Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/

Flozins, inhibitors of type 2 renal sodium-glucose co-transporter – not only antihyperglycemic drugs

Grzegorz Mizerski, Pawel Kicinski*, Andrzej Jaroszynski

Department of Family Medicine, Medical University of Lublin, Staszica 11, 20-081 Lublin, Poland

ARTICLE INFO

Received 17 June 2015
Accepted 14 August 2015

Keywords:
type 2 diabetes mellitus,
pharmacotherapy,
flozins.

ABSTRACT

The kidneys play a crucial role in the regulation of the carbohydrate metabolism. In normal physiological conditions, the glucose that filters through the renal glomeruli is subsequently nearly totally reabsorbed in the proximal renal tubules. Two transporters are engaged in this process: sodium-glucose co-transporter type 1 (SGLT1), and sodium-glucose co-transporter type type 2 (SGLT2) – this being located in the luminal membrane of the renal tubular epithelial cells. It was found that the administration of dapagliflozin, a selective SGLT2 inhibitor, in patients with type 2 diabetes, is associated with the reduction of HbA_{1c} concentration by 0.45-1.11%. Additional benefits from the treatment with dapagliflozin are the reduction of arterial blood pressure and a permanent reduction of body weight. This outcome is related to the effect of osmotic diuresis and to the considerable loss of the glucose load by way of urine excretion. Dapagliflozin may be successfully applied in type 2 diabetes monotherapy, as well as in combined therapy (including insulin), where it is equally effective as other oral anti-diabetic drugs. Of note: serious adverse effects of dapagliflozin administration are rarely observed. What is more, episodes of severe hypoglycaemia related with the treatment occur only sporadically, most often in the course of diabetes polytherapy. The most frequent effects of the SGLT2 inhibitors are inseparably associated with the mechanism of their action (the glucuretic effect), and cover urogenital infections with a mild clinical course. At present, clinical trials are being continued of the administration of several subsequent drugs from this group, the most advanced of these being the use of canagliflozin and empagliflozin.

INTRODUCTION

The kidneys play a crucial role in the regulation of the carbohydrate metabolism in that therein, the processes of gluconeogenesis and glucose reabsorption take place. Moreover, they are the site of glucose utilization [4,13]. In normal physiological conditions, the glucose that filters through the renal glomeruli, is subsequently nearly totally reabsorbed by way of the proximal renal tubules. As the cellular membrane, consisting mainly of phospholipids and cholesterol, is non-permeable for glucose, two transporters are involved in this process: sodium-glucose co-transporter type 1 (SGLT1) (present in the *intestinal epithelial cells)*, and sodium-glucose co-transporter type 2 (SGLT2) (located in the luminal membrane of the renal tubular epithelial cells). Their activity depends on the Na^+/K^+-ATPase pump. The SGLT2 transporter is located in the S1 segment of the nephron, and, although showing a lower affinity for glucose, it is responsible for 90% of all reabsorption, whereas the SGLT1, active in the segment S2/3 of the nephron, is characterised by its high affinity, but low capacity [Fig. 1] [4,13]. From the renal tubular cell, glucose passively flows into the blood by means of transporters from the glucose transporters (GLUT) family. In this action, SGLT2 cooperates with GLUT2, while SGLT1 does so with GLUT1 [Fig. 2] [4,13].

An inactivating mutation in the *SGLT2* gene leads to the occurrence of the tubular dysfunction described as 'familial renal glycosuria' (FRG). In these patients, the daily loss of glucose by way of urine excretion reaches 160-180 g. To-date, 21 mutations in the *SGLT2* gene have been detected; however, no defects have been found in these patients other than glycosuria [4]. Of note, patients with type 2 diabetes evidence an increased expression of the *SGLT2* and *GLUT2* genes.

