Liraglutide, a once-daily human GLP-1 analogue

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Abstract

Glucagon-like peptide-1 (GLP-1) is an incretin hormone physiologically playing a role in glucose homeostasis, together with the partner incretin, glucose dependent insulinotropic peptide (GIP). Active concentrations of this hormone are not maintained for long because of its very rapid degradation and elimination. The effects of the hormone are of potential therapeutic value in type 2 diabetes; therefore, analogues of GLP-1 have been developed that are characterised by a prolonged circulating half-life relative to the naturally occurring hormone. One such long-acting analogue is liraglutide. The effects of liraglutide are maintained over 24 h, allowing once-daily dosing. Liraglutide provides all of the beneficial actions of endogenous GLP-1: glucose-dependent stimulation of insulin secretion, glucagon suppression, deceleration of gastric emptying, appetite suppression/weight loss and, in animal models, inhibition of β-cell apoptosis and promotion of β-cell regeneration. Because liraglutide stimulates insulin secretion and suppresses glucagon secretion only when blood glucose levels are elevated, the risk of treatment-associated hypoglycaemia is low. In clinical studies, liraglutide substantially lowered fasting and postprandial glucose concentrations, with an overall reduction in haemoglobin A1c of up to 1-2%. In some studies, liraglutide has decreased several biomarkers of cardiovascular risk and lowered triglyceride levels significantly. Side effects most commonly are gastrointestinal symptoms; they are usually mild to moderate and resolve over time. Long-term clinical trials are needed to assess whether the effects of liraglutide on the β cell translate into a durable improvement in β-cell function and mass in patients with type 2 diabetes and, if so, whether this will slow or halt disease progression and help prevent complications.

Key words: glucagon-like peptide-1, haemoglobin A1c, liraglutide, type 2 diabetes, weight loss

Introduction

Type 2 diabetes is a progressive disease characterised by insulin resistance and pancreatic β-cell dysfunction, leading to insulin deficiency and hyperglycaemia. Loss of metabolic control is also attributed to increased hepatic glucose release in the fasting and postprandial states, with increased gluconeogenesis. Increased glucagon levels and a reduced response of GLP-1 to meals have been described. Potential sequelae include an increased risk of vascular complications, which account for about two-thirds of deaths in persons with diabetes.

The importance of glucose-lowering therapy to prevent complications in type 2 diabetes was established in the landmark UK Prospective Diabetes Study. In that 10-year trial of 3,867 patients with newly diagnosed type 2 diabetes, intensive pharmacotherapy aimed at reducing FPG to below 6 mmol/L (108 mg/dL) provided a 25% reduction in the risk of microvascular complications compared with conventional therapy. Despite improvements in diabetes treatment, however, glycaemic control, particularly adequate long-term control, is elusive for many patients. An analysis of data from the National Health and Nutrition Examination Survey 1999–2000 reported that only 37% of adults with diabetes in the USA had reached the American Diabetes Association goal of HbA1c under 7%, despite a marked increase in the percentage of those receiving pharmacological treatment. Thus, there is an
urgent need for effective new approaches to improve glycaemic control and thereby help prevent microvascular and macrovascular complications.

Among the new avenues of treatment being investigated are analogues of GLP-1, an incretin hormone secreted from intestinal mucosa in response to food ingestion. As discussed in greater detail in the accompanying article by Jens Holst (pp. S10–S18), GLP-1 helps regulate glucose homeostasis by stimulating insulin secretion and inhibiting glucagon secretion. Both of these actions are glucose-dependent. However, in its endogenous form, GLP-1 has a very short half-life because of rapid degradation by DPP-4 and renal elimination. Longer-acting analogues have been developed that circumvent this problem and are making it possible to take advantage of the beneficial actions of GLP-1 in patients with type 2 diabetes. In contrast other insulinotropic agents such as the sulphonylureas, the insulinotropic effect of GLP-1 depends even more closely on the actual glucose concentration, thereby facilitating normalisation of glucose parameters without the risk of hypoglycaemia.

Liraglutide is an acylated GLP-1 analogue. It has a fatty acid molecule, which is covalently attached to the GLP-1 sequence (figure 1). This binds to albumin, prolonging the half-life of the circulating complex without otherwise changing its biological activity.8 Also, apparently, the fatty acid molecule may sterically inhibit DPP-4 from degrading liraglutide. Liraglutide is now in phase III clinical trials (the Liraglutide Effect and Action in Diabetes trial, comprising 3,800 patients), with initial results being reported in 2008.

