International Journal of Health Sciences and Research
Vol.13; Issue: 8; August 2023
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

Role of Empagliflozin - A New Sodium Glucose Co-Transporter 2 Inhibitor as a Monotherapy for Type 2 Diabetes Mellitus

Dr. P. Sharmila Nirojini[1], Kowsalya V[2], Kalpitha Mrinali V B[3], Lavanya S[4], Dharshini. S[5]

[1]Professor and Head, Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Namakkal, Tamil Nadu, India
[2,3,4]Pharm.D. Intern, Swamy Vivekanandha College of Pharmacy and Vivekanandha Medical Care Hospital, Namakkal, Tamil Nadu, India
[5]B.Pharm. IV year, Swamy Vivekanandha College of Pharmacy, Namakkal, Tamil Nadu, India

Corresponding Author: Dr. P. Sharmila Nirojini

DOI: https://doi.org/10.52403/ijhsr.20230810

ABSTRACT

In 2010, around 4 million people worldwide lost their lives to diabetes-related causes. Inhibitors of SGLT2 are effective at controlling type 2 diabetes mellitus. By weakening the kidney's tubular barrier, empagliflozin lowers the amount of glucose excreted in urine. Empagliflozin was not related to increase in episodes of hypoglycemia as compared to placebo, with the exception of those taking a baseline sulfonylurea or insulin. The most common side effects of empagliflozin combinations were mild to moderate such as UTI, genital infection, and dysuria. Similar to the placebo, there was an equivalent rate of volume depletion in most cases. It is not suggested to be used during pregnancy or while lactating. It lowers cardiovascular disease mortality and heart failure hospitalizations in persons with type 2 diabetes.

KEYWORDS: Chemistry, Pharmacology, SGLT2 Inhibitor, Treatment, Safety, Efficacy.

INTRODUCTION

Diabetes mellitus is characterized by anomalies in the secretion of various islet hormones, reduced function of the pancreatic b-cell which leads to inadequate insulin levels and additionally, peripheral tissues become resistant towards insulin. Around 4 million people died from diabetes-related causes worldwide in 2010, and millions more suffer from the disease's severe complications such as heart attack, cerebrovascular accident, renal failure, complete vision loss, and lower limb amputations.[1] A wide range of therapy alternatives are available for type 2 diabetes glycemic management, which is a subject of rising complexity. Current anti diabetic medication works to lower blood sugar level by either enhancing insulin sensitivity or its production.[2] Each 1% raise in glycated haemoglobin (HbA1c) is associated with mortality risk that is up to 38% higher for people with elevated level of hyperglycemia which is connected to a greater probability for vascular complications.[3] The SGLT2, is in charge of drawing glucose back into the body from glomerular filtrate which presents in the proximal convoluted tubule of the nephron. Although it moves against its own concentration gradient, the movement of sodium along its gradient of concentration makes it easier for glucose to pass through the membrane.[4] One class of anti-diabetic drugs (ADAs) with a strong

track record for controlling the type 2 diabetes mellitus (T2DM) is SGLT2 inhibitors, sometimes referred as glifozins. Jardiance®, an SGLT2 inhibitor, has received approval for treating people with T2 DM in various countries globally including the EU, USA, and Japan.[5]

CHEMISTRY:

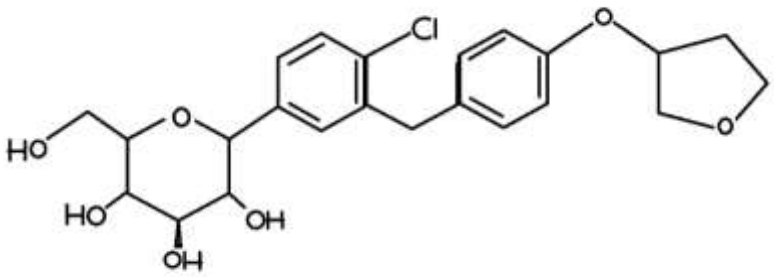

Fig 1., STRUCTURE OF EMPAGLIFLOZIN

Chemically, empagliflozin is known as D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3furanyl]oxy]phenyl]methyl]phenyl]-, (1S).The molecular weight of the chemical compound is 450.91 g/mol, and its chemical formula is C23H27ClO7.In comparison with dapagliflozin (more than 1,200 fold) and canagliflozin (more than 250 fold), empagliflozin demonstrated the most preference for SGLT2 over SGLT1 (more than 2,500-fold).[6]

