Liraglutide pharmacokinetics and dose-exposure response in Asian subjects with Type 2 diabetes from China, India and South Korea

S.H. Ingwersen a,*, K.C. Petri a, N. Tandon b, K.-H. Yoon c, L. Chen d, J. Vora e, W. Yang f

a Novo Nordisk A/S, Søborg, Denmark
b All India Institute of Medical Sciences, New Delhi, India
c Catholic Medical Center, The Catholic University of Korea, South Korea
d Department of Endocrinology, Wuhan Union Hospital, Wuhan, Hubei, China
e Royal Liverpool University Hospitals, Liverpool, UK
f Department of Endocrinology, China-Japan Friendship Hospital, Beijing, China

A R T I C L E   I N F O

Article history:
Received 10 June 2014
Received in revised form
2 September 2014
Accepted 4 January 2015
Available online 19 January 2015

Keywords:
Liraglutide
Population pharmacokinetics
Type 2 diabetes
Exposure-response

A B S T R A C T

Aims: To investigate the population pharmacokinetics and exposure-response relationship of liraglutide, a human glucagon-like peptide-1 (GLP-1) analogue, in Asian subjects with Type 2 diabetes mellitus.

Methods: Data were derived from a published 16-week, randomized, double-blind, double-dummy, active-controlled, parallel-group trial of liraglutide in China, India and South Korea. The analysis utilized 2061 pharmacokinetic (PK) samples from 605 subjects exposed to liraglutide 0.6, 1.2 or 1.8 mg once daily. Demographic factors (body weight, age, gender, country) of importance for liraglutide clearance were evaluated. An exploratory exposure-response analysis was conducted to investigate effects on glycated haemoglobin (HbA1c) and body weight.

Results: Estimated liraglutide exposure (area under the curve; AUC) appeared to increase proportionally with increasing liraglutide dose (0.6–1.8 mg). The covariate analysis confirmed previous findings in a global clinical trial. Body weight was a predictor of liraglutide exposure; compared to a reference subject of 67 kg, exposure was 32% lower for maximum (115 kg) and 54% higher for minimum (37 kg) observed body weights. Gender, age and country had no relevant effect on exposure. Exposure-response analysis supported the use of 1.2 mg as maintenance dose with the option of individual dose escalation to 1.8 mg to optimize treatment outcomes.

Conclusions: Exposure appeared to increase proportionally with increasing liraglutide dose in Asian subjects with Type 2 diabetes mellitus. The only PK relevant predictor of exposure was body weight. The exposure-response relationships for HbA1c and body weight in Asian subjects were similar to observations in global populations.

© 2015 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Correspondence to: Quantitative Clinical Pharmacology, Novo Nordisk A/S, Vandtårnsvej 108-110, 2860 Søborg, Denmark.
Tel.: +45 30794847; fax: +45 44436740.
E-mail address: si@novonordisk.com (S.H. Ingwersen).
http://dx.doi.org/10.1016/j.diabres.2015.01.001
0168-8227/© 2015 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

Liraglutide is an injectable human glucagon-like peptide-1 (GLP-1) analogue with a glucose-dependent mechanism of action and has been approved for the treatment of adults with Type 2 diabetes mellitus [1,2]. Liraglutide dosing is initiated at 0.6 mg once daily with subsequent escalation to 1.2 mg once daily after one week. If necessary for optimal glycaemic control, the dose may be further escalated to 1.8 mg once daily after one week [1,2]. US regulatory approval of these two maintenance doses was based on the fact that liraglutide 1.2 mg provided inadequate plasma concentrations to obtain full clinical effect in some patients [3], and was further supported by the higher proportion of patients who achieved the American Diabetes Association glycated haemoglobin (HbA1c) target of < 7% (< 53 mmol/mol) with liraglutide 1.8 mg (51%) than 1.2 mg (43%) following 52 weeks of monotherapy [4].

