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REVIEW ARTICLE

Liraglutide in Type 2 Diabetes Mellitus: Clinical Pharmacokinetics and Pharmacodynamics

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Abstract Liraglutide is an acylated glucagon-like peptide-1 analogue with 97 % amino acid homology with native glucagon-like peptide-1 and greatly protracted action. It is widely used for the treatment of type 2 diabetes mellitus, and administered by subcutaneous injection once daily. The pharmacokinetic properties of liraglutide enable 24-h exposure coverage, a requirement for 24-h glycaemic control with once-daily dosing. The mechanism of protraction relates to slowed release from the injection site, and a reduced elimination rate owing to metabolic stabilisation and reduced renal filtration. Drug exposure is largely independent of injection site, as well as age, race and ethnicity. Increasing body weight and male sex are associated with reduced concentrations, but there is substantial overlap between subgroups; therefore, dose escalation should be based on individual treatment outcome. Exposure is reduced with mild, moderate or severe renal or hepatic impairment. There are no clinically relevant changes in overall concentrations of various drugs (e.g. paracetamol, atorvastatin, griseofulvin, digoxin, lisinopril and oral combination contraceptives) when co-administered with liraglutide. Pharmacodynamic studies show multiple beneficial actions with liraglutide, including improved fasting and postprandial glycaemic control (mediated by increased insulin and reduced glucagon levels and minor delays in gastric emptying), reduced appetite and energy intake, and effects on postprandial lipid profiles. The counter-regulatory hormone response to hypoglycaemia is largely unaltered. The effects of liraglutide on insulin and glucagon secretion are glucose dependent, and hence the risk of hypoglycaemia is low. The pharmacokinetic and pharmacodynamic properties of liraglutide make it an important treatment option for many patients with type 2 diabetes.

Key points

Liraglutide is a glucagon-like peptide-1 receptor agonist with pharmacokinetic properties that make it suitable for once-daily dosing in patients with type 2 diabetes mellitus.

Dosing regimens for liraglutide do not generally need to be adjusted based on age, race, ethnicity, body weight, sex or injection site, and the clearance mechanism implies a low potential for drug–drug interactions.

The beneficial pharmacodynamic actions of liraglutide, including improved glucose-dependent glycaemic control, reduced appetite and energy intake, and lowered postprandial lipid profiles, make it a suitable treatment option for many patients with type 2 diabetes.

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1 Introduction

Type 2 diabetes mellitus is a major global health concern, and a leading cause of morbidity and mortality across the world [1]. In 2014, an estimated 387 million people had diabetes, which is expected to reach 592 million by 2035, and 4.9 million mortalities were associated with diabetes worldwide. Type 2 diabetes accounts for approximately 90 % of all cases of diabetes and its prevalence is increasing in every country [1, 2]. Type 2 diabetes increases the risk of cardiovascular disorders, blindness, renal failure and amputation; in addition, it is associated with increased cancer risk, cognitive decline and chronic liver disease [1, 3]. Overall, the economic burden of diabetes is increasing, accounting for 11 % of worldwide healthcare expenditure in 2014 [1]. It is a disease of heterogeneous nature and its pathophysiology is only partly understood [3]. Control of hyperglycaemia is suboptimal in many patients, with only around 50 % achieving glycaemic targets, even in resource-rich settings [4]. Hence, new treatment options are necessary to prevent diabetic complications.

Metformin is generally the recommended first-line oral anti-hyperglycaemic agent for type 2 diabetes therapy; it is considered weight neutral and to be associated with a low risk of hypoglycaemia [3, 5]. If glycaemic control is not achieved with monotherapy, two- and then three-drug combination therapy may be implemented, commonly involving metformin, sulphonylureas, thiazolidinediones, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin [3, 5]. Insulin therapy is generally initiated with basal insulin, and rapid insulin analogues prescribed if postprandial glucose control is required [3]. In all cases, anti-hyperglycaemic agents should be selected on a patient-specific basis, dependent on the benefit-to-risk profile of patients to minimise unwanted effects [5].

The GLP-1 receptor agonists constitute a well-established group of therapeutics for type 2 diabetes that promote glucose-dependent insulin secretion and inhibit glucagon release [3]. Predominant in clinical use is the GLP-1 receptor agonist liraglutide (Victoza®), which has demonstrated high levels of glycaemic benefit in head-to-head studies vs. other GLP-1 receptor agonists [6–9].

Liraglutide was extensively studied in the Liraglutide Effect and Action in Diabetes (LEAD) phase III trial programme [6, 10–14]. In these studies, liraglutide was associated with clinically significant reductions in glycated haemoglobin (HbA_{1c}) of 0.8–1.5 %, whether given as monotherapy or as combination therapy with metformin, glimepiride, rosiglitazone or insulin [15, 16]. Liraglutide also has several other clinical benefits, including reductions in body weight and systolic blood pressure and low rates of hypoglycaemia [15–17].

Liraglutide is dosed once daily using a prefilled pen [18, 19]. Treatment is initiated at 0.6 mg per day for 1 week. This initial dose is intended to reduce gastrointestinal symptoms. After 1 week, the dose is increased to 1.2 mg, and can be further increased to 1.8 mg based on individual glycaemic control.

Previously, the most recent review of the pharmacokinetic and pharmacodynamic properties of liraglutide underlying its clinical benefits was published in 2009 [20]. The aim of the current paper is therefore to provide a wide-ranging and updated review of the pharmacokinetic and pharmacodynamic properties of liraglutide for the treatment of type 2 diabetes. Among the large number of clinical pharmacology studies published on liraglutide, this updated review has prioritised, where available, the most recent studies conducted in subjects with type 2 diabetes and those using the recommended treatment doses of 1.2 and 1.8 mg. When relevant and for completeness, studies in other populations or using lower liraglutide doses are included. An overview of key studies for this review is provided in the table in the online supplementary material.

2 Liraglutide Structure and Mechanism of Protracted Action

Liraglutide is an acylated human GLP-1 analogue, with 97 % amino acid homology to native GLP-1 (Fig. 1). GLP-1 enhances meal-induced insulin secretion, the so-called 'incretin effect', and has several other actions that are desirable for an anti-diabetic agent [21]. However, although intravenous infusion of native GLP-1 can normalise plasma glucose levels in patients with type 2 diabetes [22, 23], it is not a practical option for exogenous therapy. This is because of its very short half-life ($t_{½}$) [<2 min following intravenous administration], as a result of rapid degradation by the enzymes DPP-4 and neutral endopeptidase (NEP), as well as efficient clearance by the kidneys [21, 24–27].

Liraglutide differs from the native compound by acylation of the lysine residue at position 26 with a hexadecanoyl-glutamyl side chain, and a single lysine-to-arginine amino acid substitution at position 34 (Fig. 1). Possibly because of the high level of amino acid homology to native GLP-1, liraglutide has low immunogenicity [28]. However, the subtle differences in sequence compared with native GLP-1, as well as the acylation, lead to a greatly protracted action profile. Following injection, liraglutide is highly

