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Joseph Chinnappa Raj J
Department of pharmacy practice, JKKMMRF'S-Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Namakkal dt-638183, Tamil Nadu, Affiliated by the Tamilnadu Dr MGRMedical University, Chennai, Tamil Nadu, India

Dr. Arul Prakasam KC
Department of pharmacy practice, JKKMMRF'S-Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Namakkal dt-638183, Tamil Nadu, Affiliated by the Tamilnadu Dr MGRMedical University, Chennai, Tamil Nadu, India

Balaji S
Department of pharmacy practice, JKKMMRF'S-Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Namakkal dt-638183, Tamil Nadu, Affiliated by the Tamilnadu Dr MGRMedical University, Chennai, Tamil Nadu, India

Jebin Mishael Davis S
Department of pharmacy practice, JKKMMRF'S-Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Namakkal dt-638183, Tamil Nadu, Affiliated by the Tamilnadu Dr MGRMedical University, Chennai, Tamil Nadu, India

Corresponding Author:
Department of pharmacy practice, JKKMMRF'S-Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Namakkal dt-638183, Tamil Nadu, Affiliated by the Tamilnadu Dr MGRMedical University, Chennai, Tamil Nadu, India

A focus on urinary tract infections dapagliflozin in type 2 diabetes mellitus: Mechanism of action, pharmacology, efficacy, adverse effects and safety

Joseph Chinnappa Raj J, Arul Prakasam KC, Balaji S and Jebin Mishael Davis S

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Abstract
A novel strategy for treating type 2 diabetic mellitus (T2DM) is dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor that increases renal glucose excretion without the need for insulin. In the proximal renal tubule, dapagliflozin selectively inhibits SGLT2, which effectively lowers blood glucose, reduces body weight, and moderately lowers blood pressure. Major clinical trials like DAPA-CKD and DECLARE-TIMI 58 have demonstrated that it has cardioprotective and renoprotective effects in addition to glycemic management. Dapagliflozin is pharmacologically well absorbed, with a 78% bioavailability, and is mostly converted to inactive metabolites in the liver and kidney. Despite being generally safe, using it increases the risk of genital mycotic infections and, to a lesser extent, UTIs. However, the majority of these infections are mild to moderate, and routine treatment works well for them. There has been no discernible increase in severe UTIs or renal impairment linked to dapagliflozin, according to studies. Although there are certain controllable safety issues, dapagliflozin provides a variety of therapeutic advantages in the treatment of type 2 diabetes.

Keywords: Dapagliflozin, type 2 diabetes mellitus, sodium-glucose cotransporter-2 (SGLT2) inhibitor, urinary tract infection.

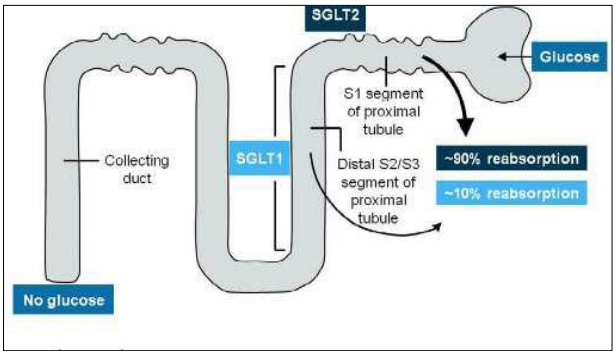
Introduction
Insulin resistance in various insulin target tissues, such as the liver, adipose tissue, and skeletal muscle, as well as insufficient insulin secretion by pancreatic β-cells, are characteristics of type 2 diabetes mellitus (T2DM), a complex metabolic disease that is also linked to other metabolic disorders like obesity, dyslipidemia, hyperuricemia, and non-alcoholic fatty liver disease. Thus, optimal hypoglycemic medications were thought to help with both glycemic control and comorbid metabolic disorders. Because of this, a variety of novel hypoglycemic medications, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, have been developed recently.Insulin resistance in different target tissues of insulin, including the liver, adipose tissue, and muscle, and inadequate insulin secretion by pancreatic β-cells, are features of type 2 diabetes mellitus (T2DM), a multi-factorial metabolic disorder that is also associated with other metabolic disorders such as obesity, dyslipidemia, hyperuricemia, and non-alcoholic fatty liver disease. Accordingly, best-in-class hypoglycemic agents were believed to assist not only in glycemic regulation but also in comorbid metabolic disease. Due to this, several novel hypoglycemic agents, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, have been created recently.90% of the glucose reabsorbed by the kidneys is due to SGLT2, an active glucose transporter in the early proximal renal tubule. Diabetic patients and animal models of the disease have increased expression of this protein. By raising urine glucose the elimination in a way that is independent of insulin, SGLT2 inhibitors produce hypoglycemic effects. Nowadays, a wide range of SGLT2 inhibitors with steadily growing clinical use are available on the market worldwide. Evidence about the beneficial impact of SGLT2 inhibitors beyond their glucose-lowering properties has attracted increasing attention. Such effects include reducing the risk of heart failure, kidney disease, and cardiovascular disease and decreasing serum uric acid (SUA) concentrations and gout flares among T2DM patients.

