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SGLT2 INHIBITORS: PROMISING NEW DRUGS FOR TYPE 2 DIABETES MELLITUS

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ABSTRACT

Due to change in life style there is a growing pandemic of Type 2 diabetes mellitus. Currently it affects more than 3 million people worldwide and this number is expected to grow to more than 5 million by the year 2030. Sodium glucose transporter 2 (SGLT2) is a new class of antidiabetic drugs which unlike many other antidiabetic drugs acts by insulin dependent mechanism and hence less prone to cause clinically significant hypoglycemia. Canagliflozin is the prototype drug of this group. It was first approved by food and drug administration in 2013. Other SGLT2 inhibitors approved by FDA for type II diabetes mellitus are dapagliflozin, and empagliflozin. The mechanism of action of these drugs is by inhibition of SGLT2 which is a low- affinity, high capacity glucose transporter which is located in the proximal tubule in the kidneys. This co-transporter is responsible for majority of the glucose reabsorption from proximal tubule. Inhibition of SGLT2 leads to increase in glucose excretion from proximal tubules of kidney. This increase in excretion consequently cause reduction in blood glucose levels. In addition to increased excretion SGLT2 inhibitors also act by increasing insulin sensitivity and increase glucose uptake in muscle cells. It further decrease gluconeogenesis. The advantages of SGLT2 include weight reduction, low incidence of hypoglycemic episodes and reduction in blood pressure levels. While it is usually well tolerated it may increase the propensity to develop urinary tract infections by virtue of increasing glucose excretion. Another major side effect associated with the use of this class of drugs is lactic acidosis. Taking into consideration pros and cons SGLT2 inhibitors appears to be a promising new treatment for patients of Type II diabetes mellitus in whom first and second line drugs are not working or are contraindicated for some reason.

KEYWORDS: Type 2 diabetes mellitus, SGLT2 inhibitors, Lactic acidosis, Urinary tract Infections.

INTRODUCTION

Diabetes Mellitus is one of the most common non-communicable diseases in india with over 60 million patients in India itself.[1] India is having the largest number of patients suffering from diabetes followed by china and united states of America.[1] People with Type 2 diabetes are at increased risk for neuropathy, retinopathy and nephropathy. In addition to end organ damage they are also prone to develop stroke, myocardial infarction and other vascular complications .[2] More than 60 % of the deaths in type 2 diabetes mellitus are due to cardiovascular complications.[3] The risk of end-organ damage and adverse cardiovascular status is directly proportional to intensive glycemic control in patients with type 2 diabetes mellitus. Intensive glycemic control not only reduces the risk of micro and macro vascular complications but also reduces the risk of sudden death owing to reduces cardiovascular complications.[4,5,6] With Increasing numbers of type 2 diabetes mellitus and rise in life expectancy due to improved healthcare the challenge of managing patients with type 2 diabetes mellitus is now faced with the problem of reduced efficacy of oral hypoglycaemic drugs and more and more patients not controlled on sulfonylureas and metformin are requiring third line drug therapy for type 2 diabetes mellitus.][7] These factors are expected to seriously hamper the ability of treating physician to maintain a state of tight glycemic control. Moreover with sulfonylureas and metformin there is always a risk of development of lactic acidosis and hypoglycemia.[8] Due to failure of first and second oral hypoglycaemic drugs and the risk of lactic acidosis and hypoglycaemia many patients are being switched to other classes of anti diabetic drugs. SGLT-2 inhibitors are one of the options in such patients. SGLT-2 inhibitors as the name suggests inhibit the sodium glucose co-transporter 2 receptors (SGLT-2). SGLT-2 receptors are located in proximal tubule of the nephron. The mechanism of action of this class of drugs is to reduce the reabsorption of glucose from the proximal portion of nephron back into the bloodstream, by inhibiting the SGLT-2 receptor which is responsible for glucose reabsorption from proximal convoluted tubule. By this mechanism these drugs increase glucose excretion from renal system.[9] In United Kingdom dapagliflozin,

canagliflozin and empagliflozin, are the SGLT-2 inhibitors approved by the National Institute for Health and Care Excellence.[10] US food and drug administration has approved the use of canagliflozin, dapagliflozin, and empagliflozin "for use with diet and exercise to lower blood sugar in adults with type 2 diabetes".[11] Treatment with SGLT2 inhibitors is associated with reduction in weight , lowered blood pressure levels , and low incidence of hypoglycemia. Overall, canagliflozin, dapagliflozin, and empagliflozin are well tolerated. Lactic acidosis and serious urinary tract infections are the major side effects seen with the use of SGLT-2 inhibitors and in May-2015 Food and drug administration of United States revised labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections.[12]

