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REVIEW ARTICLE

A Comprehensive Review on Sodium Glucose Co-Transporter-2 Inhibitors-Empagliflozin

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ABSTRACT:

Diabetes is one of the most common global illness affecting millions of people in the world. SGLT2 is newly classified anti-diabetic drug, it is highly selective novel approach for type –II diabetes patients because it as low affinity to plasma proteins and high capacity transport of glucose protein compared to SGLT1. Empagliflozin is highly selective for SGLT2, which is sold under the brand name of Jardiance it is mainly recommended for type II DM. The studies have proven that empagliflozin shows both Cardio protective and Reno protective effects and well established for the management of weight loss in diabetes mellitus. Pharmacokinetic studies are well achieved and shown no major drug interactions and less side effects. SGLT2 inhibitors have given novel approach about orally administered drug and more or less this can benefit the patients for easy life style without leading to further complications.

KEYWORDS: -Anti-diabetic drug, Empagliflozin, SGLT2 inhibitors, Cardio protective and Reno protective.

INTRODUCTION:

As per 2018 reports of the World Health Organisation, Diabetes is one of the most common global illness affecting 69.9 million people in the world. Currently several oral hypoglycaemic agents as well as various forms of insulin are available for the management of diabetes mellitus. Commonly available OHA'S include,Sulfonylureas (Glimepiride), Biguanides (Metformin), Thiazolidinediones (Rosiglitazone), α-glucosidase inhibitors (acarbose, miglitol), DPP-4 inhibitors (Sitagliptin) and SGLT2 inhibitors. Canagliflozin was the first identified SGLT2 inhibitors in the year march 2013 by Janssen Inc.The normal glucose homeostasis requires a complex highly integrated interaction among the Liver, Muscle, Adipocytes, pancreas and Neuroendocrine system.[9,14,15]

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Sodium Glucose-Co-Transporter Inhibitors:

Sodium glucose co transporter 2 inhibitors are newly analysed classification of anti-diabetic drugs for the management of type- II diabetes which is emphasized in the recent guidelines. This class of drug has a low affinity to plasma proteins and high capacity transport of glucose protein compared to SGLT1, where it has high affinity and low capacity in which 10% of the drug is reabsorbed; So SGLT2 is highly selective novel approach for type –II diabetes patient.[3] This class of drug is unique from all the other antidiabetic drug because of its insulin independent mechanism. It can be combined with other anti-diabetic drugs such as exogenous insulin.[8,3]

Animal Studies have proven that SGLT2 inhibitors reduce the plasma glucose levels resulting in improved β –cell function and enhance the insulin sensitivity in the liver and muscle.[5] Human studies have shown results of reduced levels of HbA1c for improving glucose control. However long-term efficacy and safety of SGLT2 inhibitors remains under study but as all drugs have

adverse effects even this class of drug has moderate adverse effects which can be treated in early stage.

Kidney plays a vital role on glucose homeostasis and has recently become the target organ for the management of diabetes mellitus. In normal conditions the kidney reabsorb all the glucose from the glomerular filtrate and back into the blood. The Sodium glucose co transporter 2 inhibitors (SGLT2) reduce the blood glucose concentration by inhibiting the glucose transport which is located mainly in the S1 segment of the proximal convoluted tubule which is present in the nephron. Since there is an adaptive mechanism that ensures sufficient energy which is available during fasting periods this mechanism becomes maladaptive in diabetes. As a result there about 20% of the individual with poorly controlled diabetes has increase in glucose reabsorption when using SGLT-2, where 80-90 % of glucose is filtered back and in increasing threshold of renal glucose excretion in the kidney.[15]

Therefore, they not only reduce the renal blood glucose levels they also have good cardio protective properties. Studies have proven that taking SGLT2 drugs can actually reduce the risk of developing stroke and myocardial infarction including patients with diabetes mellitus along with cardiovascular diseases. They have benefited for obese patient suffering from type-II diabetes for the use of diet and exercise. Although studies have shown it can cause mild to moderate adverse effects related to the mechanism of action.[4]

SGLT2 inhibitors currently come under four classes which is approved by the US Food and Drug Administration (FDA) and the European medicines agency for the treatment of T2DM either as a monotherapy or in combine therapy with other antihyperglycemic agents. They are Canagliflozin, Dapagliflozin, Empagliflozin and Ertugliflozin. In this class Dapagliflozin and Empagliflozin is highly selective for SGLT2, while Canagliflozin has dual blockade of SGLT1 and SGLT2.[13]

Approach of Empagliflozin:

Under the classification of SGLT2 inhibitors one such drug which is highly recommended in North America and Japan is the Empagliflozin..It is an orally administered drugbelongs to the solid brand name Jardiance which is a potent, highly selective drug and well established in the treatment of diabetes mellitus. It is recommended for Type -II diabetes and not for Type -1.The major mechanism is it acts as an inhibitor of sodium glucose co transporter mainly sited at the proximal tubule of the nephron where it inhibits the sodium and glucose reabsorption leading to glycosuria.[1,11.]