An increasing body of research indicates that patients with type 2 diabetes mellitus (DM) benefit from sodium-glucose cotransporter-2 inhibitors (SGLT2i) in specific ways, including improved cardiovascular and renal outcomes. Empaliflozin was shown to lower the risk of worsening kidney injury in patients with type 2 diabetes (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal replacement therapy, or death from renal disease) in the EMPA-REG outcome trial. In a more recent DAPA-CKD trial, dapagliflozin (DAPA) significantly reduced renal hard endpoints when compared to a placebo, even in CKD patients without diabetes mellitus. DAPA has been authorized for use in CKD patients in Japan based on the efficacy and safety of the medication as demonstrated by multiple clinical trials. According to research, SGLT2i inhibits the course of chronic kidney disease by attenuating glomerular hyperfiltration through the tubuloglomerular feedback loop. When patients with type 1 diabetes begin DAPA medication, the phenomenon is seen as the immediate decrease in the initial dip in their estimated glomerular filtration rate (eGFR). It is still unclear, nevertheless, whether DAPA medication is the cause of the initial eGFR decrease and which clinical traits in CKD patients without DM are independent of it. Therefore, we have looked backwards to see what clinical factors affect the occurrence of the initial EGFR dip in the current study.

Mechanism of action

Sodium-glucose co-transporter-2 inhibitors work by inhibiting SGLT2 in the proximal convulsed tubule, which prevents glucose reabsorption and facilitates the easier excretion of the body through urine. All glycaemic indicators get better when the plasma levels of glucose reduce as it gets eliminated. The mechanism of action of its activity is not dependent on blood glucose levels like thiazolidinedione (mediated by GLUTs) but rather on insulin. Hypoglycemia is thus unlikely, and no risk of beta cell overstimulation or exhaustion also exists. As SGLT2i's action is based on intact renal glomerular-tubular function, its efficacy is reduced in patients with renal impairment. SGLT2 mediates approximately 90% of active renal glucose reabsorption in the S1 segment of the early proximal tubule in the kidney. Dapagliflozin is a reversible and selective SGLT2 inhibitor, which dramatically reduces blood glucose and glucose reabsorption without insulin requirement. Dapagliflozin also enhances insulin sensitivity, but in T2DM patients, it also enhances endogenous glucose production. Loss of body weight has been associated with dapagliflozin's lowering of reabsorption of glucose, possibly due to reduced body caloric intake. It has also been shown that the drug decreases blood pressure due to its osmotic diuretic effect and the resulting fall in body weight.

The human kidney can reabsorb almost all of the glucose in the filtrate as soon as 34 weeks of gestation. Daily, this translates to 180 g of glucose. SGLT2, as expressed by the epithelial cells covering the first segment of the proximal convoluted tubule, reabsorbs 90% of the filtered glucose, only 1% of which enters the urine. In the lower segment of the nephron, SGLT1 reabsorbs the last 10%. The luminal surface of the epithelium of the proximal tubule is where the process of glucose reabsorption starts, as SGLT2 actively takes up glucose from the glomerular filtrate into the epithelial cells. As sodium is being actively pumped out of the basolateral cells by the Na+/K+-adenosine triphosphatase pump, glucose is being transported with sodium by the cotransporters. Glucose is transported out of the cell through the basolateral membrane by glucose transporters (GLUTs), which are transporters that are passive. This is done along the concentration gradient. The ultimate effect of this whole process is the return of glucose to the circulation from the proximal tubule. To comprehend more fully how the SGLT2/GLUT2 transporter molecules work, two genetic disorders23 have been discovered: Renal glycosuria in families and Fanconi-Bickel syndrome.