* **Corresponding author**
e-mail: pawelkici@wp.pl
tel./fax: +48 81 532 34 43

DOI: 10.1515/cipms-2015-0063

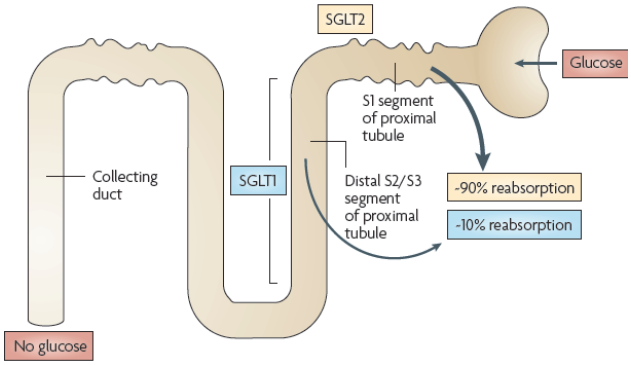

Figure 1. Localization of sodium-glucose co-transporters type 1 and type 2 (responsible for 90% of glucose re-absorption) in nephron

Reprinted by courtesy of Macmillan Publishers, Ltd. *Nature Rev. Drug Discov.* 2010; 9: 551-559, © 2010

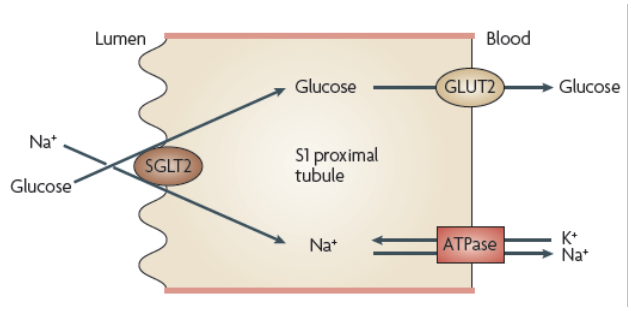

Figure 2. Glucose transfer in the proximal renal tube: active transport from the lumen of the renal tube (SGLT2) and passive transport from the renal tubular cell to the blood (GLUT2)

Reprinted by courtesy of Macmillan Publishers, Ltd. Nature Rev. *Drug Discov.* 2010; 9: 551-559, © 2010

SGLT2 INHIBITORS

Experimental pharmacological studies have demonstrated that administration of florizin, a non-selective SGLT inhibitor, brings about the blocking of the renal reabsorption of glucose [2]. This substance was discovered as early as 1835 in the roots of apple trees; however, it did not find clinical application due to its poor bioavailability after oral administration, as well as its displayed important adverse effects (disorders in the absorption of glucose, and a diarrhoea related to SGLT1 inhibition) [2,4].

Dapaglifozin, a newer development, has been found to be a selective SGLT2 inhibitor (its affinity for SGLT2 is over 1,200 times higher than for SGLT1). It is now registered for the treatment of type 2 diabetes [4], while other SGLT2 inhibitors are at the stage of clinical trials. That which are in most advanced stages of research are canagliflozin and empagliflozin. All three substances are characterized by having favourable pharmacokinetic properties: very high bioavailability after oral administration (irrespective of the meal), and a long period of half-life allowing once-daily dose administration [19].

It should be emphasized that the effectiveness of dapagliflozin depends on renal function, and it considerably deceases in patients with a moderate to severe degree of renal insufficiency [11,12]. In patients with mild impairment of the filtration function of the kidneys, however, a reduction of the drug dose is not necessary. According to most guidelines, the use of dapagliflozin is not recommended in the case of an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2. However, Kaku *et al.* have demonstrated that the efficacy of dapagliflozin in patients with chronic kidney disease with eGFR not less than GFR > 45 ml/min was not reduced, when compared to individuals with normal renal function [9].

DAPAGLIFLOZIN MONOTHERAPY IN TYPE 2 DIABETES

A team of Japanese researchers directed by Kaku [9] has evaluated the effectiveness of dapagliflozin monotherapy in 261 patients with type 2 diabetes, in whom diet and modification of life style did not ensure an optimum control of glycaemia. The patients enrolled in the study had relatively low initial glycated haemoglobin (HbA_{1C}) values (mean 7.5%). The study saw that the use of dapagliflozin (5 mg or 10 mg once a day), compared to placebo, was associated with a significantly higher reduction in HbA_{1C} (-0.45% for dapagliflozin 10 mg, -0.41% for dapgliflozin 5 mg and -0.06% for placebo) and a decrease in body weight (2.13-2.22 kg versus 0.84 kg). What is more, the therapeutic effect did not depend on gender, age, body weight index and renal function (only patients with mild and moderate chronic kidney disease, with eGFR >45 ml/min, were enrolled to the study). However, it was noted that patients with the initial highest values of HBA_{1c} benefited most. In the subgroup of patients with HbA_{1c} within the range 8-9%, after the administration of dapagliflozin, its reduction was obtained by 0.94%. Adverse effects during the study were very rarely observed – hypoglycaemia occurred only in 2 patients, and infection in 4 patients treated with dapagliflozin.