This article will review the current understanding of liraglutide, with regard to its pharmacokinetics, GLP-1-like effects, efficacy in type 2 diabetes at various doses, adverse event profile and positive effects on the cardiovascular profile. Avenues of future study will also be described.

Pharmacokinetics

Single and multiple-dose studies have confirmed that liraglutide has a half-life between 11 and 15 h, which means that once-daily dosing in humans is appropriate.9,10 Elbrønd and colleagues conducted a double-blind, randomised study with eight different single doses of liraglutide (1.25, 2.5, 5.0, 10.0, 12.5, 15.0, 17.5 and 20.0 µg/kg), injected subcutaneously in healthy men (n=72). They found a clear dose–response relationship in the AUC measurements for plasma liraglutide. After doses of 2.5–20 µg/kg, plasma liraglutide increased steadily, reaching a peak concentration after 9.3–12 h.10 Elimination half-life was 11–15 h. At a dose of 5 µg/kg, the time to maximum concentration was 9.3 h and the half-life, 15 h.

A double-blind, randomised, dose-escalation, placebo-controlled study in 30 healthy subjects likewise concluded that the pharmacokinetic profile of liraglutide supports once-daily dosing. Subjects were randomly assigned to receive liraglutide, in doses of 1.25–12.5 µg/kg subcutaneously, or placebo. Liraglutide was administered on day 1 and days 5–11, while the 84-h pharmacokinetic and 24-h glucose and insulin profiles were assessed on days 1 and 11.9 Steady state was reached after three doses; half-life

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**Figure 1.** Comparative structures of GLP-1 and liraglutide. There is one arginine instead of lysine in the sequence of GLP-1 and there is another amino acid plus a free fatty acid attached to GLP-1. These differences prolong the half-life of liraglutide but do not change its biologic activity.


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**Abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<tr>
<td>DPP-4</td>
<td>dipeptidyl peptidase-4</td>
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<td>FPG</td>
<td>fasting plasma glucose</td>
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<td>GIP</td>
<td>glucose-dependent insulinotropic peptide</td>
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<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
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<tr>
<td>HbA1c</td>
<td>glycosylated haemoglobin A1c</td>
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**Key:** DPP-4 = dipeptidyl peptidase-4; GLP = glucagon-like peptide-1

**Legend:**

- **DPP-4** = dipeptidyl peptidase-4
- **GLP-1** = glucagon-like peptide-1
- **HbA1c** = glycosylated haemoglobin A1c
- **Proteolytic inactivation (DPP-4)**
- **Albumin**
- **C-16 free fatty acid (non-covalent binding to albumin)**
- **GLP-1 (7–36) Amide**
- **Liraglutide Amide**
was approximately 12 h at end of study in all dose groups. Before steady state, a slight but statistically significant accumulation was observed at doses of 7.5 µg/kg or more, as indicated by an accumulation index of 1.4–1.5. Figure 2 presents data from a patient receiving daily doses of 5 µg/kg.

Liraglutide: GLP-1-like effects
Although in the development of liraglutide the GLP-1 molecule was altered to extend its half-life, the beneficial effects of GLP-1 in diabetic patients have been preserved.

Beta-cell sensitivity
Studies show that a single dose of liraglutide is sufficient to reinstate the insulin response to glucose to a level similar to that in healthy non-diabetic persons. Chang and colleagues assessed the effect of liraglutide on β-cell sensitivity in a double-blind, crossover study of 10 patients with type 2 diabetes. Ten healthy subjects were included as controls. Nine hours before the study, patients with type 2 diabetes received a single subcutaneous dose of liraglutide (7.5 µg/kg) or a single dose of placebo; the control group did not receive any medication. In addition, all groups received a small intravenous bolus of insulin (0.007–0.014 U/kg). This bolus reduced blood glucose to approximately 5 mmol/L (90 mg/dL) in healthy control subjects and 6 mmol/L (108 mg/dL) in the type 2 diabetic group. The following day, subjects received a graded glucose infusion to create gradually rising plasma glucose levels ranging from 5 to 12 mmol/L (90–216 mg/dL) over 3 h. As shown in figure 3, insulin secretion increased concomitantly with increases in glucose concentration in all groups. However, in patients receiving liraglutide, the effect was more pronounced than in those receiving placebo (insulin AUC 1,130±150 vs. 668±106 pmol/kg; p<0.001). The secretion rate in the patients with type 2 diabetes who received liraglutide was similar to that in the non-diabetic controls. These findings indicate that liraglutide restored β-cell sensitivity to physiological hyperglycaemia in patients with type 2 diabetes.11

