Lixisenatide resensitizes the insulin-secretory response to intravenous glucose challenge in people with type 2 diabetes – a study in both people with type 2 diabetes and healthy subjects†

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Aims: Glucagon-like peptide-1 (GLP-1) receptor agonists improve blood glucose control by enhancing glucose-sensitive insulin release, delaying gastric emptying and reducing postprandial glucagon secretion. The studies reported here investigated the insulin response to an intravenous (iv) glucose challenge after injection of lixisenatide (LIXI) 20 μg or placebo.

Methods: Two single-centre, double-blind, randomized, placebo-controlled, single-dose, crossover studies were performed in healthy subjects (HS) and people with type 2 diabetes mellitus (T2DM). Participants received subcutaneous LIXI or placebo 2h before an iv glucose challenge. Study endpoints included first- and second-phase insulin response, insulin concentration (INS), glucagon response and glucose disposal rate (Kglucose). LIXI exposure was measured over 12h.

Results: LIXI 20 μg reached maximum concentration after 2h and resensitized first-phase insulin secretion by 2.8-fold in T2DM to rates comparable with those in HS on placebo, and raised second-phase insulin secretion by 1.6-fold in T2DM. INS rose correspondingly and glucose disposal was accelerated by 1.8-fold in T2DM. First-phase insulin secretion and glucose disposal were also augmented by LIXI in HS, whereas second-phase insulin secretion reduced blood glucose concentrations to below fasting levels and then ceased, accompanied by a rapid, short-lasting rise in glucagon. Otherwise, suppression of glucagon release subsequent to augmentation of insulin release was unaffected in T2DM and in HS.

Conclusions: LIXI resensitized the insulin response to an iv glucose challenge in people with T2DM, thereby accelerating glucose disposal to nearly physiological intensity, and did not impair counter-regulation to low glucose levels by glucagon.

Keywords: healthy subjects, insulin response, lixisenatide, pharmacodynamics, pharmacokinetics, type 2 diabetes mellitus

Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists are an established therapeutic option for people with type 2 diabetes mellitus (T2DM), and both short- and long-acting agents are available [1]. GLP-1 receptor agonists enhance insulin secretion in a glucose-dependent manner, which differentiates them from insulin therapy and insulin secretagogues, such as sulphonylureas and glinides, and results in a much lower risk of hypoglycaemia [1,2]. Even though they share the same basic mechanism of action, long- and short-acting GLP-1 receptor agonists have different impacts on prandial and fasting plasma glucose (FPG), owing to differences in their pharmacokinetic and pharmacodynamic properties [1]. Short-acting GLP-1 receptor agonists act predominantly on postprandial plasma glucose (PPG), attributable to intermittent activation of the GLP-1 receptor and slowed gastric emptying [1]. Long-acting GLP-1 receptor agonists have a greater impact on FPG due to their sustained activation of the GLP-1 receptor, and lesser impact on gastric emptying owing to tachyphylaxis [1,3–6].

In healthy individuals, insulin secretion following a meal occurs in two distinct phases: a first phase that occurs during the first 10 min following a sudden rise in plasma glucose concentration, which reduces basal glucagon secretion and hepatic glucose production; and a second phase that is sustained until normoglycaemia is restored [7,8]. Early-phase insulin secretion is critical for the maintenance of glucose homeostasis, with
studies suggesting that an early insulin rise restrains excessive glucose excursions after nutrient ingestion \[9,10\]. The first-phase insulin response is characteristically absent or severely blunted in people with T2DM, owing to impaired \( \beta \)-cell function \[7,9–11\]. The GLP-1 receptor agonists, exenatide and lixisenatide, both augment first- and second-phase insulin secretion in response to an intravenous (iv) glucose bolus \[12,13\]. Lixisenatide (LIXI) is a once-daily, short-acting prandial GLP-1 receptor agonist that has been demonstrated to significantly improve glycaemic control, with a pronounced effect on PPG and a low incidence of hypoglycaemia \[14–20\]. In order to understand its effect on insulin secretion, the two complementary phase I studies reported here were undertaken, investigating the impact of LIXI on first- and second-phase insulin responses after a standardized iv glucose load in both healthy subjects (HS) and in people with T2DM.

