Drug Update

Liraglutide (Incretins)

A Goud* M S Pandharipande** A Sondoule*R W Joshi**P P Joshi***

Abstract:

Normoglycemia or near normoglycemia is the desired , but often elusive goal for most of the patients of diabetes mellitus as the complications of diabetes are related to glycemic control. Insulin secretagogues , biguanides , alpha glucosidase inhibitors , thiazolidinediones GLP-1 receptor agonists , DPP-IV inhibitors , and insulin are approved for monotherapy of type 2 diabetes mellitus. "Incretins" have unique ability to suppress glucagon secretion and amplify glucose stimulated insulin secretion . Agents in this class do not cause hypoglycemia and slow gastric emptying . GLP-1 receptor agonists do not promote weight gain; in fact, most patients experience modest weight loss and appetite suppression. At present , two synthetic GLP1 receptor agonists viz. Exenatide and Liraglutide are approved for management of type 2 diabetes mellitus . Exenatide is a synthetic version of a peptide initially identified in the saliva of the Gila monster. Liraglutide another GLP-1 receptor antagonist, is almost identical to native GLP-1 except for an amino acid substitution and addition of a fatty acyl group (coupled with *Y* – glutamic acid spacer) that promote binding to albumin and plasma proteins and prolong its half life., Liraglutide was approved by the FDA in January 2010.

Introduction:

Current strategies in Type2 diabetes mellitus address issues of insulin resistance and absolute/relative insulin deficiency. Because the complications of DM are related to glycemic control, normoglycemia or near normoglycemia is the desired goal for most of the patients. Insulin secretagogues , biguanides , alpha glucosidase inhibitors , thiazolidinediones , GLP-1 receptor agonists , DPP-IV inhibitors , and insulin are approved for monotherapy of type2 diabetes mellitus. Increasing understanding of "Incretin Axis"and its role in glucose homeostasis have paved way to development of few exciting agents collectively called Incretin based therapies. They have unique ability to augment insulin secretion and to suppress glucagon secretion in a glucose dependent manner .Incretins have shown great promise in preservation of beta cell function both in animal and human studies. At present, two synthetic GLP-1 receptor agonists viz. Exenatide and Liraglutide are approved for management of Type 2 diabetes mellitus .

Exenatide, first therapeutically prepared molecule amongst incretins is a synthetic version of a peptide initially identified in the saliva of the Gila monster (exendin -4) is an anologue of GLP-1.Unlike native GLP-1, which has a half life of <5 min, differences in the Exenatide amino acid sequence render it to resistant to the enzyme that degrades GLP-1 (dipeptidyl peptidase IV, or DPP IV). Exenatide has prolonged GLP-1 like action and binds to GLP-1 receptors found in islets, the gastrointestinal tract, and the brain. Exenatide is approved for monotherapy and for use as a combination therapy with metformin, sulfonylureas and thiozolidindediones .Treatment with these agents should start as a low dose to minimize initial side effects, especially nausea. Some patients taking insulin secretagogues may require a reduction in the dose to prevent hypoglycemia.GLP-receptor agonists should not be used in patients taking insulin. The major side effects are nausea, vomiting, and diarrhea; pancreatitis and reduced renal function have been reported in surveillance data with exenatide. Liraglutide carries a black box warning from the FDA because of an increased risk of thyroid C cell tumors and is contraindicated in individuals with medullary carcinoma of the thyroid and multiple endocrine neoplasia. Because GLP-1 receptor agonists slow gastric emptying , they may influence the absorption of other drugs. Although reported as physiological effects in the studies. Whether GLP-1receptor agonists enhance beta cell survival, promote beta cell proliferation, or alter natural history of type 2 diabetes mellitus is exactly not known.

