

Empagliflozin: the latest SGLT2 inhibitor on the block**Sangeeta Bhanwra^{1*}, Kaza Ahluwalia²**¹Department of Pharmacology,
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commercial use, distribution,
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medium, provided the original
work is properly cited.**ABSTRACT**

Empagliflozin, the latest SGLT2 inhibitor is a selective, highly potent and competitive inhibitor of SGLT2 leading to the lowering of plasma glucose level by letting the sugar pass in the urine. It has a good safety and efficacy profile and is quite convenient to use for the patient as well, except for some increase in the urinary and genital mycotic infections in the recipients.

Keywords: Empagliflozin, Blood sugar, SGLT 2 inhibitor**INTRODUCTION**

The worldwide incidence of diabetes has been increasing in the last few decades because of combination of factors like prolonged longevity, heightened inactivity, increased obesity accompanied by the increased life of patients affected with diabetes, due to recent advances in the treatment.¹ The sodium glucose transporter inhibitors (SGLT2 inhibitors) are the latest treatment options for type 2 diabetes mellitus patients, with their advantage being that they work through kidneys, rather than influencing insulin secretion or glucose absorption in the gut. This new class of drugs increases the excretion of glucose from the urine by inhibiting its reabsorption in the proximal tubule of the kidney, leading to significantly lower blood glycaemic levels, with an added advantage of weight loss in type 2 diabetes patients.² SGLT2 inhibitors include empagliflozin, canagliflozin, dapagliflozin,

ipragliflozin, out of which, canagliflozin was the first one to get USFDA approval on march 2013.³ This was followed by approval of dapagliflozin (Farxiga), on January 2014, and empagliflozin (Jardiance) on 1st august 2014.^{4,5} This novel class of drugs have been quite effective in controlling the blood sugar levels especially in obese diabetics.

Metformin has been the heart of treatment of patients with type 2 diabetes mellitus, which was followed by addition of other antidiabetic medications like sulfonylureas, biguanides, thiazolidinediones, glucagon like peptide 1 agonists, Dipeptidyl peptidase IV (DPP-4) inhibitors, insulin etc.⁶ SGLT2 inhibitors offer advantage in the treatment because they have an insulin independent mechanism of action to bring down blood sugar levels, thereby rarely causing hypoglycemia, along with beneficial effect of lowering of blood pressure. They

block the SGLT2 transporter in the proximal tubules of kidney, which is responsible for more than 90% of glucose reabsorption; thereby excreting the sugar in the urine.⁷ The risk of hypoglycaemia is low because the action of this group of drugs is not dependent on beta cells or insulin.

Empagliflozin: Pharmacology

This latest SGLT2 inhibitor is a selective, highly potent and competitive inhibitor of SGLT2 leading to the lowering of plasma glucose level by letting the sugar pass in the urine. The selectivity of empagliflozin for SGLT2 over SGLT1 is more than 2500 fold and is the greatest among all the other SGLT2 inhibitors with canagliflozin having 250 folds and dapagliflozin having 1200 fold selectivity.⁸ This selectivity is an important feature of this group because SGLT1 is extensively expressed in intestine and is responsible for glucose reabsorption there and if it is blocked, it can lead to glucose galactose malabsorption causing severe diarrhoea.

Empagliflozin has a multi-pronged action in patients of type 2 diabetes, as it brings down fasting and post-prandial blood sugar levels by increasing excretion of sugar in urine, helps in improving the functioning of insulin secreting beta cells of pancreas and shifts the substrate utilization in the body from glucose to lipid.⁹

Pharmacokinetics

Empagliflozin is given as an oral tablet, which is rapidly absorbed and has an approximate bioavailability of 78% and is mainly metabolized by glucuronidation.¹⁰ It doesn't have any active metabolites. The plasma protein binding of empagliflozin is 82-84%, mainly to albumin. After oral administration, time taken to achieve maximum concentration is 1.5 hours and the intake of food might decrease the absorption a bit, which is not relevant clinically.¹¹ The elimination half life is around 13 hours, with majority of drug being excreted in the urine itself, in 24 hours. Approximately 18% of the drug is excreted unchanged in the urine.¹²

Pharmacodynamics

The recommended dose of empagliflozin is 10mg/day for the patients with type 2 diabetes mellitus. It can be increased to 25 mg/day if need be. Empagliflozin is not to be used in the patients with type 1 diabetes mellitus. A 10 mg dose is said to inhibit approximately 40% of glucose reabsorption in the kidney. As the dose increases, the amount of glucose which is not reabsorbed also increases, until at the dose of 100 mg/day, after which it plateaus.¹⁰