Glucagon suppression
In type 2 diabetes, excessive glucagon secretion in relation to plasma glucose stimulates hepatic glucose production and therefore contributes to fasting hyperglycaemia. It is important that treatments for type 2 diabetes carry a low risk of hypoglycaemia because this condition can restrict efforts to achieve glycaemic targets. Because GLP-1 analogues suppress glucagon secretion, there has been concern that they could disturb hypoglycaemia counterregulation. Several clinical studies of liraglutide affirm that this is not the case (table 1), with a reported risk of minor events ranging between 0 and 2.8 % in patients not receiving sulphonylurea drugs.12–14 The low risk of hypoglycaemia is probably due to the glucose-dependent insulino tropic action of liraglutide.

Evidence for the low risk of liraglutide-associated hypoglycaemia was provided by a study of 11 patients with type 2 diabetes.15 All received a single subcutaneous dose of liraglutide, 7.5 µg/kg at midnight. In the morning, regular insulin infusions of 2 mU·kg⁻¹·min⁻¹ were administered to provide fasting euglycaemia. With use of a hypoglycaemic clamp, capillary glucose concentrations were sequentially maintained at 4.3, 3.7, 3.0 and 2.3 mmol/L (77, 67, 54 and 41 mg/dL) for 60 min each. Glucagon secretion increased to a similar extent with liraglutide and placebo as the glycaemic plateau was reduced. Furthermore, the glucose infusion required to maintain the specified glycaemic plateau did not differ during treatment with placebo and liraglutide (figure 4). As the glucose plateau was lowered, there was a similar increase in cortisol and catecholamines with
both treatments. Growth hormone also increased in both groups, although this increase was slightly but significantly lower during liraglutide treatment (p=0.034).

**Gastric emptying and appetite suppression**

The potent dose-dependent inhibition of gastric emptying observed after GLP-1 infusion in human subjects with type 2 diabetes will produce significant lowering of meal-related glycaemic concentrations, even without any increase in levels of circulating insulin. This may in part explain the ability of GLP-1 to suppress appetite and promote weight loss. Most current type 2 diabetes treatments are associated with weight gain, which is detrimental to the course of the disease. This issue is discussed in more detail in this supplement by Philip Larsen (pp. S34–S41) and will be reviewed only briefly herein.

Madsbad *et al.* evaluated the effect of liraglutide therapy on weight in a multiple-dose, 12-week, multicentre, parallel-group, double-blind trial. The 193 patients with type 2 diabetes were randomised to a once-daily, morning subcutaneous injection of liraglutide (0.045, 0.225, 0.45, 0.6 or 0.75 mg) or placebo, or to open-label tablet treatment with glimepiride (dose adjusted according to control during first 4 weeks, aiming at FPG <7 mmol/L; <126 mg/dL). Oral anti-diabetic treatment was discontinued during a 4-week pretreatment washout period. Liraglutide doses were selected based on studies that showed a dose of 10 µg/kg (equivalent to approximately 0.80 mg dose) to have a significant effect on glycaemia. Lower doses were used to reduce the risk of adverse effects such as nausea.

The reduction in HbA1c relative to placebo was similar after liraglutide (0.75 mg once-daily subcutaneous injection) and glimepiride (mean daily dose 2.7 mg) treatment (approximately 0.75 percentage points). This improvement in glycaemic control was associated with a decrease in weight of 0.39 kg in the liraglutide group, compared with an increase of 0.94 kg in the glimepiride group (figure 5). Thus, liraglutide and glimepiride offered similar glycaemic control but liraglutide was associated with a weight reduction that was not observed during glimepiride treatment.

**GLP-1 analogues: extended half-life**

A benefit of GLP-1 analogues over endogenous GLP-1 is their longer half-life, making them practical for clinical use. Exenatide, the only GLP-1 receptor agonist currently available for clinical use, has a half-life of 2.4 h and is approved for twice-daily dosing as a subcutaneous injection. Since liraglutide has a longer half-life, it is anticipated that once-daily dosing will be recommended.

