doi.org/10.1002/pdi.1509

9. Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin, a novel SGLT2 inhibitor, induces dose dependent glycosuria in healthy subjects. *Clin Pharmacol Ther* 2009;**85**:520–6. http://dx.doi.org/10.1038/clpt.2008.251

10. Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin, a novel, selective SGLT2 inhibitor improved glycaemic control over 2 weeks in patients with type 2 diabetes mellitus. *Clin Pharmacol Ther* 2009;**85**:513–19. http://dx.doi.org/10.1038/clpt.2008.250

11. Sha S, Devineni D, Ghosh A *et al*. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increased urinary glucose excretion in healthy subjects. *Diabetes Obes Metab* 2011;**13**:669–72. http://dx.doi.org/10.1111/j.1463-1326.2011.01406.x

12. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care* 2009;**32**:650–7. http://dx.doi.org/10.2337/dc08-1863

13. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial. *Diabetes Care* 2010;**33**:2217–24. http://dx.doi.org/10.2337/dc10-0612

14. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010;**375**:2223–33. http://dx.doi.org/10.1016/S0140-6736(10)60407-2

15. Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers. *Diabetes Care* 2009;**32**:1656–62. http://dx.doi.org/10.2337/dc09-0517

16. UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;**317**:703–13. http://dx.doi.org/10.1136/bmj.317.7160.703

Diary

2012

24th – 27th March	ACC 12 – 61st Annual Scientific Session and Expo of the American College of Cardiology, Chicago, USA website: www.accscientificsession.org
18th – 20th April	Association of Cardiothoracic Anaesthetists & Society for Cardiothoracic Surgery in Great Britain and Ireland - 2012 Annual Meeting and Cardiothoracic Forum, Manchester email: sctsadmin@scts.org website: www.scts.org
24th May	'My patient with Dizzy Spells' Conference, Harrogate District Hospital website: www.hdft.nhs.uk email: strayside-education@hdft.nhs.uk
28th – 30th May	British Cardiovascular Society Annual Conference 2012, Manchester website: www.bcs.com
27th – 29th June	HEART UK 26th Annual Conference, Newcastle upon Tyne email: wheldonvents@btconnect.com website: www.heartuk.org.uk
25th – 29th August	European Society of Cardiology (ESC) Congress 2012, Munich, Germany website: www.escardio.org
10th – 13th October	2012 Cardiometabolic Health Congress, Boston, USA email: info@cardiometabolichealth.org website: www.cardiometabolichealth.org
29th and 30th November	British Society for Heart Failure (BSH) 15th Annual Autumn Meeting, London email: info@bsh.org.uk website: www.bsh.org.uk