Empagliflozin causes increased excretion of sugar in the urine, thereby bringing down the blood sugar levels as well as causing weight loss, due to loss of calories in the urine. The amount of glucose that is excreted in the urine is directly proportional to the dose given and it doesn't

increase after the dose has reached 100 mg/day.¹³ Intake of food along with this drug didn't affect the clinical action.¹¹

The effect of empagliflozin on decreasing the fasting plasma glucose is significant and after a period of time, it is said to bring down the glycosylated haemoglobin values as well, though the fall might not be statistically significant.⁹

It can be safely given in the patients with hepatic impairment without the need for adjusting the doses.¹⁴ In a study to see the effect of renal impairment on the pharmacodynamics of empagliflozin, it was clearly seen that the effect of empagliflozin decreased with the decrease in glomerular filtration rate, hence, caution has to be exercised while prescribing empagliflozin in patients with renal impairment and renal function will have to be monitored when the drug is being given.¹⁵

Drug interactions, adverse effects and toxicity

Since the patients with type 2 diabetes mellitus are on multiple medications for the purpose of achieving desirable blood sugar levels, it is not unlikely that empagliflozin would be given with these drugs to bring down the fasting plasma glucose levels to the normal range. Various studies have been done therefore, to see the drug interactions, if any between empagliflozin and other antidiabetic medications and it was seen that there is no need for any sort of dose adjustment of empagliflozin when given concomitantly with antidiabetic agents like metformin, sitagliptin, glimepiride etc and when given together, these drugs helped in decreasing fasting plasma glucose levels to a greater extent.¹⁶⁻¹⁸

Similarly, empagliflozin can be safely administered along with other medications like diuretics, antihypertensives, statins and digoxin etc.¹⁹⁻²²

Various clinical trials of empagliflozin have been conducted to establish its safety and efficacy in patient with type 2 diabetes. In a study conducted by Heise T et al, it was seen that as the dose of empagliflozin is increased so does the urinary glucose excretion increases, till a plateau is reached at 100 mg dose of empagliflozin.²³ However, in a phase 2 study it was seen that there was no increase in urinary excretion of glucose after the dose was increased from 25 mg to 100 mg, thereby establishing that the clinically relevant dose of empagliflozin is upto 25 mg per day.⁹

The most common adverse drug reaction reported with all the SGLT2 inhibitors is the increased risk of genital mycotic infections and to a lesser extent urinary tract infections. This adverse effect is basically an extension of its pharmacological effect. There was no risk of hypoglycaemia. The risk of volume depletion is there, causing hypotension, hence the precaution needs to be

there when this drugs needs to give along with diuretics, especially the loop diuretics. Rather, empagliflozin had been seeing to provide a beneficial effect to blood pressure, though not statistically significant. Other adverse effects include drug hypersensitivity reactions, ketoacidosis, nasopharyngitis, headache and constipation.^{9,24} The effect of empagliflozin on LDL cholesterol is not very clear and overall cardiovascular safety has been established with the SGLT2 inhibitors.

Contraindications and precautions

It must not be given to the patients with renal impairment, end stage renal disease or dialysis. Caution needs to be exercised in conditions which cause volume depletion/ contraction as these drugs themselves cause decrease in blood volume. Additionally, there is risk of hypoglycaemia if used along with insulin or insulin analogs.

It comes under category C for pregnancy and should be given only if benefit outweighs the risk. Similarly caution needs to be exercised in lactating mothers as well as young population under 18 years of age as the safety of empagliflozin is not established in this groups.²⁴

CONCLUSION

The SGLT2 inhibitors have an edge over the other available antidiabetics because they do not function through beta cells of pancreas and nor through the gut. They are unique in their mechanism, as they simply lead to the fall in fasting plasma glucose levels by excreting glucose in the urine. Hence the risk of hypoglycaemia is negligible with them with added benefits of weight loss and a better control of blood pressure. This mechanism enables these drugs to be used at any stage of treatment of type 2 diabetes, as a single therapy or as an add on therapy, with no risk of hypoglycaemia. Till date, three SGLT2 inhibitors have been USFDA approved and there has been no study which involves head to head comparison of these drugs. The only pharmacological difference among these drugs is their degree of selectivity for SGLT2 over SGLT1. All in all, empagliflozin has a good safety and efficacy profile and is quite convenient to use for the patient as well, except for the some increase in the urinary and genital mycotic infections in the recipients.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Bhanwra S, Ahluwalia K. Empagliflozin: the latest SGLT2 inhibitor on the block. *Int J Basic Clin Pharmacol* 2016;5:539-42.