**Patients and Methods**

The two individual, parallel, single-centre, double-blind, randomized, placebo-controlled, single-dose, two-period, two-treatment, two-sequence, crossover studies compared the insulin response to an iv glucose challenge after injection of LIXI 20 \( \mu \)g with the response after placebo injection. One study was performed in HS and the other study was performed in people with T2DM. These studies were carried out at the PROFIL Institut für Stoffwechselforschung GmbH, Neuss, Germany. The studies were approved by the institutional review boards or ethics committees and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants gave written informed consent to participate in the studies.

**Study Design**

In both studies, participants were randomized 1:1 to one of two treatment sequences (LIXI 20 \( \mu \)g in study period 1 and placebo in study period 2 or vice versa). The two study periods were separated by a washout period of between 1 and 7 days. During each study period, participants fasted overnight (at least 10 h for HS and 13 h for people with T2DM) to adjust blood glucose to euglycaemic levels [about 5.5 mmol/l (100 mg/dl)]. In the study in people with T2DM, an iv infusion of insulin [soluble human insulin (Actrapid\textsuperscript{®}), NovoNordisk, Mainz, Germany] could be given to people who did not reach euglycaemia. Participants in both studies received a subcutaneous injection of LIXI 20 \( \mu \)g or placebo in the left or right abdominal wall. Two hours after LIXI or placebo injection, participants received an iv bolus of glucose (0.3 g/kg body weight; 50% aqueous solution) over a period of 30 s.

**Study Participants**

Both studies combined included a total of 42 participants: 20 (14 male, 6 female) in the healthy study and 22 (13 male, 9 female) in the T2DM study. In the study in HS, the mean age, weight and body mass index (BMI) were 35.6 years, 75.7 kg and 24.5 kg/m\(^2\), respectively. Screening included FPG and glycated haemoglobin (HbA1c). In the T2DM study, all subjects were confirmed as having T2DM by HbA1c determination and being treated with metformin and/or lifestyle modifications. In the study in people with T2DM, the mean age, weight and BMI were 54.6 years, 88.7 kg and 29.9 kg/m\(^2\), respectively. In this study, baseline FPG ranged from 4.9 to 7.7 mmol/l (881–139 mg/dl), with a mean value of 6.3 ± 0.5 mmol/l (114 ± 11 mg/dl), and baseline HbA1c ranged from 44 to 64 mmol/mol (6.2–8.0%), with a mean value of 52 ± 1 mmol/mol (6.9 ± 0.5%). HbA1c of people with T2DM treated with lifestyle modifications only was 49–55 mmol/mol (6.2–7.2%).

**Statistical Analyses**

The primary analysis population comprised all subjects with completed profiles on both study days and with both treatments. Per protocol, INS-AUC\(_{0–10 \text{ min}}\) served as primary endpoint in the study in T2DM and ISR-AUC\(_{0–10 \text{ min}}\) in the subsequent study in HS.

A sample size analysis determined that at least 18 volunteers were required in the T2DM study to detect a threefold increase in INS-AUC\(_{0–10 \text{ min}}\) after subcutaneous injection of
LIXI relative to placebo with a statistical power of 90% and a type 1 error of 5%, assuming a within-subject standard deviation of 0.9. Twenty subjects were enroled into the study to allow for dropouts. These assumptions were based on data reported by Fehse et al. for INS-AUC\(_{0–10}\) min observed after iv administration of exenatide relative to placebo [12]. For the study in HS, the sample size analysis determined that at least 16 volunteers were required to detect a 1.5-fold increase in ISR-AUC\(_{0–10}\) min after subcutaneous injection of LIXI relative to placebo with a statistical power of 90% and a type 1 error of 5%, assuming a within-subject standard deviation of 0.3. These assumptions were based upon the study in people with T2DM. Eighteen subjects were enroled into the study to allow for dropouts. Naturally log-transformed ISR-AUC\(_{0–10}\) min, ISR-AUC\(_{10–120}\) min, INS-AUC\(_{0–10}\) min, INS-AUC\(_{10–120}\) min, C-PEP-AUC\(_{0–10}\) min, C-PEP-AUC\(_{10–120}\) min and \(K_{\text{glucose}}\) were analysed using linear mixed models with fixed terms for sequence, period, sex and treatment, and with an unstructured R matrix of treatment variances and covariances for subject within sequence blocks (using SAS PROC MIXED). Estimates and 90% confidence intervals (CIs) for the ratios of geometric means of LIXI versus placebo were calculated within the linear mixed-effect model framework. The pharmacokinetic parameters of maximum plasma concentration (\(C_{\text{max}}\), \(t_{\text{max}}\) (time to \(C_{\text{max}}\)), half-life (\(t_{1/2}\)), area under the curve at the last quantifiable time-point (LIXI-AUC\(_{\text{last}}\)) and LIXI-AUC were calculated using non-compartmental methods from plasma concentration data of LIXI, and were summarized by descriptive statistics. All data are presented as mean ± standard deviation unless otherwise stated.

