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ANALYSIS OF THE DEVELOPMENT OF MYCOTIC INFECTIONS IN PATIENTS USING CANAGLIFLOZIN AND DAPAGLIFLOZIN: A NARRATIVE REVIEW

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Abstract: SGLT-2 inhibitors are very useful and effective medications for treating hyperglycemia and reducing cardiovascular risk. However, it is responsible for increasing the IGM index, especially in women, three to four times when compared to a placebo group. As such, it is imperative that healthcare professionals are aware of the benefits, risks, and strategies for increasing safety and efficacy, and managing SGLT2 inhibitor-related issues. The incidence, risk factors, prevention and management of IGMs associated with SGLT2 inhibitors must be discussed as part of shared decision-making models. Furthermore, risk mitigation must include optimizing glycemic, metabolic, and cardiovascular management strategies, as well as providing personal hygiene advice, avoiding unnecessary discontinuation of therapy with SGLT2 inhibitors.

UNRAVELING THE SGLT-2 INHIBITORS

The kidney is a key player in glucose metabolism, filtering, under physiological conditions, approximately 180 L of plasma per day. When plasma glucose levels are between approximately 90 to 100 mg/dL, almost all of the glucose is filtered and reabsorbed, mainly in the proximal tubule, returning to the circulation.[1] However, at glucose concentrations greater than 160-180 mg/dL, the maximal glucose transport capacity of the proximal tubule is exceeded, resulting in the excretion of glucose in the urine.[2] This reabsorption is regulated by sodium-glucose transporters (SGLTs) and glucose-facilitating transporters (GLUTs). Whereas GLUTs facilitate the movement of glucose from the extracellular space to the intracellular space without consuming energy, SGLTs transport glucose against its concentration gradient using the energy provided by sodium cotransport.[3]

The SGLT1 transporter is responsible for

approximately 10% of glucose reabsorption. On the other hand, SGLT2 is a high-capacity transporter, reabsorbing about 90% of the glucose in the proximal tubule.[4,5] Under normal conditions, these transporters reabsorb an average of 375 mg/min of glucose. However, disorders such as diabetes mellitus can increase the reabsorption threshold, contributing to increased hyperglycemia.[1,2]

The first model of active transport of glucose and other molecules was proposed by Bob Crane in 1960 in Prague, where he described the sodium-glucose cotransport hypothesis. According to Crane, glucose would be actively transported across the plasma membrane by a Na+/glucose cotransporter.[6] This process can be blocked directly by inhibiting phlorizin-mediated cotransport. Experimental data support the presence of higher and lower affinity Na+/glucose transporters at different sites, suggesting the presence of at least two Na^+/glucose transporters: SGLT1 and SGLT2.

Phlorizin was isolated from apple tree bark in 1835 by the French chemist Petersen with the first reports on its glycosuric action, being the first SGLT inhibitor to be identified.[7] Phlorizin is a flavonoid of the dihydrochalcone group and inhibits both SGLTs in the proximal tubule with 6 times greater affinity for SGLT2 than for SGLT1. The main disadvantages of phlorizin are its limited bioavailability and gastrointestinal adverse effects.[2]

The first orally available derivative of phlorizin was developed in 1999.[8] However, due to lack of selectivity and security concerns, development was discontinued. The discovery of C-glycoside derivatives, such as canagliflozin and dapagliflozin, made it possible to circumvent the susceptibility and degradation of glucosidase, thus reducing the gastrointestinal side effects of these compounds.[1] Currently, at least eight SGLT2 inhibitors with different characteristics have been developed and are being tested in clinical trials.