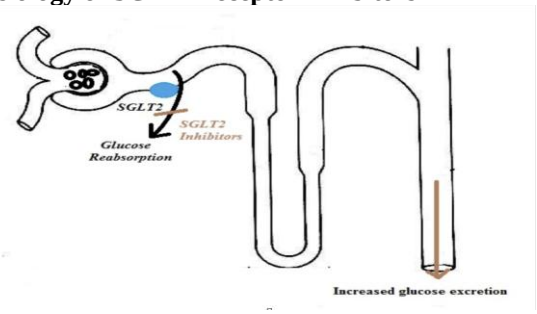
DISCUSSION

sodium-glucose linked transporter (SGLT) are a family of glucose transporter receptors found in the mucosa of small intestine (SGLT1) and the proximal convoluted tubule of the nephron (SGLT2). In the kidneys maximum amount of the filtered glucose (almost 98% in healthy individuals) is reabsorbed in proximal convoluted tubule via SGLT-2 receptors. In patients having severe hyperglycaemia these receptors are saturated with glucose and consequently there is excretion of glucose in urine ie glucosuria. Knowledge of this mechanism had led to development of novel group of drugs called SGLT2 inhibitors. Examples include canagliflozin, dapagliflozin and empagliflozin.

History of SGLT Inhibitors

The first SGLT inhibitor which was discovered was phlorizin (13). It was a naturally occurring compound derived from apple tree bark. The problem with this compound was that it was a non selective blocker of SGLT and hence caused blockade of both SGLT1 (gastrointestinal) and SGLT2 (Renal). Blockade of SGLT1 receptors by this compound was responsible for severe gastrointestinal side effects. Due to this and to its poor oral bioavailability, work on its development could not continue (14) . Drugs which specifically inhibit SGLT2, and thereby avoid gastrointestinal effects related to SGLT1 inhibition, have now been developed and approved by FDA.

Physiology of SGLT2 receptor inhibitors



One of the important physiological consideration for the use of SGLT2 receptor inhibitors for the treatment of diabetes mellitus is increased plasma glucose concentration. As expected in patients of type 2 diabetes mellitus there is generally an increase in plasma glucose level. This leads to increased filtration of glucose and increase sugar in proximal convoluted tubule. Another important factor about the action of these group of drug is presence of a good Glomerular filtration rate (GFR) because the filtration of glucose from glomerulus needs good GFR(15). Because the filtration of glucose is dependent upon the plasma glucose level there is less chances of development of hypoglycaemia in the patients on SGLT2 inhibitors because a low plasma glucose level will reduce the sugar filtration from glomerulus and hence the excretion of glucose in urine is automatically reduced.[16] In addition to the beneficial effect of having low incidence of hypoglycaemia SGLT-2 inhibitors also lead to calories loss due to loss of sugars in urine. This has a beneficial effect of reducing body weight and fat in patients of diabetes mellitus.[17] SGLT-2 inhibitors also induce diuresis secondary to urinary glucose excretion.[18] This diuresis is responsible for modest lowering of blood pressure. Diuresis, loss of calories and fat mass reduction have an overall beneficial effect on patients being treated with SGLT-2 inhibitor.[19]

Canagliflozin

It is prototype SGLT2 inhibitor. The recommended initial dose is 100 mg once daily, which can be gradually increased to 300 mg once daily in patients tolerating canagliflozin and who require additional glycemic control . The maximum dose of 300 mg once daily can only be given if the estimated GFR (eGFR) is ≥60 mL/min/1.73 m2. This dose need to be reduced to 100mg if eGFR is 45 to <60 mL/min/1.73 m2. The use of canagliflozin is contraindicated in patients who has GFR less than 45 mL/min/1.73 m2. The half life of canagliflozin is 14 to 16 hours which is consistent with once daily dosing.[20] Though canagliflozin is a SGLT2 inhibitor, in higher doses ie 300 mg once daily it may also inhibit SGLT1 in intestine and reduce postprandial glucose absorption thereby blunting postprandial rise in blood sugar levels.[21] In various clinical trials canagliflozin is found to reduce HbA1c and fasting blood glucose levels when used as mono therapy as well as add-on therpay (22). It was responsible for reduction in systolic and diastolic blood pressures and hence was especially useful in type2 diabetes mellitus patients who also had hypertension.[23] Major drug interactions include rifampicin and digoxin. Canagliflozin may cause increase exposure to digoxinn and hence patients on digoxin should be monitored if canagliflozin is started in these patients.[24]

The common side effects associated with the use of canagliflozin include genital and urinary tract infections specially in women, osmotic diuresis consequent upon increased glucose excretion through proximal convoluted tubule, hyperkalemia especially if co-administered with potassium sparing diuretics like spironolactone and amiloride. As with other SGLT-2 inhibitors risk of serious hypoglycemia is very little with canagliflozin.[25]

