EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 1
276-281
Year: 2021

EMPAGLIFLOZIN AS POTENTIAL INHIBITOR OF POLYOL PATHWAY IN DIABETIC RETINOPATHY THROUGH SODIUM-GLUCOSE CO-TRANSPORTER-2 AS AN ACTIVATOR OF NITRIC OXIDE SYNTHASE

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Article Received on 12/11/2020 **Article Revised on 02/12/2020** **Article Accepted on 22/12/2020**

ABSTRACT

Empagliflozin is an inhibitor of sodium-glucose co-transporter-2 (SGLT2), the transporters primarily responsible for the reabsorption of glucose in the kidney. It is used clinically as an adjunct to diet and exercise, often in combination with other drug therapies, for the management of type 2 diabetes mellitus. The first known inhibitor of SGLTs, phlorizin, was isolated from the bark of apple trees in 1835 and researched extensively into the 20th century, but was ultimately deemed inappropriate for clinical use given its lack of specificity and significant gastrointestinal side effects. Attempts at overcoming these limitations first saw the development of O-glucoside analogs of phlorizin (e.g. remogliflozin etabonate), but these molecules proved relatively pharmacokinetically unstable. The development of C-glucoside phlorizin analogs remedied the issues observed in the previous generation, and led to the FDA approval of canagliflozin in 2013 and both dapagliflozin and empagliflozin in 2014. As the most recently approved of the "flozin" drugs, empagliflozin carries the highest selectivity for SGLT2 over SGLT1 (approximately 2700-fold).

KEYWORDS: Polyol pathway, Aldose reductase inhibitor, SGLT2 inhibitor, Sorbitol, Sorbitol dehydrogenase, Retinopathy, Pyran, Oxolan.

INTRODUCTION

CAS Number: 864070-44-0FDA. Empagliflozin [Jardiance] is first approved August 1, 2014 by FDA manufactured by company: Boehringer Ingelheim Pharmaceuticals, Inc. for treatment of diabetes, type 2. Jardiance (empagliflozin) is a sodium glucose co-transporter-2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes, and to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.[1-4]

Empagliflozin [(2S,3R,4R,5S,6R)-2-[4-Chloro-3-[[4-[(3S)-oxolan-3-yl] oxyphenyl] methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol], sold under the brand name **Jardiance** among others, is a medication used together with diet and exercise to treat type 2 diabetes. It can be prescribed instead of metformin and has benefits over sulfonylureas. It may be used together with other medications such as metformin or insulin. It is not recommended for type 1 diabetes. It is taken by mouth. Common side effects include urinary tract infections, fungal infections of the groin, and joint pains. Rarer but more serious side effects include a skin infection of the groin called Fournier's gangrene and a form of diabetic ketoacidosis with normal blood sugar levels. Use in pregnancy and breastfeeding is not recommended. Use is not recommended in those with significant kidney disease, though it may help slow the progression of mild kidney problems. Empagliflozin is an inhibitor of the sodium glucose co-transporter-2 (SGLT-2), and works by increasing sugar lost in the urine. Empagliflozin was approved for medical use in the United States and in the European Union in 2014. In 2017, it was the 228th most commonly prescribed medication in the United States, with more than two million prescriptions.

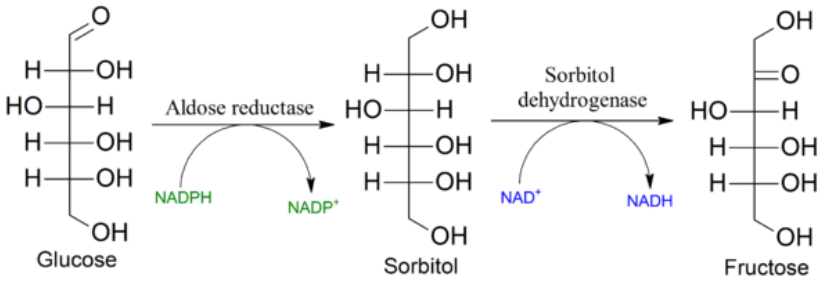
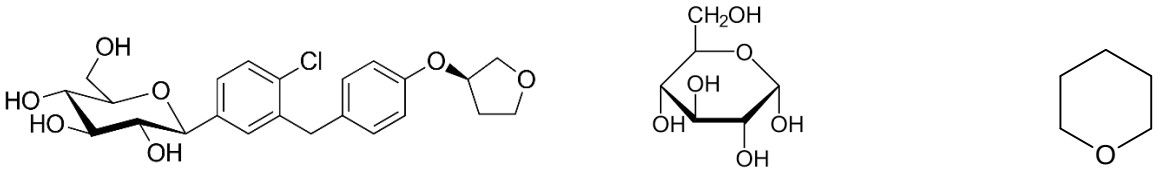


Figure-1: Polyol pathway.

