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SGLT2 inhibitors – new oral hypoglycemic drugs

Inhibitory SGLT2 – nowe doustne leki przeciwcukrzycowe

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S u m m a r y

The prevalence of diabetes increases worldwide and glycemia in many patients Dos not meet the targets precised by American or Polish Diabetes Association. These two fact stimulate development of new treatment possibilities in diabetes. One of them, described below, are kidney sodium and glucose transporter inhibitors. From the one side they increase urinary glucose excretion (mimicking the natural defense mechanism of the organism) resulting in decrease of glycemia and in negative energy balance, favoring decrease of weight, from the other icreased sodium excretion decreases blood pressure. The price for that effects is however increased frequency of genitourinary tract infections. The first marketed drug belonging to this group is dapagliflosine.

Key words: diabetes, diabetic nephropathy, SGLT2 inhibitors

S t r e s z c z e n i e

Liczba chorych na cukrzycę na całym świecie wzrasta. Równocześnie glikemia u wielu chorych nie spełnia kryteriów wyrównania podawanych przez Amerykańskie lub Polskie Towarzystwa Diabetologiczne. Te dwa fakty przyczyniają się do burzliwego rozwoju nowych możliwości terapeutycznych w cukrzycy. Jedną z takich możliwości opisano w poniższym artykule. Są to leki hamujące transport glukozy i sodu w nerkach. Z jednej strony nasilają one wydalanie glukozy z moczem (naśladując naturalny mechanizm obronny organizmu), powodując zmniejszenie glikemii i ujemny bilans energetyczny, sprzyjający zmniejszeniu masy ciała, z drugiej wzmożone wydalanie sodu z moczem powoduje spadek ciśnienia tętniczego. Ceną za te efekty lecznicze jest jednak zwiększona częstość zakażeń układu moczowego i dróg rodnych. Pierwszym lekiem z tej grupy dopuszczonym na rynek jest dapagliflozyna.

Słowa kluczowe: cukrzyca, nefropatia cukrzycowa, inhibitory SGLT2

The kidney is one of important players regulating the homeostasis of glucose and carbohydrates. One of the involved mechanisms is glucose excretion and reabsorption, mediated by sodium-glucose cotransporters, mainly type 2 (SGLT2), located in the S1 segment of the proximal tubule. This transporter is encoded by SLC5 (specifically SCL5A2) gene (1). It is characterized by high capacity, but low affinity for glucose, and is responsible for about 90% of the reabsorption of glucose from the tubuli (2, 3) (the remaining 10% of glucose is in the physiological conditions reabsorbed by type 1 transporter, SGLT1, located in the S2/S3 segment of proximal tubule (4). The molar ratio of transferred glucose to transferred to sodium is 1:1 for the SGLT2 transporter (1:2 for SGLT1) (2, 5). Sodium-glucose transporter type 2 is sodium-dependent, one-way co-transporter, expressed on the luminal side of the nephron proximal tubule cells (5, 6). It is responsible for active glucose transport from the lumen of renal proximal tubule to renal epithelial cells, against the concentration gradient. Transported to epithelial cells glucose produces gradient between the cell and interstitial fluid, which is then used by GLUT transporters (7, 8).

The mechanism of action of SGLT inhibitors

SGLT2 inhibitors are structurally similar to fenyloglukozide called phlorizin, a non-selective blocker that blocks both type 1 and 2 receptor (9). There is evidence that it acts on SGLT in a double manner: by carbohydrate group and by sugar-free part of the aromatic ring.

It seems that glucose-free parts of of SGLT proteins, having a polar structures located on a large transmembranous loop, with the help of which they can interact with glucose-free parts of the inhibitors, play a key role in the mechanism of blocking. On this basis phlorizine binds to nonspecific hydrophobic pocket formed in the last part of the loop (9-11). It should be noted that the SGLT 2 is a protein composed of 672 amino acids which form fourteen transmembranous segments arranged in loops (12, 13).

Pharmacokinetics of SGLT2 inhibitors

All SGLT2 inhibitors are administered orally. Pharmacokinetical parameters such as rate of absorption, time to maximal serum concentration after exposure, time of dissociation from the receptor are different in different drugs of the class. For example, dapagliflozine and ipragliflozine are rapidly absorbed. Peak serum dapagliflozine concentration is achieved after about 1 hour of exposure (12). Ipragliflozin is similarly absorbed and its half-time is about 12 hours (13, 14). The relationship between the dose, plasma concentration and time is linear. Ipragliflozine has several inactive metabolites, called M1, M2, M3, M4 and M6, the main metabolite is M2 (13). Seragliflozine is rapidly absorbed and also rapidly metabolized, maximum concentration is achieved after 30-45 minutes after exposure. The half-life is approximately 0.5 hours to 1 hour (15). Pharmacokinetic of canagliflozine is dose dependent, but much longer than in case of previously mentiod SGLT2 inhibitors. The half-life is approximately 12-15 hours, and time peak concentration after exposure is achieved after similar time (16).