**Results**

In the healthy study, all 20 participating subjects completed the study, with no study discontinuations; however, only 18 were included in the pharmacodynamic analysis as two subjects had incomplete pharmacodynamic profiles. In the T2DM study, 22 subjects were enroled and 20 subjects completed the planned study period. The two remaining subjects discontinued due to AEs, neither of which was considered to be related to study treatment.

Three participants who completed the T2DM study required intermediate low-dose iv infusions of insulin to stabilize glycaemic levels on the first study day that were discontinued 30 min prior to glucose challenge. Two of these participants randomized to the placebo–LIXI sequence also required stabilization on the second study day and therefore received insulin infusions matching day one to enhance comparability. These insulin infusions did not interfere with the response pattern as verified by strong individual differences in insulin responses to iv glucose following placebo and LIXI treatments.

**Pharmacodynamics – Fasting State**

People with T2DM presented with elevated FPG 180 min prior to LIXI or placebo administration – mean (s.d.) 7.51 (1.11) and 7.49 (0.92) mmol/l [135 (20) and 135 (17) mg/dl], respectively – which gradually decreased to 6.60 (0.69) and 6.65 (0.76) mmol/l [119 (12) and 120 (14) mg/dl] immediately prior to injection of medication. LIXI administration was associated with a small increase in fasting basal insulin secretion and INS, and a sizeable decrease in basal blood glucose levels in both HS and people with T2DM (Figure 1B, C). Both effects were short-lived in HS but were more sustained in T2DM, establishing euglycaemia prior to the iv glucose challenge. The resulting baseline FPG were 6.09 (0.68) mmol/l [110 (12) mg/dl] 120 min after placebo and 4.56 (0.97) mmol/l [82 (17) mg/dl] 120 min after LIXI in people with T2DM, and 4.97 (0.27) and 4.36 (0.25) mmol/l [90 (5) and 78 (5) mg/dl] in HS.

**Pharmacodynamics – iv Glucose Bolus**

Pharmacodynamic outcomes from both studies are shown in Table 1. Treatment with LIXI significantly increased first-phase insulin secretion (ISR-AUC\(_{0–10}\) min) by 2.4-fold (90% CI: 1.9–3.0) increase in glucose disposal rate (\(K_{\text{glucose}}\)) in both HS and in people with T2DM receiving LIXI (Figure 1B). A 2.3-fold (90% CI: 1.9–3.0) increase in \(K_{\text{glucose}}\) was seen in HS, and a 1.8-fold (90% CI: 1.6–1.9) increase was seen in people with T2DM treated with LIXI compared with placebo.

As a result of the increase in insulin secretion, INS-AUC\(_{10–120}\) min increased in both HS and in people with T2DM (Figure 1C). A 3.2-fold (90% CI: 2.7–3.8) increase was seen in HS compared with placebo and a 6.6-fold (90% CI: 5.0–8.7) increase was observed in people with T2DM compared with placebo. INS-AUC\(_{10–120}\) min was also significantly (p < 0.001) increased in both HS [3.4-fold increase (90% CI: 2.7–4.2]); p < 0.001] and people with T2DM [3.0-fold increase (90% CI: 2.7–3.3)]; p < 0.001].