The sustained blood glucose-lowering action of liraglutide was demonstrated in a study of 13 patients with type 2 diabetes. Patients received 1 week of once-daily subcutaneous liraglutide injections (6 µg/kg) and 1 week of once-daily placebo injections in a double-blind, crossover trial. Oral antidiabetic agents were discontinued 2 weeks before the study treatment period. After 1 week of liraglutide treatment, plasma glucose was consistently lower during a 24-h test period than after placebo treatment, including after an overnight fast. This finding was confirmed statistically in an assessment of AUC (mmol·L⁻¹·h) for this 24-h test period (187.5 for liraglutide vs. 232.3 for placebo; p=0.01).19

**Effectiveness of various doses of liraglutide**

Liraglutide has a dose-dependent effect on glycaemic control. In early studies, relatively small doses of this agent were used, and results were not impressive. At larger doses, however, 0.6–0.75 mg given as a single daily subcutaneous injection, the impact on HbA1c was similar to that of a sulphonylurea, but without the increase in weight characteristic of sulphonylureas.
In the study by Madsbad et al., HbA\textsubscript{1c} progressively decreased during the course of the trial and was still falling at week 12 when the trial ended.\textsuperscript{12} Thus, even greater therapeutic benefit may be achievable with longer-term treatment.

Because of the dose–response relationship seen with liraglutide, achieving the effective dose as rapidly as possible is desirable. However, patients may initially experience gastrointestinal events. Nauck and colleagues showed that, by increasing the dosage by 0.5 mg per week, the patient can be safely titrated to a substantially higher and well-tolerated dose. In 144 patients with type 2 diabetes who had received metformin treatment (1,000 mg twice daily), the patients were randomised to 5 weeks of treatment (double-blind) with metformin plus liraglutide, liraglutide or metformin, or metformin plus glimepiride (open label). The dose of liraglutide was increased weekly from 0.5 to 2 mg once daily. Liraglutide added to metformin monotherapy was associated with a significant reduction in fasting serum glucose (−3.9 mmol/L; −70 mg/dL) and HbA\textsubscript{1c} levels (−0.8%) after 5 weeks.\textsuperscript{14} Furthermore, liraglutide in combination with metformin or metformin plus glimepiride significantly reduced fasting serum glucose (−1.2 mmol/L; −22 mg/dL). Body weight was significantly lower with metformin plus liraglutide than with metformin plus glimepiride, even after only 5 weeks (−2.9 kg). There were no confirmed episodes of hypoglycaemia with liraglutide treatment. Nausea was the most common adverse event with liraglutide therapy, but it was transient and led to withdrawal of only 4% of the patients treated.\textsuperscript{14}

While the study by Nauck et al.\textsuperscript{14} showed reductions in HbA\textsubscript{1c} with liraglutide alone or in combination, the study was only 5 weeks long. In a 14-week study of 377 patients, doses of 1.25 and 1.9 mg/day of liraglutide given as monotherapy yielded decreases of about 1.7% in HbA\textsubscript{1c} (p<0.0001 vs. placebo) (figure 6).\textsuperscript{20} Body weight decreased by 3.0 kg in patients receiving 1.9 mg of liraglutide, and the weight loss was dose-dependent.\textsuperscript{20} This weight loss occurred regardless of the gastrointestinal side effects, which were, in any event, transient.\textsuperscript{20}

As would be expected, in view of its pharmacokinetic profile, liraglutide continued to reduce FPG after an overnight fast.

While the effect is dose dependent, even at the lowest dose used in this study the effect was significantly (p<0.05) different from placebo (figure 7).\textsuperscript{20}

### Adverse event profile of liraglutide

Liraglutide is well tolerated, with nausea and diarrhoea as the most common treatment-emergent adverse events.\textsuperscript{20,21} As discussed earlier and as shown in table 1, the risk of hypoglycaemia during treatment with liraglutide is low.\textsuperscript{12,13} The incidence of hypoglycaemia is similar to that reported with metformin and lower than that reported with glimepiride, despite similar glycaemic control. In a 5-week study involving larger doses of liraglutide (0.5–2 mg), there were no reported hypoglycaemic events of any type in patients receiving liraglutide or metformin monotherapy. One patient reported a symptoms-only event during treatment with liraglutide plus metformin, and three reported hypoglycaemia (one minor, two symptoms only) during treatment with glimepiride plus metformin (n=36) (table 1).\textsuperscript{14}