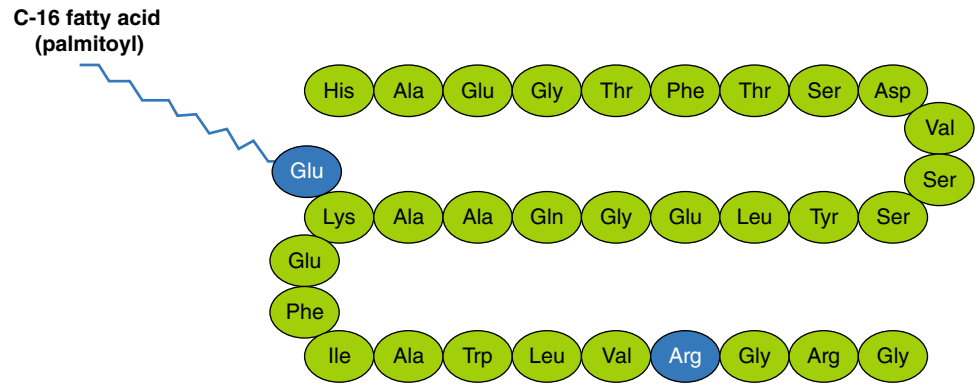

Fig. 1 Primary structure of liraglutide. Compared with native GLP-1 (7–37), liraglutide has lysine replaced with arginine in position 34, and the lysine at position 26 is acylated on its ε-amino group with the γ-carboxyl group of *N*-palmitoyl-L-glutamic acid. *GLP-1* glucagon-like peptide-1. Republished with permission of © Dove Medical Press Ltd. from Deacon. Vasc Health Risk Manag. 2009;5:199–211 [21]; permission conveyed through Copyright Clearance Center, Inc

Table 1 Mechanisms of protraction of liraglutide

Effect	Mechanism
Slowed absorption from the subcutis	Liraglutide exists predominantly in a self-associated heptameric state, even at sub-micromolar concentrations in the formulation [31]. Hydrophobic interactions between the fatty acid side chains on each liraglutide molecule are the main driver of this association; by contrast, the non-acylated precursor molecule of liraglutide remains largely in a monomeric state [31]. The formation of strongly self-associated oligomers seems particularly important for the protracted absorption of liraglutide after subcutaneous injection. The binding of liraglutide to albumin in the subcutis may also slow the absorption rate [85]. The slowed absorption from the subcutis results in a longer half-life following subcutaneous administration (13 h) compared with intravenous injection (8.1 h) [45]
Decreased rate of elimination	Stabilisation against enzymatic degradation:
	Liraglutide is metabolised by DPP-4 and NEP in a manner that is similar to the degradation of native GLP-1 [32]. However, the rate at which this occurs has been demonstrated in vitro to be much slower for liraglutide than for native GLP-1 [Novo Nordisk, data on file]. The binding to albumin further slows the rate of liraglutide degradation, possibly by hindering the enzymatic access to the molecule [Novo Nordisk, data on file]
	Decreased renal elimination:
	The high degree of binding of liraglutide to albumin is also thought to play a role in causing a reduced glomerular filtration of the peptide within the kidneys [21]

DPP-4 dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1, *NEP* neutral endopeptidase

non-covalently bound to the dominant plasma protein, human serum albumin (>99 % in vitro) [29], which is most likely via a fatty acid-binding site [30]. The following main mechanisms underlie the protraction of liraglutide: (1) slowed absorption following subcutaneous injection [31]; and (2) reduced elimination rate owing to slowed metabolism and renal filtration [30, 32]. These mechanisms are described in more detail in Table 1.

From a pharmacokinetic perspective, these prolongation mechanisms lead to a delayed time to maximum concentration (t_{max}) and a much elongated $t_{½}$ compared with native GLP-1 [21]. As a consequence, liraglutide is suitable for once-daily dosing, and because its plasma concentrations are determined by the mechanisms mentioned in Table 1, it has a low susceptibility for pharmacokinetic variations across (sub)populations.

3 Liraglutide Pharmacokinetic Properties

The pharmacokinetics of liraglutide has been evaluated in several single- and multiple-dose clinical pharmacology trials. This characterisation is summarised in the following sections. To support the pharmacokinetic evaluation, sparse sampling for liraglutide assay was taken in two phase III studies that included patients with type 2 diabetes: one trial conducted in America, primarily including USA sites with doses of 1.2 and 1.8 mg [10, 33] and one trial

conducted in Asia (China, India and South Korea) with doses of 0.6, 1.2 and 1.8 mg [34, 35].

3.1 Liraglutide Assay

A validated two-site enzyme-linked immunosorbent assay has been developed, using two monoclonal antibodies directed against different liraglutide epitopes [36]. The two antibodies used for the assay are directed against the N- and C-terminal regions of the liraglutide molecule, respectively. The lower limit of quantification was initially 30 pM, and was later reduced to 18 pM. Cross-reactivity with endogenous GLP-1 has been eliminated.

3.2 Absorption, Distribution, Metabolism and Excretion

Studies in healthy subjects and in patients with type 2 diabetes have demonstrated that the pharmacokinetic properties of liraglutide make it suitable for once-daily dosing. Across studies and populations, liraglutide has shown to be slowly absorbed following subcutaneous injection, with a t_{max} of approximately 12 h (range 7–14 h) [32, 36–44], and an absolute bioavailability of around 55 % [45]. The plasma $t_{½}$ has been estimated at approximately 13 h (range 11–15 h) [32, 36–44].

In healthy subjects, with multiple doses up to 12.5 μg/kg (~0.9 mg) daily, steady state was reached after approximately 3 days, with a mean accumulation ratio of 1.4–1.5 [36]. Pharmacokinetic profiles of liraglutide following steady-state doses of 0.6, 1.2 and 1.8 mg in healthy subjects are shown in Fig. 2 [42].

In a population pharmacokinetic study based on seven single- and multiple-dose trials, the pharmacokinetics of liraglutide was shown to be similar in healthy subjects and subjects with type 2 diabetes regardless of the dose levels used [46]. Moreover, the 24-h pharmacokinetic coverage was found to be suitable for once-daily dosing (Fig. 3).

Dose proportionality was established for the exposure of liraglutide in healthy subjects (in terms of the area under the concentration–time curve [AUC]) and maximum concentration [C_{max}]) for doses ranging from 0.6 to 1.8 mg (Fig. 4) [42]. This is in line with results from several pharmacokinetic evaluations in healthy and subjects with type 2 diabetes, which also indicated dose proportionality [35, 36, 40, 45].

Estimates of clearance and volume of distribution ranged from 0.6 to 1.2 L/h [32, 33, 36–42, 44] and from 11.0 to 24.7 L [32, 36–42], respectively, and were consistent across populations: healthy/type 2 diabetes, race groups, age groups, injection sites and dose levels. The relatively small volume of distribution suggests that liraglutide is mainly distributed in the intravascular fluid and extracellular compartment, which aligns with its high degree of albumin binding.

Based on data from a population pharmacokinetic analysis in subjects with type 2 diabetes, the inter-patient variability of clearance has been estimated at 36 %, without accounting for demographic covariates; this was reduced to 28 % after correcting for differences in body weight and sex (the two most important covariates) [33].

The effect of the site of injection (abdomen, upper arm or thigh) on the pharmacokinetic profile of liraglutide has been investigated in healthy subjects [43]. Bioavailability was found to be equivalent in comparisons of upper arm vs. both abdomen and thigh, but slightly lower with administration in the thigh compared with the abdomen. However, this minor difference was not considered to be clinically