The study by Ji *et al.* [8] covered Asian patients with type 2 diabetes with initial HbA_{1C} values of 7-10.5%, who previously had not undergone pharmacological treatment. Following randomization, the patients were administered dapagliflozin (5 mg or 10 mg) or placebo for 24 weeks. After 24 weeks of treatment, a higher reduction in HbA_{1C} was obtained in the group of patients who were treated with dapagliflozin, compared to those who received placebo (1.04-1.11%, according to the dose, versus 0.29%). In addition, a reduction in body weight was seen (1.64-2.25 kg versus 0.27 kg). Undesirable events were rarely noted. However, episodes of hypoglycaemia were more frequent in patients who were administered dapagliflozin (0.8-1.5%, according to the dose, versus 0.8%); yet, these episodes did not lead to the discontinuation of therapy in any of the patients. Besides the aforementioned, infections of the genital system (3.1-4.5% versus 0.8%) and the urinary system (3.9-5.3% versus 3%) occurred more often. Similar to the study by Kaku, no cases of *interstitial nephritis* were found.

An interesting study was conducted by Henry *et al.* [6], who analyzed three various models of initiating the pharmacotherapy of type 2 diabetes (extended-release metformin, dapaglflozin at a dose of 5 mg or 10 mg, or a combination

of both drugs). Their work showed that a higher dose of dapagliflozin was as equally effective in the reduction of HbA_{1C} as was metformin (1.45% versus 1.44%). Furthermore, in accordance with expectations, the combination of both drugs was the most effective (reduction of HbA_{1c} by 1.98%). During this study, no episodes of severe glycaemia were observed. However, in patients treated with dapagliflozin, infections of the urogenital system were more frequent (*vulvovaginitis*, *balanitis* and *urocystitis*, but not *pyelonephritis*). In turn, the treatment with metformin was more often related with diarrhoea and nausea.

DAPAGLIFLOZIN IN COMBINATION THERAPY FOR TREATING TYPE 2 DIABETES

Strojek *et al.* [20], in a randomized placebo-controlled study, analyzed the safety and effectiveness of a combined therapy based on derivatives of sulphonylurea and dapagliflozin. Their work enrolled patients who received monotherapy with glimepiride in whom an optimum metabolic control was not obtained (HbA_{1c} 7-10%). In the study group, glimepiride was combined with dapagliflozin, whereas in the control group, glimepiride with placebo was administered. After 24 weeks of treatment, a significant decrease in HbA_{1c} was observed in the study group, from 0.41%-0.73% (according to the applied dose of dapagliflozin of 2.5-10 mg daily). In the control group (glimepiride + placebo), the HbA_{1c} reduction was 0.04%. The beneficial effect of therapy with glimepiride in combination with dapagliflozin on body weight, was also confirmed (a reduction by 1.36-2.41 kg in the study group, and by 0.77 kg in the control group). However, within the group of patients who received placebo, hypoglycaemia was more rarely observed (6.8% versus 9.7-11%), as was urogenital infections (1.4% versus 5.2-8.6%).

In another study conducted by Nauck *et al.* [14] among patients with type 2 diabetes inadequately controlled with metformin, glypizide or dapagliflozin was combined into the treatment. Patients within this study commenced treatment with dapagliflozin at 2.5 mg or glipizide at 5 mg, and could be up-titrated to a maximum tolerated dose of 10 mg and 20 mg, respectively. No changes in metformin dose were allowed during the study. After two years of observations, it was found that the dapagliflozin administration added to the therapy was related with a permanent reduction in the value of systolic arterial blood pressure and body weight. In the group receiving glipizide, an increase in arterial blood pressure was noted (a difference by 3.9 mm Hg, to the advantage of dapagliflozin), as well as an increase in body weight (a difference by 5.1 kg, to the benefit of patients treated with dapagliflozin). Most importantly, the addition of dapagliflozin was more effective than the addition of glipizide (reduction in HbA_{1c} by 0.18% after two years). Episodes of hypoglycaemia were more than ten times rarer in patients who received dapagliflozin, compared to glipizide administration (4.2% versus 45.8%). In turn, infections of the genital and urinary systems were more frequent in patients who were administered dapagliflozin, and not glipizide (14.8% versus 2.9%, and 13.5% versus 9.1%, respectively). What is understandable is that the infections more frequently occurred in females. From the clinical point of view, it is important to note that in the case of therapy with dapagliflozyin, the infections concerned the lower urinary tract, while acute pyelonephritis was less frequently noted, however, recurrent infections of the urinary bladder were more often observed. It is an interesting to note that an increased risk of urogenital infections was elevated during the first 52 weeks of treatment, and later did not differ from the risk found in the control group.