Therapeutic effect of SGLT2 inhibitors

It has been proven that patients with type 2 diabetes have a higher expression of SGLT2 receptors compared to healthy subjects (11, 17, 18). Blocking of these transporters leads to increased urinary excretion of glucose and reduction of both fasting and postprandial plasma glucose concentration. It is estimated that SGLT2 inhibitors may block the reabsorption of glucose at about 60%. Therefore, these compounds may be used in the treatment of diabetes-especially type 2 diabetes mellitus. Indeed, dapagliflozine is the first drug of the calss which is accepted by European Medicine Agency and may be marketed in the European Union.

SGLT2 inhibitors reduce blood glucose not influencing insulin levels, however they may also improve insulin sensitivity and reduce gluconeogenesis in the liver (18). They seem not only to improve glucose control (percentage of glycated hemoglobin, fasting and postprandial plasma glucose) but also body weight as well systolic blood pressure (18). The two latter effects seem to be dependent on the diuretic effect of these medications. This effect, in turn, is probably dependent on the osmotic effect exerted by glucosuria, however it may also result from natriuresis. Sodium excretion occurs in the last parts of nephrons as a rebound after the sodium reabsorption in the proximal parts. There is no evidence up to date that SGLT2 inhibitors may increase natriuresis directly (17, 18).

There is a tendency to the use of selective SGLT2 inhibitors. Non-selective inhibitor of SGLT, such as phlorizine hydrolyzes in the intestine to the aglycone called phloretin, which potently blocks not only SGLT1 transporters, but also GLUT proteins, which causes undesirable adverse effects such as exacerbation of insulin resistance and hypoglycemia in the CNS (17-19).

Possible side effects

Selective SGLT2 inhibitors appear to be safe. The risk of hypoglycemia is low. They may, however, increase the risk of urogenital infections. In women the infections are rather bacterial and fungal, in men fungal balanitis is probably most important. In some patients these diuretic drugs may cause an increase in hematocrite value, but they rather do not increase a frequency of hypovolemia. It also appears that they do not result in impairment of renal function, although they may lead to an increase of serum urea concentration (18, 19). It is not entirely clear yet whether there is a higher incidence of cancer in subjects using these drugs. Because of slightly higher incidence of breast and bladder cancer FDA has not yet approved dapaglifozine, although the European Medicines Agency (EMA), however, approved the drug judging that it is probably safe and the difference in cancer incidence between dapagliflozin and placebo treated subjects is non significant.

Dapagliflozine as model representative of SGLT2 inhibitors

Dapagliflozine is currently the first-from-the-class drug approved for treating diabetes. It is a selective SGLT2 inhibitor with about 100 times higher affinity to this protein than to SGLT1. The main (non-active) metabolite of dapagliflozine is its glucuronide (12). Dapagliflozine is rapidly absorbed, peak plasma concentration is reached from 0.5 to 1.3 hours after exposure to the drug (12). Time of dissociation of dapagliflozine from the transporter is much longer than this of galactodapagliflozine (half-life time of the latter is 20-30 s) (20-22).

Dapagliflozine, as other drugs from this class improves diabetes control and reduces glycated hemoglobin by about 0.5-0.9% (20, 22). It decreases also blood pressure and improves lipid profile. It may also influence serum C – peptide and uric acid (20), reduces body weight (of approximately 2 kg in 24 weeks) and waist circumference (of about 1.5 cm in 24 weeks). There is evidence that decrease of body weight is caused not only, and even not predominatly by the diuretic effect. It was shown that dapagliflozine leads to a decrease of the visceral (258.4 cm^3 at 24 weeks), and subcutaneous (184.8 cm^3 to 24 weeks) fat. In 26.2% of patients treated with dapagliflozine a weight loss of at

least 5% was observed (22). In the course of drug therapy a decrease of uric acid level (about 0.2-1 mg/dL) also occurs (12).