In the study in people with T2DM, 15 completers were receiving metformin and five were treated with lifestyle modification alone, prior to the study. Of the 15 participants treated with metformin, seven were strong responders to LIXI (INS-AUC\(_{0–10}\) min > 3800 pmol/min/l), while only one participant who had previously been treated with lifestyle modification alone was identified as a strong responder. The baseline HbA1c of the metformin-treated strong responders was 44–53 mmol/mol (6.2–7.0%), and the baseline HbA1c of the lifestyle-treated strong responder was 48 mmol/mol (6.5%). The baseline HbA1c levels for the participants identified as weaker responders to LIXI (INS-AUC\(_{0–10}\) min < 2000 pmol/min/l) were 48–64 mmol/mol (6.5–8.0%).

The increase in insulin secretion was reflected in the C-PEP levels, with LIXI increasing first- and second-phase C-PEP parameters of maximum plasma concentration (\(C_{\text{max}}\), \(t_{\text{max}}\)) half-life (\(t_{1/2}\)), area under the curve at the last quantifiable time-point (LIXI-AUC\(_{\text{last}}\)) and LIXI-AUC were calculated using non-compartmental methods from plasma concentration data of LIXI, and were summarized by descriptive statistics. All data are presented as mean ± standard deviation unless otherwise stated.
Figure 1. Plots of mean values for (A) insulin secretion rate, (B) blood glucose concentration, (C) insulin concentration, (D) C-peptide concentration and (E) glucagon concentration, all during iv glucose challenge following injection of lixisenatide 20 μg or placebo. ISR, insulin secretion rate; HS, healthy subjects; T2, type 2 diabetes mellitus; SC, subcutaneous; IV, intravenous.
Table 1. Pharmacodynamic comparisons for lixisenatide versus placebo.

|                          | People with T2DM (n = 20) | Healthy subjects (n = 18) |
|--------------------------|---------------------------|--------------------------|
|                          | Placebo 20μg | Geometric mean ratio LIXI/PBO (90% CI) | Placebo 20μg | Geometric mean ratio LIXI/PBO (90% CI) |
| Insulin response         |              |                                      |              |                                      |
| ISR-AUC<sub>0–10min</sub>, pmol/kg | 48 (19) 133 (49) | 2.8 (2.5, 3.1) | 112 (30) 268 (78) | 2.4 (2.1, 2.6) |
| ISR-AUC<sub>10–120min</sub>, pmol/kg | 593 (158) 925 (210) | 1.6 (1.4, 1.7) | 370 (111) 341 (118) | 0.9 (0.8, 1.0) |
| INS-AUC<sub>0–10min</sub>, pmol min/l | 503 (385) 2835 (1778) | 6.6 (5.0, 8.7) | 2620 (1253) 8269 (3758) | 3.2 (2.7, 3.8) |
| INS-AUC<sub>10–120min</sub>, pmol min/l | 10 402 (5158) 31 602 (17 307) | 3.0 (2.7, 3.3) | 6371 (2327) 21 885 (8841) | 3.4 (2.7, 4.2) |
| C-peptide response       |              |                                      |              |                                      |
| C-PEP-AUC<sub>0–10min</sub>, pmol min/l | 1809 (1432) 7796 (3990) | 6.1 (4.2, 8.8) | 8661 (3406) 19 726 (6685) | 2.3 (2.0, 2.7) |
| C-PEP-AUC<sub>10–120min</sub>, pmol min/l | 81 555 (25 986) 167 725 (42 743) | 2.1 (1.9, 2.3) | 65 029 (20 726) 97 208 (24 885) | 1.5 (1.3, 1.7) |
| Glucose disposal         |              |                                      |              |                                      |
| Glucose disposal, K<sub>glucose</sub>, % per min | 0.57 (0.11) 0.98 (0.11) | 1.8 (1.6, 1.9) | 1.6 (0.8) 3.8 (1.8) | 2.3 (1.9, 3.0) |

All data are reported as arithmetic mean ± s.d. (standard deviation) unless otherwise stated. AUC, area under the curve; CI, confidence interval; ISR, insulin secretion rate; ISR-AUC<sub>0–10min</sub>, first-phase insulin secretion; ISR-AUC<sub>10–120min</sub>, second-phase insulin secretion; INS-AUC<sub>0–10min</sub>, first-phase insulin concentration; INS-AUC<sub>10–120min</sub>, second-phase insulin concentration; K<sub>glucose</sub>, glucose disposal constant; LIXI, lixisenatide; PBO, placebo; T2DM, type 2 diabetes mellitus.

levels in both HS and people with T2DM compared with placebo (Figure 1D).