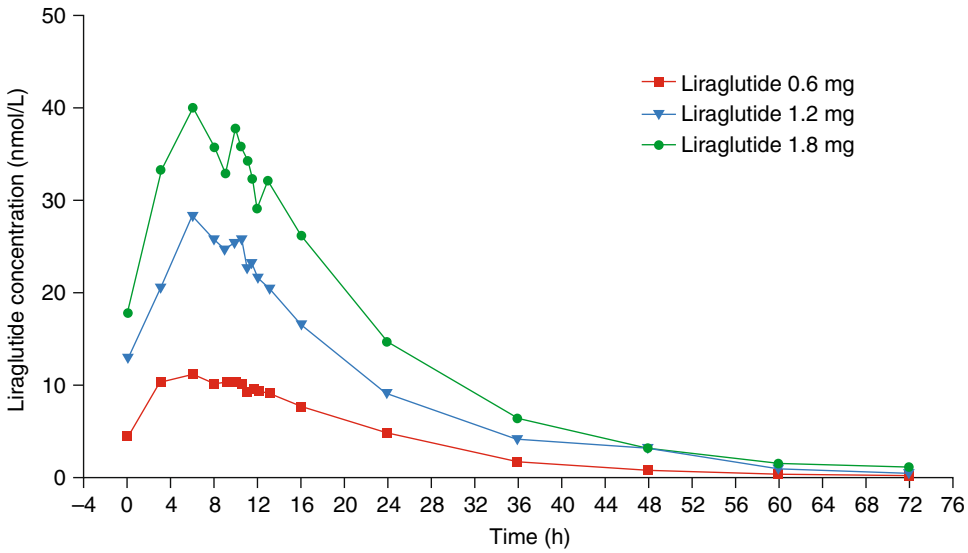

Fig. 2 Mean concentration profiles of liraglutide following steady-state doses of 0.6 mg ($n = 9$), 1.2 mg ($n = 9$) and 1.8 mg ($n = 8$) in healthy male Chinese subjects. With permission of © John Wiley & Sons, Inc. from Jiang et al. J Clin Pharmacol. 2011;51:1620–7 [42]

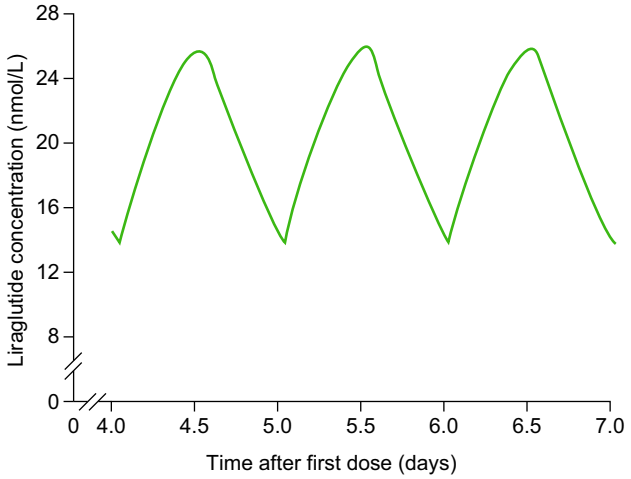

Fig. 3 Model-derived steady-state concentration profile of liraglutide (20 μg/kg) dosed once daily. With permission of © John Wiley & Sons, Inc.; adapted from Watson et al. Population pharmacokinetics of liraglutide, a once-daily human glucagon-like peptide-1 analog, in healthy volunteers and subjects with type 2 diabetes, and comparison to twice-daily exenatide. J Clin Pharmacol. 2010;50:886–94 [46]

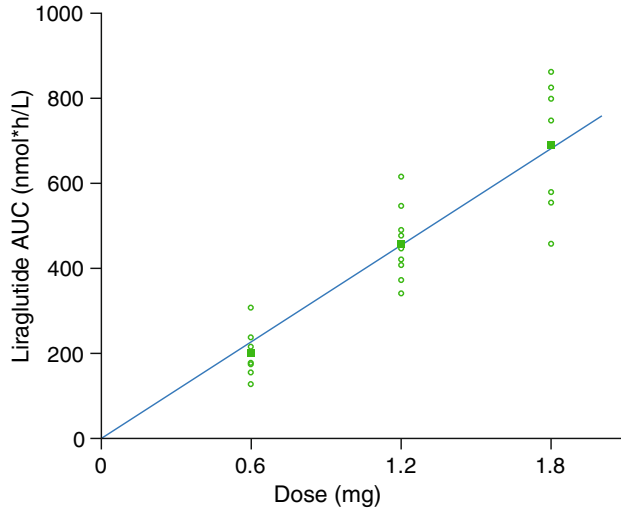

Fig. 4 Dose-proportionality plot of liraglutide exposure at steady state. *Open circles* represent individual study subjects. *Squares* represent mean values at each dose in healthy male Chinese subjects. The line represents the regression line from a linear model with logarithmic transformed AUC and dose under the assumption of dose proportionality ($r^2 = 0.96$). *AUC* area under the concentration–time curve in a dosing interval (24 h). Data from Jiang et al. The pharmacokinetics, pharmacodynamics, and tolerability of liraglutide, a once-daily human GLP-1 analogue, after multiple subcutaneous administration in healthy Chinese male subjects. J Clin Pharmacol 2011;51:1620–7 [42] © John Wiley and Sons, analysis results from data on file

relevant [43]. In clinical practice, administration of liraglutide can be interchanged between the three sites without dose adjustment [18, 19].

The metabolism of liraglutide appears to follow a similar pathway to native GLP-1 (albeit at a much slower rate), with cleavage by DPP-4 and NEP into several metabolites [32]. In a study with radiolabelled liraglutide, no intact liraglutide was excreted in urine or faeces, and low levels of metabolites were detected in plasma, indicating that the drug is completely degraded into peptides, amino acids and fatty acid fragments within the body [32].

4 Pharmacokinetics: Demographic Covariates and Special Populations

Liraglutide pharmacokinetics have been investigated in several sub-populations covering a range of demographic factors. Overall, body weight and sex are the only two factors of importance for the exposure of liraglutide. The influence of each individual factor is summarised below.

4.1 Body Weight

Two population pharmacokinetic analyses have investigated the influence of demographic covariates on liraglutide pharmacokinetics at steady state with doses up to 1.8 mg [33, 35]: one based on data from a phase III study conducted in the USA [10], and one using data from a phase III study conducted in Asia [34]. In both, mean exposure (based on AUC values) decreased with increasing body weight [33, 35]. However, there was substantial overlap in exposure values between individuals within low- and high-body weight subgroups, and hence dose adjustment according to body weight (or body mass index) is not required [35]. Instead, dose escalation from 1.2 to 1.8 mg should be based on the individual clinical response.

4.2 Sex

Exposure (AUC and C_{max}) was equivalent between male and female healthy subjects when correcting for body weight following a single dose of 1 mg of liraglutide [37]. In two population pharmacokinetic analyses of subjects with type 2 diabetes, mean liraglutide exposure was greater for female than male individuals after correction for differences in body weight [33, 35]. In the USA population study, the sex effect was outside the acceptance interval for bioequivalence (AUC, 0.8–1.25) [33]; however, in the Asian population study, the sex effect was in the same direction but within the acceptance interval for bioequivalence [35] (Fig. 5). As there was generally a large overlap in exposure values among individual male and female subjects, dose adjustment according to sex is not considered to be meaningful [33, 35].

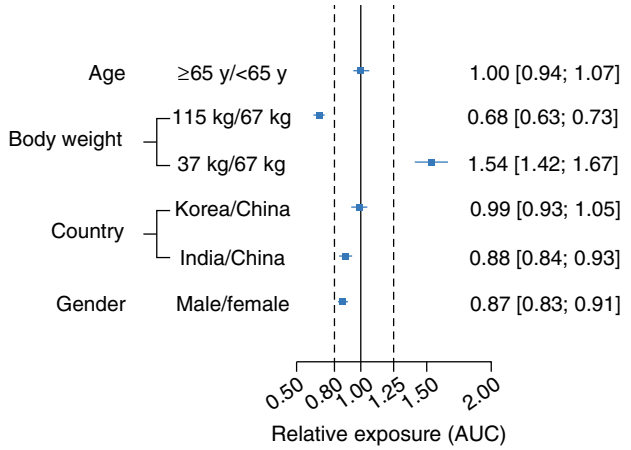

Fig. 5 Forest plot of covariate effects on liraglutide dose-normalised exposure (AUC) relative to a reference subject (Chinese female individual aged <65 years and with a body weight of 67 kg). Data are mean (90 % CI). *Vertical dotted lines* indicate bioequivalence limits of 0.8–1.25. The column to the right provides numerical values of geometric mean relative exposures with 90 % CIs obtained by likelihood profiling. *AUC* area under the concentration–time curve, *CI* confidence interval, *y* years. Reprinted from Ingwersen et al. Diabetes Res Clin Pract. 2015;108:113–9 [35], with permission from © Elsevier Ireland Ltd

4.3 Age

Liraglutide exposure has been shown to be unrelated to age. In a single-dose study in healthy subjects, the AUC (adjusted for body weight) was equivalent in young (age 18–45 years, both included) and older (age ≥65 years) subjects [37]. Similarly, in two population pharmacokinetic analyses, liraglutide exposure following therapeutic doses at steady-state did not differ between older (age >65 years) and younger subjects with type 2 diabetes [33, 35].

