A critical appraisal of antihyperglycemic and cardioprotective activities of liraglutide: A glucagon-like peptide-1 analog

INTRODUCTION

Oral glucose load enhances the release of insulin than the similar quantity if administered intravenously and a difference of 40%-60% in the area-under-the-curve of the insulin time concentration graph is registered. This difference is known as “incretin effect” which enhances the availability of insulin and decreases blood glucose.[1] Owing to this effect, liraglutide GLP analogue has been approved by Food and Drug Administration for treatment of type 2 DM.[2]

Liraglutide is substituted product in the native hormone glucagon-like peptide-1 (GLP-1) obtained by the substitution of Lys 34 to Arg and by addition of a C16 fatty acid at 26th position using an α-glutamic acid spacer. Due to substitution of only one amino acid, liraglutide shares homology with native hormone native GLP-1. Since there is only one amino acid replacement, the resultant molecule shares 97% (36/37 amino acids) sequence identity with native human GLP-1. In contrast to this, exenatide that was originally identified as a derivative of Gila monster (Heloderma suspectum) venom, shares only 53% sequence identity with native GLP-1.[3,4] The aim of this review is to compile the antidiabetic and cardioprotective mechanism of liraglutide [Figure 1, adapted from Russell 2009].

PHYSIOLOGY

The incretins are the peptide hormones and the peptides are short polymers formed by the linking, in a defined order, of α-amino acids. In humanGLP-1 and glucose-dependent insulino tropic polypeptide (GIP), the uppermost incretins which are secreted into circulation immediately after eating. GLP-1 and GIP are usually secreted by L and K cells subsequently, (L cell located in the ileum and colon while K cell located in Duodenum). [5-11]
Both incretins produce hormonal effects on multiple organs, important ones are the endocrine pancreas, gut, and the brain. Their most frequent effect is the regulation of energy homeostasis. Both, GIP and GLP-1 influence their actions by binding with specific receptors. The GIP receptors (GIPR)\(^{[12,13]}\) and GLP-1 receptors (GLP-1R)\(^{[14,15]}\) belong to G protein coupled receptor family and they stimulate insulin secretion in a glucose-dependent manner, delay gastric emptying, and suppress appetite.\(^{[16]}\) Aggregation of these effects plays an important role in glucose homeostasis, specifically in the control of postprandial glucose.\(^{[16]}\) Subsequent studies show that incretins improve glucose sensitivity of pancreatic β cell and, promote pancreatic β cell proliferation, and reduce β cell cardiac cell apoptosis.\(^{[6,7]}\)

The incretins act through G-protein-coupled receptors, the GLP-1 receptor, which is predominant in pancreatic islet and β cells, heart, central nervous system, kidney, lungs, and gastrointestinal tract. The GIP receptor, however, is highly observable in the pancreatic islet β cells and less in the central nervous system and in adipose tissues\(^{[6,16,17]}\) [Figure 2].

The response of incretin to a meal lasts approximately 2-3 hours even short half-life (1-2 min) because there is ongoing production of incretins due to presence of nutrients in the gut. Dipeptidylpeptidase-4 (DPP4), an enzyme that is ubiquitously expressed in endothelial cells, is responsible for incretin metabolism.\(^{[7,17]}\)

**PHARMACOLOGY**

**Mechanism of action**

Liraglutide contains fatty acid molecule at 26\(^{th}\) position that have affinity to bind with albumin and enhances the life of molecule than endogenous GLP-1 molecule which is degraded easily with DPP4 and creates minimum insulin secretion. GLP-1 receptors are predominant in pancreatic alpha and beta cells, the central and peripheral nervous systems, the heart, lung, and the gastrointestinal tract where they enhance insulin release. GIP and GLP-1 are secreted once after the food ingestion and leads to the glucose-dependent insulin secretion. Once released, GIP and GLP-1 are subjected to degradation by DPP4 on lymphocytes and on endothelial cells of blood vessels. Due to presence of C16 fatty acid liraglutide action is prolonged and the binding of incretin ligands or agonist to the incretin receptors results in production of cAMP via adenylyl cyclase (AC) activation, which leads to elevation of intracellular calcium levels the enhance in intracellular calcium concentrations tend to fusion of insulin-containing vesicles to the plasma membrane and exocytosis of insulin from β cell [Figure 3].\(^{[7,18,19]}\)

**Pharmacodynamic drug interactions**

According to European Medical agency, liraglutide shows synergistic effects in combination with the γ-peroxisome proliferator-activated receptor (PPAR\(^{\gamma}\)) agonist pioglitazone, and also with the sulfonylurea glipizide.\(^{[20,21]}\)

**PHARMACOKINETICS**

In isotonic solution, the liraglutide should be administered subcutaneously. According to European Medical agency the peak concentration of liraglutide approaches between 3 and 9 h and the half-life is 13 h after single administration. However, endogenous administration of GLP-1 has the half-life of approximately 2 min due to DPP4 degradation. Presence of fatty acid chain in liraglutide molecule forms heaptamers at injection site depot and allows reversible binding to serum albumin may probably be responsible for delayed absorption of liraglutide and resistance to metabolism by DPP4, and reduces renal clearance. For such extended mode of action once daily dose is sufficient.\(^{[5,20-22]}\)

**ADVANTAGES**

- Hypoglycemia: It was found that incretin mimetics have low risk of hypoglycemia than other class of antidiabetic drugs due to the induction of insulin secretion in a glucose-dependent way.
- Effect on beta-cell health: Prevent cellular apoptosis and maintain β cell morphology.
- Effect on postprandial hyperglycemia: Incretins can maintain this crucial parameter by direct inhibition of the glucagon release and enhanced insulin release.\(^{[5,20-22]}\)