Resident* Assistant Professor** Professor and HOD***
Dept of Medicine,
Indira Gandhi Govt.Medical College,Nagpur
Address for correspondence
M. S. Pandharipande
Email: madhuri.pandharipande@gmail.com

Liraglutide:

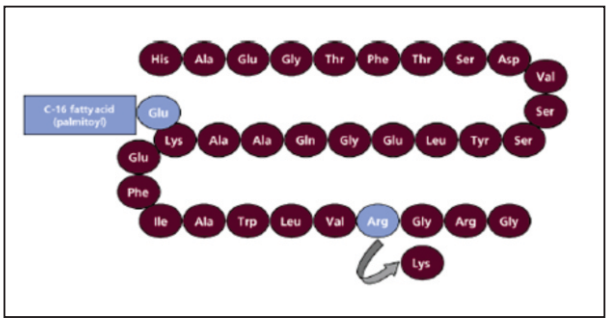
Liraglutide is a once daily human GLP-1 analogue developed for the treatment of type 2 DM.It improves first phase insulin secretion and maximal beta cell insulin secretory capacity by restoring beta cell insulin secretory capacity by restoring beta cell glucose sensitivity . It also suppresses glucagon secretion from alpha cells of the pancreas. However both insulin secretion and glucagon

suppression are switched off at lower glucose concentrations , thereby avoiding hypoglycemia . Liraglutide has a plasma half life of approximately 13 hours and therefore is suitable for once daily administration. Liraglutide is marketed under the brand name Victoza in the U.S., India, Canada, Europe Phase I trials of an oral variant of Victoza (NN9924) have already been started .

The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae , has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. Liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP), leading to insulin release in the presence of elevated glucose concentrations.

Pharmacokinetics:

Liraglutide is a once-daily GLP-1 derivative for the treatment of type 2 diabetes. GLP-1, in its natural form, is short-lived in the body (the half-life after intramuscular injection is approximately half an hour), so it is not very useful as a therapeutic agent. However, Liraglutide has a half-life after subcutaneous injection of 11–15 hours, making it suitable for once-daily dosing The prolonged



action of Liraglutide is achieved by attaching a fatty acid molecule at one position of the GLP-1 molecule, enabling it to bind to albumin within the subcutaneous tissue and bloodstream. The active GLP-1 is then released from albumin at a slow, consistent rate. Binding with albumin also results in slower degradation and reduced elimination of Liraglutide from the circulation by the kidneys compared to GLP-1

Preparations:

Multiple dose pre-filled pen: 18 mg in 3 ml (6 mg/ml)

Storage:

Liraglutide should be refrigerated between 2-8 C (36-46 F) prior to first use. After the first use it can be stored at room temperature 15-30 C (59-86 F) or refrigerated at 2-8 C (36-46F).

Dosing:

Liraglutide is injected under the skin of the abdomen, thigh, or upper arm. Each pre-fiilled pen can deliver 0.6, 1.2, and 1.8 mg doses. The initial dose is 0.6 mg daily for one week. After one week the dose is increased to 1.2 mg daily. The maximum dose is 1.8 mg daily.

Drug Interactions:

Liraglutide slows down transit of food and drugs through the intestine and, therefore, may reduce the absorption of drugs that are taken orally. Although Liraglutide did not significantly affect the absorption of oral dugs tested in studies, it is still prudent to separate administration of Liraglutide and oral medications. Combining liraglutide with insulin or drugs that stimulate release of insulin may cause hypoglycemia. The dose of insulin release stimulating drug should be reduced.

Pregnancy:

There are no adequate studies of Liraglutide in pregnant women.

Nursing Mothers:

There are no adequate studies of Liraglutide in nursing mothers, and it is not known whether Liraglutide is excreted in human breast milk.

Side Effects:

The most common side effects of liraglutide are nausea, vomiting, diarrhea, constipation, upper respiratory tract infection, and headache. Patients also may experience flu like symptoms, dizziness , sinusitis, back pain, and reactions at the injection site.

There are reports about increased risk of thyroid cancer with the use of Liraglutide and increased risk of pancreatitis with Incretins. However, final recommendation from studies and report by USFDA are awaited

The Victoza label carries a Black Box Warning: **"**Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risks**"** Liraglutide has multiple direct effects on human physiology.