Pharmacology of action

Taken once a day, dapagliflozin is an oral, reversible, and highly selective SGLT2 inhibitor. The human absolute bioavailability of dapagliflozin is 78%. With a time to maximum plasma concentration of 0.5-1.3 hours, it is rapidly absorbed. With a mean volume of distribution of 118 liters, dapagliflozin has extensive extravascular distribution. Age, ethnic group, gender, body weight, or the presence of type 2 diabetes are not determinable in affecting dapagliflozin exposure. Nonetheless, patients younger than 18 years and older than 75 are not recommended to start treatment with dapagliflozin because of a lack of data [European Commission, 2012]. Food does not have significant effects on drug pharmacokinetics and action. Uridine diphosphate glutaronidasyltransferase 1A9 (glucuronidation) in the liver and the kidney metabolizes dapagliflozin into a substantial inactive metabolite (dapagliflozin 3-O-glucuronide, D3OG), which is primarily excreted by the kidney. Hepatic impairment affects the plasma concentration of dapagliflozin. Patients with mild, moderate, or severe hepatic impairment had mean peak plasma concentrations of dapagliflozin 12% lower and 12% and 40% higher, respectively, than in the healthy group, based on a trial in which a single oral dose of the drug (10 mg) was employed. Individuals with mild to severe hepatic impairment do not require a change in their medication dosing. But when patients with extensive liver damage are administered dapagliflozin, physicians should exercise care, in whom 5 mg should be used as a starting dose which may be titrated up to 10 mg in case of good tolerability.

The kidney mainly clears dapagliflozin and its inactive metabolite. Renal impairment is one of the key determinants of dapagliflozin's metabolism and efficacy. In accordance with a study, patients with mild, moderate, and severe renal impairment had increased peak plasma concentrations of dapagliflozin (4%, 6%, and 9%) and D3OG (20%, 37%, and 52%, respectively) compared with patients who have normal kidney function. Nevertheless, in patients with renal impairment, the pharmacodynamic effects of dapagliflozin were considerably reduced, resulting in decreased efficacy. individuals with moderate to severe renal impairment

(creatinine clearance <60 ml/min or estimated glomerular filtration rate < 60 ml/min/1.73 m2) should avoid the use of dapagliflozin, but should be used in individuals with mild renal impairment.

Pharmacokinetics

Dapagliflozin is rapidly and well absorbed when administered orally. 38 and 39 after a fast-dose administration, maximum plasma levels occur within two hours. Bioavailability is 78% with a once-daily (OD) dose of 10 mg. Food and food are fine to take it with. Forty Hepatic or renal disease has minimal impact on its 91% protein-bound status. The enzyme uridine diphosphate-glucuronosyltransferase 1A9 metabolizes dapagliflozin in the liver and kidney to yield its inactive metabolite, dapagliflozin 3-O-glucuronide. Dapagliflozin's average terminal plasma half-life is 13 hours (10 mg dose). Dapagliflozin and its metabolites are primarily excreted by the urine, and renal impairment hinders this excretion; 2% are excreted unchanged by the urine and 15% are excreted unchanged by the feces.

Pharmacodynamics

Higher diuresis of 375 mL/day on average and dose-dependent glycosuria are linked to dapagliflozin. Serum sodium does not seem to be impacted by the brief increase in sodium excretion in the urine. Urinary uric acid excretion rises momentarily, while serum uric acid levels fall over time. Although the exact cause of the decreased serum uric acid levels is unknown, it was recently suggested that either suppression of uric acid absorption at the renal tubule's collecting duct or glycosuria-induced uric acid release via GLUT9 isoform 2 in the proximal tubule are to blame. This could also be because dapagliflozin causes weight loss.

Efficacy of Dapagliflozin in T2DM

Based on their pharmacological profiles, SGLT2 inhibitors should possess an acceptable safety profile. All drugs in this class exhibited the identical adverse effects observed during clinical trials.Gestural side effects have not been observed, and no intestinal mucosa SGLT1 transporter blockage can be anticipated with their high selectivity for the SGLT2 transporter. In addition, SGLT2 pharmacologic inhibition would not be anticipated to cause polyuria, nocturia, or contraction of volume since patients with homozygous mutations in the SGLT2 gene are asymptomatic despite the occurrence of very marked glucosuria (> 50-100 g/24 h). Clinical trials have not indicated any of these adverse effects. There was a slight rise in urine output (200-400 mL/d) during the 12-24 weeks when dapagliflozin was administered to individuals. Initial two to three days of treatment. No evidence of over excretion of sodium, potassium, or other electrolytes was detected in the urine. A modest rise in plasma urea nitrogen to creatinine ratio and hematocrit (1-2 volume percent) have been observed, which is in keeping with moderate volume contraction. Plasma electrolyte concentrations were unaltered following dapagliflozin. As noted earlier, type 2 diabetes patients have exhibited moderate reductions in systolic and diastolic blood pressure.Lastly, hypoglycemia is not anticipated in diabetic or non-diabetic animals, and SGLT2 inhibitors are not associated with hypoglycemia in type 2 diabetic individuals or diabetic animals as they do not impact the glucose counterregulatory mechanisms.