Population PK analysis using data from a Phase 3 liraglutide study appeared to indicate dose-exposure proportionality and no relevant effects on exposure from age group (>65 years), race (Black or other) and ethnicity (Hispanic or non-Hispanic) [3]. Although lower body weight and female gender correlated with greater exposure, dose adjustments based on these effects were not considered meaningful [3]. It was previously shown that liraglutide exposure appears to be dose proportional in healthy males of Japanese [5] and Chinese [6] ethnicity.

By contrast with traditional PK studies that use data from highly selected subjects with minimal inter-individual variability, a population PK approach collects information from patients representative of the target population and supports inclusion of studies that are not amenable to standard PK analysis. As such, population PK analysis can measure and explain PK variability by identifying factors (demographic, pathophysiological, environmental, drug-related) that influence the dose-exposure relationship, thus determining the need for dose modification in certain subgroups [7–9]. While population PK data are available for Caucasian and other populations, to date, no such analyses have been published on liraglutide within the Asian population.

Expanding on the above mentioned clinical pharmacology data, a clinical trial was conducted to compare the safety and efficacy of liraglutide with glimepiride in Asian subjects with Type 2 diabetes from China, India and South Korea (n = 929) [10]. This study demonstrated comparable efficacy and tolerability to those reported in the global Liraglutide Effect and Action in Diabetes (LEAD) trial programme, with statistically significant dose-dependent reductions in estimated mean HbA1c from baseline to Week 16 (1.14%, 1.36%, 1.45% [13, 15, 17 mmol/mol] for liraglutide 0.6, 1.2 and 1.8 mg, respectively). Liraglutide was also associated with dose-dependent weight reduction (estimated mean reduction: 1.80 kg, 2.35 kg and 2.44 kg, respectively, vs. 0.08 kg weight gain in the glimepiride group [P < 0.0001]).

Using data from this study, the present analysis examined population PK and exposure-response relationships for HbA1c and body-weight effects of liraglutide in Asian subjects with Type 2 diabetes from China, India and South Korea [10].

2. Methods

2.1. Subjects/data source

Data were obtained from a previously published randomized, controlled trial (NCT00614120) [10], which investigated the safety and tolerability of once-daily liraglutide, compared with glimepiride, in combination with metformin in Asian subjects with Type 2 diabetes (n = 929). Details of the trial design have been described previously [10] and are only briefly summarized here. The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines [11,12]. Subjects provided written informed consent before initiation of any trial-related activities. The trial protocol was approved by local institutional review boards [10]. The trial was a 16-week, randomized, double-blind, double-dummy, active-controlled, four-arm, parallel-group, multicentre, multinational trial conducted in 17 sites in China, 10 sites in South Korea and 24 sites in India [10]. Subjects discontinued all pre-trial oral antidiabetic drugs except metformin before entering a 3-week run-in with forced escalation of metformin to 2000 mg/day followed by a 3-week maintenance period. Subjects with fasting plasma glucose between 7.0 and 12.8 mmol/l at the end of the maintenance period were randomized to receive either liraglutide 0.6 mg, 1.2 mg, 1.8 mg or glimepiride 4 mg, all once daily [10].

Four blood samples for the liraglutide PK assay were obtained from each subject at four separate visits (Week 2, 4, 12, and 16) using unrestricted sampling times. The time and date of sampling were recorded by the investigator in the case report form. Dosing information (dose level and time of dosing) was recorded for the two doses prior to blood sampling. Bioanalysis of liraglutide from collected samples was performed using a validated enzyme-linked immunosorbent assay (ELISA) method [13]. Efficacy data were obtained at baseline and 4, 8, 12 and 16 weeks after treatment initiation. The 16-week data from these subjects formed the PK data-set population for this analysis.

2.2. Population pharmacokinetic analysis

The population PK analysis was performed using 2061 PK samples collected from 605 subjects exposed to liraglutide. The analysis was conducted using a pre-specified approach [14–16]. The structural PK model was a one-compartment model with first-order absorption and elimination. As the data did not support estimation of the absorption rate constant (ka), it was fixed to a mean value of 0.202 h⁻¹, obtained from a clinical trial with full PK profiles in Chinese subjects [6]. The sensitivity of the results from the population PK analysis with regard to the value of this fixed parameter was evaluated as part of the model qualification procedure.