With regard to paediatric patients with type 2 diabetes, liraglutide exposure in subjects aged 10–17 years has been shown to be similar to that observed in adults [47]. Liraglutide C_{max} increased linearly with dose [48]. An ongoing phase III study is examining the efficacy and safety of liraglutide up to 1.8 mg in a paediatric population with type 2 diabetes. Liraglutide is currently not recommended for treatment of a paediatric population.

4.4 Race and Ethnicity

In a population pharmacokinetic analysis based on the USA phase III trial, race (Caucasian, African-American and Asian) and ethnicity (Hispanic and non-Hispanic) were found to have no effect on liraglutide exposure [33]. Furthermore, in the Asian phase III trial, exposure was similar among patients from the three countries (China, India and South Korea) [35]. The pharmacokinetic profile of liraglutide in healthy Japanese [40] and Chinese [42] subjects was also found to be consistent with other race groups.

4.5 Renal Impairment

In a single-dose study with liraglutide 0.75 mg in subjects with varying degrees of renal function (classified with mild, moderate or severe impairment, end-stage renal disease or normal renal function), renal impairment was associated with somewhat lower liraglutide exposure than in healthy subjects (Fig. 6). However, there was no clear trend for a relationship between creatinine clearance and exposure of liraglutide [41]. These results suggest that patients with type 2 diabetes also experiencing renal impairment can use standard liraglutide treatment regimens [41].

A randomised controlled trial of 277 subjects with type 2 diabetes and moderate renal impairment demonstrated the efficacy and safety of liraglutide 1.8 mg compared with placebo [49]. Based on these data, liraglutide is approved in Europe for patients with type 2 diabetes and mild or moderate renal impairment, and no dose adjustment is required [19]. In addition, haemodialysis did not alter the pharmacokinetic profile of liraglutide evaluated in 10 subjects with type 2 diabetes and end-stage renal disease who received liraglutide 0.6 mg or 0.9 mg [50]. In contrast, however, in a study of subjects with type 2 diabetes and end-stage renal disease undergoing dialysis treatment, plasma liraglutide concentrations were higher than in subjects with type 2 diabetes and normal renal function [51].

However, liraglutide is currently not recommended, or should be used with caution, in patients with severe renal impairment or end-stage renal disease [18, 19].

4.6 Hepatic Impairment

In a single-dose study of liraglutide 0.75 mg in subjects with mild, moderate or severe hepatic impairment or normal hepatic function, hepatic impairment was not associated with increased liraglutide exposure but was instead somewhat decreased compared with subjects with normal hepatic function (Fig. 6) [38]. Hence, the data indicate that patients with type 2 diabetes also experiencing hepatic impairment may use a standard liraglutide dosing regimen. However, therapeutic experience in these patients remains limited and liraglutide is not currently recommended, or should be used with caution, in this group of patients [18, 19].

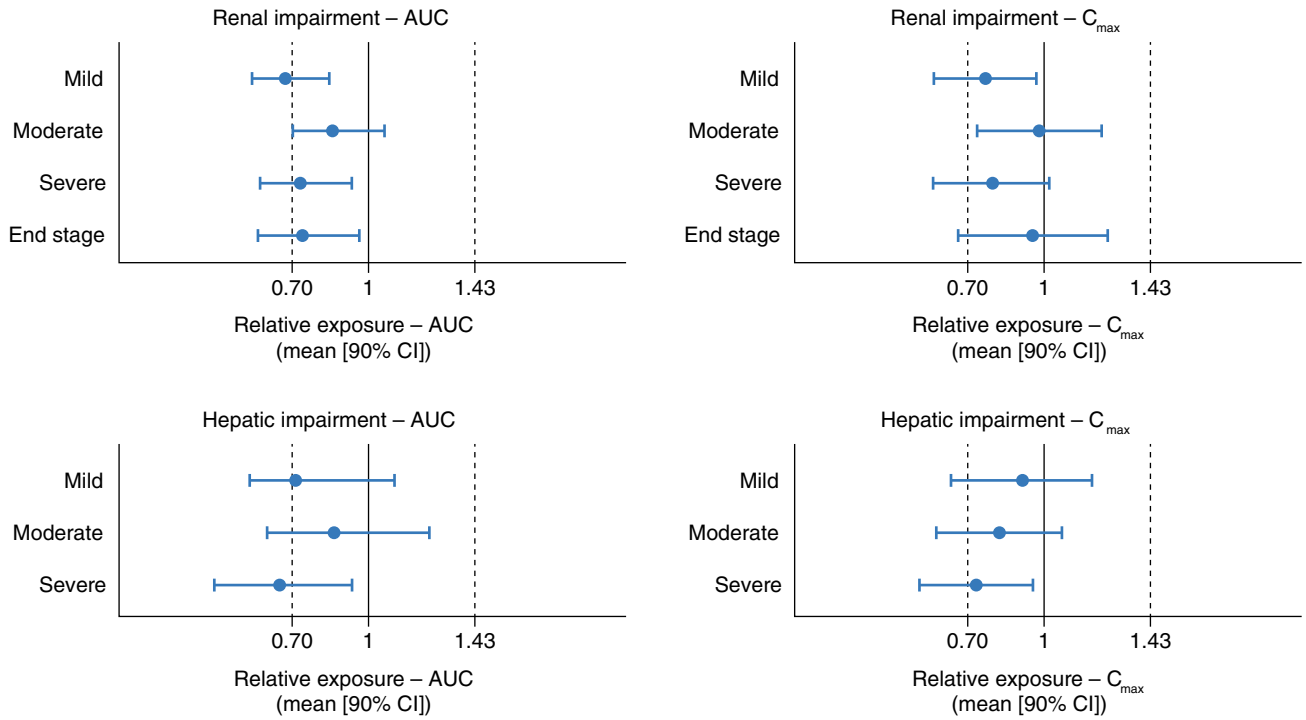

Fig. 6 Liraglutide exposure (AUC and C_{max}) following liraglutide 0.75 mg in subjects with renal or hepatic impairment relative to healthy controls. Data are mean exposures (with 90 % CI) for each group ($n = 5$–7 per group) relative to healthy subjects. *Broken vertical lines* illustrate the no-effect boundaries (0.70–1.43) used in the assessment. *AUC* area under the concentration–time curve, *CI* confidence interval, C_{max} maximum concentration. Renal impairment data from Jacobsen et al. Br J Clin Pharmacol. 2009;68:898–905 [41]. Hepatic impairment data from Flint et al. Br J Clin Pharmacol. 2010;70:807–14 [38]

5 Drug–drug Interactions

Being a protein, liraglutide has low potential for interactions with drugs cleared by cytochrome P450. This has been confirmed in non-clinical in vitro and in vivo studies [18, 19] (Novo Nordisk, data on file]. The underlying protraction and clearance mechanisms of liraglutide also give rise to a low potential for drug–drug interaction.

