HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2024; 11(3):1483-1489

UDC: 615.015:616.379-008.64

doi:10.5937/hpimj2403483D

Education Article

The Influence of The Pharmacodynamic Properties of Drugs on Indications For Their Use - Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2 Inhibitors)

Nikola I. Denda[1], Nemanja Z. Maletin[1], Marko B. Atanasković[1], Biljana A. Vučković[2,3], Aleksandar L. Rašković[1]

[1] Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad
[2] Department of Pathophysiology and Laboratory Medicine, Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia
[3] Center of Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Serbia

SUMMARY

Introduction: Sodium-glucose cotransporter type 2 (SGLT2) inhibitors play a crucial role in type 2 diabetes treatment, exerting effects on proximal tubules to reduce glucose reabsorption and enhance urinary excretion, offering cardiovascular and renoprotective benefits. This study aims to explore the pharmacodynamic advantages of SGLT2 inhibitors, expanding their therapeutic indications and assessing variations in pharmacological effects among different representatives.

Methods: A thorough review of literature from 2000 to 2023 via PubMed focused on SGLT2 inhibitors' pharmacology and clinical impact on T2DM, heart failure, and chronic kidney disease. Twenty relevant studies were analyzed to understand differences between these inhibitors, refining their efficacy and safety profiles.

Topic: On May 20, 2024, 16 original human studies examining the effects of SGLT2 inhibitors were found. Additionally, 4 original animal studies investigating the impact of SGLT2 inhibitors on laboratory mice were discovered.

Conclusion: SGLT2 inhibitors show promise in improving patients' quality of life and reducing diabetes-related complications. Continuous safety and efficiency monitoring is crucial for optimizing their therapeutic use, given limited data on their long-term safety and comparative effectiveness.

Keywords: Diabetes Mellitus, SGLT2 Inhibitors, Diabetic Complications

Corresponding author:
Full Professor Aleksandar L. Rašković, MD, PhD
Specialist in Clinical Pharmacology
Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine Novi Sad, University of Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia
E-mail: aleksandar.raskovic@mf.uns.ac.rs

INTRODUCTION

There are various pharmacological approaches to the treatment of diabetest type 2 (T2DM). Strict glycemic control with older diabetes medications, such as metformin, thiazolidinediones, sulfonylureas, meglitinides, and DPP-4 inhibitors reduces microvascular complications but has no significant effect on macrovascular complications. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown cardioprotective effects and a reduction in cardiovascular outcomes. SGLT2 inhibitors work by blocking the transporter for sodium and glucose in the renal proximal tubule, leading to glucose elimination through urine and a decrease in serum glucose levels.

Cardiovascular disease and chronic kidney disease are key comorbidities that influence the choice of therapy. Currently, four SGLT2 inhibitors are approved for the treatment of T2DM by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA): canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, while empagliflozin and dapagliflozin are additionally approved for the treatment of heart failure and chronic kidney disease [http://www.fda.gov; http://www.ema.europa.eu].

By inhibiting the SGLT2 transporter, the reabsorption of glucose is blocked, which facilitates its excretion and ultimately lowering blood glucose levels. In addition, the elimination of glucose via the kidneys does not cause the negative metabolic effects associated with the removal of endogenous glucose. This mechanism contributes to weight loss due to calorie loss. Also, the action on the SGLT2 transporter affects the excretion of sodium, which affects the reduction of arterial blood pressure. The favorable cardiovascular effects of these drugs are also explained by eliminating the influence of sympathetic nerves on the heart and blood vessels. All these factors suggest that SGLT2 transporter inhibition may provide a more effective treatment of diabetes with associated cardiovascular disorders compared to existing therapies [1]. SGLT2 utilizes one sodium ion per glucose molecule, while SGLT1 uses two sodium ions per glucose molecule [2]. Therefore, SGLT2 uses less energy than SGLT1. Therefore, the most energetically efficient adaptation to hyperglycemia is to increase the amount of SGLT2. Studies in humans with T2DM and genetic rodent models of T2DM and T1DM support an increase in renal SGLT2 expression [3-5]. SGLT2 inhibitors lower HbA1c, uric acid, and body weight, reducing risk factors for adverse cardiovascular outcomes.

