Overview of Dapaglifluzin as a New Oral Anti-Hyperglycemic Agents[1]

Hala K. Mageed, Noor A. Shahatha, Islam T. Qasim
College of Pharmacy, University of Mosul, Mosul, Iraq

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ABSTRACT

Dapagliflozin, also known as Farxiga, has emerged as one of the newest pharmaceutical compounds being considered for its potential in combating hyperglycemia. This antidiabetic drug is part of a class called sodium-glucose cotransporter-2 (SGLT) inhibitors which work by impeding glucose reabsorption through kidneys leading to increased urine excretion thereby lowering blood sugar levels. The use of dapagliflozin offers hope for individuals suffering from type 2 diabetes due to its unique mechanism of action compared to traditional insulin therapy.
The development of dapagliflozin stems from years of extensive research into novel methods of treating hyperglycemia. Researchers have been particularly interested in SGLTs since they play crucial roles in renal glucose handling. Studies showed that blocking these transporters could lead to enhanced glycosuria without significant changes observed in other metabolites like potassium and magnesium. Consequently, the FDA approved dapagliflozin as monotherapy or combination therapy for adult patients with type 2 diabetes mellitus along with established cardiovascular disease risk factors. Despite the promising results obtained so far regarding efficacy and safety profiles, concerns remain over certain aspects related to this medication's usage. For instance, there are worries about potential side effects such as genital tract disorders and bone fractures associated with SGLT inhibition. Furthermore, it should be noted that dapagliflozin might interact negatively with other drugs used concurrently, necessitating careful consideration before prescribing. In conclusion, while dapagliflozin holds promise in managing hyperglycemia among people living with type 2 diabetes, further investigation is needed to fully understand its benefits and risks. As medical science continues to evolve, more innovative therapeutics will likely come onto the market offering diverse approaches towards tackling this global health crisis.

Keywords: *Diabetes mellitus; SGLT; Dapagliflozin.*

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders of multiple etiologies which characterized by the presence of hyperglycemia which are due to impairment of insulin secretion, defective insulin action or both. These chronic hyperglycemia may lead to dysfunction, damage and failure of different organs in the body when persist for long period. As a result, long term complications of diabetes were done and may include retinopathy, nephropathy, neuropathy and others cardiovascular disorders [1, 2].

The majority of diabetes cases can be mainly classified into two categories: type 1 diabetes mellitus (T1DM) which is due to absolute deficiency of insulin secretion and type 2 diabetes mellitus (T2DM) which is mainly due to a combination of insulin resistance and an inadequate compensatory insulin secretory response. Another type of diabetes is Gestational diabetes (GDM) which is occurs during the pregnancy [2].

Despite the wide available of different medications for DM treatment, most diabetic patients do not reach the ideal recommended level of glycemic control [1]. Many oral anti-hyperglycemic drugs (OADS) act by increasing in insulin sensitivity or enhance insulin secretion or both, and due to the progressive nature of the disease, these drugs often lose their efficacy over time [3]. Only about half of patients with T2DM achieve their glycemic, hemoglobin A1c (HbA1c), blood pressure (BP), or lipid goals, and less than 20% meet all these. Medication adverse effects, drug–drug interactions, concurrent illnesses, and hospitalizations can all cause hyperglycemia and result in difficulty maintaining

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glycemic control [4]. For all of these problems we need a new class of OADS which can meet these requirements. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new class of OADS whose efficacy is independent on insulin sensitivity and secretion [3].

The efficacy of most OADS including biguanide, sulfonylureas, α-glycosidase inhibitors, thiazolidinediones, glucagon-likepeptide-1 analog and dipeptidyl peptidase-4 inhibitors is insulin-dependent and therefore, their efficacy was diminishes when the function of pancreatic islet β-cells declines during the progression of T2DM [5].

DM is a worldwide problem that is growing in prevalence. An estimated 347 million people worldwide are diagnosed with diabetes, and 90–95% of those have T2DM. As by 2025, its prevalence will be an increase 24% as compared with 2003. There will be 72% increase diabetics by 2030 in individuals of 20 to 79 years of age. Environmental factors like obesity, physical inactivity, diet and socioeconomic factors are responsible for development of DM. As a result of these factors, the number of diabetic patients is expected to rise to 592 million by 2035 [6].

Increasing DM prevalence could lead to increase morbidity, including continued high rate of renal disease, ageing-related disability, and cancers. On the other hand long-term complications of diabetes are divided into microvascular like retinopathy, nephropathy which may lead to renal failure; and neuropathy which may be a risk of foot ulcers and macrovascular complications such as hypertension and abnormalities of lipoprotein metabolism which are often found in people with diabetes. All these complications will increase mortality in diabetic patients [7].

The most effective management of DM should include both lifestyle modifications with balanced diet, exercise and pharmacologic therapies which are very necessary to meet individualized glycemic goals. Lifestyle modifications must be combined with OADS for optimal glycemic control, particularly as T2DM progresses with continued loss of pancreatic β-cells function and insulin production. OADS with different mechanisms of actions and synergistic effects which can be obtained when used OADS together in combination are necessary to extend the number of treatment options available to patients with T2DM [8].

