Glucagon-like peptide 1 receptor agonists: a new approach to type 2 diabetes management

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Keywords: type 2 diabetes, GLP-1 receptor agonists

Abstract

Despite advances in options for the treatment of type 2 diabetes, optimal glycaemic control is often not achieved. Hypoglycaemia and weight gain that are associated with many antidiabetic medications may interfere with the implementation and long-term application of treatment strategies. Glucose homeostasis is dependent on a complex interplay of multiple hormones and gastrointestinal peptides, including glucagon-like peptide 1 (GLP-1). Abnormal regulation of these substances may contribute to the clinical presentation of diabetes. GLP-1-based therapies affect glucose control without causing hypoglycaemia through several mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, regulation of postprandial glucagon and reduction of food intake.

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Introduction

The management of patients with type 2 diabetes mellitus (diabetes) is becoming increasingly complex.[1] The focus of treatment has been on increasing insulin availability, either through direct insulin administration or through oral agents that promote insulin secretion or improve sensitivity to insulin, or on delaying the delivery and absorption of carbohydrate from the gastrointestinal tract.[2] Although the use of metformin has been the initial medical therapy for most patients, the progressive nature of type 2 diabetes implies that pharmacological agents, in addition to metformin, are required for successful glycaemic control.[1]

Incretin-based therapies represent a therapeutic class with which to achieve the treatment goals of type 2 diabetes.[3] Incretin-based therapies consist of two classes: glucagon-like peptide 1 (GLP-1) receptor agonists, an injectable, which solely acts on the GLP-1 receptor, and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) which are available as oral medications that raise endogenous GLP-1 and other hormone levels by inhibiting the enzyme DPP-4.[4] The focus of this article will be to review the actions and appropriate place in therapy of the GLP-1 receptor agonists, exenatide and liraglutide.

Incretin-based therapy

Incretins are hormones which are found in the gut that are secreted from enteroendocrine cells into the blood within minutes after eating. One of their many roles is to increase insulin secretion and suppress glucagon secretion from the β and α cells of the pancreas after eating. The net effect is to increase insulin-mediated glucose uptake in peripheral tissues, and to suppress hepatic glucose production, both of which result in the lowering of blood glucose.[5]

The incretin effect

According to the incretin effect, oral glucose has a greater stimulatory effect on insulin secretion than intravenous glucose. This is mediated by several gastrointestinal peptides, particularly GLP-1. GLP-1 also suppresses glucagon production, and in pharmacological doses, can delay gastric emptying and reduce food intake.[5]

Glucagon-like peptide 1 agonists

GLP-1 levels are abnormally low in patients with type 2 diabetes. Endogenous GLP-1 has a short half-life of 1-2 minutes as a result of rapid degradation by the enzyme DPP-4. GLP-1 levels can be raised therapeutically by the use of injectable GLP-1 receptor agonists that are resistant to enzymatic degradation, or by an oral DPP-4 inhibitor. When used as monotherapy, these agents do not cause hypoglycaemia because the effect on insulin and glucagon secretion is glucose-dependent.[5]

GLP-1 receptor agonists work by binding to GLP-1 receptors that are located throughout the body, especially on pancreatic α and β cells. An injection of a GLP-1 receptor agonist "floods" the binding sites of the receptors to a much greater degree than the DPP-4 inhibitors. Thus, these drugs tend to reduce blood glucose levels, decrease weight, slow gastric emptying and lower glucagon levels more substantially than DPP-4 inhibitors.[3] GLP-1 receptor agonists are an attractive choice in patients in whom promotion of weight loss is a major consideration and when the level of blood glucose control [haemoglobin A_{1c}

(HbA_{1c})] is moderately elevated (8%) and where insulin is not required.[3] Exenatide and liraglutide are the two GLP-1 receptor agonists that are currently available in South Africa.[6] The GLP-1 agonists are available only as injectables in the form of pen devices.[5] These agents are not to be used in the treatment of type 1 diabetes.[6]