Jabbour *et al.* [7] confirmed that dapagliflozin (at a dose of 10 mg), when added to the therapy with dipeptidyl peptidase-4 inhibitor – sitagliptin (in combination with metformin or alone), and compared to placebo, after 24 weeks, resulted in a significant reduction in the percentage of HbA_{1c} (0.5% in patients receiving dapagliflozin + sitagliptin ± metformin, versus 0% in patients treated with sitaplitin ± metformin and placebo), and in body weight (2.1 versus 0.3 kg, respectively). Similar to the studies discussed above, a typical complication of treatment with dapagliflozin was that genital system infections were more frequently observed (9.4% versus 0.4%), whereas infections of the urinary system occurred with a similar frequency (6.7% versus 6.2%).

In their study, Wilding *et al.* [21] evaluated insulin therapy combined with dapagliflozin at 2.5 mg or 5 mg (and switched to 10 mg after 48 weeks) or 10 mg, with a part of the patient study group simultaneously receiving other oral anti-diabetic drugs (a point that should be underlined). After two years of observations, it was found that in the group treated with dapagliflozin used as an add-on therapy to insulin, the percentage of HbA_{1c} decreased by 0.6-0.8% depending on the dose (versus 0.4% with insulin + placebo). A dose-dependent reduction in body weight by 0.9-1.4 kg was also noted (versus body weight gain by 1.8 kg in the group treated with insulin and placebo). Importantly, during the use of dapagliflozin, the doses of insulin remained on a constant level, whereas in patients who were administered placebo, the insulin dose increased by 18.3 units/daily during the period of two years. In this study, urogenital infections were more frequently noted in patients who received dapagliflozin; however, the majority of episodes occurred within the first 24 weeks of treatment.

Despite such adverse effects, the use of dapagliflozin for a period of two years did not induce a deterioration of the quality of life of the patients, compared to placebo [5].

Not withstanding certain initial concerns, the studies *in vitro*, *in silico* and *in vivo* also did not confirm any carcinogenous potential of dapagliflozin. Moreover, neither dapagliflozin nor its metabolites had any genotoxic effect. Also, chronic glycosuria did not induce the processes of overgrowth of the transitional epithelium of the urinary bladder [18].

OTHER SGLT2 INHIBITORS

Canagliflozin was approved for use by the Food and Drug Administration (FDA) in the United States [10]. Serious adverse effects of canagliflozin are rare and do not differ from those observed while applying other SGLT2 inhibitors [1,16,17]. The effectiveness of canagliflozin was confirmed both in the monotherapy and in the combined therapy of

type 2 diabetes [1]. As with dapagliflozin, this drug induces a permanent reduction of body weight and arterial pressure. A further effect on the lipid profile was also demonstrated (an increase in the level of LDL cholesterol, a decrease in the concentration of triglycerides, and an increase in the level of HDL cholesterol [1,16,17]. Of note: a contraindication against the use of canagliflozin is seen in chronic kidney disease, in stages IV-V [17]. Yale *et al*., in a randomized placebo-controlled study, confirmed the effectiveness (seen as a reduction in the percentage of HbA_{1c} that is accompanied by a reduction of body weight and arterial blood pressure), and good tolerance of canagliflozin monotherapy in patients with type 2 diabetes, and chronic kidney disease, with eGFR at 30-50 ml/min/1.73 m^2 [22]. Beyond the aforementioned, at present, an interesting study is on-going (CANVAS) in which the effect of canagliflozin on the risk of cardiovascular events is being evaluated [15]. It should be mentioned that in Japan, two subsequent drugs from this group have been approved: ipragliflozin and luseogliflozin [10], and currently several other drugs are at the stage 3 of clinical research (empagliflozin, tofogliflozin) [3].