In HS, the suppression of glucagon release was augmented following LIKI administration but returned to normal levels more rapidly than after placebo (Figure 1E). Glucagon levels are affected by both INS and blood glucose levels, and the drop in glucagon levels observed in HS is the result of a drop in blood glucose levels. Glucagon release recovered faster in the few participants with blood glucose levels <3.9 mmol/l (<70 mg/dl) attributable to normal feedback pathways. In the study in people with T2DM, glucagon suppression was not affected by LIKI.

Pharmacokinetics

The mean LIKI plasma concentration profile over time, following a single subcutaneous dose of LIKI 20μg in HS and people with T2DM, is shown in Figure 2 and Table 2. Maximum LIKI concentrations (C<sub>max</sub>) were achieved 2 h after a single 20μg LIKI injection in both people with T2DM and HS, and then declined with a similar mean (s.d.) half-life of 2.6 (0.7) and 2.1 (0.4) h, respectively. However, a greater peak plasma concentration was recorded in HS [LIKI-C<sub>max</sub>; mean (s.d.) 145 (63.6) pg/ml] compared with people with T2DM [LIKI-C<sub>max</sub>; mean (s.d.) 83.9 (21.3) pg/ml].

Safety and Tolerability

In the study in HS, 20 treatment-emergent adverse events (TEAEs) were reported by eight participants, seven (35%) while receiving LIKI and four (20%) while receiving placebo, with some participants experiencing TEAEs in both study arms; all were mild-to-moderate in intensity. The most frequent TEAEs with LIKI treatment were gastrointestinal, which were reported by five participants [nausea (n = 5), vomiting (n = 3), diarrhoea (n = 1)], followed by headache (n = 2).

Discussion

In this study, conducted under experimental conditions, a single dose of LIKI enhanced first-phase insulin secretion by 2.8-fold and second-phase insulin secretion by 1.6-fold in response to an iv glucose challenge in people with T2DM. This enhanced insulin secretion was seen to result in 6.6-fold elevated INS and an acceleration of glucose
Table 2. Pharmacokinetic characteristics of lixisenatide.

| Parameter mean (s.d.) | People with T2DM* | Healthy subject† |
|-----------------------|-------------------|-----------------|
| LIIXI-Cmax, pg/ml     | 83.9 (21.3)       | 145 (63.6)      |
| tmax, h†              | 2.0 (1.50–2.25)   | 2.0 (1.98–2.75) |
| t1/2x, h              | 2.6 (0.7)         | 2.1 (0.4)       |
| LIIXI-AUC0-last, pg h/ml | 449 (149)       | 611 (216)       |
| LIIXI-AUC0-last, pg h/ml | 529 (165)       | 661 (216)       |

LIXI-AUC, area under the curve extrapolated to infinity; LIIXI-AUC0, area under the curve at the last quantifiable time point; LIIXI-Cmax, maximum plasma concentration; s.d., standard deviation; T2DM, type 2 diabetes mellitus; tmax, time to LIIXI-Cmax; t1/2x, terminal plasma half-life (i.e. time from LIIXI-Cmax to half LIIXI-Cmax).