Numerous preclinical studies have confirmed their anti-inflammatory, antiproliferative, antioxidant, metabolic and vascular role, as well as their contribution to reducing negative cardiac remodeling [6,7]. SGLT2-inhibitors are studied at the molecular, mitochondrial, interstitial and electrolyte levels. Although originally developed to treat hyperglycemia in people with diabetes, recent placebo-controlled outcome trials have shown that empagliflozin and canagliflozin reduce the risk of cardiovascular disease in individuals with T2DM at high risk for such outcomes.. Exploratory analyzes have also suggested that they may reduce the progression of kidney disease in this population [8-10] Increased elimination of sodium via renal tubules reduces intraglomerular pressure, which underpins the nephroprotective effect of SGLT2 inhibitors.

Most patients usually tolerate this drug class well, and the most common side effects of SGLT2 inhibitors recorded in their post-registration monitoring are predictable and related to their mechanism of action. Glycosuria can lead to an increased risk of bacterial, particularly fungal, infections of the genitourinary tract increases, which are generally mild to moderate and respond well to therapy.

Orthostatic hypotension is possible due to hyponatremia and water loss, which, in severe cases, can lead to circulatory disorders in peripheral areas, potentially resulting in gangrene e. SGLT2 inhibitors are not recommended for use in pregnancy. An increased risk of lower limb amputation and bone fracture has been reported in clinical practice in a trial with canagliflozin [11].

Several SGLT2 inhibitors h ave received approval for T2DM treatment, while others are still undergoing pre-registration in clinical trials. There are three selective SGLT2 inhibitors on the market - canagliflozin (Invokana®), dapagliflozin (Farkiga®) and empagliflozin (Jardiance®) - which are approved by the Food and Drug Administration (FDA) as mono, dual and triple therapy for T2DM. In addition to these, several other similar compounds are in the development process and may be approved soon. Empagliflozin, among these three approved drugs, shows the highest selectivity for SGLT2 compared to SGLT1, while canagliflozin is the least selective [11].

A highly selective SGLT2 inhibitor, ertugliflozin (Steglatro®), has been registered by the European Medicines Agency, from the group of SGLT2 inhibitors, for the treatment of T2DM. Although they are primarily registered as drugs for the treatment of T2DM, given their proven potential for cardioprotective and beneficial effects on kidney function, the indications for dapagliflozin and empagliflozin have now been expanded to include heart failure and chronic kidney disease. Therefore, these two representatives of SGLT2 inhibitors are examples of drugs that, due to their proven beneficial pharmacodynamic effects and safety of use, the indications have been extended to the mentioned indications regardless of T2DM.

This educational article aims to examine the impact of the potentially beneficial pharmacodynamic properties of sodium-glucose cotransporter 2 inhibitors on the expansion of indications for the use of these drugs. In addition, the educational article aims to show the connection between the differences in the pharmacological effects of individual representatives of SGLT2 inhibitors and the differences in the indication spectrum within the group of these drugs.

METHODS

A thorough review of literature from 2000 to 2023 via PubMed focused on SGLT2 inhibitors' pharmacology and clinical impact on T2DM, heart failure, and chronic kidney disease. Twenty relevant studies were analyzed to understand differences between these inhibitors, refining their efficacy and safety profiles.

TOPIC

Analysis of clinical studies of efficacy and safety of SGLT2 inhibitors

Author	Study design	Number of respondents	The most significant results of the study
Donnan K. et al., [11].	A systematic literature review		Metformin and SGLT2 inhibitors do not carry a high risk of hypoglycemia when used alone or in combination with other antihyperglicemic grugs. However, the risk of hypoglycemia is significantly increased when used concomitantly with insulin or an insulin secretagogue [11].
Bonora B. et al., 2020. [12].	A randomized clinical trial	7,020	We believe that a combination of different mechanisms may play a role in the overall cardioprotective and nephroprotective benefits of SGLT2 inhibitors in diabetic patients. Clinicians treating patients with T2DM, especially those with cardiovascular or renal risk factors, or established cardiovascular or renal disease, must carefully consider this evidence [12].
Antonio S. et al., 2020. [13].	A meta-analysis	39,593	In the available long-term randomized trials, SGLT2 inhibitors significantly reduce all causes mortality of T2DM patients [13].

