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DAPAGLIFLOZIN: SELECTIVE SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITOR IN TYPE 2 DIABETES

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ABSTRACT
Dapagliflozin is a promising new drug that targets the so far untapped renal glucose reabsorption. By inhibiting sodium-glucose co-transporter-2 (SGLT2) which is mainly localized in the S1 segment of the proximal tubule, Dapagliflozin promotes renal glucose excretion and reduces hyperglycemia in an insulin-independent manner. Dapagliflozin also produces pronounced weight loss which may be an advantage in patients on sulfonylureas and insulin. Dapagliflozin has the potential to be used as monotherapy, as well as in combination with all approved antidiabetic agents.
KEYWORDS: Dapagliflozin, type 2 diabetes, sodium-glucose co-transporters

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia, which contributes to micro and macrovascular complications including retinopathy, neuropathy and accelerated cardiovascular disease.[1] Clinical studies have shown that intensive efforts to meet treatment goals significantly reduce the risks of microvascular and macrovascular complications.[2] However, despite various therapeutic options only about 42% of individuals with diabetes have a good glycemic control reflected by A1C levels <7%.[3] The currently used drugs are also laden with various concerns, including weight gain, high risk of hypoglycemia, poor postprandial control, and failure to maintain long-term glycemic control. The conventional and newer oral antidiabetic drugs (OADs) as well as insulin therapy are also associated with worsening insulin resistance and progressive failure of insulin secretion. Even insulin-combinations therapies are far from being completely effective in controlling hyperglycemia.[4] Overall; there is a need for novel agents that can be safely administered to help achieve glycemic targets without increasing the risks of the currently available drugs.

A novel approach for treating hyperglycemia, targets receptors for renal glucose reabsorption.[5] The kidneys play an important but underappreciated role in the overall regulation of blood glucose levels in the body. In normal individuals, glucose present in the plasma is filtered by the kidneys, but virtually all of it is reabsorbed, such that less than 1% of glucose is excreted in urine.[6,7] In patients with T2DM who have hyperglycemia, a greater amount of glucose is filtered and paradoxically the glucose resorptive capacity of the kidneys is increased despite the fact that this retention process contributes to sustaining the hyperglycemia of diabetes.[8] This leads to glucotoxicity, which worsens insulin resistance and contributes to dysfunction in the beta cells of the pancreas. This method of controlling hyperglycemia appears to minimise deleterious effects that exacerbate T2DM complications.

Transport of glucose across cell membranes is accomplished by two gene families: the facilitative glucose transporters (GLUTs) and the active sodium-dependent transport process mediated by the sodium–glucose co-transporters (SGLTs). The SGLTs are a large family of membrane proteins involved in the transport of glucose, amino acids, vitamins, osmolytes, and some ions across the brush-border membrane of the intestinal epithelium and the proximal renal tubules. Inhibition of the SGLTs is complicated by differences in two important isoforms: SGLT1 and SGLT2. SGLT1 is highly expressed in the gastrointestinal tract and is the major transporter of dietary glucose and galactose. SGLT1 is also expressed in the liver, lung, and kidney, while SGLT2, for which glucose is the primary substrate, appears to be selectively expressed in the kidney.[9,10] SGLT2 expression in the kidney is localized to the S1 segment of the proximal tubule, where more than 90% of renal glucose reabsorption occurs; whereas SGLT1 is present in the more distal S3 segment of the proximal tubule.[5]

The inhibition of renal glucose reabsorption is a novel approach to the treatment of diabetes.

In humans, mutations in SGLT2 are associated with familial renal glucosuria (OMIM 233100)[11,12] a benign syndrome in which glucose excretion occurs in the absence of hyperglycemia. Thus, SGLT2 appears to be the major transporter responsible for renal glucose transport, mediating glucose reuptake from the glomerular filtrate. Hence selective inhibition of SGLT2 vs. SGLT1 will promote renal glucose excretion and reduce hyperglycemia without the potential for gastrointestinal side effects predicted with SGLT1 inhibition.[13] Pre-clinical models have shown that SGLT2 inhibition lowers blood glucose independently of insulin.[14] Dapagliflozin, a highly selective inhibitor of SGLT2, has demonstrated efficacy, alone and in combination with metformin, pioglitazone and insulin in reducing hyperglycemia in patients with type 2 diabetes.[15,16]

Chemistry

Dapagliflozin is a potent, selective renal SGLT2 inhibitor. Chemical name of Dapagliflozin(C-aryl glucoside 6) is (2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-chloro-3- (4-ethoxybenzyl)phenyl]-6-(hydroxymethyl) tetrahydro-2*H*-pyran-3,4,5-triol 2*S*)-propane-1,2-diol (1:1) monohydrate.[17]

Pharmacodynamics

Dapagliflozin is the first in a new class of oral selective SGLT2 inhibitors designed for treating T2DM. Dapagliflozin decreases hyperglycemia by inhibiting renal glucose reabsorption through SGLT2. SGLT2 is a sodium-solute co-transport protein located in the kidney proximal tubule that reabsorbs the majority of glomerular-filtered glucose.[18] Dapagliflozin, both as monotherapy and in combination with other OADs and/or insulin, produced decreases in HbA1C, Fasting plasma glucose (FPG) and Post prandial plasma glucose (PPG). While fall in FPG was dose-related, changes in A1C and PPG were not.[16,19] Dapagliflozin also produces pronounced weight loss at all doses, more acute during the first week of therapy. Diuresis may partly be responsible for weight loss and mild hypotensive effects.[18]

Pharmacokinetics

It contains a C-glucoside for increased in vivo stability, characteristics that prolong half-life and produce consistent pharmacodynamic activity. [17]

Adverse effects

The most common adverse effects reported are genital infections (2-7% compared to 0% in the placebo treated group) and urinary tract infections (5-12% compared to 6% in the placebo treated group).[18]

Indications

Dapagliflozine (10-20 mg) could be a novel agent for patients of T2DM as monotherapy or combination therapy in patients poorly controlled with high insulin doses and/or OADs with the added advantage of improvement in weight status.

Merits

1. Selective SGLT2 inhibitors offer a potential effect only in the kidneys, allowing excretion of glucose and creation of a negative energy balance without a potential gastrointestinal side effect profile.[17,20]

2. Dapagliflozin has a 1200-fold selectivity for SGLT2 over SGLT1 as compared with phlorizin's 10-fold selectivity.[17]

Demerits

Urinary frequency (pollakiuria), backache, nasopharyngitis, nausea, headache, and upper respiratory tract infection

Though most oral antidiabetic drugs and insulin cause weight gain, Dapagliflozin causes weight loss in an excessive and aggressive manner, to the extent of approximately 4kg weight loss in three months. This may lead to muscular weakness and fatigue and patient compliance may be affected over a long term.

Normally, in healthy individuals, the kidneys filter a large volume of glucose and actively reabsorb virtually all of it. Glucose reabsorption is necessary to retain calories, but becomes counterproductive in type 2 diabetes. The degree of sustained hyperglycemia is directly related to diabetic microvascular complications and may also contribute to macrovascular complications. In this way, hyperglycemia appears to perpetuate a vicious cycle of deleterious effects that exacerbate type 2 diabetes.

CONCLUSION

Sodium glucose co-transporters 2 (SGLT2) inhibitors represent a promising approach to the treatment of T2DM. They have the potential to be used as monotherapy, as well as in combination with all approved antidiabetic agents. Since their mechanism of action is independent of the severity of beta cell dysfunction or insulin resistance, efficacy should not decline with progressive beta cell failure or in the presence of severe insulin resistance.

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