In vitro studies in human plasma showed that liraglutide protein binding was not changed in the presence of a number of highly protein-bound drugs [Novo Nordisk, data on file]. Furthermore, therapeutic plasma concentrations of liraglutide are relatively low (up to 25–50 nM) compared with plasma albumin concentrations (typically around 500–700 μM in humans), and hence it is unlikely that liraglutide will alter the protein binding of other drugs. The binding of liraglutide to albumin is most likely via the fatty acid-binding sites [30].

As a result of the above information, clinical investigations of liraglutide drug–drug interactions have focussed primarily on the slowed gastric emptying with liraglutide, which may affect the absorption of concomitantly administered oral drugs. The selected drugs represent a range of drugs of different solubilities and permeabilities including all four classes (I–IV) in the Biopharmaceutics Classification System [52]. These studies have shown minor effects on overall exposure but delayed initial absorption of a variety of concurrent oral medications such as paracetamol, atorvastatin, griseofulvin, digoxin, lisinopril and an oral combination contraceptive (Fig. 7). These effects were not considered to be clinically relevant [44, 53, 54] and dose adjustments for co-administered drugs are not required [18, 19].

GLP-1 analogues are often used in combination with insulin products, and liraglutide in combination with insulin detemir and insulin degludec has been shown to provide good glycaemic control, sustained weight loss and low rates of hypoglycaemia [16, 55].

An interaction study was conducted to investigate potential pharmacokinetic and pharmacodynamic interactions between liraglutide and insulin detemir when administered together. Co-administration of liraglutide 1.8 mg (at steady state) and insulin detemir (single dose) in patients with type 2 diabetes produced an additive glucose-lowering effect without affecting the pharmacokinetic profile of either agent (as evaluated by AUC, C_{max} and t_{max}) [56]. This suggests that the addition of insulin detemir in patients already being treated with liraglutide does not

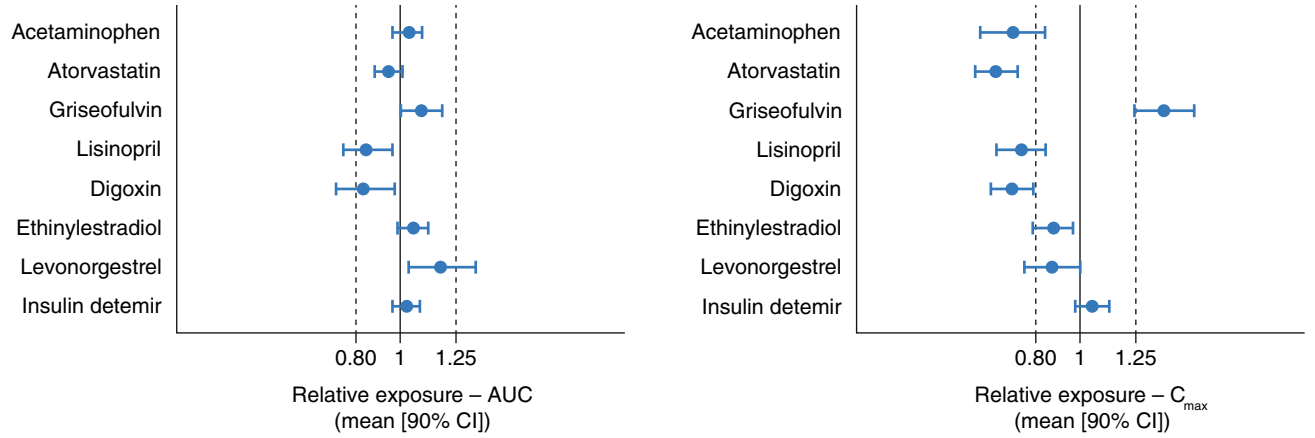

Fig. 7 Effects of liraglutide 1.8 mg on the exposure of selected co-administered drugs. Data are mean relative exposures (with 90 % CI) when co-administered with liraglutide vs. co-administration with placebo. The trials consisted of healthy subjects (atorvastatin $n = 42$, griseofulvin $n = 27$, lisinopril $n = 38$, digoxin $n = 26$, ethinylestradiol/levonorgestrel $n = 21$) and subjects with type 2 diabetes (acetaminophen $n = 18$ and insulin detemir $n = 32$). *Broken vertical lines* illustrate the no-effect boundaries (0.80–1.25) used in the assessment. Ethinylestradiol and levonorgestrel were administered as a combination product. *AUC* area under the concentration–time curve, C_{max} maximum concentration. Data from Malm-Erjefält et al. Mol Pharm. 2015; doi: 10.1021/acs.molpharmaceut.5b00278 [44]; Jacobsen et al. J Clin Pharmacol. 2011;51:1696–703 [53]; Kapitza et al. Adv Ther. 2011;28:650–60 [54]; Morrow et al. Diabetes Obes Metab. 2011;13:75–80 [56]

require a different insulin titration algorithm from that used when combined with oral anti-diabetic agents. This is in agreement with the different clearance mechanisms of insulins and GLP-1 analogues.

Using a fixed-dose combination of liraglutide and insulin degludec (IDegLira) with preserved pharmacokinetic properties of the two active components, treatment benefits were seen across the entire dose and exposure range compared with each component dosed alone [57].

6 Clinical Pharmacodynamics

The pharmacodynamic properties of liraglutide have been investigated in both single-dose [58–60] and multiple-dose [39, 61–65] studies. For the latter, steady-state maintenance doses of 1.2 mg and 1.8 mg were preceded by weekly dose escalations at increments of 0.6 mg (0.6 to 1.2 to 1.8 mg daily). One multiple-dose study used doses of 6 μg/kg (~0.55 mg) liraglutide [66].

6.1 Fasting and Postprandial Glucose

Glycaemic control by liraglutide is mediated by stimulation of insulin secretion and glucagon suppression and also involves a minor delay of gastric emptying. These effects have been examined via their impact on fasting and postprandial glucose.

Early studies employed relatively low liraglutide doses (typically below 0.9 mg; doses were converted from μg/kg to mg dose using individual body weights), which showed substantially improved fasting and postprandial glycaemia in subjects with type 2 diabetes [58]. Similarly, liraglutide dosed at approximately 0.55 mg daily was shown to significantly improve 24-h glycaemia in subjects with type 2 diabetes after 8 days of treatment, based on glucose AUC values. This effect was mediated by modification of insulin secretion and suppression of prandial glucagon secretion [66].

A crossover study in subjects with type 2 diabetes has demonstrated that treatment with liraglutide (assessed at the dose escalation steps of 0.6, 1.2 and 1.8 mg) reduces fasting as well as postprandial glucose excursions following a standardised meal, relative to placebo [61]. Compared with placebo, the postprandial plasma glucose $AUC_{0–5h}$ was 35 % lower after liraglutide 1.2 mg and 39 % lower after liraglutide 1.8 mg [61]. Mean postprandial glucose profiles are shown in Fig. 8. Two other crossover studies conducted in subjects with type 2 diabetes confirmed the fasting and postprandial glucose lowering effect with liraglutide, given at an approved dose level of 1.8 mg (with 3–4 weeks of treatment, including 2 weeks of dose escalation) [39, 62].