Urinary tract infections have been demonstrated to increase by approximately 50% in type 2 diabetic subjects on doses of dapagliflozin of 5 (N=1145) and 10 (N=1193) mg once daily. Whether the glucosuria caused by SGLT2 inhibitors promotes bacterial growth is yet to be determined. SGLT2 treatment did not increase the incidence of urinary bacteruria in one study that sampled urine midstream. In addition to this, SGLT2 inhibitor drug augments vulvovaginitis and balanitis frequencies by approximately three times.It has been shown that SGLT2 inhibitors have no negative influence on renal function, as evidenced by elevation in blood creatinine or the development of tubular proteinuria or albuminuria in T2DM patients with normal GFR. There was increased breast cancer and bladder cancer incidence in phase 3 dapagliflozin studies. However, there were only ten occurrences in total (10 for both cancers). This outcome was surprising because the SGLT2 transporter is not expressed in breast or bladder tissue. In addition, extensive 2-year animal carcinogenic studies did not indicate any neoplastic or preneoplastic activity.

The significance of the increased frequency of the above two cancers is unknown to date because exposure to dapagliflozin was temporary (generally for less than one year), while breast and particularly bladder cancer develop in a period of years. In addition, the high frequency of UTI testing could have led to detection of microscopic hematuria, which may have introduced detection bias against bladder cancer. However, due to this potential carcinogenic signal, the FDA asked for additional safety data on cancer risk related to dapagliflozin therapy before authorizing the drug for use in clinical practice.

All randomized participants who received at least one dose of double-blind trial medication and for whom at least a baseline and one postbaseline efficacy value were available were included in the full analysis set, which was employed in the efficacy analyses. Change from baseline in HbA1c at Week 24 was the primary effectiveness analysis, and it was analyzed using a mixed effects model with repeated measures (MMRM) with "direct likelihood" that assumed missing data were missing at random. Before double-blind study medication was interrupted or rescue medication was given, measures were included in the primary analysis. Treatment, week, randomization stratification factor (glucose-lowering treatment stratum), and treatment-by-week interaction were all fixed categorical effects in the model. Baseline measurement and baseline measurement-byweek interaction were also continuous fixed covariate effects.Point estimates and 95% CIs of each treatment group's mean change were estimated, and mean change estimates of the dapagliflozin and placebo groups were compared. At the nominal level, P values were also calculated and reported for the differences in estimates between dapagliflozin and placebo groups at Week 24. Secondary efficacy endpoint tests (between-baseline difference for body weight, FPG, and seated SBP) were not conducted unless the comparison of the primary endpoint and all previously ordered secondary comparisons were significant. This sequential testing strategy was employed to aid in multiple comparisons. Like the main analysis model, an MMRM was used to analyze exploratory and secondary endpoints. Exploratory analyses for outcomes collected at baseline and at the end of therapy with the last observation carried forward (LOCF) using analysis of covariance (ANCOVA). ANCOVA models were a fixed covariate

effect for baseline measurement and fixed categorical effects for treatment and randomization stratification factor.