MECHANISM OF ACTION:

The neuroendocrine system, liver, muscles, adipocytes, and pancreas all contribute to maintain normal glucose homeostasis. Furthermore, investigations revealed that by reabsorbing the filtered glucose, the kidneys ensure the supply of enough energy throughout times of fasting and play an essential function in the regulation of glucose homeostasis. Because of the increase in SGLT2 expression and activity brought on by hyperglycemia in the kidney's proximal tubule of diabetes patients, thereby this route becomes inappropriate. The gradient generated by the movement of sodium ions passing over the lumen membrane, facilitates the passive entry of glucose to the cell through SGLT2 process. Afterwards, sodium-potassium pump, which is driven by adenosine triphoshatase, returns the sodium to blood, whereas GLUT2 promotes the diffusion of glucose to the circulation. [7] Empagliflozin improves the glucose urinary excretion by significantly lowering kidney's tubular barrier for glycosuria. The lessened hypoglycemic effect occurs with effective glucose management by causing a daily loss of 240–400 kcal in urine, which is linked to weight reduction and 60–100 g/day of glucose excretion. Reduction in blood pressure occurred as a result of major sodium loss in urine and glucose osmotic diuresis. [8] Empagliflozin decreased the probability of cardiovascular events in high-risk patients with type 2 diabetes mellitus.[9] Plasma volume is decreased by empagliflozin, which appears to be its primary action for significantly reducing blood pressure with measurements of 3 to 4 mmHg after 12 weeks. [10]

PHARMACOKINETICS:

After oral dosing, empagliflozin was quickly absorbed and reached its highest levels between 1.5 and 3 hours later. Following that, a faster phase of distribution and a less rapid phase of elimination characterise the biphasic decline in plasma

levels. Over the 25 to 100 mg dosage range, both AUC and Cmax increased almost proportionately with dose.[11] The main mechanism for empagliflozin metabolism in pre-clinical species was oxidative metabolism. "Empagliflozin undergoes glucuronidation by specific UGT isoforms (UGT1A3, UGT1A8, UGT1A9, and UGT2B7) in humans, resulting in the production of three main conjugates of glucuronides (2-0-, 3-0- and 6-0-)". [12] Each make up less than 10% of overall drug consumption in human plasma, and they are perceived to be less efficient [12]. With empagliflozin 10 mg and 25 mg, t12 value at steady state ranged 13.9 hours (52.9%) and 12.1 hours (24.1%) respectively. At steady state, empagliflozin accumulated by up to 17%, which is consistent with its half-life. The average proportion of empagliflozin dose was eliminated in unaltered form in urine at steady state with dose of 10 mg and 25 mg, respectively. [13]

PHARMACODYNAMICS:

Empagliflozin 25 mg QD was administered in single or multiple doses, and both quickly increased urine glucose excretion, resulting in 506 mmol/d mean urine glucose excretion on the first day and a 642 mmol/d mean excretion on day 5. With single and several doses of empagliflozin, significant reductions of blood glucose levels from baseline were observed. Urinary excretions of sodium raised by a mean of 45.3 mmol/d following an individual dosage of Empagliflozin in comparison to baseline, but after receiving numerous doses, it recovered to baseline values. Single and several dosages of empagliflozin produced insignificant drops in the pH of urine and capillary blood. [14] By lowering the reabsorption of filtered glucose, inhibiting renal SGLT2 reduces the renal glycemic barrier and increases the kidneys' ability to excrete glucose in urine. An insulin-independent decline in aberrant blood sugar levels is brought on by increased urinary glucose outflow (70-100 g/day) in people with type 2 diabetes patients using gliflozins. [15]

POTENTIAL DRUG INTERACTIONS:

When used concurrently with other glucose-lowering medications or with cardiovascular medications frequently prescribed to type 2 diabetic patients, empagliflozin was not linked to any negative drug-drug interactions. Based on in vitro investigations. UGT1A1 or CYP450 (CYP450) enzymes are not inhibited, inactivated, or stimulated by empagliflozin. Due to the potential risk of decreased efficacy, empagliflozin treatment in conjunction with known UGT enzyme inducers (such as phenytoin, carbamazepine) should be avoided. [1]