6.2 Insulin and Glucagon

Following 8 days of treatment with low-dose liraglutide (6 μg/kg once daily [~0.55 mg]), fasting and postprandial insulin levels were comparable to those in placebo-treated subjects with type 2 diabetes, despite lower glucose levels

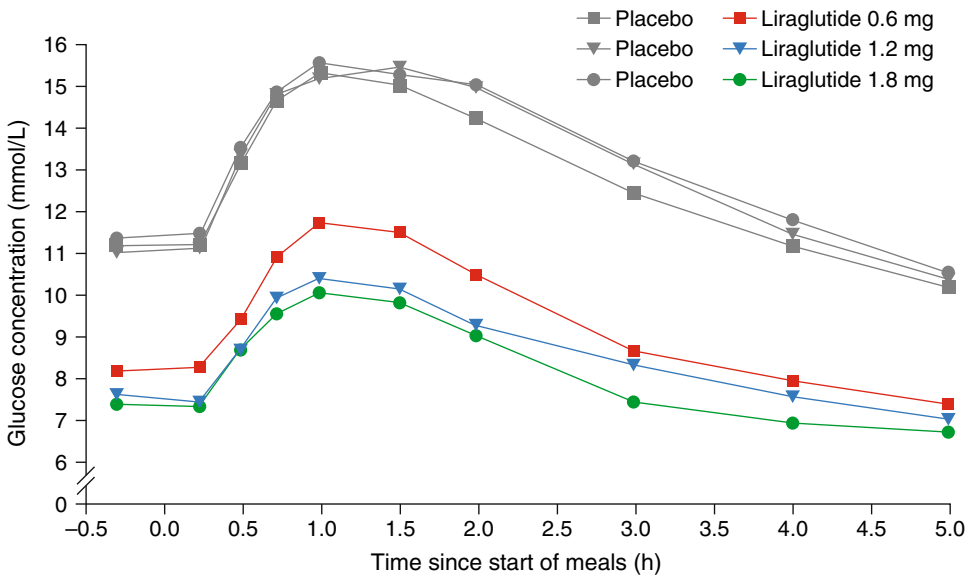

Fig. 8 Mean postprandial glucose profiles during a standardised meal test performed in 18 subjects with type 2 diabetes dosed with liraglutide or placebo. During each 3-week treatment period, the liraglutide/placebo dose was escalated weekly in 0.6-mg increments from 0.6 to 1.2 mg and 1.8 mg. Postprandial glucose measures were performed at steady-state liraglutide 0.6-mg (*red squares*), 1.2-mg (*blue triangles*), and 1.8-mg (*green circles*) doses, and for placebo (*matched grey lines*). © With kind permission from Springer Science + Business Media: Advances in Therapy, The once-daily human glucagon-like peptide-1 (GLP-1) analog liraglutide improves postprandial glucose levels in type 2 diabetes patients. 2011;28:213–26, Flint et al., Fig. 1 [61]

during active treatment, which suggests a relative increase in insulin secretion [66].

In more recent studies, liraglutide 0.6, 1.2 and 1.8 mg were all shown to increase insulin concentration relative to placebo in patients with type 2 diabetes, following a standardised meal [39, 61]. This effect appeared to be dose dependent, see Fig. 8 [61].

First- and second-phase as well as arginine-stimulated insulin responses have been assessed in subjects with type 2 diabetes treated with low-dose liraglutide (~0.55 mg) or placebo for 9 days [66]. Liraglutide stimulated both phases of insulin response relative to placebo (Fig. 9). Similarly, 14 weeks of treatment with therapeutic doses of liraglutide was associated with increases in first- and second-phase insulin secretion, together with increases in arginine-stimulated insulin secretion during hyperglycaemia [63].

Furthermore, in a graded glucose infusion study, in which insulin secretion was assessed in subjects with type 2 diabetes in response to gradually rising plasma glucose levels from ~5 to 12 mmol/L, a single administration of low-dose liraglutide (7.5 μg/kg [~ 0.66 mg]) stimulated insulin secretion in a glucose-dependent manner [59]. After treatment with liraglutide, insulin secretion rates were similar to those in healthy controls undergoing the same glucose infusion protocol and roughly double those of placebo-treated patients with type 2 diabetes (Fig. 10). Overall, liraglutide appeared to restore β-cell responsiveness to physiological hyperglycaemia without unwanted insulin secretion at euglycaemia.

Glucagon release was reduced after 8 days of treatment with low-dose liraglutide, primarily resulting from a marked reduction in postprandial concentrations following a protein-rich meal [66]. Mean postprandial glucagon levels were also found to be decreased following a standardised fat-rich meal in patients pre-treated with liraglutide 1.8 mg, compared with placebo [39].

The glucose-dependent action of liraglutide on insulin secretion is in line with the low risk of hypoglycaemia observed in clinical trials with liraglutide [15].

6.3 Counter-regulatory Hormones during Hypoglycaemia

Subjects with type 2 diabetes underwent two hyperinsulinaemic, stepwise hypoglycaemic clamp experiments: one following a single dose of liraglutide (7.5 μg/kg; ~0.68 mg), the other after placebo [60]. Liraglutide did not impair the hypoglycaemic counter-regulatory response compared with placebo, as measured by glucagon as the primary parameter or by cortisol, adrenaline and noradrenaline, although the growth hormone response was slightly impaired. Insulin secretion was stimulated by liraglutide in a glucose-dependent manner [60]. This means that stimulation of insulin secretion by liraglutide is markedly reduced during hypoglycaemic conditions.

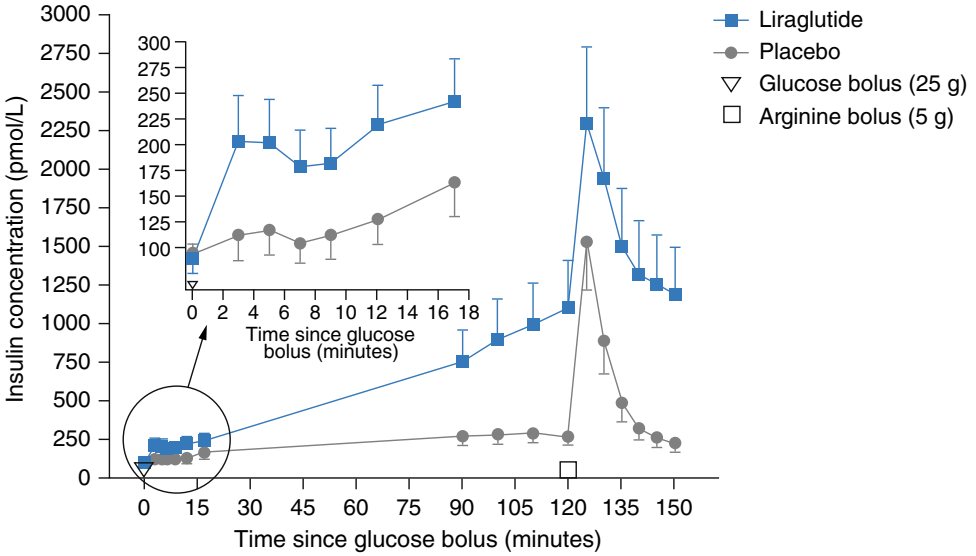

Fig. 9 Mean insulin profiles following glucose bolus injection (inserted), during a hyperglycaemic clamp and following an arginine stimulation test in 13 subjects with type 2 diabetes treated for 9 days with liraglutide 6 μg/kg (~0.55 mg) or placebo. Glucose bolus (first phase): 0–17 min; hyperglycaemic clamp (second phase): 90–120 min; arginine stimulation test (maximum insulin secretion): 120–150 min. © American Diabetes Association. Diabetes, American Diabetes Association, 2004. Copyright and all rights reserved. Material from this publication has been adapted with the permission of the American Diabetes Association from Degn et al. Diabetes. 2004;53:1187–94 [66]