CANAGLIFLOZIN AND DAPAGLIFLOZIN

Canagliflozin was approved by the Food and Drug Administration (FDA) in 2013 for the treatment of type 2 diabetes, the appropriate dosage being dependent on kidney function.[9] A patient with an estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1,73 m^2 You can start with a dose of 100 mg/day, with the possibility of increasing it up to 300 mg. In those with a GFR ≤ 60 mL/min/1.73 m^2 the recommended dose is up to 100 mg per day. Canagliflozin is contraindicated in patients with a GFR < 45 mL/min/1.73 m2, pregnant women and children under 18 years of age. [2]

Treatment with canagliflozin as monotherapy or combined with other oral agents such as metformin, sulfonylurea and pioglitazone or with insulin results in a significant reduction in HbA1c and fasting plasma glucose levels. Adverse side effects include polyuria, hypotension, increased LDL cholesterol, increased serum creatinine levels, decreased GFR, electrolyte disturbances (such as hyperkalemia, hypermagnesemia, and hyperphosphatemia), and a slightly higher incidence of fracture compared with placebo. In addition, another very common effect is infections of the genital mucosa and urinary tract.[1,2]

Dapagliflozin (Forxiga) was approved by the European Medicines Agency in 2012 and by the FDA in 2014.[10] In addition to monotherapy, dapagliflozin is also recommended in combination with metformin, insulin and insulin sensitizers, generating a reduction in HbA1c levels regardless of the duration of diabetes. The drug also contributes to the reduction of fasting and postprandial glycemia and HbA1c, but it is not recommended for patients with GFR < 60 mL/min/1.73 m^2.[11] Adverse effects include

increased risk of vulovaginitis and balanitis due to glycosuria, as well as hypotension associated with dehydration.

IS THERE EVIDENCE OF AN INCREASE IN GENITOURINARY INFECTIONS?

It was hypothesized that the use of SGLT2 inhibitors would negatively increase mycotic genital and urinary tract infections resulting from the intentional induction mechanism of glycosuria. From this, randomized studies evaluating the efficacy of SGLT2 inhibitors investigated the incidence of genitourinary infections as a secondary safety outcome. Prescribing information indicates that each SGLT2 inhibitor may increase the risk of developing IMGs and considers infections to be a common adverse reaction, defined as having an incidence greater than 2% in clinical trials, compared to 1% to 2% in treated groups with placebo.[12-15]

A retrospective study examined the rates of IMGs in patients over 6 months taking SGLT2 inhibitors (n = 1977) compared to similar patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors (n = 1964). Results showed a significantly greater risk of IMGs in those taking SGLT2 inhibitors compared to those taking DPP-4 inhibitors (2.9% vs 0.9%; hazard ratio [HR] = 3.50; CI of 95% = 1.95-5.89).[16] However, there was a lack of diversity in the SGLT2 inhibitors used, with 93% of patients using dapagliflozin, 3% canagliflozin and 4% empagliflozin. Differentiating infection rates for each individual drug from the data presented in this study is not possible due to lack of diversity.

When separately comparing the risk of developing genital mycotic infections (GMI) in patients using canagliflozin, it was found that patients using 100mg per day of the drug had an incidence of IGM of 7.4%. This value increased to 7.8% in those who used 300mg of medication. Furthermore, there was a dignified difference between patients of different sexes. Men who used 100mg and 300mg had an incidence of 4.2% and 3.8%, respectively. Women had an incidence two to three times higher; 10.6% in those who used 100mg daily and 11.6% in those who used the medication at a dose of 300mg.[12]

Elderly patients are also subject to infections. A retrospective cohort of adults aged 66 years and older evaluated the occurrence of IMGs within 30 days of starting an SGLT2 inhibitor (n = 21,444; mean age = 71.8 years) or a DPP4 inhibitor (n = 22,463; mean age = 74.8 years). The absolute difference in risk of IMGs between new users of SGLT2 inhibitors and new users of DPP4 inhibitors was 1.21%.[17]

To clarify these doubts, a meta-analysis published in 2018 evaluated the risk of various infections in patients with type 2 diabetes using SGLT2 inhibitor therapy compared to placebo. This study included 86 RCTs, which involved a total of 50,880 patients and analyzed the class as well as each agent individually. Results across the class show a significantly greater risk of IGMs in those taking SGLT2 inhibitors compared with those taking placebo. Furthermore, this study evaluated each agent individually and found that the increased risk of IGM versus placebo was similar across all SGLT2 inhibitors: relative risk 3.91 (95% CI = 2.89-5.29) for canagliflozin and 3.45 (95% CI = 2.55-4.66) for dapagliflozin.[18]