THERAPEUTIC EFFICACY:

When compared to sitagliptin or the placebo at week 76, Fasting Plasma Glucose reductions were larger with both dosages of empagliflozin. At week 76, empagliflozin at both dosages resulted in larger HbA1c reductions such as below 7% than placebo and also weight loss was reported with 10 mg and 25 mg of empagliflozin. In the initial evaluation, empagliflozin reduced systolic blood pressure (SBP) compared to the control group, however this effect was not observed in sensitivity tests. [16] In comparison to those who received placebo (8.6%), a higher percentage of patients (32.6%) who had macroalbuminuria at baseline had an improvement to microalbuminuria with empagliflozin. The substantial reduction in A1C is observed with empagliflozin of 0.53% from baseline is the greatest drop in A1C. A decrease in UACR from baseline was one of empagliflozin's documented positive renal effects.[17] Hospitalisations for HF and death in T2DM patients have been considerably decreased by SGLT2 inhibitors. Kidney disease, a disorder that is usually related to diabetes, is progressed more slowly by SGLT2 inhibitor. The group treated with empagliflozin experienced a substantial decrease in the risk of receiving renal

replacement therapy, with a reduction of 55% and showed a 44% drop in probability for doubling serum creatinine levels compared to placebo. [18]

MONOTHERAPY:

The main goal of monotherapy studies was to assess how glycemic control was affected by various therapeutic doses of empagliflozin according via decreases in fasting blood glucose and hemoglobin A1C, as well as to provide further information on body mass index and blood pressure. All empagliflozin groups experienced a major decrease in HbA1c, with variations from placebo differing between 0.7% with an intake of 5 mg to 0.9% dose of 50 mg. Along with Fasting plasma glucose decreased to 1.5 to 2 mmol/L, average weight reduction of 1.6 to 2.2 kg occurred, and systolic blood pressure dropped from 1.5 to 4 mmHg for all doses. [19]

In people with type 2 diabetes mellitus. Except for patients using a baseline sulfonylurea or insulin, empagliflozin wasn't related to increased episodes of hypoglycemia compared to placebo. Most of the adverse events of empagliflozin combinations were UTI, genital infection aWith an excellent tolerability profile, Glycated hemoglobin and Fasting plasma glucose was clinically improved with 5–50 mg once daily dose of empagliflozin as monotherapy compared to control group. With empagliflozin, non-glycemic advantages, such as a considerable decrease in body weight and waist circumference were attained and enabling more patients to lose 5% of their body weight. When administered as a monotherapy, it results in enhanced glycemic management, body weight reduction, SBP in Japanese patients and also reported a favourable safety profile. The most suitable doses of empagliflozin are 10 and 25 mg, according to benefit-risk analysis. [20] Empagliflozin monotherapy was shown to be linked with changes in the concentration of glycated haemoglobin, with average declines of up to -0.78%, at 10 and 25 mg are the two dosages of empagliflozin that are permitted. [21]

COMBINATION THERAPY:

Empagliflozin And Metformin:

Patients with T2DM are advised to use metformin as their first-line glucose-lowering medication so it is a clear possibility of empagliflozin combo therapy. Treatment with 10 and 25 mg of empagliflozin combination significantly reduced HbA1c, systolic and diastolic blood pressure and body mass in comparison to placebo plus metformin. [21] Regardless of a patient's ability to deal with the highest dose of metformin, the initial dosage of empagliflozin - metformin combination could serve as helpful therapy option for people with recently uncovered type 2 diabetes, especially those with glycated hemoglobin level more than 8.5%. Empagliflozin + metformin twice-daily regimens drastically decreased the level of HbA1c more than the dose of once daily empagliflozin and metformin twice per day programme. [22]

Empagliflozin And Linagliptin:

"Both empagliflozin 25mg/linagliptin 5mg and empagliflozin 10mg/linagliptin 5mg showed larger adjusted mean reductions in HbA1c from baseline against empagliflozin or linagliptin as monotherapy as an adjunct to metformin".[23] Those who are reluctant to comply with metformin or alternative oral hypoglycemic medication might benefit from combination regimen using empagliflozin+linagliptin. Numerous studies have shown that this combination therapy is more effective in lowering HbA1c and FPG levels compared to employing each drug individually. The risk of hypoglycemia and tolerability was not affected by the once per day oral dose combination of Empagliflozin-linagliptin. [24]

