LIRAGLUTIDE: THE FIRST HUMAN GLP-1 ANALOGUE

Doina Catrinoiu

Diabetes Clinic, University of Medicine and Pharmacy" Ovidius" Constanţa

Abstract

Conventional treatment strategies for type 2 diabetes fail to address the progressive decline in beta-cell function. The difficulty in achieving and sustaining good glycemic control with current therapies and their inherent risks and drawbacks has led to interest in the development of new therapeutic options.

The incretin hormones are intestinal peptides that enhance insulin secretion following ingestion of nutrients. GLP-1 is the better characterized incretin hormone, and has been shown to play a critical role in normal carbohydrate metabolism.

Two therapeutic approaches, the incretin mimetics and dipeptidyl peptidase-IV (DPP-4) inhibitors, have been in development over the last few years.

Liraglutide is a potent, long-acting GLP-1 analogue based on the structure of native GLP-1, which is obtained by derivatising GLP-1 with a fatty acid, providing a compound with pharmacokinetic properties that are suitable for once-daily dosing.

Liraglutide has demonstrated lasting improvement of HbA1c levels, weight reduction and improved β-cell function in patients with Type 2 diabetes mellitus. Liraglutide is well tolerated; the adverse events that are most frequently reported being transient nausea and diarrhoea.

This article reviews the mechanisms of action and efficacy of liraglutide for the treatment of Type 2 diabetes mellitus.

***Keywords**: Type 2 diabetes, GLP-1, liraglutide*

Introduction

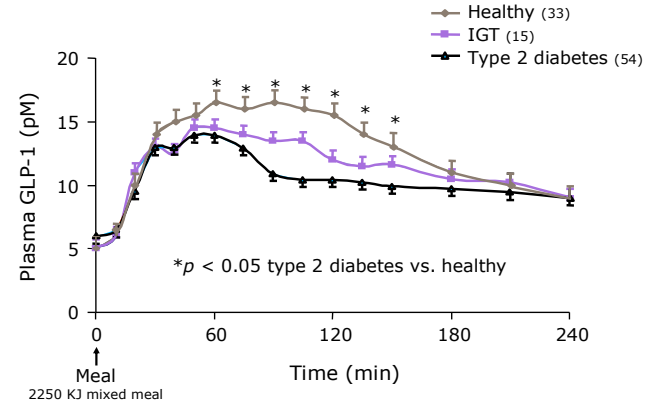
The incidence of type 2 diabetes has reached epidemic proportions and moreover, this estimate is expected to at least double by 2030 to affect more than 350 million people worldwide [1]. The main sources of morbidity and mortality are microvascular and macrovascular complications, which account for the major proportion of the healthcare cost associated with the disease [2]

Insulin resistance and beta-cell dysfunction are considered to be the two main pathophysiologic factors that contribute to the hyperglycemia of type 2 diabetes.

Abnormalities of the secretion of the beta-cell hormone amylin, and the incretin hormones, particularly glucagon-like peptide-1 (GLP-1), may also contribute to the overall pathophysiologic state [3,4].

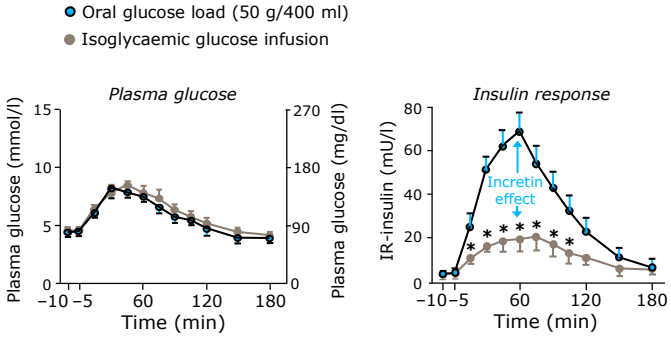
Excess glucagon secretion due to abnormal beta-cell function together with abnormal gastric emptying, are additional contributors to excess blood glucose excursions.