A covariate analysis for the influence of demographic variables on liraglutide clearance (Cl/F) was conducted as part of the population PK analysis. It comprised a full covariate
model that was pre-specified to comprise the following categorical covariates: liraglutide dose, age group (≥65 vs. <65 years), country and gender, with body weight (allometric relationship) as a continuous covariate. The importance of each covariate effect was visualized by the estimated mean (90% confidence interval [CI]) for the effect of the covariate on dose-normalized exposure at steady state (area under the curve [AUC]ₖₛ) relative to a reference subject.

The relationship between liraglutide dose and plasma exposure was presented as median, 25th and 75th percentiles, and 5th and 95th percentiles of AUC values for each of the three dose levels.

The population PK model was qualified by means of goodness-of-fit plots, using an evaluation of the estimated model parameter values, by likelihood profiling, by an assessment of shrinkage for the random effects; and by means of sensitivity analyses for excluded outliers and for the fixed value of kₚ used in the model.

### 2.3. Exposure-response analyses

The dataset used for the exposure-response analysis for HbA₁c and body weight comprised subjects who completed the trial and were included in the population PK analysis. In contrast with the statistical evaluation used in the previous publication [10], no imputation (last observation carried forward) was performed.

For this analysis, liraglutide AUC values were binned into four quartiles with the median AUC plotted against the corresponding mean responses for each quartile.

The exposure-response analysis was based on an analysis of covariance (ANCOVA). The effects on HbA₁c and body weight vs. liraglutide dose or exposure were presented as the mean change from baseline with baseline HbA₁c and body weight as covariates, respectively. The effects on HbA₁c and body weight vs. liraglutide exposure were presented as change from baseline vs. liraglutide AUC in a dosing interval at steady state, as obtained from the population PK model.

### 2.4. Software

S-PLUS version 8.2 (TIBCO, Palo Alto, CA, USA) was used for data file compilation, statistical and graphical analysis. NONMEM version 7.1.2 (ICON Development Solutions, Ellicott City, MD, USA) was used for the population PK analysis. Standard error estimates for the ANCOVA analysis were determined using R (Version 2.14.2) [17] with the add-on package ‘doBy’ (version 4.5-3) [18].

### 3. Results

#### 3.1. Baseline characteristics

The demographics for the final data-set are shown in Table 1. As might be expected, females had a lower body weight than males. Only small differences in body weight, body mass index (BMI) and age existed between countries.

#### 3.2. Population PK analysis

The PK parameter estimates obtained from the population PK model are shown in Table 2. Estimated liraglutide exposure (AUC) appeared to increase proportionally with increasing liraglutide dose (0.6–1.8 mg) (Fig. 1a). Median exposure values in terms of AUCs in a dosing interval at steady state were

### Table 1 - Baseline characteristics of the patient population (n = 605).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th>China</th>
<th>India</th>
<th>Korea</th>
<th>Overall median (minimum–maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>Female</td>
<td>61.0</td>
<td>64.7</td>
<td>67.4</td>
<td>67.6 (37.0–114.7)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>71.1</td>
<td>68.2</td>
<td>74.2</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Female</td>
<td>24.6</td>
<td>27.4</td>
<td>27.1</td>
<td>25.2 (17.1–44.8)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>24.8</td>
<td>24.5</td>
<td>25.6</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Female</td>
<td>55.0</td>
<td>50.0</td>
<td>52.0</td>
<td>53.0 (21.0–77.0)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>54.0</td>
<td>51.0</td>
<td>55.5</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index.