The risk of hypoglycemia in the course of the therapy is low. Hypoglycemias occurred in 3.5% of patients treated with dapagliflozine during 52 weeks of follow-up (22), and usually were not great. Blood glucose concentration is usually below 63 mg/dl, but above 54 mg/dl. The patients do not require interventions of third person in any form. Most episodes of hypoglycemia are observed in the course of combination therapy with glimepiride or insulin (19). Other side effects of the drug are increased hematocrit, and urogenital infections. Studies have shown that infection in the form of balanitis or valvulovaginitis occurred in approximately 3.3% of patients, and urinary tract infection in approximately 6.6%. One of the most controversial possible side effects linked to the drug is breast and bladder cancer. It has been shown initially that breast cancer occurred in 9 patients treated with dapagliflozine (0.2%) as compared to the placebo group (one patient, 0.1%). Similarly, occurrence of bladder cancer was 0.3% in dapagliflozine treated patients in comparison with 0.05% in the placebo group (23, 24). However, data recently submitted to the European Medicines Agency show that in the course of further observation, this ratio has changed, as there occurred new cases of cancer in the placebo group. Based on those data EMA approved lastly dapagliflozine for the European market, both as monotherapy and combination therapy, arguing that the benefits of its use outweigh the risk of complications (23).

Results of published clinical studies using dapagliflozine

In a 12 week-long, prospective randomized trial that enrolled 389 patients with type 2 diabetes, dapagliflozine used in 5 doses (2.5 mg, 5 mg, 10 mg, 20 mg or 50 mg) was compared with metformin XR (initial 750 mg dose, increased to two per week to 1500 mg) and with placebo. Inclusion criteria were as follow: age 18-79 years, the level of glycated hemoglobin between 7-10%, the concentration of C-peptide greater than 1 ng/ml, BMI below 40 kg/m^2, GFR greater than 60 ml/min/1,73 m^2, serum creatinine less than 1.5 mg/dl in men and 1.4 mg/dl in women, and microalbuminuria of less than 300 mg/day. HbA1c was reduced by 0.55 to 0.9% in patients treated with dapagliflozine in comparison with 0.18% in the placebo group, but about 0.73% in the metformin treated group. Glycated hemoglobin level of less than 7% was achieved in 40-59% of patients treated dapagliflozine, 32% in the placebo and 54% in the metformin group. Decrease of fasting glucose during the study was 16-31 mg/dl in dapagliflozin-treated patients and was dose-dependent. In the placebo group the decline was 6 mg/dl, and the metformin group 18 mg/dl. The greatest weight loss (about 2.5-3.4%) was observed in patients treated with dapagliflozine in comparison to 1.2% of weight loss in the placebo group and 1.7% in patients treated with metformin. Similarly, in patients treated with dapagliflozine the greatest reduction was achieved in waist circumference, and the largest proportion of patients who achieved weight loss 0 > 5%. The drug was safe, although the above mentioned side effects were observed. There was no effect on serum sodium, potassium and calcium concentrations, but magnesium level decreased by about 0.1 mEq/l (25).

Another prospective, multicenter study with randomization included 71 patients of which 23 received placebo, 24 patients 10 mg dapagliflozyna in combination with insulin and 24 patients 20 mg dapagliflozyna in combination with insulin. In the 12-week of observation glycated hemoglobin decreased of -0.7% in the 10 mg-group, and of 0.78% in the 20 mg-group. Among patients treated with dapagliflozine 65.2% achieved a reduction of HbA1c of more than 0.5%, while in the placebo group such effect was achieved in only 15.8% of patients. In the course of therapy, in addition to the typical side effects, there was also one case of renal failure probably because of dehydration, in patient treated with dapagliflozine, but also with enalapril, carvedilol and furosemide. After rehydration renal function normalized. A tendency to vomiting and nausea was also observed, especially in patients treated with 20 mg of the drug (26).

In the last time a systematic review of the literature was published that included seven randomized trials with SGLT2 inhibitors, in 6 of which dapagliflozine was used (in one it was canagliflozine). The median observation time was 24 weeks, the patients suffered from type 2 diabetes and were over 18 years of age. It was shown that the treatment with 10 mg of dapagliflozine significantly reduced HbA1c by 0.54%. Both dapagliflozine and canagliflozine reduced body weight (of 1.81 kg and 2.04 kg, respectively). Both drugs reduced also systolic blood pressure (27).

SUMMARY

It seems that SGLT2 inhibitors are promising class of drugs, due to a specific, distinct than in the case of other drugs mechanism of action, to their pleiotropic effects and to the potential to use both in monotherapy as well as in combination therapy.

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