SGLT2 inhibitors are a new therapeutic class of OADS for the treatment of T2DM. This therapeutic class currently includes six agents: canagliflozin, dapagliflozin, empagliflozin, ertuglifluzin, ipraglifluzin and tofoglifluzin. The last two drugs were approved in japan [9].

Dapagliflozin was approved in the US FDA on 8 January 2014 and has previously been approved in 2011 by EU and is used in 38 other countries, including Europe, under the trade name Forxiga (Bristol-Myers Squibb Company, Middlesex, UK). A fixed-dose combination of dapagliflozin and metformin (Xigduo [Bristol-Myers Squibb Company, Middlesex, UK]) was also recently approved in Europe [10].

Dapagliflozin is an oral active agent, highly reversible selective SGLT2 inhibitors which has been shown to significantly improve glycemic control. SGLT2 inhibitors reduce glucose reabsorption in the kidneys and facilitate its excretion in the urine by inhibiting the high capacity glucose transporter SGLT2 that located in the proximal convoluted tubule, this result in lowering glucose levels which are independent on insulin action [11]. This unique mechanism of action of SGLT2 inhibitors when compared with other OADS make it to be used in combination with other OADS. On the other hand, dapagliflozin increase the amount of glucose excreted in the urine and improved both fasting plasma glucose (FPG) and post prandial plasma glucose levels in type 2 diabetic patients [12].

MECHANISM OF ACTION

Dapagliflozin competitively, reversibly, and highly selectively inhibits SGLT2. SGLT2 are expressed in the kidney and on the epithelial lining of the S1 segment of the proximal convoluted tubule. Physiologically, these transporters are responsible for approximately 90% of renal glucose absorption. By blocking SGLT2 with dapagliflozin, reabsorption of glucose into the bloodstream is reduced. Finally, dapagliflozin promotes glucose filtration through the kidneys and into the urine which lead to eliminate glucose from the body [13]. In T2DM renal glucose reabsorption is increased. SGLT2 has a low-affinity, high-capacity transporter located in the S1 segment of the proximal convoluted tubule of the nephron that mediates the majority of renal glucose reabsorption from the glomerular filtrate [14].

Several studies have demonstrated that 24 hour urine glucose excretion with dapagliflozin represents only about 40–50% of the human filtered glucose load. One potential reason for this ceiling effect is that when SGLT2 is inhibited, sodium glucose cotransporter-1 (SGLT1) may compensate by increasing reabsorption of glucose [15].

This type of mechanism of action mean that, dapaglifluzin does not act through increasing insulin secretion or decreasing insulin receptor resistance, therefore, therapy with this class of agents neither causes hypoglycemia nor depends on the duration of T2DM. Thus it can be initiated as a monotherapy in newly diagnosed diabetic patients or in combination with other OADS or insulin in patients with long standing diabetes [16].

THERAPEUTIC EFFECTS

Treatment with dapagliflozin as a monotherapy or in combination with other OADS was associated with reductions in HbA1c and FPG as well as reductions or stabilization of body weight and systolic BP in patients with T2DM. Dapagliflozin improved glycemic control, stabilized insulin dosing and reduced body weight without increasing major hypoglycaemic episodes over several weeks in patients whose T2DM was inadequately controlled with insulin [17].

For patients with T2DM, multiple OADS with different mechanisms of action are often required to adequately manage hyperglycemia. Most currently available OADS act by increasing insulin secretion or sensitizing tissues to insulin action and therefore depend upon pancreatic β-cells function for efficacy. Due to a progressive loss of β-cells function, many patients eventually require multiple agents to achieve target HbA1c levels. Many currently available agents are associated with hypoglycemia and/or weight gain that act as barriers to the achievement of glycemic and weight control. Therefore, we need to add a new agent that are not effect on body weight or lead to loss of weight without causing hypoglycemia. Dapaglifluzin meets the most of these requirements and therefore, has been used in the management of T2DM [18].

Glycemic control and body weight reduction

Dapagliflozin as a monotherapy or in combination with other OADS, including sulfonylureas, glinides, metformin, a-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists has beneficial effect on glycemic control. In the recent research dapaglifluzine can be added to insulin in the treatment of diabetic patients .In patients with T2DM who received dapagliflozin in doses between 2.5mg and 20 mg. as a result, glucose excretion after 1 day ranged between 38 and 77 g and after 14 days ranged between 42 and 73 g [19].

Omoroski et al state that as dapagliflozin may provide additional glycemic control when used with insulin in patients with advanced β-cells failure. Moreover, energy loss and osmotic diuresis secondary to increased urinary glucose excretion and natriuretic may counter insulin-related weight gain and fluid retention, respectively [20].

In other studies as in Japan Kaku et al demonstrate that, in patients with T2DM, the efficacy of dapagliflozin on glycemic parameters and body weight has been studied over 3–6 months and they found that there are improvement for both parameters [21].