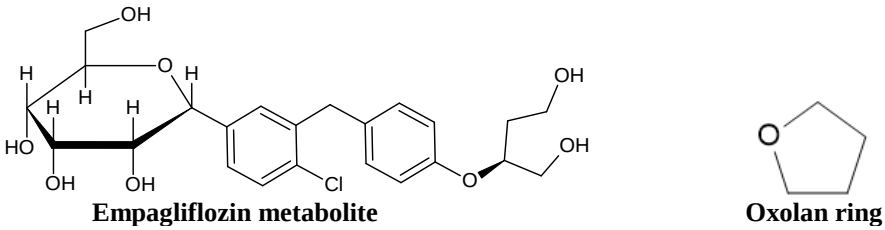
The polyol pathway is a two-step process that converts glucose to fructose. In this pathway glucose is reduced to sorbitol, which is subsequently oxidized to fructose. It is also called the sorbitol-aldose reductase pathway. The pathway is implicated in diabetic complications, especially in microvascular damage to the retina, kidney, and nerves. Sorbitol cannot cross cell membranes, and, when it accumulates, it produces osmotic stresses on cells by drawing water into the insulin-independent tissues. Cells use glucose for energy. This normally occurs by phosphorylation from the enzyme hexokinase. However, if large amounts of glucose are present (as in diabetes mellitus), hexokinase becomes saturated and the excess glucose enters the polyol pathway when aldose reductase reduces it to sorbitol. This reaction oxidizes NADPH to NADP+. Sorbitol dehydrogenase can then oxidize sorbitol to fructose, which produces NADH from NAD+. Hexokinase can return the molecule to the glycolysis pathway by phosphorylating fructose to form fructose-6-phosphate. However, in uncontrolled diabetics that have high blood glucose - more than the glycolysis pathway can handle - the reactions mass balance ultimately favors the production of sorbitol. Activation of the polyol pathway results in a decrease of reduced NADPH and oxidized NAD+; these are necessary co-factors in redox reactions throughout the body, and under normal conditions they are not interchangeable. The decreased concentration of these NADPH leads to decreased synthesis of reduced glutathione, nitric oxide, myo-inositol, and taurine. Myo-inositol is particularly required for the normal function of nerves. Sorbitol may also glycate nitrogens on proteins, such as collagen, and the products of these glycations are referred-to as AGEs - advanced glycation end-products. AGEs are thought to cause disease in the human body, one effect of which is mediated by RAGE (receptor for advanced glycation end-products) and the ensuing inflammatory responses induced. They are seen in the hemoglobin A1C tests performed on known diabetics to assess their levels of glucose control.[5-8]



Empagliflozin **Glucose** **Pyran ring**

Figure-2: Empagliflozin and Guocose and Pyarn ring.

Empagliflozin and Glucose both have six membered pyran ring chromophore unit. Glucose under goes reduction into sorbitol by aldose reductase which on oxidation by sorbitol dehydrogenase into fructose by polyol pathways. Sorbitol formation from glucose is inhibited by empagliflozin by competitive inhibition on aldose reductase by inhibiting polyol pathway due to structural similarity.



Empagliflozin metabolite **Oxolan ring**

Figure-3: Drug metabolite.

The drug undergoes metabolic process in liver where the five membered oxolan [tetrahydrofuran] ring is opened at ether linkage [-O-] into two alcohol units having [-CH_2-OH] units which becomes structurally similar to glucose and inhibits polyol pathway by competitive inhibition of aldose reductase enzyme by blocking the specific receptor and for this sorbitol formation is inhibited and formation of cataract on diabetic retinopathy is also inhibited.