Type 2 diabetes patients have impaired GLP-1 secretion



Adapted from Toft-Nielsen et al. J Clin Endocrinol Metab 2001;86:3717–3723.

The incretin effect



- Insulin response is greater following oral glucose than i.v glucose, despite similar plasma glucose concentration

Adapted from Nauck et al. Diabetologia 1986;29:46–52, *p ≤ 0.05. n=8 healthy volunteers

Conventional treatment strategies for type 2 diabetes fail to address the progressive decline in beta-cell function. Moreover, these therapies are often associated with weight gain in overweight or obese patients with type 2 diabetes. Exogenous insulin and insulin secretagogues are also associated with an increased risk of hypoglycemia.

The difficulty in achieving and sustaining good glycemic control with current therapies and their inherent risks and drawbacks has led to interest in the development of new therapeutic options. Two therapeutic approaches, the incretin mimetics and dipeptidyl peptidase-IV (DPP-4) inhibitors, that leverage the favourable pharmacologic effects of the incretin response, have been in development over the last few years.

Incretin hormones and the incretin efect

The incretin effect was described in the 1960s when investigators recognized that administration of glucose via the oral route

elicited a significantly greater insulin secretory response compared to an isoglycemic intravenous glucose load. The significant increase in insulin secretion was described to the gut-delivery of glucose and was described as intestinal secretion of insulin or the "incretin effect". The incretin effect was subsequently attributed to the insulinotropic effects of two gut-derived hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon- like peptide-1 (GLP-1), termed the "incretin hormones" [5-9]. In healthy human subjects, GIP and GLP-1 are secreted within minutes of food ingestion. Moreover, GIP and GLP-1 stimulate the secretion of insulin only in the hyperglycaemic state, and thus have a so-called "glucose-dependent" insulin secretory effect [7-9]. It is thought that approximately 60% of the insulin response to oral glucose is due to the insulin-potentiating effects of the incretin hormones [7].

GIP is secreted by K-cells from the intestinal epithelium, and in humans and rodent models has been demonstrated to be a significant contributing factor to the maintenance of normal glucose homeostasis in the postprandial period [7- 15]. GLP-1 is the better characterized incretin hormone, and has been shown to play a critical role in normal carbohydrate metabolism. GLP-1 is secreted from L-cells in the lining of the colon and ileum, in response to consumption of a meal [16-18].

Glucoregulatory Effects of GLP-1 consists of [19-21]:

- Enhances glucose-dependent insulin secretion
- Suppresses inappropriately elevated postprandial glucagon secretion
- Regulates postprandial gastric emptying
- Suppresses appetite resulting in reduced food intake
- Promotes weight reduction
- Promotes beta-cell proliferation and neogenesis

Moreover, GLP-1 has been shown to have trophic effects on primary islet cultures, beta-cell lines, and on beta-cells from animal models of type 2 diabetes. In pre-clinical studies, GLP-1 has been demonstrated to promote beta-cell proliferation and neogenesis, and reduce apoptosis [22]. In addition, GLP-1 promotes differentiation of non-insulin secreting cells into cells capable of synthesizing and secreting insulin.

In healthy human subjects, GIP and GLP-1 contribute equally to the incretin response when secreted in their normal physiologic ranges [7].

However, in patients with type 2 diabetes, the incretin effect appears to be reduced or even absent, most notably with a defective GLP-1 secretory response at mealtime [8]. In contrast, the effect of GIP is diminished in patients with type 2 diabetes, despite its near normal secretion. It has been speculated that GLP-1 deficiency may play a role in the inexorable decline in beta-cell function over time in type 2 diabetes. This is as yet unproven; however exogenous administration of GLP-1 to type 2 diabetes patients can elicit a potent glucose-lowering effect, whereas GIP administration elicits little or no response.