### Table 2 - Pharmacokinetic (PK) parameter estimates obtained from the population PK model.

<table>
<thead>
<tr>
<th>Fixed-effects parameters</th>
<th>Estimate</th>
<th>RSE (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>kₚₖ, absorption rate constant (h⁻¹)</td>
<td>0.202 (fixed)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CL/F, clearance (L/h)</td>
<td>0.769</td>
<td>2.22</td>
<td>[0.736; 0.803]</td>
</tr>
<tr>
<td>V/F, volume of distribution (L)</td>
<td>19.3</td>
<td>8.72</td>
<td>[16.0; 22.6]</td>
</tr>
<tr>
<td><strong>Between-subject variability parameters (CV%)</strong></td>
<td></td>
<td>Shrinkage (%)</td>
<td></td>
</tr>
<tr>
<td>Absorption rate constant</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clearance</td>
<td>23.0</td>
<td>26.6</td>
<td>–</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>38.0</td>
<td>66.7</td>
<td>–</td>
</tr>
<tr>
<td><strong>Residual variability parameters</strong></td>
<td></td>
<td>Shrinkage (%)</td>
<td></td>
</tr>
<tr>
<td>CV%</td>
<td>22.7</td>
<td>6.1</td>
<td>–</td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, coefficient of variation; RSE, relative standard error.
Fig. 1 – (a) Dose versus steady-state liraglutide exposure based on estimates of clearance. Data are median, 5th, 25th, 75th and 95th percentiles. Crosses are individual observations outside the 5th and 95th percentiles. The solid line represents the linear regression line on a linear scale. (b) Forest plot of covariate effects on liraglutide dose-normalized exposure in patients with Type 2 diabetes from China, India and South Korea. Effects are expressed as exposure (AUC) relative to a reference subject (Chinese female, <65 years of age, body weight of 67 kg). Data are mean (90% CI). 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 curve; CI, confidence interval; y, years.

201 nM h at 0.6 mg, 375 nM h at 1.2 mg and 524 nM h at 1.8 mg, corresponding to average liraglutide concentrations of 8 nM, 16 nM and 22 nM, respectively, at the three dose levels investigated in the trial. Dose proportionality was not formally tested, since the trial was not powered to formally test for dose proportionality.

The effect of selected demographic covariates (age, body weight, gender and country) on liraglutide exposure relative to a reference subject (<65 years, 67 kg, female of Chinese origin) is shown in the forest plot in Fig. 1b. Liraglutide exposure was independent of age group (>65 vs. <65 years).

Body weight had an impact on liraglutide exposure. The mean relative liraglutide exposure fell outside the acceptance interval for bioequivalence (0.8–1.25), indicating that liraglutide exposure was affected by body weight to a pharmacokinetically relevant extent. The AUC of liraglutide decreased with increasing body weight. For the maximum (115 kg) and minimum (37 kg) observed body weights in the trial, the exposure was 32% lower and 54% higher, respectively, relative to a reference subject with a body weight of 67 kg (median body weight in the trial).

While liraglutide exposure was 13% lower in males vs. females, the change in exposure was within the bioequivalence interval (limits: 0.8–1.25) and therefore not considered relevant from a PK perspective.

Effects of ethnicity were not directly investigated; however, country was included as a covariate in this analysis. For subjects from South Korea, the exposure was similar

Fig. 2 – The effect of dose and exposure on change in HbA1c from baseline to Week 16. HbA1c data are from an ANCOVA model with country, prior treatment and liraglutide dose (a) or AUC quartile (b) as fixed effects and baseline HbA1c as covariate. ANCOVA, analysis of covariance; AUC, area under the curve; SE, standard error.
compared with subjects from China. Subjects from India had a 12% lower exposure relative to a reference subject from China. These effects were within the bioequivalence interval and were not considered to warrant dose adjustments.