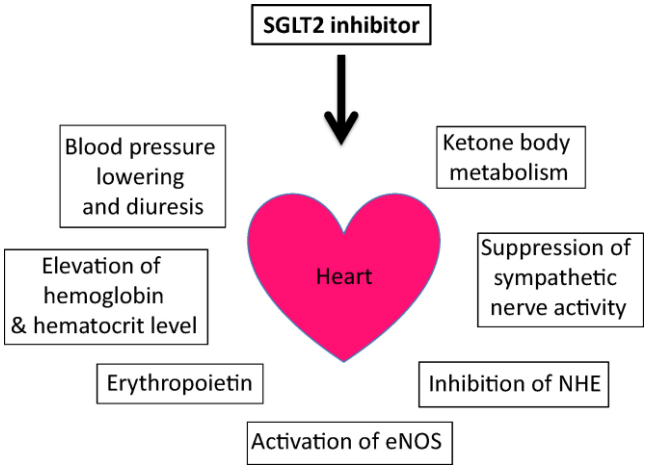


Figure-4: SGLT2 as NO activator.

Endothelial NOS (eNOS), also known as nitric oxide synthase 3 (NOS3) or constitutive NOS (cNOS), is an enzyme that in humans is encoded by the NOS3 gene located in the 7q35-7q36 region of chromosome 7. This enzyme is one of three isoforms that synthesize nitric oxide (NO), a small gaseous and lipophilic molecule that participates in several biological processes. The other isoforms include neuronal nitric oxide synthase (nNOS), which is constitutively expressed in specific neurons of the brain and inducible nitric oxide synthase (iNOS), whose expression is typically induced in inflammatory diseases. eNOS is primarily responsible for the generation of NO in the vascular endothelium, a monolayer of flat cells lining the interior surface of blood vessels, at the interface between circulating blood in the lumen and the remainder of the vessel wall. NO produced by eNOS in the vascular endothelium plays crucial roles in regulating vascular tone, cellular proliferation, leukocyte adhesion, and platelet aggregation. Therefore, a functional eNOS is essential for a healthy cardiovascular system.

Pharmacodynamics

Empagliflozin lowers blood glucose levels by preventing glucose reabsorption in the kidneys, thereby increasing the amount of glucose excreted in the urine. It has a relatively long duration of action requiring only once-daily dosing. Patients should be monitored closely for signs and symptoms of ketoacidosis regardless of blood glucose level as empagliflozin may precipitate diabetic ketoacidosis in the absence of hyperglycemia. As its mechanism of action is contingent on the renal excretion of glucose, empagliflozin may be held in cases of acute kidney injury and/or discontinued in patients who develop chronic renal disease.The overexcretion of glucose creates a sugar-rich urogenital environment which increases the risk of urogenital infections - including urosepsis, pyelonephritis, mycotic infections, and even Fournier's gangrene - in both male and female patients - monitor closely for signs and symptoms of developing infection.

Mechanism of action

The vast majority of glucose filtered through the glomerulus is reabsorbed within the proximal tubule, primarily via SGLT2 (sodium-glucose linked co-transporter-2) which is responsible for ~90% of the total glucose reabsorption within the kidneys. Na^+/K^+-ATPase on the basolateral membrane of proximal tubular cells utilize ATP to actively pump Na+ ions into the interstitium surrounding the tubule, establishing a Na^+ gradient within the tubular cell. SGLT2 on the apical membrane of these cells then utilize this gradient to facilitate secondary active co-transport of both Na+ and glucose out of the filtrate, thereby reabsorbing glucose back into the blood – inhibiting this co-transport, then, allows for a marked increase in glucosuria and decrease in blood glucose levels. Empagliflozin is a potent inhibitor of renal SGLT2 transporters located in the proximal tubules of the kidneys and works to lower blood glucose levels via an increase in glucosuria.[9-12]

Empagliflozin also appears to exert cardiovascular benefits - specifically in the prevention of heart failure - independent of its blood glucose-lowering effects, though the exact mechanism of this benefit is not precisely understood. Several theories have been posited, including the potential inhibition of Na^+/H^+ exchanger (NHE) 1 in the myocardium and NHE3 in the proximal tubule, reduction of pre-load via diuretic/natriuretic effects and reduction of blood pressure, prevention of cardiac fibrosis via suppression of pro-fibrotic markers, and reduction of pro-inflammatory adipokines.