**CARDIOPROTECTIVE MECHANISM OF LIRAGLUTIDE**

Caspase (cysteine aspartic protease) have important roles in apoptosis. Protease is an enzyme which is responsible for proteolysis.
Liraglutide may modulate gene function during apoptosis and exhibits cardioprotective actions by activating cardioprotective signaling pathways in the heart. Further, it inhibits the enzyme caspase which play significant role in the conversion of stimulus to death receptors for apoptotic signals.[23] Caspase can be categorized as inhibitor and effector (8, 9, 10, 2) and (3, 7, 6) subsequently.[24] Caspase initiator gets activated after binding with specific oligomeric adaptor protein and effector activation is brought about due to initiator caspase activation through proteolytic cleavage followed by effector caspses which proteolytically degrade a host of intracellular protein to progress cell death.[24] Liraglutide inhibits the caspase-3 which usually occurs at high level during doxorubicin-induced cardiotoxicity and coronary artery occlusion in mice.[23] Marre et al., found a higher level of caspase-3 in these mice which plays an important role in cell apoptosis it was also found a declined concentration of caspase-3 when coronary artery occludes diabetic mice was treated with liraglutide.[23]

Liraglutide acts on GLP-1R modulate adenylcylase consequently phosphatidylinositol 3-kinases (Pi3k) become activated.[23] This activation leads to phosphorylation of Akt (protein kinase-B). Akt is responsible for autophosphorylation of Becl2 associated death promoter (BAD). Phosphorylation of BAD results in inhibition of cell apoptosis which finally increases the transcription of antioxidants and cardioprotective factors such as peroxisome proliferator activated receptor (PPARβα), nuclear respiratory factor-2 (Nrf2), and heamoxigenase-1(Ho-1).[23,24] [Figure 4].

**DOSAGE AND ADMINISTRATION**

Liraglutide can be injected through abdomen subcutaneously or through thigh or upper arm at any time in a day independent of the time and meal adherence. The 0.6 mg dose should be started as per recommendations and then it may be titrated 1.2 or 1.8 mg once daily with respect to the desired HbA1c goal. While initiating the treatment with liraglutide, a dose reduction of concomitantly administered insulin secretagogues (such as sulfonylureas) should be considered to reduce the risk of hypoglycemia.[22,26]

**ADVERSE EFFECTS ASSOCIATED WITH LIRAGLUTIDE**

**Gastrointestinal and hypoglycemia**

Gastrointestinal problem such as diarrhea, nausea, dyspepsia, constipation, and nervous system disorders such as headache and dizziness, particularly during the first 4 weeks are the most predictable adverse events that occurred during the clinical trial on the effects and action of liraglutide in diabetes (LEAD-1). The occurrence of nausea was highest (10.5%), whereas the hypoglycemia major and hypoglycemia minor were found to be at 0% and 9.2% subsequently in LEAD-1 clinical trial. Hypoglycemic episode required third party assistance was considered as hypoglycemia major and self-treated were considered as hypoglycemia minor.[25]

**Pancreatitis**

Pancreatitis was reported in the cohort study conducted by Noel et al., whereas diabetes has prevalence to develop pancreatitis. Therefore, it is difficult to establish that liraglutide is the real culprit in pancreatitis.[26,29]

**Immunogenicity**

Treatment with liraglutide may probably be responsible for generation of antiliraglutide antibody formation such as the antirifampin antibody,[31] which has been reported in phase 3 clinical trial in 4%-13% patients.[27,31]

**Lipohypertrophy**

Long-term insulin therapy is main cause of lipohypertrophy.[30] However, incidence of lipohypertrophy with liraglutide is not
reported in the clinical trials conducted on diabetic subjects; however, the urticarial reactions were not ruled out.[23]

PATIENT COUNSELLING INFORMATION

Risk of thyroid c-cell tumors

Patients counseling should be done for thyroid tumors symptoms such as a lump in the neck, hoarseness, dysphagia, or dyspnea.[20,13]

Pancreatitis

Patients should be informed regarding the symptoms of pancreatitis which may lead to severe abdominal pain with vomiting. Patients should be advised to contact the concerned physician.[20,13]

Instructions

Patients should be counseled that nausea is most common with the initiation of liraglutide therapy while starting liraglutide initially, but decreases over time in the majority of patients and does not typically require discontinuation of liraglutide. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom or if any known symptom persists or worsens.[20,13]

CONCLUSION

Liraglutide-based therapies are relatively new options for the treatment of patients with type 2 diabetes. These agents have low risk associated with hypoglycemia and weight gain in contrast to those drugs which are generally used in the treatment of type-2 diabetes mellitus and shows cardioprotective effect. The monotherapy of GLP-1 receptor agonists and DPP-4 inhibitors have a low risk of hypoglycemia because they stimulate insulin secretion in a glucose-dependent manner. Also, the DPP-4 inhibitors generally do not have any effect on weight, while GLP-1 receptor agonists may cause weight loss. The cause that weight loss may enhance insulin sensitivity and, therefore, have significant benefit in the treatment of type 2 diabetes. GLP-1 receptor agonists may be useful in those patients who are overweight and have risks for developing hypoglycemia and cardiovascular complication. However, the diligent postmarketing surveillance is required to confirm the safety and efficacy of these promising agents, and to determine risk factors associated with the development of the adverse drug reactions.

REFERENCES