Dapagliflozin

Its a highly selective inhibitor of SGLT2.[26] Dapagliflozin was approved for the treatment of Type 2 Diabetes Mellitus by FDA in 2014. In the European Union and other countries in it has been in use since 2012 . The recommended starting dose is 5 mg once daily, which can be increased to 10 mg once daily in patients tolerating it well. Many studies have concluded the usual dose of dapagliflozin to be 10 mg OD.[27] Kidney function should be done before starting dapagliflozin. Because it is known to cause reduction in GFR it should not be used in patients with an eGFR <60 mL/min/1.73 m2. In patients who have already been on dapagliflozin it should be discountinued if GFR falls below 60 mL/min/1.73 m2.[28] It is given orally since its bioavailability is high. Its t1/2 of 14 hrs allows for once daily dose.[29] It can be given with or without food and food is not expected to affect absorbtion of this drug.[30] It can also be used as add-on therapy with metformin, pioglitazone, glimepiride, and sitagliptin. Combination of these drugs demonstrated significant reductions in HbA1c, fasting blood glucose, and body weight compared with placebo. In the studies that were conducted over years, dapagliflozin demonstrated sustained improvements in efficacy , which is an important finding given the chronic nature of T2DM.[31] The addition of dapagliflozin in patients of type 2 diabetes who has already been on insulin demonstrated that it has synergistic effect with insulin and helps in maintaining lower blood sugar levels. It was hypothesised that because dapagliflozin works independently of the of insulin , it is responsible for synergistic reduction in blood sugar level in patients who are inadequately controlled on insulin monotherapy. In the many trials where simultaneous treatment with insulin and dapagliflozin was studied they were found to be efficacious for longer duration of time over a range of patients with type 2 diabetes mellitus.[32] The adverse effects of dapagliflozin include hypoglycemia, hypotension, reduced GFR, urinary tract infections, Genital infections, increase in LDL and blood urea notrogen and rarely bladder cancer. Some studies have concluded that there is no such casual relationship between dapagliflozin and bladder cancer.[33] Hypoglycemia cause by dapagliflozin is minor and may be seen if it is given with sulphonylureas.[34]

Empagliflozin

Empazliflozin has been in use since FDA approved it in 2014.[35] The usual dose is 10 mg to 25 mg. The long T1/2 is consistent with once daily dosing. Like in other SGLT2 inhibitors empagliflozin may cause reduction in GFR and hence it should be avoided in patients having GFR less than 45 mL/min/1.73 m2. The mechanism of action is inhibition of SGLT2 in proximal tubule by which it increases excretion of glucose through urine. Like Canagliflozin and dapagliflozin it can also be used as mono therapy, addo-on therapy or along with insulin. There are no significant interactions of empagliflozin with metformin,hydrochlorothiazide or digoxin.[36] Used as mono therapy it was found to reduce HbA1c levels as well as systolic and diastolic blood pressures.[37] The adverse effects of empaglilozin are similiar to other 2 SGLT2 inhibitors. The incidence of serious hypoglycemia is very rare with empagliflozin. Hypoglycemia was seen when it was added to other oral hypoglycemics rather than when used as mono therapy.[38] As with other SGLT2 inhibitors the incidence of genital and urinary tract infections especially in females and in those patients who have chronic kidney disease.[39] There was no or very small change in HDL and LDL levels in patients who have been on empagliflozin treatment.[40]

Summary

Canagliflozin, dapagliflozin, and empagliflozin are novel anti diabetic drugs which act by inhibition of SGLT2 receptors located in proximal convoluted tubules of nephrons. The unique property of this group of drugs is their ability to lower blood glucose levels independent of secretion and action of insulin. SGLT2 receptors can be used as mono therapy in patients for whom other first and second line oral hypoglycaemic drugs are contraindicated or not tolerated for any reason. In Other patients these drugs can be used as add-on therapy in addition to first and second line oral hypoglycemics. Canagliflozin, dapagliflozin, and empagliflozin reduce HbA1c, Fasting and postprandial blood glucose levels in patients having different stages of Type 2diabetes mellitus by increasing excretion of glucose through proximal convoluted tables of nephrons. As their mechanism of action is independent of insulin secretion and action they can be used in patients inadequately controlled on other drugs like metformin, sulfonylurea or even in patients on insulin. The additional benefits of SGLT2 inhibitors other than lowering of blood sugar levels are reduction in blood pressure, weight loss and diuresis. An increase in HDL-C is also noted in many studies which again is beneficial for the patient. The mechanism of action of these drugs is dependent upon sugar content of glomerular filtrate which in turn is dependant upon blood sugar levels. A decrease in blood sugar level automatically cause reduction in sugar levels of glomeruli filtrate and hence episodes of clinically significant hypoglycemia is very rare in patients receiving SGLT2 canagliflozin, dapagliflozin or empagliflozin. The only major concern in use of these drugs is the incidence of urinary tract and genital infetions specially in women. By virtue of increasing glucose levels in urine these drugs tend to predispose the patient for development of urinary tract infections but these infections in general are mild to moderate and expected to resolve with standard treatment. The other limitation of SGLT2 inhibitors is they tend to reduce GFR and hence should be avoided in patients having GFR at lower side of normal and these drugs are contraindicated in patients who have significantly reduced GFR. The other concerns of these drugs causing neoplasia of urinary bladder has already been refuted.

CONCLUSION

Despite concerns with incidence of urinary tract infections SGLT2 inhibitors appear to be novel and promising group of drugs. Because of their action being independ-

ent of insulin action they have a definite role in patients not adequately controlled on first and second line therapy. In addition to glycemic control they have additional beneficial effects of diuresis, lowered blood pressure levels and weight loss.

Conflict Of Interest: None

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