Absorption

Following oral administration, peak plasma concentrations are reached in approximately 1.5 hours (T_{max}). At steady-state, plasma AUC and C_{max} were 1870 nmol·h/L and 259 nmol/L, respectively, following therapy with empagliflozin 10mg daily and 4740 nmol·h/L and 687 nmol/L, respectively, following therapy with empagliflozin 25mg daily. Administration with food does not significantly affect the absorption of empagliflozin.

Volume of distribution
The estimated apparent steady-state volume of distribution is 73.8 L.

Protein binding
Empagliflozin is approximately 86.2% protein-bound in plasma.

Metabolism
Empagliflozin undergoes minimal metabolism. It is primarily metabolized via glucuronidation by 5'-diphospho-glucuronosyltransferases 2B7, 1A3, 1A8, and 1A9 to yield three glucuronide metabolites: 3-O-, 4-O-, and 5-O-glucuronide. No metabolite represented more than 10% of total drug-related material. It has 5 chiral points having -OH linkages in 3R,4R,5S positions which forms O-glucuronide.

Hover over products below to view reaction partners
Empagliflozin: Empagliflozin-3-glucuronide, Empagliflozin-4-glucuronide, Empagliflozin-5-glucuronide.

Route of elimination
After oral administration of radiolabeled empagliflozin approximately 41.2% of the administered dose was found eliminated in feces and 54.4% eliminated in urine. The majority of radioactivity in the feces was due to unchanged parent drug while approximately half of the radioactivity in urine was due to unchanged parent drug.

Half-life
The apparent terminal elimination half-life was found to be 12.4 h based on population pharmacokinetic analysis.

Clearance
Apparent oral clearance was found to be 10.6 L/h based on a population pharmacokinetic analysis.

Medical uses
Type 2 diabetes: Empagliflozin is used in combination with proper diet and exercise to help people with type 2 diabetes lower their blood sugar levels. It can be used alongside other medications for type 2 diabetes such as metformin, sulfonylureas, and insulin. When compared to a placebo, empagliflozin led to a drop of 0.7% in hemoglobin A1c, a long-term marker of blood glucose levels.

Weight and blood pressure
Empagliflozin cause moderate reductions in blood pressure and body weight. These effects are likely due to the excretion of glucose in the urine and a slight increase in urinary sodium excretion. In clinical trials, patients taking empagliflozin lost an average of 2% of their baseline body weight. A higher percentage of people taking empagliflozin achieved weight loss greater than 5% from their baseline. The medication reduced systolic blood pressure by 3 to 5 millimeters of mercury (mmHg). The effects on blood pressure and body weight are generally viewed as favorable, as many patients with type 2 diabetes have high blood pressure or are overweight or obese.

Heart kidney disease
SGLT2 inhibitors, including empagliflozin, appear to reduce the likelihood of hospitalization for heart failure or progression of chronic kidney disease in persons with type 2 diabetes. Empagliflozin may reduce the likelihood of death due to cardiovascular causes in people with type 2 diabetes who have known cardiovascular disease. One concern regarding the trial on which these claims are based is that the different arms received different amounts of other medications; thus, the reduced risk cannot necessarily be attributed to empaglifozin. In some countries it has also been approved to reduce the risk of death from cardiovascular causes in people with type 2 diabetes and heart disease. Treatment guidelines: Guidelines by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend SGLT-2 inhibitors like empagliflozin as second-line medications after metformin for type 2 diabetes in people with heart failure or chronic kidney disease. For type 2 diabetes with established cardiovascular disease, the guidelines recommend either a SGLT-2 inhibitor or a GLP-1 agonist as second-line medications after metformin. In all other type 2 diabetes cases, SGLT-2 inhibitors like empagliflozin can be appropriate second-line options if blood glucose control or weight loss are treatment priorities. They are less appropriate if cost is a major factor. In the United Kingdom empagliflozin is typically only recommended together with metformin if a sulfonylurea cannot be taken.