The management of type 2 diabetes

Diabetes requires the medical management of each patient to be approached comprehensively, based on the patient's unique medical history and risk factors, behaviour, and ethnocultural background and environment. Glucose targets should be individualised and should take into account the patient's age, duration of disease, the presence or absence of microvascular complications and macrovascular disease (including risk factors for cardiovascular disease and the risk of severe hypoglycaemia). The usual target of HbA_{1c} levels for patients with type 2 diabetes remains less than 7%. Cardiovascular disease risk reduction is important for all patients with type 2 diabetes. The primary goal for lipids is to reduce low-density lipoprotein cholesterol in patients with or without coronary artery disease. One of the most important goals in the management of type 2 diabetes is weight loss of 5-10% of body weight as this provides benefit in improving hyperglycaemia, dyslipidaemia and hypertension. Medical nutrition therapy continues to be the cornerstone of efforts to improve outcomes for patients with type 2 diabetes. Patients should be encouraged to moderate calorie and carbohydrate intake, reduce saturated fat and increase fibre intake. Since lifestyle interventions may not be durable enough for patients to achieve or maintain HbA_{1c} goals, concurrent treatment with metformin, sulphonylureas, insulin, thiazolidinediones (glitazones) or incretin-based therapies has been recommended by various diabetes associations.[3]

Exenatide

Exenatide (Byetta®) is indicated as an add-on therapy for patients with type 2 diabetes mellitus who are inadequately controlled by lifestyle modification and other oral antidiabetic therapy.[6,7] Exenatide is a short-acting GLP-1 receptor agonist which is available in 5-µg and 10-µg pens and administered twice a day before meals.[3,5] The primary effect of short-acting GLP-1 receptor agonists, such as exenatide, is the lowering of post-prandial glucose levels.[3]

Liraglutide

Liraglutide (Victoza®) is indicated as an adjunct to diet and exercise to achieve glycaemic control patients with in type 2 diabetes.[6] This long-acting GLP-1 receptor agonist is administered subcutaneously once a day. More profound reductions in HbA_{1c} levels have been observed with liraglutide, a longer-acting agent, than with the twice-a day exenatide. This has an effect on both fasting plasma glucose and postprandial glucose levels. When compared directly with a long-acting insulin analog, liraglutide resulted in statistically significant better glucose lowering, without the risk of hypoglycaemia or weight gain.[3]

Both exenatide and liraglutide are associated with weight loss. However, weight loss is more profound in patients with greater starting body mass indices. GLP-1 receptor agonists also have a beneficial effect on blood pressure and a significant improvement in very low-density lipoprotein, free fatty acids, and triglycerides.[3]

Place in therapy

A treatment algorithm has been developed by the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) for the clinical use of GLP-1 receptor agonists. The formulation of the current guideline takes into consideration the challenge that type 2 diabetes is not a homogenous disease and is poorly managed. Less than 50% of patients achieve glycaemic targets. The aim of therapy is to achieve and maintain the HbA_{1c} below the patient's individualised target level.[5]

The newer incretin-based therapies, including GLP-1 receptor agonists, have been included as part of the diabetes treatment algorithm because of their efficacy, without the burden of weight gain and hypoglycaemia. However, they are relatively new and no long-term outcome data are available. Therefore, the newer therapies should be reserved as alternate therapies when conventional therapies are not suitable.[5]

All of the following criteria must be met for add-on therapy with a GLP-1 receptor agonist as part of a three-drug regimen:[5]

- Inadequate glycaemic control using combination therapy with maximally tolerated doses of metformin and sulphonylureas.
- The patient must not be a candidate for a third oral agent.
- The patient must be a poor candidate for insulin therapy.
- A reduction in HbA_{1c} less than 1.5% is required in order to reach the patient-specific goal.

Both of the following criteria must be met for add-on therapy as part of a two-drug regimen:[5]

- The patient has not achieved desired HbA^{1c} with one oral agent and is not a candidate for any other available agent (oral or insulin).
- A reduction in HbA_{1c} less than 1.5% is required in order to reach the patient-specific goal.

Table I is a treatment algorithm for patients with type 2 diabetes, according to SEMDSA.