Liraglutide and Cardiovascular System- It increases glucose uptake in myocardium through non insulin mechanism. It increases nitric oxide synthesis, p38MAP kinase activity and GLUT-1 translocation, induces nitric oxide mediated vasorelaxation , reduces TNF-alpha

mediated PAI-1 secretion . Liraglutide has demonstrated increased survival, reduced cardiac rupture and improved cardiac function in mice

Liraglutide and Central Nervous system – Liraglutide improves spatial and associative memory when adminidtered in to the CNS. Its most striking effect on the CNS is reduced intake of food and increased satiety by its action on the hypothalamus. This results in striking weight loss and may have a salutary impact in achieving glycemic control, improving cardiovascular outcomes and management of obesity.

Liraglutide and gastrointestinal system—

It delays gastric emptying and decreases food intake. Nausea is also commonly observed with administration of Liraglutide.

Liraglutide and the endocrine pancreas—

Evidence of increased beta cell mass has been clearly demonstrated in animal studies with Liraglutide. It stimulates beta cell proliferation from the existing beta cells and also to some extent increase neogenesis from the ductal epithelial cells at the same time it reduces apoptosis of beta cells , net result being increased beta cell mass.

In clinical studies on humans, Liraglutide improved beta cell function as assessed by HOMA-B and proinsulin:insulin ratio . This could reflect preservation of beta cell function and may be responsible for longer durability of glycemic control ,however , needs to be confirmed in long term clinical trials.

Clinical trials on Liraglutide

Liraglutide has been extensively studied in phase 3 trials, both as monotherapy and in combination with other oral antidiabetic drugs.(LEAD: Liraglutide effect and action in diabetes).The LEAD trial was performed on 4000 patients with type 2 diabetes mellitus ,designed to investigate the efficacy of Liraglutide at each step in the treatment continuum from monotherapy to combination with two oral antidiabetic drugs. Published data demonstrated Liraglutide delivers immediate, substantial and sustained reduction in HbA1C combined with visible weight loss , meaningful reduction in systolic blood pressure as well as improved beta cell function. Average HbA1C reduction ranged from 1.2 to 1.6%. In LEAD trials,44 to 68 % subjects could achieve ADA target of 7%.Other remarkable benefit shown in LEAD programme was near .absence of hypoglycemia. Weight loss of approximately 5 to 8 kg was observed in LEAD studies..Consistent reduction in systolic blood pressure 3 to 6.6 mmHg was also observed.

Safety issues

Mast common side effect noted during studies on Liraglutide was nausea.As part of safety regulations all subjects in LEAD programme were monitored for pancreatitis None of the reported cases had any casual relationship with Liraglutide

Liraglutide versus other incretin therapies

Currently DPP-IV inhibitors are not compared directly with Liraglutide. However , studies show that levels of GLP-1 receptor agonist, Liraglutide are higher than achieved with a DPP IV inhibitors. Liraglutide caused significant weight loss , whereas DPPIV inhibitors were weight neutral. Nausea was more common with Liraglutide. Liraglutide administered once daily achieved better and sustained GLP-1 concentration as compared to Exenatide. Significant HbA1C reduction was seen with Liraglutide as compared with Exenatide. Weight loss was comparable with two agents, nausea was more frequent and prolonged with Exenatide

Liraglutide was approved by the FDA in January 2010. **Liraglutide** (NN2211), marketed under the brand name **Victoza**, is a long-acting glucagon-like peptide-1 agonist (GLP-1 agonist) developed by Novo Nordisk. The product was approved by the European Medicines Agency (EMA) on July 3, 2009, and by the U.S. Food and Drug Administration (FDA) on January 25, 2010.

Liraglutide is marketed under the brandname Victoza in the U.S., India, Canada, Europe and Japan.

Conclusion :

Liraglutide is a synthetic GLP -1 receptor agonist developed for treatment of type 2 DM. Liraglutide has ability to augment insulin secretion and to suppress glucagon secretion in a glucose dependent manner .It has an advantage of once daily administration, promote weight loss and does not cause hypoglycemia. However, it is available in the injectable form, is associated with nausea and is contraindicated in medullary carcinoma of thyroid and multiple endocrinal neoplasia.

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