SAFETY AND TOLERABILITY:

Patients taking monotherapy of empagliflozin witnessed a decreased overall

incidence of ADRs at baseline compared to those undergoing dual therapy. Patients on empagliflozin or dual treatment experienced hypoglycemia in 0.05% and 0.57% of cases. The most common side effects such as polyuria (1.50% and 0.65%) infections of the urinary tract (1.14% and 0.82%) and vaginitis (0.79% and 0.22%) were seen in combination therapy than monotherapy. Volume depletion in both groups such as monotherapy or combination therapy occurred similarly. [25] With an exception of a greater frequency with empagliflozin 25 mg versus control group, occurrence of diminished volume shared similarities with both treatments among age groups. Both the placebo and empagliflozin groups had identical rates of malignancies with onset of 6 months after the commencement of treatment. In contrast to a slight increase in the placebo group, those receiving empagliflozin reported a decrease in serum uric acid. [26]

CONCLUSION

Overall in regular clinical setting, empagliflozin exhibited an improved glycemic control and appeared to be tolerated effectively as a mono therapy and in conjunction with other glucose lowering oral medications. 10 and 25 mg of empagliflozin had positive effects and dysuria which were found to be mild to moderate. Volume depletion occurred at a similar rate to placebo. It is not advised to be used while lactating or in pregnancy conditions. In people with type 2 diabetes, it decreases mortality from cardiovascular disease and hospitalizations for heart failure.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCE

1. Scott LJ. Empagliflozin: a review of its use in patients with type 2 diabetes mellitus. Drugs. 2014 Oct; 74:1769-84.
2. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, Bekiari E, Tsapas A. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2014 Oct;16(10):984-93.
3. Neumiller JJ. Empagliflozin: a new sodium-glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. Drugs in context. 2014;3.
4. Riggs MM, Seman LJ, Staab A, MacGregor TR, Gillespie W, Gastonguay MR, Woerle HJ, Macha S. Exposure− response modelling for empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in patients with type 2 diabetes. British journal of clinical pharmacology. 2014 Dec;78(6):1407-18.
5. Frampton JE. Empagliflozin: a review in type 2 diabetes. Drugs. 2018 Jul; 78:1037-48.
6. Ndefo UA, Anidiobi NO, Basheer E, Eaton AT. Empagliflozin (Jardiance): a novel SGLT2 inhibitor for the treatment of type-2 diabetes. Pharmacy and Therapeutics. 2015 Jun;40(6):364.
7. Forycka J, Hajdys J, Krzemińska J, Wilczopolski P, Wronka M, Młynarska E, Rysz J, Franczyk B. New Insights into the Use of Empagliflozin—A Comprehensive Review. Biomedicines. 2022 Dec 19;10(12):3294.
8. Chawla G, Chaudhary KK. A complete review of empagliflozin: Most specific and potent SGLT2 inhibitor used for the treatment of type 2 diabetes mellitus. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2019 May 1;13(3):2001-8.
9. Salsali A, Kim G, Woerle HJ, Broedl UC, Hantel S. Cardiovascular safety of empagliflozin in patients with type 2 diabetes: a meta-analysis of data from randomized placebo-controlled trials. Diabetes, Obesity and Metabolism. 2016 Oct;18(10):1034-40.
10. Kowalska K, Walczak J, Femlak J, Młynarska E, Franczyk B, Rysz J. Empagliflozin—A New Chance for Patients with Chronic Heart Failure. Pharmaceuticals. 2021 Dec 30;15(1):47.
11. Heise T, Seman L, Macha S, Jones P, Marquart A, Pinnetti S, Woerle HJ, Dugi K. Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of empagliflozin in patients with type 2 diabetes mellitus. Diabetes therapy. 2013 Dec; 4:331-45.