Table 1. Antihyperglycemic potential and analysis of the efficacy and safety of SGLT2 inhibitors in the treatment of T2DM

Author	Study design	Number of respondents	The most significant results of the study
Suzuki et al., 2022. [14].	A retrospective, cohort study	25,315	Risks for later development of heart failure, myocardial infarction, angina pectoris, stroke and atrial fibrillation did not differ between representatives SGLT2 inhibitors. This is the first study that compared a wide range of cardiovascular outcomes in patients with DM treated with SGLT2 inhibitors in the post-registration period [14].
Tikkanen I, et al 2015. [15].	A double-blind, randomized clinical trial	825	Empagliflozin was associated with clinically significant reductions in blood pressure and HbA1c compared to placebo and was well tolerated in patients with T2DM and hypertension [15].

Table 2. Cardioprotective potential and analysis of the efficacy and safety of SGLT2 inhibitors in the treatment of heart failure

Chrysant, et al., 2017. [16].	A systematic literature review		A cardiovascular outcome study of empagliflozin reported a significant reduction in the risk of death, myocardial infarction, and stroke. [16].
Xie Yafei et al., 2023. [5].	A systematic literature review		A large body of evidence has shown that SGLT2 inhibitors can reduce hospitalization for heart failure in patients with or without diabetes [5].
Butler J et al., 2020. [17].	A meta-analysis	18,265	SGLT2 inhibitors significantly improve cardiovascular outcomes. A trend towards the benefit of this group of drugs was observed in patients with heart failure with preserved ejection fraction [17].
Inzucchi SE et al., 2018. [18].	A randomized clinical trial	7,020	A 38% reduction in the risk of CV death was observed with empagliflozin versus placebo in patients with T2DM and established cardiovascular disease in the trial [18].

Table 3. Nephroprotective potential and analysis of the efficiency and safety of SGLT2 inhibitors in the treatment of chronic kidney disease.

Author	Study design	Number of respondents	The most significant results of the study
Jasna Klen et al., 2023. [19].	a double-blind, randomized, placebo-controlled clinical trial	4,401	SGLT2 inhibitors can reduce albuminuria, the progression of diabetic nephropathy, thus reducing the need for dialysis by over 40%. The molecular mechanisms underlying these beneficial effects of SGLT2 inhibitors extend beyond their glucose-lowering effects [19].
Palmer et al., 2023. [20].	A systematic literature review		SGLT2 inhibitors are part of clinical practice guidelines for slowing the progression of chronic kidney disease in patients with and without diabetes mellitus. Inhibition of glucose transport not only lowers the concentration of glucose in the plasma, but also triggers other hemodynamic metabolic pathways that mediate the protective effect of the kidney [20].
Bailey et al., 2022. [21].	A systematic literature review		SGLT2 inhibitors improve tubular oxygenation and metabolism and reduce renal inflammation and fibrosis. SGLT2 inhibitors did not increase the risk of urinary tract infections or the risk of acute renal failure [21].

Table 4. Analysis of preclinical studies of pharmacological properties of SGLT2 inhibitors

Author	Type of preclinical study	A species of laboratory animals	The result of the study
Tahara et al., 2016. [22].	Comparison of pharmacokinetics and pharmacodynamics of representative SGLT2 inhibitors	Normoglycemic (C57BL/6) and diabetic (KK/Ay T2DM) mice	According to the duration of action, SGLT2 inhibitors are divided into long-acting and representatives of medium-long action with rapid and delayed onset of action. All investigated SGLT2 inhibitors exhibit significant antihyperglycemic activity, but differ from each other in the quality of daily blood glucose control as well as in the duration and onset of the pharmacological effect, which may be related to the different efficacy of T2DM control [22].
Kimura Y et al. , 2019. [23].	Comparison of pharmacokinetics and pharmacodynamics of representative SGLT2 inhibitors	Normoglycemic and diabetic mice treated with canagliflozin	Findings suggest that treatment with SGLT2 inhibitors with a fasting period protects the kidney from cardiorenal syndrome possibly by reducing oxidative stress mediated by b-hydroxybutyrate, in type 2 diabetic rats [23].