When the results were broken down by dose, there were no obvious differences between the highest and lowest clinical doses of each agent. In the general population, the IMG rate is about 1% to 2%, depending on patient-specific factors. However, in patients using SGLT2 inhibitors, the overall incidence is increased 3 to 4 times compared to placebo.

RISK FACTORS AND INCIDENCE OF RECURRENCE

Predispositions to IMGs are important to properly distinguish the increased incidence of genitourinary infections with SGLT2 inhibitors. There are certain factors that can predispose an individual to symptomatic candidiasis such as: female gender, pregnancy, use of hormonal contraceptives, recent use of antibiotics, and other factors that can weaken the immune system such as immunosuppressant medications, HIV infections or diabetes. On the other hand, circumcised male patients have the lowest risk of developing symptomatic candidiasis.[19] In general, patients with diabetes, specifically those who do not meet glycemic targets, are considered immunosuppressed, as hyperglycemia impairs the immune system, promoting an increased susceptibility to infection.[20]

A study that compared 2671 individuals with DM2 and 8907 without DM2 found that the chances of women developing fungal vaginitis and the chances of men developing fungal balanitis were higher in the group with DM2, with an odds ratio of 1.90 and 2.25, respectively. Furthermore, the T2DM group had an increased risk of recurrent genital infections compared to the general population. High BMI, greater atherosclerotic development and lower socioeconomic status were also indicated as predisposing risk factors for genital infections.[21]

A retrospective study, which analyzed 1,049 individuals treated with dapagliflozin, found that most infections (98%) occurred in the first months after initiation, especially in women ($p<0.001$) and patients with previous IMG ($p< 0.05$). However, no other variables, including duration of diabetes, glycated hemoglobin, estimated glomerular filtration rate, and past urinary problems, were associated with an increased risk of infection in this study.[22]

STRATEGIES OF PREVENTION

According to the literature, modifiable and non-modifiable risk factors predispose patients to develop IMGs. Viable prevention strategies include reducing modifiable risk factors when possible. In general, patients with diabetes have an increased risk of infection, and this risk of infection may be increased by factors such as obesity (BMI > 30 kg/m2) and increased development of atherosclerotic plaque.

Optimize diabetes care according to the American Diabetes Association recommended comprehensive care for T2DM to maintain target blood glucose levels (premeal glucose 80 to 130 mg/dL, peak postmeal glucose less than 180 mg/dL dL for many adults), lowering BMI if overweight or obese and lowering the risk of cardiovascular accidents is imperative in lowering FMIs. In addition, personal hygiene education must be recommended for all patients initiating SGLT2 inhibitors.

A study demonstrated that the chance of patients without personal hygiene to develop IGM when compared to those who practice hygienic methods is about eight times more in the first 6 months of treatment with ISGLT2 ($p <0.05$).

However, even with appropriate prevention strategies, it is inevitable that some patients taking SGLT2 inhibitors will develop an IMG during the course of treatment. Therefore, it is imperative that the infection be properly controlled. According to the prescribing information, drug discontinuation was not necessary in most cases, as these are generally mild infections that resolve quickly with appropriate treatment. Mild infections can be treated through self-care with topical or oral antifungals and/or antibiotics.

CONCLUSION

SGLT-2 inhibitors are very useful and effective medications for treating hyperglycemia and reducing cardiovascular risk. However, it is responsible for increasing the IGM index, especially in women, three to four times when compared to a placebo group. As such, it is imperative that healthcare professionals are aware of the benefits and risks, strategies to increase safety and efficacy, and management of SGLT2 inhibitor-related issues.

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CONFLICT OF INTERESTS

There is not any.

FINANCING

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