12. Tomlinson B, Hu M, Zhang Y, Chan P, Liu ZM. Evaluation of the pharmacokinetics, pharmacodynamics and clinical efficacy of empagliflozin for the treatment of type 2 diabetes. Expert Opinion on Drug Metabolism & Toxicology. 2017 Feb 1;13(2):211-23.
13. Zhao X, Cui Y, Zhao S, Lang B, Broedl UC, Salsali A, Pinnetti S, Macha S. Pharmacokinetic and pharmacodynamic properties and tolerability of single-and multiple-dose once-daily empagliflozin, a sodium glucose cotransporter 2 inhibitor, in Chinese patients with type 2 diabetes mellitus. Clinical Therapeutics. 2015 Jul 1;37(7):1493-502.
14. Heise T, Jordan J, Wanner C, Heer M, Macha S, Mattheus M, Lund SS, Woerle HJ, Broedl UC. Pharmacodynamic effects of single and multiple doses of empagliflozin in patients with type 2 diabetes. Clinical therapeutics. 2016 Oct 1;38(10):2265-76.
15. Faillie JL. Pharmacological aspects of the safety of gliflozins. Pharmacological research. 2017 Apr 1; 118:71-81.
16. Roden M, Merker L, Christiansen AV, Roux F, Salsali A, Kim G, Stella P, Woerle HJ, Broedl UC. Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naïve patients with type 2 diabetes: a double-blind extension of a Phase III randomized controlled trial. Cardiovascular diabetology. 2015 Dec;14(1):1-1.
17. Kelly MS, Lewis J, Huntsberry AM, Dea L, Portillo I. Efficacy and renal outcomes of SGLT2 inhibitors in patients with type 2 diabetes and chronic kidney disease. Postgraduate medicine. 2019 Jan 2;131(1):31-42.
18. Garcia-Ropero A, Badimon JJ, Santos-Gallego CG. The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors for type 2 diabetes mellitus: the latest developments. Expert Opinion on Drug Metabolism & Toxicology. 2018 Dec 2;14(12):1287-302.
19. Hedrington MS, Davis SN. The role of empagliflozin in the management of type 2 diabetes by patient profile. Therapeutics and clinical risk management. 2015 May 5:739-49.
20. Kadowaki T, Haneda M, Inagaki N, Terauchi Y, Taniguchi A, Koiwai K, Rattunde H, Woerle HJ, Broedl UC. Empagliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, 12-week, double-blind, placebo-controlled, phase II trial. Advances in therapy. 2014 Jun; 31:621-38.
21. Hershon KS. Options for empagliflozin in combination therapy in type 2 diabetes mellitus. International Journal of General Medicine. 2016 May 25:155-72.
22. Hadjadj S, Rosenstock J, Meinicke T, Woerle HJ, Broedl UC. Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016 Oct 1;39(10):1718-28.
23. Goldman JD. Combination of empagliflozin and metformin therapy: A consideration of its place in type 2 diabetes therapy. Clinical Medicine Insights: Endocrinology and Diabetes. 2018 Jul 9; 11:1179551418786258.
24. Triplitt C, Solis-Herrera C, Cersosimo E, Abdul-Ghani M, Defronzo RA. Empagliflozin and linagliptin combination therapy for treatment of patients with type 2 diabetes mellitus. Expert opinion on pharmacotherapy. 2015 Dec 12;16(18):2819-33.
25. Kaku K, Nakayama Y, Yabuuchi J, Naito Y, Kanasaki K. Safety and effectiveness of empagliflozin in clinical practice as monotherapy or with other glucose-lowering drugs in Japanese patients with type 2 diabetes: subgroup analysis of a 3-year post-marketing surveillance study. Expert Opinion on Drug Safety. 2023 May 18
26. Kohler S, Salsali A, Hantel S, Kaspers S, Woerle HJ, Kim G, Broedl UC. Safety and tolerability of empagliflozin in patients with type 2 diabetes. Clinical therapeutics. 2016 Jun 1;38(6):1299-313.

How to cite this article: P. Sharmila Nirojini, Kowsalya v, Kalpitha Mrinali V B, Lavanya S, Dharshini. S. Role of empagliflozin - a new sodium glucose co-transporter 2 inhibitor as a monotherapy for type 2 diabetes mellitus. *Int J Health Sci Res.* 2023; 13(8):64-69. DOI: *https://doi.org/10.52403/ijhsr.20230810*

******