Type 1 diabetes
Empagliflozin is not recommended for type 1 diabetes. One trial studied its use in addition to insulin in people with type 1 diabetes. The medications delivered modest improvements in blood glucose control and body weight but were associated with an increased risk of diabetic ketoacidosis, a dangerous complication of diabetes. Empagliflozin is not approved by the U.S. Food and Drug Administration (FDA) for use in type 1 diabetes. Contraindications: History of a severe allergic reaction to empagliflozin, End-stage kidney disease, Diabetic ketoacidosis.[13-16]

Side effects: Common: Empagliflozin increases the risk of genital fungal infections. The risk is highest in people with a prior history of genital fungal infections. Urinary tract infections (UTIs) may be more common with empagliflozin. Certain individual clinical trials have demonstrated an increase risk but cumulative data across multiple trials show no increase in UTI risk. Empagliflozin reduces systolic and diastolic blood pressure and can increase the risk of low blood pressure, which can cause fainting and/or falls. The risk is higher in older people, people taking diuretics, and people with reduced kidney function. Slight increases

in LDL cholesterol can be seen with empagliflozin, in the range of 2% to 4% from baseline.

Figure-5: Empagliflozin formulation.

Diabetic ketoacidosis (DKA): a rare but potentially life-threatening condition, may occur more commonly with empagliflozin and other SGLT-2 inhibitors. While DKA is usually associated with elevated blood glucose levels, in people taking SGLT-2 inhibitors DKA may be seen with uncharacteristically normal blood glucose levels, a phenomenon called euglycemic ketoacidosis. The absence of elevated blood glucose levels in people on an SGLT-2 inhibitor may make it more difficult to diagnose DKA. The risk of empagliflozin-associated DKA may be higher in the setting of illness, dehydration, surgery, and/or alcohol consumption. It is also seen in type 1 diabetes who take empagliflozin, which notably is an unapproved or "off-label" use of the medication. To lessen the risk of developing ketoacidosis (a serious condition in which the body produces high levels of blood acids called ketones) after surgery, the FDA has approved changes to the prescribing information for SGLT2 inhibitor diabetes medicines to recommend they be stopped temporarily before scheduled surgery. Empagliflozin should each be stopped at least three days before scheduled surgery. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, and trouble breathing.

Fournier's gangrene: a rare but serious infection of the groin, occurs more commonly in people taking empaglflozin and other SGLT-2 inhibitors. Symptoms include feverishness, a general sense of malaise, and pain or swelling around the genitals or in the skin behind them. The infection progresses quickly and urgent medical attention is recommended. Empagliflozin can increase people' risk of low blood sugar when it is used together with a sulfonylurea or insulin. When used by itself or in addition to metformin it does not appear to increase the risk of hypoglycemia.

CONCLUSION

Empagliflozin is in a class of medications called sodium-glucose co-transporter 2 (SGLT2) inhibitors, according to MedlinePlus. The drug lowers blood sugar by causing the kidneys to get rid of more glucose (blood sugar) in the urine. Heart failure is a chronic, progressive condition where the heart muscle isn't able to pump enough blood to meet the body's needs for blood and oxygen, according to the American Heart Association (AHA). In heart failure, the heart goes through something called "adverse remodeling," which is when the left ventricle, the thickest of the heart's chambers which pumps oxygenated blood to tissues in the body, becomes thicker, more spherical, and pumps in a weaker way than usual, Santos-Gallego explains. But empagliflozin reduces and reverses adverse remodeling. It specifically reduces the dilation and thickness of the left ventricle, helps it pump more strongly, and makes the left ventricle less spherical. In September, the FDA granted empagliflozin fast track designation to improve outcomes following a heart attack. Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need, per the FDA. Sodium glucose cotransporter 2 (SGLT2) inhibitors are antidiabetic drugs that increase urinary excretion of glucose, thereby improving glycemic control and promoting weight loss. SGLT2 inhibitors trigger multiple mechanisms that could predispose to diabetic ketoacidosis. When SGLT2 inhibitors are combined with insulin, it is often necessary to decrease the insulin dose to avoid hypoglycemia. The lower dose of insulin may be insufficient to suppress lipolysis and ketogenesis. Furthermore, SGLT2 is expressed in pancreatic α-cells, and SGLT2 inhibitors promote glucagon secretion. Finally, phlorizin, a nonselective inhibitor of SGLT family transporters decreases urinary excretion of ketone bodies. A decrease in the renal clearance of ketone bodies could also increase the plasma ketone body levels. Based on the physiology of SGLT2 and the pharmacology of SGLT2 inhibitors, there are several biologically plausible mechanisms whereby this class of drugs has the potential to increase the risk of developing diabetic ketoacidosis. Future research should be directed toward identifying which patients are at greatest risk for this side effect and also to optimizing pharmacotherapy to minimize the risk to patients.

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