Molecular, pharmacological and clinical aspects of liraglutide, a once-daily human GLP-1 analogue

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ABSTRACT

Liraglutide, a human glucagon-like peptide 1 (GLP-1) analogue with high homology to native GLP-1, has structural modifications sufficient to amend pharmacokinetics for once-daily administration without compromising biological activity. Data from large, controlled, clinical studies have confirmed the therapeutic profile of liraglutide, with robust reductions in HbA1c, low risk of hypoglycaemia and clinically relevant reductions in body weight and systolic blood pressure.

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1. Introduction

Glucagon-like peptide 1 (GLP-1) is one of two insulinotropic hormones secreted in response to oral ingestion of glucose. GLP-1, together with glucose-dependent insulinotropic polypeptide (GIP), is secreted by enteroendocrine cells in the gut following oral, but not intravenous, glucose administration. The increased secretion of insulin resulting from the effects of these hormones on the pancreatic beta cells – known as the incretin effect – accounts for up to 60% of the postprandial insulin response in healthy individuals (Doyle and Egan, 2007).

GLP-1 has a number of acute effects on glucose sensing and insulin secretion by the beta cell, including closure of KATP channels, shifting membrane potential and sensitising beta cells to glucose (Holz et al., 1992), reduction of activity of the Kv channel (MacDonald et al., 2002), release of Ca2+ from internal stores (Bode et al., 1999), and an increase in the number of readily releasable insulin secretory vesicles. In addition, chronic effects include increased insulin mRNA levels (Drucker et al., 1987), via regulation of insulin transcription (Fehman and Habener, 1992), and via stabilisation of insulin mRNA, and increased levels of transcription factor PDX-1 mRNA and protein (Perfetti et al., 2000; Stoffers et al., 2000). GLP-1 thus provides both an immediate effect on insulin secretion and longer-term stimulation of insulin synthesis. Yet longer-term effects of GLP-1 are at the level of beta-cell neogenesis, increased via differentiation of duct cells (Perfetti et al., 2000) and via proliferation of existing beta cells (Farilla et al., 2003) and of lipotoxicity- and cytokine-mediated beta-cell apoptosis, reduced by GLP-1 which protects beta-cells against glucolipotoxicity (Buteau et al., 2004).

The physiological role of GLP-1, together with a deficiency of GLP-1 secretion seen in type 2 diabetes, suggest it as a promising potential therapy for that disease, and indeed infusion of GLP-1 can lower levels of blood glucose (Rachman et al., 1997). However, native GLP-1 has an exceptionally short half-life of less than 2 min following administration in vivo, being rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP-4). Therapeutic administration of GLP-1 is thus impractical, and efforts have focused on amending the pharmacokinetic properties of GLP-1 in a series of derivatives and analogues.

2. Liraglutide: structure and pharmacology

Native GLP-1 is a 30-amino acid peptide produced by cleavage of the transcription product of the preproglucagon gene (Bell et al., 1983). Liraglutide was obtained by substitution of Lys 34 to Arg, and by addition of a C16 fatty acid at position 26 using a H9253-glutamic acid spacer (Fig. 1). Structure-activity data supporting the specific modifications in the liraglutide molecule were reported by Knudsen et al. (2000) and Madsen et al. (2007). Knudsen et al. (2000) and Madsen et al. (2007) varied the position of attachment of the γ-glutamic acid spacer and C16 fatty acid, achieving half-lives of up to 20 h. Madsen et al. (2007) prepared a series of analogues with varying lengths and structures of fatty acid moiety, which protracts circulating lifetime of acylated peptides by binding to albumin. Their data indicated a close relationship between fatty acid length and half-life, ranging from 0.8 h
for a C10 fatty acid to 21 h for a C18 fatty acid. Potency for the GLP-1 receptor was unaffected by chain length for fatty acids up to C16 but was reduced for the analogue with C18 fatty acid. Altering the spacer region (for example omitting the γ-glutamic acid or substituting triethylene glycol or sulphonamide) tended to reduce potency of the analogue series, but had little effect on protraction, an effect also seen when hydrophilicity of the omega-terminal of the fatty acid moiety was increased. In contrast, adding polarity to the fatty acid did not impair potency but reduced protraction.

Liraglutide is administered as an isotonic solution by subcutaneous injection. Pharmacokinetics of liraglutide are suitable for once-daily administration, with a $T_{\text{max}}$ of 9–13 h and a $T_{1/2}$ of 13 h. Protraction of liraglutide concentration is believed to be due to a combination of albumin binding in the circulation, aggregation at the injection site, and reduced susceptibility to DPP-4 degradation (Knudsen et al., 1999; Steensgaard et al., 2008). The 24-h duration of action was confirmed by Degn et al. (2004), who found a sustained glucose-lowering effect 24 h after last dose of liraglutide at steady-state achieved after three doses.

Stimulation of insulin secretion with liraglutide shows a glucose dependency. Nauck et al. (2003) conducted a series of stepwise hypoglycaemic clamps in 11 people with type 2 diabetes following injection of liraglutide or placebo. They found that insulin secretion was increased by liraglutide relative to placebo at higher glucose levels (4.3 and 3.7 mmol/L) but not at lower glucose levels (3.0 or 2.3 mmol/L; Fig. 2). They also found that the glucagon response to hypoglycaemia was unaffected by liraglutide treatment.