It produces a dose dependent urinary glucose excretion with increase up to 90g of glucose excreted per day.Since Empagliflozin does not require any dose adjustment because they based on their pharmacokinetic studies.

In the past few years a study outcome was introduced called the EMPA-REG OUTCOME which set up a land mark for the cardiovascular studies, it had proven that empagliflozin had shown both cardio protective and Reno protective effects in reducing the risk of blood pressure, stoke and other cardiovascular outcomes. It has been beneficial in reducing the hospitalisation for the risk of heart failure. It is not recommended along with insulin as it can cause severe hypoglycaemia. A study shown that empagliflozin with metformin improved glucose control of T2DM patients without the risk of hypoglycaemic.[1,4,7]

DESCRIPTION:

IUPAC name-(2S,3R,4R,5S,6R)-2-[4 chloro-3-[{4-[(3S)-Oxolan-3- yl]oxyphenyl] methyl]phenyl]-6(hydroxy methyl)oxane-3,4,5,triol.It is an C –glycosyl compound consisting of a beta – glycosyl residue having a (4 chloro-3-{4-[(3s) tetrahydrofuran-3yloxy] benzyl} phenyl group at the anomeric centre.Empagliflozin is a white yellowish non hygroscopic powder, water soluble sparingly soluble in methanol less soluble in ethanol and acetonitrile. Practically insoluble in toluene.[13]

Pharmacology:

Dosage And Administration:

Recommended Dosage:

It is treated with 10mg in the morning and the dose is increased to 25mg if tolerated.

Patient with Renal Impairment:

Empagliflozin should not be given to patients with estimated GFR less than 45ml/min/1.73m2 no dose adjustment is needed in patients greater than or equal to 45ml/min/1.73m2.

Mechanism of Action:

Empagliflozin is an inhibitor Sodium dependent glucose transporter. It acts on the brush border proximal convoluted tubule in the kidney. It reduces the renal reabsorption of filtered glucose thereby reducing the glucose levels in the kidney and increasing in urinary excretion of glucose (glycosuria). This results to excretion of 60-100g/day of glucose to improve the glucose control with low risk of hypoglycaemia when taken as mono-therapy or combined therapy with other anti-diabetic drugs such as metformin. This result at account of 200 -400kcal/day of urine associated with weight reduction. Glucuretic action is dependent on the blood concentrations and GFR because ofits insulin

independent mechanism. There is decrease in blood pressure due to osmotic diuresis of glucose and natriuresis of co-transported sodium.[18,11]

Pharmacokinetic Properties:

Absorption:

After oral administration it is rapidly absorbed (t max reached <2 h post dose) with 78% bioavialablity. Thereafter plasma concentration declined the biphasic manner with rapid distribution phase and slow terminal phase. Administration of high fat calorie diet intake of empagliflozin 25mg resulted in lower exposure AUC decreased around 16% and C max decreased approximately 37% compared to the fasting state. The effect of empagliflozin was considering that there was noclinically relevant difference with food.[13]

Distribution:

They are highly protein bound in healthy and distributed well in tissues and fluids. The apparent volume of distribution estimated to be 73.8L based on this analysis.

Metabolism:

Empagliflozin has no major metabolites in the blood as its metabolism takes place by glucornidation by uridine 5'- diphospho –glucuronosyltransferase isoforms of UGT1A3, UGT1A8, UGT1A9 and UGT2B7.[13] To three main glucuronide conjugates in the human plasma at,10% of the total drug circulation.

Excretion:

Excretion of renal glucose is approximately around 95% the half of the drug was eliminated in the faeces or urine in which majority of the drugs was identified in the faeces which was identifiedas the unchanged drug. The terminal half -life of empagliflozin is 12 hours in single dose and in multiple doses approximately around 18 h.This pharmacokinetics are not affected by the age, gender body mass index and race especially Asians and non-Asians.

Contraindications:

Contraindicated with patients suffering from hypersensitivity, severe renal impairment, end stage renal failure or dialysis it should not be initiated less than 45ml/min/1.73m of estimated GFR levels.

Adverse Reactions:

As empagliflozin causes some side effects they are, Hypotension, Ketoacidosis, Urinary tract infection like urosepsis, Hypoglycaemia when used with insulin or insulin secretagenous, Genital and Mycotic infections, Increased LDL levels.[1,11,13]

Polyuria can result in extra glucose which can lead to dehydration with postural hypotension especially in elderly patients on diuretics. Glycosuria predisposes patients to urinary tract infections and genital tract infection respectively. Case report has found out about euglycemic ketoacidosis with use of SGLT2 inhibitors. Empagliflozin causes osmotic diuresis therefore adverse effects relate to volume depletion ,systolic BP, Dehydration ,hypotension ,hypovolemia , impaired renal function were also reported.A recent study had found out by the FDA that empagliflozin cause diabetic ketoacidosis in 2015 but later on studies have established low risk of diabetic ketoacidosis when treated early.[1,7,13]

Drug -Drug Interactions:

The drug interaction had not significantly resulted in taking empagliflozin but only such drugs as diuretics (Furosemide) when taken along with empagliflozin can result in increased urine can lead to enhance the potential of volume depletion and also cause the risk of hypoglycaemia. When taken with insulin it causes increase of risk of hypoglycaemia but reducing the insulin levels can be monitored closely.Co-administration of empagliflozin and sitagliptin had no clinically significant interactions same as with metformin.