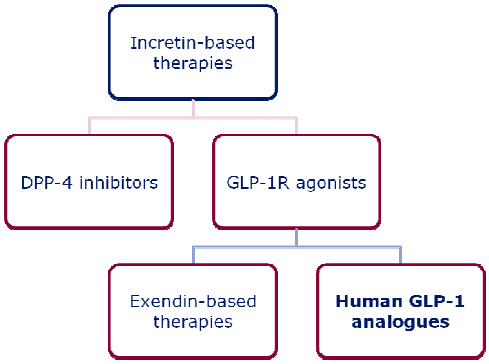
This renders GLP-1 an attractive candidate for pharmacologic development [7].

GLP-1

However, the value of GLP-1 as a pharmacotherapy for type 2 diabetes is

significantly limited due to the 2-minute half-life of the native hormone in the circulation, a result of its rapid degradation by the ubiquitous protease, dipeptidyl peptidase-4 (DPP-4) [6,23-26].

The family of incretin-based therapies



The therapeutic potential of GLP-1 has been leveraged by two novel therapeutic approaches. The first approach includes synthetic peptides that are resistant to degradation by DPP-4 — the so-called incretin mimetics. The second approach utilizes molecules that inhibit the action of DPP-4 — the so-called

DPP-4 inhibitors which increase endogenous concentrations of GLP-1 by limiting degradation in the circulation by DPP-4.

The incretin mimetics (GLP-1 Receptor agonists) consists of:

– Exendin based-derivatives as exenatide
– GLP-1 analogues as liraglutide

Liraglutide

Chemistry, pharmacokinetics and metabolism

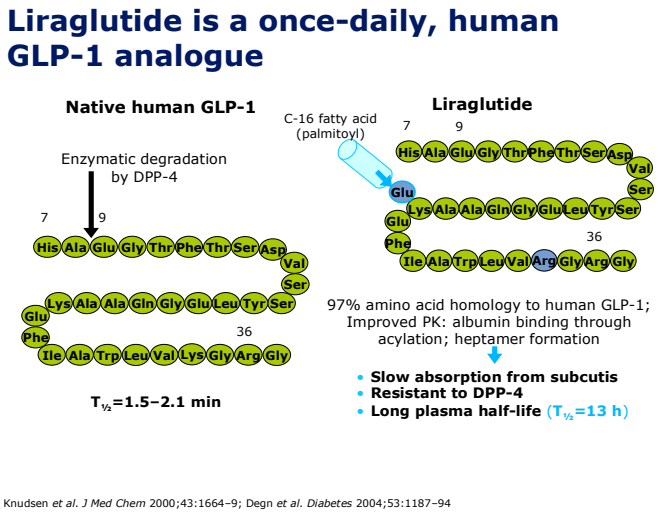
The modifications include an amino acid substitution (replacement of lysine with arginine at position 34) and an attachment of a C16 acyl chain via a glutamoyl spacer to lysine at position 26.

Liraglutide is administered subcutaneous where is slowly absorbed with a time to maximum concentration

half-life (t½) of 11 – 13 h [27], making it suitable for once-daily injection. The long half-life of liraglutide is believed to be based on albumin binding and an ability to form micellar-like aggregates in the subcutis, resulting in prolonged absorption and elimination as well as DDP IV stability.

It has been proven that liraglutide provides 24-h glycaemic control [28]. No effect of gender

or age has been seen with respect to the pharmacokinetics of liraglutide [29].



Knudsen *et al. J Med Chem* 2000;43:1664–9; Degn *et al. Diabetes* 2004;53:1187–94

Pharmacodynamics

In Phase II studies in patients with Type 2 diabetes mellitus on diet or oral antidiabetic treatment as monotherapy, liraglutide injected once daily significantly lowered fasting plasma glucose (FPG) concentrations, improved β-cell function and reduced body weight with a very low risk of hypoglycaemia [30,31].

Subcutaneous doses of liraglutide administered during induced hypoglycaemia do not impair the glucagon response or the general hypoglycaemic counter-regulatory responses and liraglutide has not been proven to be insulinotropic at hypoglycaemic plasma glucose concentrations [32].

β-cell function

Studies support that liraglutide increases β-cell mass in animals through stimulation of β-cell neogenesis, stimulation of β-cell proliferation and suppression of β-cell apoptosis.