In addition to glucose control mediated by insulinotropic action, GLP-1–based therapies potentially have beneficial effects on body weight. These are potentially mediated by central effects on satiety, and also by a reduction in gastric emptying. Studies with liraglutide in animal models confirm the effect of liraglutide: obese candy-fed rats lost a mean 14.2 g after 12 weeks liraglutide treatment, whereas control animals gained 24.3 g over the same period (Raun et al., 2007).

### 3. Clinical data with liraglutide

The clinical effects of liraglutide treatment have been investigated in the Liraglutide Effect and Action in Diabetes (LEAD) series of studies in more than 4000 people with type 2 diabetes. These were designed to mirror the typical sequence of treatment escalation in type 2 diabetes, ranging from use of liraglutide as initial drug therapy following failure of diet and exercise alone, to liraglutide combination with one or with two oral anti-diabetic drugs (OADs).

Monotherapy with liraglutide was evaluated in the LEAD 3 study, a double-blind randomised controlled trial in 746 patients whose diabetes was inadequately controlled on diet and exercise, or with no more than half-maximal dose of one OAD (which was discontinued at entry) (Garber et al., 2008). Two liraglutide dose levels, 1.8 and 1.2 mg once-daily, were compared with glibenpiride, 8 mg, and achieved reductions in HbA$_{1c}$ of 1.1% and 0.8%, respectively—each significantly more than the 0.5% reduction with glibenpiride ($p < 0.0001$ and $p = 0.0014$). Patients not receiving OAD therapy at entry had HbA$_{1c}$ reductions with liraglutide of up to 1.6% (Fig. 3). The improvement in HbA$_{1c}$ with liraglutide treatment reflected both a reduction in fasting glucose levels (reduced by 1.4 mmol/L from baseline with liraglutide 1.8 mg) and in postprandial glucose levels (reduced by 2.1 mmol/L).

Improvements in glycaemic control were also evident when liraglutide was used in combination with OAD therapy. In LEAD 2, a double-blind randomised study comparing liraglutide plus metformin with glibenpiride plus metformin or metformin alone, liraglutide 1.8 mg plus metformin reduced HbA$_{1c}$ by 1.0%, comparable to the reduction with glibenpiride/metformin and significantly more than metformin alone (change +0.09%, $p < 0.0001$) (Nauck et al., 2008). Similarly, in the LEAD 1 study, liraglutide, 1.8 mg plus glibenpiride, 4 mg, reduced HbA$_{1c}$ by 1.1%, significantly more than a 0.4% reduction with rosiglitazone plus glibenpiride ($p < 0.0001$) and a 0.2% increase with glibenpiride alone ($p < 0.0001$) (Marre et al., 2008).
When used in combination with two OADs, liraglutide 1.8 mg, achieved reductions in HbA1c of 1.5% and 1.3% when used in combination with metformin and rosiglitazone (LEAD 4) and in combination with metformin and glimepiride (LEAD 5), respectively (Zinman et al., 2008; Russell-Jones et al., 2008). In LEAD 4, the improvement with liraglutide was significantly greater than that with metformin/rosiglitazone alone (0.5%; p < 0.0001), while in LEAD 5 it was again significantly greater than metformin/glimepiride alone (1.3% vs. 0.2%; p < 0.001) and also greater than insulin glargine plus metformin and glimepiride (1.1%; p = 0.0015).

Importantly, glucose reduction with liraglutide is associated with very low levels of hypoglycaemia. In the LEAD 3 monotherapy study, there were no major hypoglycaemic events with liraglutide and a rate of minor events <0.5 per patient per year (p < 0.0001 vs. 2.0 events/(patient/year) with glimepiride). Minor hypoglycaemic event rates were similarly low in the LEAD 1, 2 and 4 trials (0.5, 0.1 and 0.6 events/(patient/year), respectively), and only slightly higher (1.2 events/(patient/year)) in the LEAD 5 study where liraglutide was used together with both sulphonylurea and metformin.

Favourable effects on body weight seen in preclinical data were confirmed in the LEAD studies: in LEAD 3, liraglutide 1.8 mg as monotherapy reduced mean body weight by 2.5 kg from a baseline of 93 kg, significantly different to a 1.1 kg increase in body weight with glimepiride (p < 0.0001). Liraglutide plus metformin in LEAD 2 resulted in a 2.8 kg weight reduction (p < 0.0001 vs. 1.0 kg increase with glimepiride/metformin); liraglutide plus glimepiride in LEAD 1 yielded a more modest decrease of 0.2 kg that was nevertheless significantly different to a 2.1 kg increase with rosiglitazone/metformin. Similarly, in combination with two OADs, liraglutide 1.8 mg treatment yielded body weight reductions of around 2 kg (2.0 kg with liraglutide plus metformin and rosiglitazone in LEAD 4; 1.8 kg with liraglutide plus metformin and glimepiride in LEAD 5).

Interestingly, data from the LEAD studies show that when used for treatment of type 2 diabetes, liraglutide was associated with a consistent, significant reduction in systolic blood pressure of 2–6 mmHg. Mechanisms for this effect are undetermined but initial analyses suggest that it may precede, and thus be unrelated to, the improvement with liraglutide.

4. Summary

Liraglutide, a human GLP-1 analogue with high homology to native GLP-1, has structural modifications sufficient to amend biological activity. Data from large, controlled, clinical studies have confirmed the therapeutic profile of liraglutide, with robust reductions in HbA1c, low risk of hypoglycaemia and clinically relevant reductions in body weight and systolic blood pressure.

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