Oh CM et al., 2019. [24].	Comparison of pharmacokinetics and pharmacodynamics of representative SGLT2 inhibitors	Laboratory mice	SGLT2 inhibitors have a protective effect in doxorubicin-induced heart failure in mice. This implies that SGLT2 inhibitor therapy could be a good treatment strategy even in heart failure patients without diabetes [24].
Takasu et al., 2014. [25].	Comparison of pharmacokinetics and pharmacodynamics of representative SGLT2 inhibitors	Normoglycemic and diabetic mice	Inhibition of sodium-glucose cotransporter 2 by ipragliflozin, alone or in combination with existing oral antidiabetic drugs, has a potent effect on blood glucose levels in a variety of mouse models of hyperglycemia [25].

CONCLUSION

The potential for significant improvement in patient's quality of life and the reduction of the risk of serious complications makes sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) a valuable tool in the fight against the diabetes epidemic and associated comorbidities. Some representatives of SGLT2 inhibitors, such as empagliflozin and dapagliflozin, in addition to being used in the treatment of diabetes, have extended indications for heart failure and chronic kidney disease that may exist independently of T2DM. However, continuous monitoring of the safety and long-term effects of these drugs remains crucial for optimizing their therapeutic use.

Although the efficacy of SGLT2 inhibitors has been confirmed by numerous randomized clinical trials (RCTs) with sufficiently large samples to establish indications for their use clearly, data from both RCTs and observational studies are lacking, which would determine the long-term and comparative safety of representatives of this drug class and explain the differences in their indications.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Uticaj farmakodinamskih svojstava lekova na indikacije za njihovu upotrebu - inhibitori natrijum-glukoza kotransportera 2 (SGLT2 inhibitori)

Nikola I. Denda[1], Nemanja Z. Maletin[1], Marko B. Atanasković[1], Biljana A. Vučković[2,3], Aleksandar L. Rašković[1]

[1] Katedra za farmakologiju, toksikologiju i kliničku farmakologiju, Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija
[2] Katedra za patofiziologiju i laboratorijsku medicinu, Medicinski fakultet Novi Sad, Univerzitet u Novom Sadu, Novi Sad, Srbija
[3] Centar za laboratorijsku medicinu, Klinički centar Vojvodine, Novi Sad, Srbija

KRATAK SADRŽAJ

Uvod: Inhibitori natrijum-glukoza kotransportera tipa 2 (SGLT2) igraju ključnu ulogu u lečenju dijabetesa tipa 2, delujući na proksimalne tubule kako bi smanjili reapsorpciju glukoze i povećali njeno izlučivanje urinom, nudeći kardiovaskularne i renoprotektivne benefite. Ova studija ima za cilj da istraži farmakodinamičke prednosti SGLT2 inhibitora, proširi njihovu terapijsku primenu i proceni varijacije u farmakološkim efektima različitih predstavnika.
Metode: Detaljan pregled literature od 2000. do 2023. godine putem PubMed-a fokusiran je na farmakologiju SGLT2 inhibitora i njihov klinički uticaj na dijabetes tipa 2, srčanu slabost i hroničnu bubrežnu bolest. Analizirano je dvadeset relevantnih studija kako bi se razumele razlike između ovih inhibitora, sa ciljem poboljšanja njihovih profila efikasnosti i bezbednosti.
Tema: Dana 20. maja 2024. godine pronađeno je 16 originalnih studija na ljudima koje ispituju efekte SGLT2 inhibitora. Takođe, otkrivene su 4 originalne studije na životinjama koje istražuju uticaj SGLT2 inhibitora na laboratorijske miševe.
Zaključak: SGLT2 inhibitori pokazuju potencijal u poboljšanju kvaliteta života pacijenata i smanjenju komplikacija povezanih sa dijabetesom. Kontinuirano praćenje bezbednosti i efikasnosti je od suštinskog značaja za optimizaciju njihove terapijske primene, s obzirom na ograničene podatke o dugoročnoj bezbednosti i komparativnoj efikasnosti.

Ključne reči: dijabetes melitus, SGLT2 inhibitori, komplikacije dijabetesa

Received: September 4, 2024
Accepted: September 24, 2024