Liraglutide, administered to human embryonic and fetal material, has been shown to increase primary β-cell number in the developing pancreas [33]; a recent study on human islets demonstrated that treatment with liraglutide inhibits cell death by regulating the expression profile of apoptosis-related genes in human islets freshly isolated from three organ donors [34].

In humans, it has been shown that a single dose of liraglutide is capable of restoring β-cell sensitivity to glucose. The method included a graded glucose infusion protocol, during which glucose is infused to create gradually rising plasma levels from 5 to 12 mM during 3 h. Patients with Type 2 diabetes mellitus (n = 10) received a single dose of liraglutide 7.5 µg/kg s.c. or a single dose of placebo in a double-blind, cross-over design 9 h before the graded glucose infusion. A group of healthy control subjects who did not receive any injections were also included. In all of the groups, insulin secretion increased

concomitantly with increases in glucose concentration; however, after a single liraglutide dosing, the effect in patients with Type 2 diabetes was significantly more pronounced than following placebo and the secretion rate was similar to that observed in the healthy control subjects [35].

Clinical development

Phase II clinical trial information are presented below.

Liraglutide monotherapy

An early, 1-week, randomised double-blind, placebo-controlled cross-over Phase II clinical trial showed a sustained blood glucose-lowering action during a 24-h test period in patients with Type 2 diabetes mellitus receiving an injection of liraglutide 6 µg/kg q.d. s.c. compared with placebo [28]. Furthermore, a randomised double-blind study examined the dose–response relationship of liraglutide on glycaemic control compared with oral antidiabetic treatment (glimepiride 1 – 4 mg). A total of 190 patients were assigned to 1 of 5 fixed-dosage groups of liraglutide (0.045 mg and ≤ 0.75 mg), placebo or open-label sulfonylurea [30]. The effect on HbA1c levels was greater with increasing doses and in the liraglutide 0.75 mg group; HbA1c significantly decreased by 0.75 percentage points and fasting glucose by 1.8 mM compared with placebo [30]. Body weight decreased by 1.2 kg with liraglutide 0.45 mg compared with placebo.

Data from a randomised, double-blind, parallel- group trial including 165 patients with Type 2 diabetes mellitus administered higher doses of liraglutide (0.65, 1.25 or 1.9 mg) for 14 weeks and demonstrated that liraglutide is capable of decreasing FPG levels between 2.7 mM (0.65 mg) and 3.4 mM (1.25 and 1.9 mg) on average when compared with placebo [31]. All three doses of liraglutide lowered both pre- and postprandial self-monitored blood glucose levels.

Interestingly, in the same study, a decrease in levels of HbA1c of ≤ 1.7 percentage points was noted and ~ 50% of the patients with Type 2 diabetes mellitus managed to reach the goal level of < 7% in HbA1c when receiving the 2 highest doses of liraglutide (1.25 and 1.9 mg) compared with only 5% in the placebo group [31]. In the highest liraglutide dose group (1.9 mg), change from baseline in body weight was -2.99 and -1.21 kg compared with placebo [31]. In the same study *in vivo*, β-cell function was evaluated in a subgroup of patients. Out of the 39 subjects randomised to the subgroup, 28 subjects completed a 14-week treatment period (0.65, 1.25 and 1.9 mg or placebo) [36]. All of the subjects were evaluated before and after the 14-week treatment period. The methods used were an insulin-modified frequently sampled intravenous glucose tolerance test and a hyperglycaemic clamp with arginine. For comparison, a non-treated group of control subjects underwent the same tests once. These studies showed that the 2 highest doses of liraglutide significantly increased the maximal β-cell secretory capacity compared with placebo by 114 and 97% with liraglutide 1.25 and 1.90 mg, respectively.

The same doses significantly increased the first-phase insulin secretion by 124% (1.25 mg) and 107% (1.90 mg). Second-phase

insulin secretion increased with the liraglutide 1.25-mg dose level but did not reach statistical significance at the highest dose level [36]. In addition, a significant reduction in systolic blood pressure of 3 – 7 mmHg was observed when liraglutide was compared with placebo [37]. Changes in diastolic blood pressure tended to be reduced. Furthermore, liraglutide treatment was associated with a decrease in triglycerides, plasminogen-activator inhibitor-1 and B-type natriuretic peptide concentrations but these observations need to be further explored [37].

