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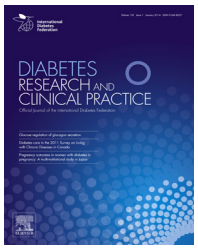

Liraglutide pharmacokinetics and dose-exposure response in Asian subjects with Type 2 diabetes from China, India and South Korea

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ABSTRACT

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 (HbA_{1c}) 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 HbA_{1c} and body weight in Asian subjects were similar to observations in global populations.

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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 (HbA_{1c}) 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 abovementioned 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 HbA_{1c} 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 HbA_{1c} 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-armed, 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 (k_a), 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