*Data are from 21 participants (one participant was excluded from AUC calculation owing to extrapolation > 30%).
†Median (interquartile range).

disposal comparable with that seen in HS on placebo, with $K_{glucose}$ increasing by 1.8-fold. The first-phase insulin secretion response in people with T2DM was comparable with that seen in HS receiving placebo. In HS, LIIXI also enhanced first-phase insulin secretion by 2.4-fold; first-phase INS was also higher by threefold and acceleration of glucose disposal was higher by 2.3-fold. However, the rise in second-phase insulin secretion was short lived and (in total) not increased, as insulin release rapidly ceased when blood glucose fell below baseline. Overall, these effects on insulin response are what would be predicted for a prandial GLP-1 receptor agonist based on previous studies with native GLP-1 or exenatide [1,12,22–30]. It is important to note, however, that this was an acute study and the effect of LIIXI on insulin secretion following longer-term use is not known.

The ability of LIIXI to resensitize glucose-dependent insulin release was observed in all people with T2DM. However, there was a trend observed for LIIXI to be more effective in those with modestly elevated HbA1c levels, indicative of the early stages of T2DM, compared with those with higher HbA1c levels. This is probably related to the greater insulin secretory capacity remaining in earlier disease stages.

Glucagon suppression was not affected in either patient population, with glucagon levels returning to normal more rapidly in HS after LIIXI than after placebo. It is likely that physiological counter-regulatory pathways are not affected by LIIXI, enabling the body to combat hypoglycaemia. The effect of LIIXI on glucagon suppression is consistent with observations from a previous 13-week study that showed enhanced suppression with LIIXI during the 4 h following a standardized meal test [31].

The iv glucose bolus coincided well with the maximum plasma concentrations of LIIXI, which occurred 2 h after subcutaneous injection of a 20 µg dose, and the terminal plasma half-life was similar between people with T2DM (2.6 h) and HS (2.1 h), which is consistent with a previous study using repeated dosing of LIIXI [32]. Higher maximum plasma concentrations of LIIXI were seen in HS compared with people with T2DM. This resulted in higher overall exposure to LIIXI in HS than in people with T2DM – reflecting the greater dose per body weight of 0.26 µg/kg in HS compared with 0.23 µg/kg in people with T2DM – yet indicates otherwise similar exposure profiles in people with T2DM and in HS.

The mechanism of action underlying the observed acute effects of LIIXI on insulin secretion probably involves direct stimulation of GLP-1 receptors located in the pancreatic islet β-cells, resensitizing the glucose concentration-dependent exocytotic release from insulin-secretory vesicles via a cyclic AMP-dependent signalling pathway [3,4,33]. Although the overall impact of GLP-1 receptor agonists on glycaemic control is likely to involve a multifactorial mechanism of action, with retardation of gastric emptying being predominant to the PPG-lowering efficacy of LIIXI, the acute effects on the insulin-secretory profile are likely to be highly relevant as they mark restoration of glucose-sensitive stimulation of insulin secretion [3,4,34–36].

At least in its early stages, T2DM is characterized by fasting hyperglycaemia despite hyperinsulinaemia and relative hyperglucagonaemia, all of which were present in people with T2DM. The sustained lowering of blood glucose from hyperglycaemic levels to those of HS after injection of LIIXI, and prior to the iv glucose challenge, which is not seen in subjects treated with placebo, is indicative of resensitizing glucose-sensitive insulin release and readjusting glucohomeostasis. This effect on fasting hyperglycaemia is effective on its own and adds to the accelerated PPG disposal. The corresponding effect in HS was short lived, which could be explained by intact glucohomeostatic regulation.

In conclusion, LIIXI resensitized the insulin response to an iv glucose challenge in people with T2DM, thereby accelerating glucose disposal to nearly physiological intensities, and did not impair counter-regulation to low glucose by glucagon. The first-phase insulin secretion response in people with T2DM was comparable with that seen in HS receiving placebo.

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Conflict of Interest

R. H. A. B. initiated the investigation, supervised the clinical part in subjects with type 2 diabetes, pooled the information, contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. R. H. A. B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J. S. joint supervised the investigation, supervised the clinical part in HS, contributed to the discussion, and reviewed and edited the manuscript. J. M. researched and deconvoluted the data, conducted the statistical evaluations and contributed to the discussion. C.
K. headed the clinical part and reviewed and edited the manuscript.

R. H. A. B., J. S. and J. M. are employees of Sanofi. C. K. is managing director and co-owner of Profil and has received honoraria from Sanofi.

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