In study done by bailey et al in 2010, a clinical presentation of duration up to 2 years in patients with T2DM was studied, they found that, dapagliflozin improved glycemic control and reduced body weight when added to metformin [22]. Other study in 2016 state that dapagliflozin as a monotherapy and in combination therapy was improve glycemic control and reducing bodyweight and BP in type 2 diabetic patients including those with high HbA1c [23].

Sulphonylureas are widely used as second line therapy for patients with T2DM. Although their efficacy as antihyperglycemic agents is established but a common side effect such as hypoglycemia and weight gain can appear. Use of dapagliflozin as second line therapy may provide an alternative option to sulphonylureas, with a more favorable side effect profile and additional beneficial effects on body weight. In study done in 2015, dapagliflozin and sulphonylurea (glipizide) provide similar efficacy with the benefits of sustained reductions in body weight and a lower rate of hypoglycemia with dapagliflozin compared to glipizide after 1 year of treatment. These effects continued to be observed in extensions of up to 4 years [24]. Other study state that, addition of dapaglifluzine to metformin in type 2 diabetic patients inadequately controlled with metformin lead to reducing of fat mass and body weight [25].

HbA1c reduction

Several studies show that, dapaglifluzin will reduce HbA1c when used for several weeks in combination with other OADS for T2DM treatment. In 2012 Henry et al demonstrate that, dapagliflozin in dose of 5mg or 10 mg per day as initial combination therapy with metformin significantly lowered HbA1c concentrations from baseline to 24 weeks compared with monotherapy with either component, without increasing the risk for hypoglycemia[26]. Jabbour et al state that, dapagliflozin was lower HbA1c when administered as a monotherapy or in combination with other OADS in patients with T2DM[27].

Systolic blood pressure reduction

Dapagliflozin can cause decreases in systolic BP via its osmotic diuretic effect. Therefore, patients receiving antihypertensive agents (especially loop diuretics) or those known to experience hypotension should be closely monitored when initiating or titrating dapagliflozin[14]. Other study shows that dapagliflozin in a dose of 10 m per day can reduce systolic BP in type 2 diabetic patients inadequately controlled and with hypertension despite receiving angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy alone for hypertension treatment[28]. In 2015, Sjöström et al shows that, dapagliflozin has also reduced blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes[29].

Improvement of cardiovascular risk factors

Several studies show that, dapaglifuzin can improves cardiovascular risk factors when used in patients with T2DM. Risk factors associated with cardiovascular disease include obesity, hypertension and dyslipidaemia, while diabetes independently increases the risk of CVD. Dapagliflozin have been shown to improve some cardiovascular risk factors, with a low risk of hypoglycemia[30]. Ptaszynska et al state that, small changes in low-density lipoprotein and high-density lipoprotein have also been observed with dapagliflozin[31].

On the other hand, in research done in 2017, among the SGLT2 inhibitors, empagliflozin and canagliflozin have shown reduced risk of major adverse cardiovascular events versus placebo in their respective cardiovascular outcomes trials [32]. Finally, a recent study in 2019 McGurnaghan et al indicate that, dapaglifluzin can reduce HbA1c, Systolic BP, body weight and body mass index [33].

ADVERSE EFFECTS

Urinary tract infections and genital infections are common side effects of dapaglifluzin which often associated with SGLT2 inhibitor treatment as a consequence of the associated glucosuria. Events suggest that, urinary tract infections and genital infections were higher in all dapagliflozin groups compared with placebo. These events were more common in women, and most occurred during the first 24 weeks of treatment. Most of these infections were classified as mild or moderate in intensity and responded to routine antibiotic treatments. Genital infection is the commonest side effect of dapaglifluzine which is mild or moderate and occur in the first 6 months of treatment. A risk of recurrence or new infection may occur with continues use. Genital infections adverse effect led to treatment discontinuation in patients receiving dapagliflozin [34, 35]. These adverse effects results were found by another recent research which done in 2018 by Jabbour et al who show that, genital infection and urinary tract infections especially pyelonephritis has also be seen after treatment with dapaglifluzin which is mainly mild or moderate but these patients rapidly respond to appropriate antibiotic therapy after withdrawal of dapaglifluzin [36].

CONTRAINDICATION AND CAUTION

Dapaglifluzin is used with caution in elderly patients with chronic renal disease because of dehydration side effect but some research demonstrate that, dapaglifluzin can be used safety in elderly patients with chronic renal disease and this differences in effects is depend on glomerular filtration rate and stage of renal failure [37]. On the other hand, in 2018 Alessandro et al state that renal functions are not affected and no changes in serum creatinine after 1 year treatment with dapaglifluzin [38].

CONCLUSION

In conclusion, dapagliflozin represents an innovative approach towards managing hyperglycemia due to its unique mechanism of action targeting SGLT2 enzymes responsible for renal glucose reuptake. Its efficacy across diverse patient groups underscores its versatility and potential therapeutic benefit. Nevertheless, caution should be exercised regarding common adverse events. As further research continues to elucidate its full range of benefits and risks, dapagliflozin promises to play a crucial role in combating diabetes worldwide.

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