Therapeutic Efficacy Of Empagliflozin:

The study aspect is shown when taken empagliflozin what happens to the parameters levels and what positive and negative results are estimated and proven.

Glycemic Control Studies:

The positive aspect of taking empagliflozin along with other oral and injectable ADAs when taken alone or in combined therapy the studies has shown taking empagliflozin 10mg and 25mg/day[1] as monotherapy and add on therapy had significantly reduced the HbA1c levels compared with placebo or add on placebo even with patients suffering from chronic kidney disease or even end stage renal failure including patients having hypertension and obese. It significantly decreased the fasting blood glucose levels vs placebo. HbA1c levels significantly diminished with decreasing baseline renal function generally preserved in patients with lower estimated GFR rate.[6]

A negative aspect of this study when patients with type - II diabetes taking empagliflozin were treated with insulin .[14] A case study were reported that a 66 year old man he was treated for HbA1c and post prandial was elevated and he was on treatment with anti-diabetics along with insulin Aspart (novo log).The dose of insulin was reduced to 20units/day. Along with that he started taking empagliflozin 25mg once daily in the morning. After 1hour of breakfast and 1 hour after dinner. The patients

developed signs of hand shaking and dizziness. So it was proven that the patient suffered from hypoglycaemia when taken with this therapy. The treatment was discontinued and taken with other ADAs to improve the therapeutic effect .

Empagliflozin Along With Metformin:

Empagliflozin has established the study when taken with metformin were glycated HbA1c levels and reduction in the weight showed decreased significant results decreasing the risk of developing systolic blood pressure. Combined therapy of these two drugs showed not risk of aetiology's.The only drawback was taking this combination can lead to unwanted effects such as lactic acidosis, hypotension when taken alcohol and severe renal problems.[5]

Cardiovascular Studies:

Empagliflozin is potent highly selective drug for the treatment of diabetes.[11] This study has shown that risk of developing myocardial infraction and stroke can decrease the risk factors when using empagliflozin the rates of CVdeaths has decreased the hospitalization mortality rates.[3,7] Risk of developing high blood pressure and other cardiovascular outcomes have reduced and established well. No further drawbacks were seen in this study as it was related to the adverse effects which are seen in the mechanism of action in empagliflozin.[2,3]

Cost Comparison:

Table I: Cost comparison[8,12]

Drug	Strength	Dosage form	Price (volume of 10 tablets
Sulfonylureas			
Gliclazide	80mg	Tab	495₹
Glimepiride	1mg,20mg	Tab	15₹,25₹
Biguanides			
Metformin	500mg,850mg	Tab	17₹
DPP-4 inhibitors			
Linagliptin	5mg	Tab	427₹
Sitagliptin	25mg,50mg, 100mg	Tab	299₹
GLP-1 receptor Analogue			
Liraglutide	2mlx3ml	Pre filled pen	2,500₹
Thiazolidinediones			
Pioglitazone	15mg,30mg	Tab	19₹,38₹
Rosiglitazone	2mg,4mg	Tab	35₹,60₹
SGLT-2 inhibitors			
Empagliflozin	10mg,25mg	Tab	376₹

Advantages:

There are several advantages when taking Empagliflozin they areIt is the newlydrug of choice which can improve patients' conditions with poorly controlled diabetes. They can reduce the renal absorption of 90% of the filtered glucose and increase in renal glucose excretion. There is low risk of hypoglycaemia since it is insulin independent unlike any other anti -diabetic drugs whenit is given has mono-therapy or combined therapy.Decrease in weight loss has benefited with patients in diabetes and has lost an average of 2 -3% of their body weight with Lower systolic blood pressure.Heart benefits since high blood sugar lead to coronary artery disease and cardiomyopathy people have the risk of developing heart attack. Jardiance was found to help to protect the heart. Patients with dialysis and kidney disease in type II diabetes reduce 39% of the worsening disease

CONCLUSION:

SGLT-2 inhibitors class of drugs brings a great advantage in improving the patients with type-II diabetes.It has become one of the most different class of drugs when compared with other anti-diabetic agents because of its insulin independent mechanism. The newly improved class of drug Empagliflozin is one such drug is potent and unique mechanism from all other ant-diabetic drugs. They can lower the glycated haemoglobin levels shown in type -II diabetes patients since they lower the blood glucose levels and increase in glycosuria. When used as mono-therapy there was no risk of hypoglycaemia. This drug has found to have drastic weight reduction and lowering the blood pressure. The cardio vascular studies are well established in empagliflozin and the rate of cardiovascular death has also reduced .Pharmacokinetic studies are well achieved and have shown results of no major drug interactions and others kinetic parameters.The major drawback of this drugs are their side effects but doesn't bring major complications if treated early. SGLT-2 inhibitors have given novel approach about orally administered drug and more or less this can benefit the patients for easy life style without leading to further complications.

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