### Effect of liraglutide on cardiovascular risk profile

One of the goals of treatment of type 2 diabetes is to reduce the risk of cardiovascular events, which is elevated in diabetic patients.\textsuperscript{22} Liraglutide may decrease this risk, as evidenced by its effect on several cardiovascular parameters. The weight loss that is characteristic of liraglutide may ultimately be found to help reduce cardiovascular risk. In addition, treatment with liraglutide has also been shown to improve several biomarkers of cardiovascular risk. In a study of 377 patients with type 2 diabetes, Vilsbøll and colleagues found that 14 weeks of treatment with liraglutide 1.90 mg/day reduced triglyceride levels by 22% (p<0.01 vs. placebo).\textsuperscript{20} C-reactive protein, a marker of inflammation, decreased by 20% (not significant); B-type natriuretic peptide, a serologic marker of myocardial vulnerability, decreased by 38% (p=0.01); and plasminogen activator inhibitor-1, a marker of impaired fibrinolysis, decreased by 25% (p=0.05) (figure 8).\textsuperscript{23}
In the same trial, systolic blood pressure decreased significantly at all three dosages, and diastolic blood pressure non-significantly (figure 9), the mechanism of this decrease is unclear. These improvements were in addition to the decrease in HbA1c of up to 1.7%, with half of the patients reaching their goal HbA1c. Further, body weight decreased with liraglutide treatment. The effect on blood pressure preceded the effect on body weight, suggesting that the effect cannot be ascribed to the decreased body weight.

**Liraglutide: future directions**

GLP-1 analogues are a relatively recent innovation in type 2 diabetes treatment – only one (exenatide) is available in the USA, and liraglutide has completed the LEAD phase III trials – and the durability of their beneficial effects has not been investigated in clinical studies. Nevertheless, there is reason to believe that therapy with liraglutide may result in long-term improved glucose control. Continued, progressive β-cell failure is a pathogenic feature of type 2 diabetes. Liraglutide is associated with improvement in β-cell function, as evidenced by enhanced β-cell neogenesis/proliferation and inhibition of apoptosis.

The effects of GLP-1 inhibitors on β-cell function are discussed in detail by Gallwitz elsewhere in this supplement (pp. S19–S25). Briefly, GLP-1 analogues improve β-cell function not only through indirect metabolic action, but also through direct recruitment of signal transduction pathways in the β cells that promote glucose-dependent insulin secretion.

Two animal studies showed that liraglutide increases β-cell mass in animals and the effect occurs within weeks of the

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**Table 1.** Percentage of patients reporting hypoglycemia in three liraglutide trials. No major hypoglycemic events were reported. Liraglutide is associated with a low risk for hypoglycemia, indicating that counterregulatory mechanisms are not adversely affected

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<tr>
<th></th>
<th>Liraglutide (0.045–2 mg OD)</th>
<th>Glimepiride (≤ 4 mg)</th>
<th>Metformin (1 g BID)</th>
<th>Liraglutide (0.5–2 mg OD) + metformin (up to 1 g BID)</th>
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**Key:** BID = twice daily; n/a = not available; OD = once daily

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**Figure 8.** Effect of 14 weeks of liraglutide treatment on biomarkers of cardiovascular risk. Data from Vilsbøll et al. 23

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**Figure 9.** Decreases in blood pressure after 14 weeks of treatment with three doses of liraglutide vs. placebo. Data from Vilsbøll et al. 23
Liraglutide is a once-daily GLP-1 analogue that has a proven a promising clinical profile including substantial improvement in glycaemic control without a risk for hypoglycaemia, and weight loss as an added benefit of liraglutide administration. In one study, Zucker diabetic fatty rats (which show insulin resistance and β-cell defects) received subcutaneous injections of 150 μg/kg liraglutide or vehicle twice daily for 6 weeks. At the end of the treatment period, β-cell mass was significantly greater in the liraglutide group. In the second study, db/db (diabetic) mice received subcutaneous injections of vehicle or liraglutide (200 µg/kg) twice daily for 2 weeks. Blood glucose tests on days 1, 8 and 15 demonstrated that mice treated with liraglutide had lower blood glucose (as measured using 24-h AUC) relative to those receiving vehicle. Furthermore, at the end of the trial, β-cell mass and proliferation rate were greater with liraglutide treatment.

Discussion
Liraglutide is a human GLP-1 analogue that has maintained a great degree of similarity to endogenous GLP-1; only one amino acid has been exchanged, and another one has been added to attach a free fatty acid. Once-daily injections cover a full 24 h, including fasting periods (e.g., sleep). Liraglutide provides substantial reductions in glucose and HbA1c, as expected in an efficacious anti-diabetic drug. At the same time, liraglutide has little or no effect on hypoglycaemia counterregulatory mechanisms via glucagon and thus has a low risk of hypoglycaemia. Unlike the sulphonylureas, which often induce some weight gain, liraglutide actually causes a decrease in weight, possibly as a result of its effect on gastric emptying and satiety. The most commonly reported adverse events have been nausea, vomiting and diarrhoea, which were usually mild to moderate and rarely lead to discontinuation of therapy. In light of the improvement in β-cell function and β-cell mass observed in preliminary studies, the long-term effects of liraglutide on progression of type 2 diabetes will be of particular interest.

References