Adverse effects: Dapagliflozin

Among individuals with type 2 diabetes, urinary tract infections (UTIs) are common. The relationship between glycosuria and UTIs in patients with poorly controlled diabetes (HbA1c > 6.5-12%) was evaluated by Johnsson *et al*. by integrating the safety data of 12 randomized placebo-controlled dapagliflozin studies. Besides Met, insulin, SU, or thiazolidinedione, patients also received either dapagliflozin (2.5 mg, 5 mg, or 10 mg) or a placebo once daily for 12-24 weeks. 3,152 patients treated with once-daily dapagliflozin at a dose of 2.5 mg (N=814), 5 mg (N=1145), or 10 mg (N=1193) as monotherapy or as an adjunct treatment and 1,393 patients treated with a placebo, had their rates of UTIs that were either clinically diagnosed or imputed from events measured. Diagnosed infection rates were 3.6%, 5.7%, 4.3%, and 3.7% for dapagliflozin at 2.5 mg, 5 mg, 10 mg, and placebo, respectively. The rate of UTIs remained steady in the face of sustained elevation in urine glucose levels in response to dapagliflozin dosages. It was suspected that most of the infections encountered were typical in diabetic individuals. Two-thirds of UTIs were detected according to their common symptoms, and most of those infections were mild to moderate and received regular care; they were cleared after a single cycle of medication. Infrequently, eight (0.3%) participants taking dapagliflozin and one (0.1%) patient on placebo withdrew due to UTIs. a history of recurring UTIs, female sex, and age >65 years, but not the baseline HbA1c, were predictors of UTIs. Furthermore, this study could not determine a definitive dosage relationship between UTI and glycosuria.

Dapagliflozin modestly reduces blood pressure but raises diuresis. Consequently, patients who are at risk of volume depletion, hypotension, and electrolyte disturbances should be administered the drug cautiously. Volume-deficient patients, like patients on loop diuretics or with an acute illness, should not be administered dapagliflozin [European Commission, 2012]. Also, patients who undergo volume depletion should discontinue the drug until the depletion is corrected. Dapagliflozin and UTI and vaginal infection incidence, which were higher among women, were dose-dependently correlated in a meta-analysis involving 52 randomized controlled trials. Genital infection and UTI are most frequent in the first 24 to 26 weeks of treatment, after which their occurrence reduces. 80Routine oral and topical antifungal therapy (standard therapy) often successfully treats these infections, which are usually uncomplicated. 80, 81 severe pyelonephritis occurs with very low frequency and is approximately the same as a placebo. It is worth mentioning that 12 cases of Fournier's gangrene-necrotizing fasciitis perineum have appeared in patients on SGLT2 inhibitors, according to the latest FDA warnings since 2013.

Safety Profile of Dapagliflozin: Focus on UTI and Beyond

Even though dapagliflozin's many clinically established benefits, concern persists regarding the incidence of adverse events (AE) related to the SGLT2 drug class. Phase III clinical study results for Urinary Tract Infections (UTI) have been variable. As SGLT inhibitors are potentially to increase the risk of genitourinary infection via increased glucosuria, this has been a debated issue. In contrast to 4.5% of patients receiving a placebo, 7.3% and 6.5% of patients taking 5 and 10 mg of dapagliflozin, respectively, reported UTI symptoms, based on results from 12 dapagliflozin type 2 diabetes clinical efficacy trials. Infections were generally mild or moderate and readily treatable, however. Though previous studies have shown there is an association between the use of dapagliflozin and a high rate of UTI occurrence, another recent evaluation done by Dave *et al*., 2019 revealed that the risk of UTIs with the addition of SGLT2 inhibitors was not significantly different from what other types of second-line antidiabetic medications are found in true clinical practice. There is a built-in 60% increased risk of UTIs in type 2 diabetic patients, and the DECLARE and DAPA-HF trials indicated that patients who were on dapagliflozin experienced fewer UTI events. Dapagliflozin use is more frequently associated with genital infections, including fungal vulvovaginitis and balanitis. In a pooled analysis of 4545 patients, the infections were noted in 4.1-5.7% of patients versus a 0.9% infection rate on placebo. Genital fungal infections are more prevalent in females; in one study, 13.2% of females and 3.3% of males had them (aOR 4.22, 95% CI 2.48-7.19, p<0.001). Genital infections were once more probable with dapagliflozin compared to a placebo (HR 8.36, 95% CI 4.19-16.68), this being confirmed by the DECLARE study. Overall, these diseases were likewise easily controlled and rarely led to drug or research withdrawal.

Conclusion

An efficient and well-tolerated oral hypoglycemic medication, dapagliflozin enhances glucose management and has extra advantages for the kidneys and heart. Because of its insulin-independent mode of action, it can be used with a variety of T2DM patients, including those who have insulin resistance. Mild vaginal and urinary infections have been reported to be more common, however these side effects are usually temporary and treatable. The overall risk of severe UTIs is nevertheless similar to that of other antidiabetic medications, according to clinical data. Thus, as long as patients are carefully chosen and closely watched for genitourinary infections, dapagliflozin continues to be an effective part of the treatment arsenal for type 2 diabetes.

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