Safety

While the GLP-1 receptor agonists do not cause hypoglycaemia on their own, the risk is increased when used in combination with other agents, such as the sulphonylureas. It is recommended that the sulphonylurea dose is reduced when a GLP-1 receptor agonist is added.[5] The most common adverse effects of these drugs relate to the gastrointestinal tract (nausea and vomiting), and may occur on initiation of therapy.[3,5] Although adverse effects can be severe and may lead to discontinuation of therapy, nausea is usually transient, lasting from 4-8 weeks,

Table I: 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa treatment algorithm for patients with type 2 diabetes[5]

Lifestyle measures plus	Preferred therapies	Alternate therapies for special circumstances		
Step 1: Initiate at least one oral drug at diagnosis	Metformin	Sulphonylurea	Dipeptidyl peptidase-4 inhibitor	Acarbose
Step 2: Combine any two drugs*	Metformin + Sulphonylurea	Incretin-based therapy	Acarbose	Basal insulin
Step 3: Combine three drugs	Metformin + sulphonylurea + basal insulin (or metformin + pre-mix insulin)	Metformin + sulphonylurea + incretin-based therapy	Metformin + sulphonylurea + acarbose	
Step 4: More advanced therapies	Refer to specialist for basal + mealtime insulin ± metformin ± acarbose ± incretin therapy	Metformin + pre-mix insulin (if not used yet)		

This algorithm should be used only if the patient does not have features of severe decompensation. [Severe decompensation includes any of the following: fasting plasma glucose > 15 mmol/l, haemoglobin A_{1c} > 11%, marked polyuria and polydipsia, weight loss > 5% or ketoacidosis. Refer the patient for specialist care (Step 4)]. Progress down this algorithm within three months if haemoglobin A_{1c} remains above 7% (or above the individualised target). Choose therapies that are likely to produce the haemoglobin A_{1c} reduction that is required to achieve the target. Do not proceed with drug therapy without annual serum glomerular filtration rate measurement.
*: If the patient's haemoglobin A_{1c} is > 9% without features of severe decompensation upon diagnosis, consideration should be given to initiating therapy at Step 2.

and can be minimised by up-titrating the dose slowly. Symptomatic relief can be achieved with the use of anti-nausea medication.[5] Patients should be advised that eating beyond satiety may trigger nausea when a GLP-1 receptor agonist is being used.[3]

There have been recent reports of pancreatitis with the use of GLP-1 receptor agonists. Patients should be warned to report symptoms that are suggestive of pancreatitis immediately, to discontinue the drug straight away on suspicion of pancreatitis, and not to restart a GLP-1 agonist if the diagnosis of pancreatitis is confirmed.[5]

Contraindications

The use of GLP-1 receptor agonists is contraindicated in the following circumstances: [5]

- There is a compelling indication for insulin therapy.
- A history of hypersensitivity.
- Renal failure.
- A personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome (liraglutide only).
- The patient has severe gastrointestinal disease, including gastroparesis.
- The patient has a history of pancreatitis.
- Triglyceride level > 10 mmol per litre, gallstones with intact gallbladder, and alcohol abuse.
- The planned treatment regimen includes a DPP-4 inhibitor.
- The patient is not obese.

Efficacy

The main advantage is that, unlike most other antidiabetic agents that are used in type 2 diabetes, the GLP-1 receptor agonists promote weight loss. According to a study which compared liraglutide 1.8 mg with exenatide 10 µg twice daily in patients who were inadequately controlled on metformin and/or a sulphonylurea, the mean weight loss over 26 weeks was 3 kg. The HbA_{1c} reduction with liraglutide was 1.1% vs. 0.8% that was achieved using exenatide.[5]

Conclusion

GLP-1 receptor agonists represent an exciting addition to the treatment of patients with type 2 diabetes when used in combination with lifestyle modification, or as part of a combination therapy strategy.[3] These agents have the potential to change the paradigm of diabetes treatment by replacing traditional treatment strategies because of superior control, freedom from hypoglycaemia and association with weight loss. Treatment with GLP-1 receptor agonists targets patients in whom other conventional agents are poorly tolerated, or for whom weight loss is more highly prized.[8]

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