3.3. Exposure-response analyses

3.3.1. HbA1c
Liraglutide appeared to provide greater HbA1c reductions with increasing dose (Fig. 2a). Mean end-of-trial change in HbA1c from baseline was −1.3%, −1.5% and −1.8% (−14, −17 and −20 mmol/mol) for liraglutide 0.6 mg, 1.2 mg and 1.8 mg, respectively. The effect of liraglutide increased with increasing exposure (Fig. 2b) and appeared to level-off at AUC levels between 400 and 600 nM·h, corresponding to average liraglutide concentrations of 16–22 nM. Less than half of the subjects who received liraglutide at the 1.2 mg dose achieved AUC values of 400 nM·h or greater, whereas >75% of subjects dosed at 1.8 mg achieved this exposure level. This suggests that a dose of 1.8 mg provides a substantial proportion of subjects with exposures in the effective part of the exposure – HbA1c relationship.

3.3.2. Body weight
Body weight was significantly reduced at all investigated doses; the magnitude of weight loss increased with increasing dose in the overall population (Fig. 3a). Mean end-of-trial change in body weight was −1.9 kg, −2.6 kg and −2.9 kg from baseline with liraglutide 0.6 mg, 1.2 mg and 1.8 mg, respectively. Effects on body weight in the overall population increased with drug exposure, and appeared to level-off at AUC levels from 400 to 600 nM·h (Fig. 3b), reaching a mean weight loss of 3.1 kg in the highest exposure quartile. Again, this suggests that a dose of 1.8 mg provides a substantial proportion of subjects with exposures in the effective part of the exposure – body weight relationship. Further subset analysis revealed that the benefit of increasing the dose from 1.2 mg to 1.8 mg was greatest in the population with BMI above 25 kg/m² (data not shown).

4. Discussion
The objective of this analysis was to investigate the PK properties of liraglutide in patients from China, India and South Korea, and to use the estimated exposure obtained from the population PK analysis to perform exposure-response analyses for the key clinical effects of liraglutide.

The finding that reductions in HbA1c and body weight appear to increase with increasing dose in the Asian population examined here is similar to observations in early PK/pharmacodynamic (PD) studies of liraglutide in healthy male subjects [13,19] and population PK studies of a global population from the Phase 3 clinical trial programme [3]. Furthermore, they were in accordance with findings from a PK/PD study of healthy male Chinese subjects (n = 37), where the dose relationships of AUC0–24h, Cmax and Ctrough at steady state did not deviate from dose proportionality in a PK-relevant manner following administration of liraglutide 0.6 mg, 1.2 mg or 1.8 mg once daily for 21 days [6].

The findings described here showed that body weight significantly influenced liraglutide exposure in an Asian population, with decreasing exposure evident with increasing body weight. The effect of body weight on liraglutide exposure was beyond the threshold for bioequivalence and therefore considered pharmacokinetically relevant. Body weight and gender were previously identified as significant covariates for liraglutide exposure in a global population [3]. Although the decreased exposure with increasing body weight was pharmacokinetically relevant, there was a large overlap in individual exposure values between subgroups of low and high body weight. Hence, it would not be meaningful to adjust the liraglutide dose according to body weight (or BMI). Increasing the liraglutide dose to 1.8 mg should be based on individual considerations.

Females had a lower clearance – and hence a higher exposure – than males in the population after correcting for body weight. However, gender only explained three
percentage points of the inter-individual variability in body weight-adjusted clearance (reduced from 31% to 28%).

While gender was found to have a small significant effect on liraglutide exposure in the present analysis, the difference was within the acceptance interval for bioequivalence and was not deemed to have PK relevance.

Age (≥65 vs. <65 years) was a non-significant predictor of liraglutide exposure in the present analysis. Similar results were found in a previous evaluation of subjects aged ≥65 years compared with those <65 years [3].

It is important to consider the impact of intrinsic (genetic, physiological and pathological) and extrinsic (socioeconomic status, culture, diet and environment) differences between ethnicities or race on the pharmacokinetics of a drug [20,21]. For example, the impact of obesity on drug pharmacokinetics may vary when using the different BMI cut-off points for Asian populations (BMI [kg/m²] for overweight: ≥23.0; obese: ≥25.0) compared to those for Europeans (BMI [kg/m²] for overweight: ≥25.0; obese: ≥30.0) [22–26]. Neither race (Black vs. others) nor evaluation of certain subsets of ethnicity (Hispanic vs. non-Hispanic) has previously been found to have statistical significance on liraglutide exposure [3]. The results reported here support this finding, with Asian subjects in this analysis demonstrating similar PK properties as reported in Caucasian and Black subjects [3]. There was no significant difference in liraglutide exposure in subjects from South Korea compared with China, and although a significant small reduction in exposure was observed for subjects from India vs. China, it was not considered to be pharmacokinetically relevant.