Recently, a Phase II trial performed in Japan, including > 200 patients with Type 2 diabetes mellitus previously treated with exercise and diet and/or single oral antidiabetic agents, demonstrated reduced HbA1c levels by ~ 2 percentage points and > 75% of the patients recruited managed to reach the ADA treatment goal of an HbA1c < 7% (press release by Novo Nordisk, 30 June 2006).

Liraglutide in combination therapy

Liraglutide as an add-on therapy to metformin was evaluated by Nauck *et al.* In total, 144 patients with Type 2 diabetes mellitus were examined and, following 2 – 6 weeks of metformin dose titration (≤ 1 g b.i.d.), randomised to treatment with: liraglutide monotherapy; liraglutide plus metformin; metformin monotherapy; metformin plus glimepiride (n = 36 for each group) for 5 weeks.

Liraglutide was initiated at 0.5 mg q.d. and increased by 0.5 mg every week if FPG was > 6 mM up to a maximum of 2 mg/day (if tolerated). Glimepiride 2 mg was initiated and increased to 4 mg in 1-mg increments during the first 2 weeks if FPG was > 6 mM. Metformin was continued at the run-in dose. Following 5 weeks of treatment, HbA1c was significantly reduced relative to baseline in all of the groups except the group receiving metformin as a monotherapy. Furthermore, combination therapy with liraglutide plus metformin resulted in significantly greater reductions in HbA1c than liraglutide or metformin monotherapy [38].

Liraglutide in combination with metformin induced a clinically and statistically significant weight loss (2.9 kg) compared with metformin plus glimepiride.

Adverse events

Hypoglycaemia

The risk of hypoglycaemia during GLP-1 treatment is very low. This is due to the strict glucose dependence of insulinotropic actions by GLP-1 combined with the fact that the suppression of glucagon – which occurs with GLP-1 during hyperglycaemic conditions – does not occur during hypoglycaemia.

GLP-1 alone can probably not cause hypoglycaemia. In fact, hypoglycaemia in response to exogenous

GLP-1 has only been observed under artificial conditions (i.e., the concomitant administration of intravenous glucose and GLP-1) [39,40]. In fasting subjects [41] or in combination with oral nutrient intake [42,43], there is a very small potential of GLP-1 to cause hypoglycaemia. This is in contrast to pharmacological properties of other insulin secretagogues (such as sulfonylureas and

meglitinides [44]) and points to a specific advantage of GLP-1 as a therapeutic agent.

So far, only a very low frequency of hypoglycaemia (defined as a blood glucose of < 3.1 mM) has been reported in all of the clinical trials with liraglutide, with a frequency approximately the same as during metformin treatment but markedly lower than during treatment with glimepiride [30,45].

No major hypoglycaemic episodes (defined as hypoglycaemic episodes requiring medical assistance) have been reported by any subject treated with liraglutide.

Gastrointestinal side effects of liraglutide treatment

The most frequently reported side effects involve the gastrointestinal system during liraglutide treatment. Gradual dose escalation of liraglutide successfully reduced the proportion of subjects experiencing dose-limiting nausea. Gastrointestinal complaints often occurred within the first week of treatment, with diarrhoea and nausea being the most frequent adverse effects. Most of the subjects reported adverse events of mild-to-moderate severity [28,30,31,38].

In a study involving liraglutide ≤ 1.9 mg or placebo as a monotherapy, gastrointestinal events were the most frequently reported events in all of the treatment groups, including the placebo group [31]. The most frequent single event was diarrhoea, which occurred with an incidence of ~ 20% in the liraglutide-treated groups and 12.5% in the placebo-treated group. Transient, mild nausea was reported in ≤ 10% of the liraglutide-treated subjects compared with 3% of the placebo-treated subjects.

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