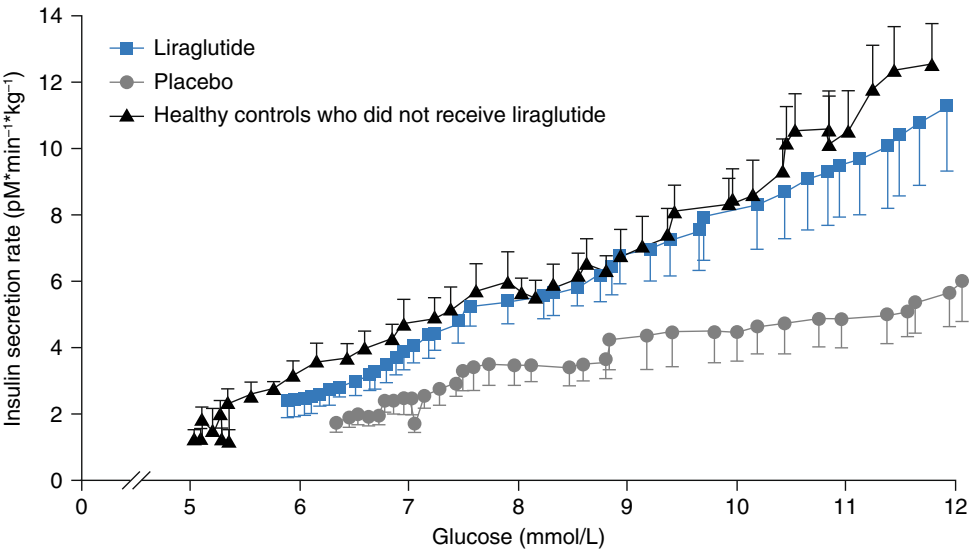

Fig. 10 Glucose-dependent stimulation of insulin secretion in subjects with type 2 diabetes treated with liraglutide. Relationship between insulin secretion rate (ISR) and plasma glucose levels during graded glucose infusion in subjects with type 2 diabetes ($n = 10$) receiving liraglutide 7.5 μg/kg (~0.66 mg; *blue squares*) or placebo (*grey circles*). Values from healthy controls ($n = 10$) who did not receive liraglutide (*black triangles*) are also shown. ISR was derived by deconvolution of C-peptide concentrations. Data are mean ± standard error; $n = 10$ for each group. © American Diabetes Association. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. From Chang et al. Diabetes. 2003;52:1786–91 [59]

6.4 Postprandial Lipids

After 3 weeks of treatment with liraglutide 1.8 mg or placebo in subjects with type 2 diabetes, postprandial levels of triglyceride and apolipoprotein B48 (a structural lipoprotein in chylomicrons, which are secreted following ingestion of lipids and used as a marker of lipid uptake from the gastrointestinal tract) were measured following a

standardised fat-rich meal [39]. Both were reduced by 28 % and 35 %, respectively, with liraglutide compared with placebo. This adds to the clinical benefits of liraglutide treatment considering that postprandial triglyceridaemia is a proven independent risk factor for cardiovascular disease in individuals with and without type 2 diabetes [67–69]. No significant treatment differences were apparent for non-esterified fatty acids [39]. The beneficial effect of liraglutide on the postprandial lipid response aligns with results from trials of native GLP-1 [70].

6.5 Gastric Emptying

GLP-1 agonists have been reported to slow gastric emptying as a result of reduced gastrointestinal motility [71].

The impact of drugs on gastric emptying is often studied by examining their effects on the absorption of orally administered paracetamol [72–75]. In particular, if a drug reduces the C_{max} and delays the t_{max} of paracetamol, it is considered to slow gastric emptying. A delay of gastric emptying may contribute to the glycaemic effects of liraglutide and may on the other hand result in delayed absorption of drugs dosed concomitantly (see Sect. 5).

In a crossover study of subjects with type 2 diabetes receiving liraglutide or placebo once daily for 3 weeks, paracetamol absorption was examined after a standardised carbohydrate-rich meal [61]. Over the first hour, paracetamol exposure was approximately 43 and 30 % lower, respectively with liraglutide 1.2 mg and 1.8 mg compared with placebo. However, this effect was less pronounced when assessed over 5 h (17 % following liraglutide 1.2 mg and 6 % [not significant] following 1.8 mg) [61]. The minor impact on gastric emptying contributes to the glycaemic effects of liraglutide but only to a modest degree [61, 76]. Similar results were achieved in a crossover study of gastric emptying after 4 weeks of treatment [62].

By contrast, in another recent analysis of subjects with type 2 diabetes treated for 3 weeks with liraglutide or placebo, there were no treatment-related differences with regard to gastric emptying assessed both by paracetamol absorption and by a ^{13}C octanoate breath test [39, 77]. However, the meal provided prior to assessment was high in fat, which is known to delay gastric emptying [78] and hence could have masked any additional effect of liraglutide.

Overall, the gastric emptying data suggest similarity between liraglutide and placebo over the full postprandial period but slower gastric emptying with liraglutide during the first hour.

In any case, it has been suggested that the effect of liraglutide on gastric emptying decreases over time, owing to tolerance development as a result of continuous activation of the GLP-1 receptor [79]. Indeed, data from a rat model showed that inhibition of gastric emptying diminished markedly over the course of 14 days of twice-daily liraglutide administration [80].

6.6 Body Weight and Body Composition

It is well known that liraglutide lowers body weight in subjects with type 2 diabetes [81]. Body weight loss was also observed in short-term clinical pharmacology studies. To further elucidate this, body composition was assessed in a subgroup of subjects with type 2 diabetes enrolled in two phase III studies, after 26 and 52 weeks of treatment, respectively [64].

In one study, fat percentage measured by low-radiation dual-energy X-ray absorptiometry was significantly reduced with liraglutide 1.2 and 1.8 mg plus metformin (−1.1 and −1.2 % change from baseline, respectively) compared with glimepiride plus metformin (+0.4 %), but not compared with placebo (−0.2 %). Visceral and subcutaneous adipose tissue areas were also significantly reduced with liraglutide (1.2 and 1.8 mg) plus metformin vs. glimepiride plus metformin. For example, the visceral adipose tissue area was reduced by 17 and 16 % with liraglutide 1.2 mg and 1.8 mg, respectively, by 5 % with glimepiride, and by 8 % with placebo [64].

Similarly, in the other phase III study, reductions in fat percentage were significantly greater with liraglutide monotherapy compared with glimepiride (−0.9 and −0.3 % with liraglutide 1.2 mg and 1.8 mg, respectively; +2.6 % with glimepiride), as were reductions in fat mass [64].

The weight reduction obtained with liraglutide (1.2 mg) in healthy obese women has been shown to be associated with increased bone formation and unchanged bone mineral content. In contrast, the control group which obtained a similar diet-induced weight reduction as the treatment group exhibited a reduced bone mineral content [82].

6.7 Appetite, Energy Intake and Energy Expenditure

To seek explanations for the body weight loss observed with liraglutide treatment, the effects of liraglutide on appetite sensations, energy intake and energy expenditure have been assessed in subjects with type 2 diabetes [62, 65]. After 3 weeks of treatment with liraglutide or placebo, reduction in hunger was significantly greater and mean energy intake was significantly lower (by 18 %) with liraglutide relative to placebo [65]. The weight loss associated with liraglutide treatment in type 2 diabetes may be mediated through these effects [65].

In a similar study, after 4 weeks of treatment, there was a trend towards lower energy intake and higher energy expenditure with liraglutide compared with placebo or glimepiride, although these effects did not reach statistical significance [62]. Fasting hunger was significantly lower with liraglutide, but other appetite measures were not significantly different between groups [62].

6.8 Corrected QT Interval

The potential effect of liraglutide on cardiac repolarisation was assessed in a thorough QT study. In a crossover design with healthy subjects given liraglutide for 3 weeks (0.6 mg/daily for 1 week followed by 1.2 and 1.8 mg) or corresponding placebo, electrocardiograms were recorded at the end of the 1.2- and 1.8-mg dosing weeks [83]. The study did not show evidence for a prolongation of the corrected QT interval. In addition, the corrected QT interval was unrelated to exposure. Hence, liraglutide has no clinically relevant effects on the corrected QT interval [83].

