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ERTUGLIFLOZIN – A NOVEL SGLT 2 INHIBITOR - A REVIEW

Pharmacology

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ABSTRACT

Glucose is the main source of energy for the entire living beings. Glucose is absorbed from various sources and are metabolized in several ways for the need of organisms. Kidneys play an important role in glucose metabolism which are responsible for the reabsorption of glucose. They contribute to glucose balance by producing glucose through gluconeogenesis, utilizing glucose in renal medulla and nearly 100% re-absorption of the filtered glucose. Number of different drugs are available for the treatment of diabetes mellitus. They are sulphonylurea, biguanides, meglitinides, alpha glycosidase inhibitor, glitazones etc. Mechanism of action of available drugs includes increasing insulin secretion, increasing insulin sensitivity, controlling hepatic glucose release or inhibiting intestinal glucose absorption. These drugs has many adverse effects mainly hypoglycaemia. The other side effects include weight loss, lactic acidosis etc.This review focusses on the novel antidiabetic drug Ertugliflozin. Sodium-dependant glucose co-transporters (SGLT1 and SGLT2), also known as co-transporters or symporters, are integral membrane proteins that mediate the transport of glucose with much lower affinity and galactose across the plasma membrane by an active transport mechanism. This transport process cotransport glucose molecule and sodium ions. The energetically favored movement of a sodium ion across the plasma membrane into the cell is driven by a concentration gradient and a membrane potential and is coupled with transport of sodium ions in to the cell across the apical cell membrane which is pumped by a sodium/potassium ATPase across the basolateral membrane via glucose transport facilitators designated GLUT-Proteins.The SGLT1 is a high affinity, low-capacity sodium–glucose symporter with sodium-to glucose coupling ratio of 2:1. The transporter is expressed mainly in intestine, heart, and kidneys. Ertugliflozin is a new Sodium–Glucose co-Transporter-2 (SGLT-2) blocker, which inhibits the re-absorption of glucose from the kidneys, thereby causing loss of glucose in the urine and reduction of blood sugar levels and weight loss.

KEYWORDS

Diabetes mellitus, Sodium Glucose Co-transporters, Ertugliflozin

Introduction

The main energy source for eukaryotic organisms is glucose. It plays a vital role in the metabolism and cellular homeostasis. Most of the mammalian cells required continuous supply of glucose. This acts as a primary source for the generation of adenosine triphosphate (ATP)[1,2]. Glucose metabolism is maintained by the coordinated regulation of three processes. First process is the absorption of glucose via small intestine, second process is the production of glucose in the liver. The third process is the consumption of glucose by all tissues[3]. Tissues such as brain need constant supply of glucose. Low blood glucose concentration results in seizures, loss of consciousness and irreversible cell damage. The excessive blood glucose concentration have an effect called glucose toxicity which cause blindness, renal failure, cardiac disease and neuropathy[4]. Glucose is the main regulator of insulin secretion and production. High concentration of glucose over a longer period cause negative effects on pancreatic beta-cell function which result in increased sensitivity to glucose, increased basal insulin release, reduced maximal secretory response and a gradual depletion of insulin stores. So concentration of glucose in blood need to be maintained within the limit of 80-110 mg/dL. The plasma membrane of eukaryotic organism is impermeable for hydrophilic molecules because of its lipid bilayer. So glucose is transported across the plasma membrane by membrane associated carrier proteins. The two different types of transporter protein that mediate glucose and othe rsugar transfer through lipid bilayer are Sodium Glucose Co-transporter System (SGLT) and facilitative glucose transporters (GLUT). SGLT and GLUT belong to the solute carrier gene series (SLC). The series consist of 43 families (SLC 1 – SLC 43) and have 498 genes[5].

Diabetes mellitus is a metabolic disorder characterized by high blood glucose level[6]. There are many drugs for diabetes mellitus treatment.This includes sulfonylurea, biguanides, alpha glycosidase inhibitor, meglitinides etc. These drugs reduce the blood sugar level by different mechanism including increasing insulin secretion, increasing peripheral utilization of glucose etc. They have many disadvantages including anaemia , hypoglycaemia , GI intolerance etc[7].

Ertugliflozin is a SGLT 2 blocker which can be used is used as drug for diabetes mellitus . It inhibits the reabsorption of glucose and thus reduce the blood glucose level. This drug was approved by FDA in 2017.