The identified exposure-response relationships of liraglutide in the Asian population were similar to those previously observed in a global population [3] for both HbA1C reductions and weight loss; greatest mean effects in the overall population were observed with the 1.8 mg dose. While liraglutide 1.2 mg may be sufficient to provide the full therapeutic effect in some patients, other patients (including those of greater body weight) would be expected to gain further benefit from the higher dose.

The additional beneficial effects on HbA1C and body weight with liraglutide 1.8 mg compared to 1.2 mg appeared greater in the present analysis compared with the main trial analysis [10]. This difference was mainly due to the exclusion of non-completers and no imputation of missing data at the end of the trial. Such imputation is likely to cause bias in the exposure-response relationships due to lack of steady-state conditions for HbA1C at time points prior to Week 16.

Population PK analysis is becoming a common practice in many clinical programmes [27] and is often requested by regulatory authorities. Carrying out well-designed population PK studies using data from Phase 3 trials can be a challenge due to the importance of accurate blood sampling and dosing information for outpatients. However, in addition to providing information on the variability of the PK of a drug across different demographic subsets of patients, the exposure-response data obtained from population PK analyses can serve as supportive evidence of drug effectiveness and add to the establishment of a rationale for dose selection.

This analysis used a structural PK model that was previously shown to adequately describe liraglutide PK in a mostly Caucasian adult population with Type 2 diabetes [3]. The good fit of model predictions to the observed data in this analysis indicates its suitability for modelling of liraglutide PK in an Asian population.

Covariate effects were restricted to effects on clearance (and hence, AUC in this analysis) due to the sparse PK sampling. This was not considered a serious limitation due to the low peak-to-trough variations for liraglutide. However, the shape of simulated concentration–time profiles obtained using the model may be slightly inaccurate.

In conclusion, this population PK analysis provided evidence that exposure to liraglutide is dose-proportional in Asian subjects with Type 2 diabetes. Age was not a predictor of liraglutide exposure; only body weight had a pharmacokinetically relevant impact, with increasing body weight resulting in decreasing exposure. The exposure-response relationship of liraglutide in Asian subjects was similar to that observed in global populations, with the greatest effects on HbA1C and body weight observed with the 1.8 mg dose. It is likely that liraglutide 1.2 mg will be sufficient to provide full therapeutic effects in some patients, whereas others would gain further benefit from escalation to the 1.8 mg dose.

5. Funding

Novo Nordisk sponsored the original clinical trial from which data were used in the present analyses, performed the analyses reported in the manuscript and also reviewed the manuscript for scientific accuracy. The authors retain full responsibility for the content of the manuscript.

Conflict of interest disclosures

SH Ingwersen and KC Petri are employees at and shareholders of Novo Nordisk A/S. K-H Yoon has served on advisory boards for AstraZeneca, Eli Lilly, Boehringer Ingelheim, Hamm, and Merck; has received research support from Merck, AstraZeneca, and Bayer; and has received speaker fees from Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Merck, and Novartis. J Vora has received support for research and attendance for national and international educational meetings and honoraria for lecturing and advisory boards from Novo Nordisk, Lilly, Sanoﬁ, MSD, Takeda, Novartis, and Abbott. N Tandon, W Yang and L Chen have no conflicts of interest to report.

Funding source

Novo Nordisk

Acknowledgements

The authors are grateful to Lene Alifrangis, Niels Rode Kristensen, Christoffer Wenzel Tornøe and Morten Donsmark for assistance in this analysis. Watermeadow is acknowledged for editorial assistance in preparing the manuscript.
REFERENCES