7 Pharmacokinetic/Pharmacodynamic Relationships

Based on data from a phase III study in the USA, as well as a dose-finding phase II study, the mean change from baseline in HbA_{1c} at 12–14 weeks was plotted for various doses of liraglutide (up to 1.8 mg and including placebo) given as monotherapy [33]. A clear dose–response relationship was observed, with maximum responses at doses $\geq$1.2 mg. There was a substantial overlap in the magnitude of effects at the two highest doses (1.2 g and 1.8 mg), largely because exposure (based on plasma concentrations at steady state) was overlapping at these doses [33]. However, the decrease in HbA_{1c} at the end of the 52-week treatment period was significantly greater with liraglutide 1.8 mg vs. 1.2 mg (1.14 vs. 0.84 %), and the proportion of patients achieving an HbA_{1c} level <7 % was significantly greater with the higher dose (51 vs. 43 %, respectively) [10].

A similar analysis based on data from a phase III study of liraglutide combined with metformin, conducted in Asian patients, also showed a clear dose–response relationship for effects on HbA_{1c} levels with liraglutide 0.6, 1.2 and 1.8 mg [35].

Liraglutide exposure–response relationships were also evaluated in both of the above analyses [33, 35]. In the USA trial, maximum HbA_{1c} response was obtained at liraglutide trough plasma concentrations at or above ~15 nmol/L (mean exposure of the third quartile in the phase II dose-range finding trial) (Fig. 11), and some

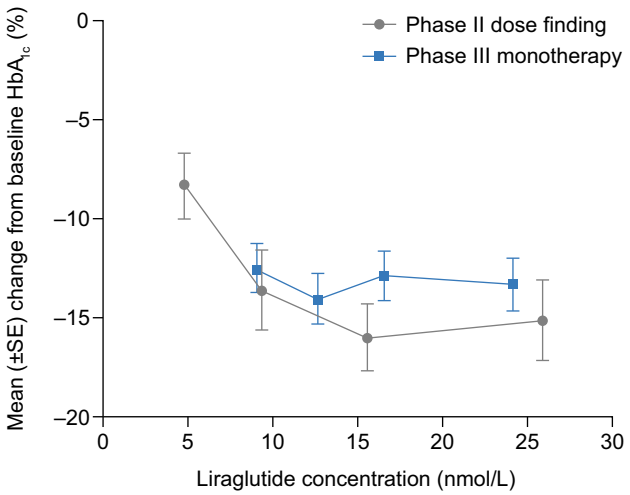

Fig. 11 Exposure–response relationship of liraglutide effects on HbA_{1c} in subjects with type 2 diabetes. Figure shows percentage change from baseline in HbA_{1c} following 14 weeks of treatment in a phase II dose-finding study (*grey circles*) and following 12 weeks of treatment in a phase III study (*blue squares*). The exposure–response relationships were evaluated by dividing liraglutide concentration values from each trial into quartiles. Exposures are trough concentrations for the phase II trial and model-derived mean concentrations for the phase III trial. *HbA_{1c}* glycated haemoglobin, *SE* standard error. With permission of © John Wiley & Sons, Inc.; adapted from Ingwersen et al. Dosing rationale for liraglutide in type 2 diabetes mellitus: a pharmacometric assessment. J Clin Pharmacol. 2012;52:1815–23 [33]

patients treated with liraglutide 1.2 mg had plasma concentrations below this level [33]. In the Asian trial, the effect of liraglutide on HbA_{1c} increased with increasing exposure before levelling off at mean liraglutide concentrations of 16–22 nmol/L; fewer than half of the subjects receiving liraglutide 1.2 mg achieved this exposure level, compared with >75 % of those receiving liraglutide 1.8 mg [35].

Similar relationships were observed for dose–response and exposure–response with regard to weight loss in the population of Asian subjects with type 2 diabetes [35]. Mean reductions in body weight increased with increasing liraglutide dose and exposure. Weight loss was largest with the 1.8-mg dose, and the benefit of a dose increase from 1.2 to 1.8 mg was greatest in patients with a body mass index >25 kg/m^2 [35].

As discussed by Niswender et al., among subjects treated with liraglutide who experienced gastrointestinal adverse events at >7, >14 and >30 days after treatment, a slightly greater weight reduction was observed in subjects with a longer duration of the adverse events [81]. This indicated that gastrointestinal adverse events may influence, but are not solely responsible for, weight loss in liraglutide-treated subjects.

Another study assessed the relationships between plasma concentrations of liraglutide and plasma glucose

(fasting plasma glucose and postprandial glucose $AUC_{0–5\ h}$) [76]. This was based on a post hoc analysis of data from subjects with type 2 diabetes randomised to 3 weeks of treatment with liraglutide (0.6, 1.2 and 1.8 mg daily, dose escalated at weekly intervals) and placebo in a crossover design. Glucose levels decreased significantly with increasing liraglutide concentration associated with doses between 0.6 and 1.8 mg. Most of this effect appeared to be reached with liraglutide 1.2 mg, but the degree of overlap between the 1.2- and 1.8-mg data points showed that some subjects would benefit from treatment with 1.8 mg [76].

No exposure–response analysis has been published for nausea, the most commonly observed adverse event with liraglutide. However, the frequency of reported nausea has been shown to be dose dependent and transient in nature, as discussed by Gough [84].

Overall, liraglutide 1.8 mg provides substantially more subjects with exposures in the most effective part of the exposure–response relationship for HbA_{1c} [33, 35]. These data therefore support the current posology of liraglutide, which allows for a dose increase from 1.2 to 1.8 mg once daily if the former does not result in acceptable glycaemic control [18, 19].

8 Conclusions

The pharmacokinetic and pharmacodynamic profiles of liraglutide at doses of up to 1.8 mg have been extensively studied, both in healthy subjects and in subjects with type 2 diabetes. The pharmacokinetic properties of liraglutide, particularly its extended plasma $t_{½}$ of around 13 h, make it suitable for once-daily dosing. Liraglutide administration can be interchanged between three injection sites (abdomen, upper arm or thigh) without dose adjustment. Age, race and ethnicity have no clinically relevant effect on drug exposure, and hence there is no need to adjust the dose based on these factors. Body weight and sex, however, are factors of importance for exposure, but do not necessitate dose adjustments per se. Exposure is somewhat decreased with renal or hepatic impairment, and standard liraglutide dose regimens are appropriate. However, liraglutide is not recommended, or should be used with caution, for patients with hepatic impairment or severe or end-stage renal impairment.

Drugs that are commonly co-administered with liraglutide show no clinically relevant changes in exposure, and dose adjustment is not required. Insulin detemir and liraglutide can be co-administered without altering the pharmacokinetic profile of either drug.

Clinical pharmacodynamic studies have demonstrated a number of beneficial actions of liraglutide, most importantly, improved fasting and postprandial glycaemic control, mediated by increased insulin and reduced glucagon levels. The effects of liraglutide on insulin and glucagon secretion are glucose dependent and thus the risk of hypoglycaemia is low. Furthermore, the counter-regulatory glucagon response was unchanged during hypoglycaemia. Liraglutide showed beneficial changes of postprandial lipid profiles and is also associated with reduced hunger and energy intake, resulting in body weight loss. As liraglutide dose and hence exposure increases, both HbA_{1c} and body weight decrease. Liraglutide at doses up to 1.8 mg has been shown to be an important treatment option for many patients with type 2 diabetes.

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Compliance with Ethical Standards

Potential conflicts of interest LVJ, AF, AKO and SHI are employees and shareholders of Novo Nordisk A/S.

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