Sodium Glucose Co-transporters

Kidney has a vital role in energy control of body. Glucose is filtered in glomerulus and the filtered glucose is reabsorbed. The reabsorbtion is carried out mainly in the S1 segment of proximal tubules. When the glucose reabsorption reaches saturation, excess glucose in excreted in urine which result in a condition called gloycosuria. Approximately 180 g of glucose in filtered daily. In this 90 % of glucose is reabsorbed in convoluted segment of proximal tube the remaining 10 % is reabsorbed in the distal straight segment. SGLT and GLUT are mainly responsible for glucose transport.

There are six types of known SGLTs. Among them SGLT1 and SGLT2 were extensively studied. SGLT1 is mainly present in the renal proximal tubule at the S2 site, has a stronger affinity for glucose. Also it has less transporting capacity than SGLT2. SGLT2 is present in proximal tubule membranes at the S1 site. It has lower affinity and greater capacity for transporting glucose. About 90% of glucose reabsorbed in the proximal tubule is mediated by SGLT2 is responsible for 90% and SGLT 1 is responsible for 10% of glucose reabsorbtion[8].

Ertugliflozin

Ertugliflozin was approved by the FDA on December 22, 2017 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It is available in 5mg and 15mg tablets.

The chemical name of ertugliflozin L-pyroglutamic acid is (1S,2S,3S,4R,5S)-5-(4-chloro-3-(4ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2S)-5 oxopyrrolidine-2-carboxylic acid. The molecular formula is C27H32ClNO10 and the molecular weight is 566.00.

Ertugliflozin L-pyroglutamic acid is a white to off-white powder that is soluble in ethyl alcohol and acetone, slightly soluble in ethyl acetate and acetonitrile and very slightly soluble in water

Mechanism of Action

SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Ertugliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Pharmacodynamics

Urinary Glucose Excretion and Urinary Volume

Dose-dependent increases in the amount of glucose excreted in urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following single- and multiple-dose administration of ertugliflozin. Dose-response modeling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE). Enhanced UGE is maintained after multiple-dose administration. UGE with ertugliflozin also results in increases in urinary volume.

Cardiac Electrophysiology

The effect of ertugliflozin on QTc interval was evaluated in a Phase 1 randomized, placebo- and positive-controlled 3-period crossover study in 42 healthy subjects. At 6.7 times the therapeutic exposures with maximum recommended dose, ertugliflozin does not prolong QTc to any clinically relevant extent.

Pharmacokinetics

The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes mellitus. The steady state mean plasma AUC and Cmax were 398 ng·hr/mL and 81.3 ng/mL, respectively, with 5 mg ertugliflozin once-daily treatment, and 1,193 ng·hr/mL and 268 ng/mL, respectively, with 15 mg ertugliflozin once-daily treatment. Steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin. Ertugliflozin does not exhibit time-dependent pharmacokinetics and accumulates in plasma up to 10-40% following multiple dosing.

Absorption

Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations (median Tmax) of ertugliflozin occur at 1 hour postdose under fasted conditions. Plasma Cmax and AUC of ertugliflozin increase in a dose-proportional manner following single doses from 0.5 mg (0.1 times the lowest recommended dose) to 300 mg (20 times the highest recommended dose) and following multiple doses from 1 mg (0.2 times the lowest recommended dose) to 100 mg (6.7 times the highest recommended dose). The absolute oral bioavailability of ertugliflozin following administration of a 15 mg dose is approximately 100%.

Effect of Food

Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin Cmax by 29% and prolongs Tmax by 1 hour, but does not alter AUC as compared with the fasted state. The observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant, and ertugliflozin may be administered with or without food. In Phase 3 clinical trials, ertugliflozin was administered without regard to meals.

Distribution

The mean steady-state volume of distribution of ertugliflozin following an intravenous dose is 85.5 L. Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.

Elimination

Metabolism

Metabolism is the primary clearance mechanism for ertugliflozin. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation to two glucuronides that are pharmacologically inactive at clinically relevant concentrations. CYP-mediated (oxidative) metabolism of ertugliflozin is minimal (12%). Excretion The mean systemic plasma clearance following an intravenous 100 µg dose was 11.2 L/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 16.6 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 40.9% and 50.2% of the drug-related radioactivity was eliminated in feces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 33.8% as unchanged ertugliflozin in feces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent[9].

Adverse effects

The most common side effects associated with ertugliflozin are female genital mycotic infections which had an observed incidence of ≥ 5%. Other warnings and precautions that are associated with ertugliflozin include: hypotension, diabetic ketoacidosis, intravascular volume contraction/depletion, acute kidney injury/renal impairment, lower limb amputation, hypoglycemia, and increase in low-density lipoprotein cholesterol (LDL)[10].

Conclusion

This new drug serves as an alternative drug for the treatment of patients with type 2 diabetes mellitus.

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