CONCLUSIONS

SGLT2 inhibitors are a group of drugs that effectively reduce glycaemia. In clinical studies, the use of dapagliflozin has been associated with a reduction in the concentration of HbA_{1c} by 0.45-1.11%. Additional benefits from the treatment with dapagliflozin are a decrease in arterial blood pressure and a permanent reduction of body weight. This comes about due to the effect of osmotic diuresis, and due to a considerable loss of the glucose load by way of urine excretion. Dapagliflozin may be successfully applied in type 2 diabetes therapy, as well as in combined therapy, including insulin, where it has been seen to be equally as effective as other anti-diabetic drugs.

Serious adverse effects of dapagliflozin are rare. However, episodes of severe hypoglycaemia related with dapagliflozin treatment occur sporadically, most often during combined therapy. This is associated mainly with two mechanisms: the lack of effect on insulin secretion and the lack of effect on the absorption of glucose in the gastrointestinal tract (by way of the co-transporter SGLT1). The most frequent effects of SGLT2 inhibition are inseparably related with the mechanism of their action (glucuretic effect), and cover urogenital infections of a mild clinical course.

In Poland, from among the SGLT2 inhibitors that are approved internationally, only dapagliflozin and cangliflozin are allowed for turnover; however, their use is limited by the lack of reimbursement and the high cost of monthly therapy.

REFERENCES

1. Bhatia K. et al.: Canagliflozin-current status in the treatment of type 2 diabetes mellitus with focus on clinical trial data. *World J. Diabetes*, 5, 399, 2014.
2. Chao E., Henry R.: SGLT2 inhibition — a novel strategy for diabetes treatment. *Nature Rev. Drug Discov.*, 9, 551, 2010.
3. Diamant M., Morsink L.: SGLT2 inhibitors for diabetes: turning symptoms into therapy. *Lancet*, 382, 917, 2013.
4. Endocrine Today. http://www.healio.com/endocrinology/diabetes/(...)sglt2-inhibitors. (accessed 15.06.2014).
5. Grandy S. et al.: Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin over 2 years. *Int. J. Clin. Pract.*, 68, 486, 2014.
6. Henry R. et al.: Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomized controlled trial. *Int. J. Clin. Pract.*, 66, 446, 2012.
7. Jabbour S. et al.: Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care*, 37, 740, 2014.
8. Ji L. et al.: Dapagliflozin as monotherapy in drug-naïve Asian patients with type 2 diabetes: a randomized, blinded, prospective phase III study. *Clin. Ther.*, 36, 84, 2014.
9. Kaku K. et al.: Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise. *Diabetes Obes. Metab.,* 16, 1102, 2014.
10. Kim G., Chung S.: Clinical implication of SGLT2 inhibitors in type 2 diabetes. *Arch Pharm. Res.*, 37, 957, 2014.
11. Kirk R.: Diabetes: Efficacy of dapagliflozin associated with renal function. *Nat. Rev. Nephrol.*, 9, 695, 2013.
12. Kohan D. et al: Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int.*, 85, 962, 2014.
13. Kokot F., Hyla-Klekot L.: Nowe potencjalne tarcze ataku farmakologicznego w cukrzycy typu 2. *Nefrol. Dializoter. Pol.*, 15, 239, 2011.
14. Nauck M. et al.: Durability of glycaemic efficacy over 2 years with dapagliflozin, versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus was inadequately controlled with metformin. *Diabetes Obes. Metab.*, 16, 1111, 2014.
15. Neal B. et al.: Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)--a randomized placebo-controlled trial. *Am. Heart J.*, 166, 217, 2013.
16. Nicolle L. et al.: Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. *Postgrad. Med.*, 126, 7, 2014.
17. Plosker G.: Canagliflozin: a review of its use in patients with type 2 diabetes mellitus. *Drugs,* 74, 807, 2014.
18. Reilly T. et al.: Carcinogenicity risk assessment supports the chronic safety of dapagliflozin, an inhibitor of Sodium-Glucose Co-Transporter 2, in the treatment of type 2 diabetes mellitus. *Diabetes Ther.*, 5, 73, 2014.
19. Scheen A.: Evaluating SGLT2 inhibitors for type 2 diabetes: pharmacokinetic and toxicological considerations. *Expert. Opin. Drug. Metab. Toxicol.*, 10, 647, 2014.
20. Strojek K. et al.: Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial. *Diabetes Ther.*, 5, 267, 2014.
21. Wilding J. et al.: Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. *Diabetes Obes. Metab.*, 16, 124, 2013.
22. Yale J. et al.: Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. *Diabetes Obes. Metab.*, 16, 1016, 2014.