



Acute Administration of the GLP-1 Receptor Agonist Lixisenatide Diminishes Postprandial Insulin Secretion in Healthy Subjects But Not in Type 2 Diabetes, Associated with Slowing of Gastric Emptying

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ABSTRACT

Introduction: It is uncertain whether lixisenatide has postprandial insulinotropic effects when its effect on slowing gastric emptying is considered, in healthy subjects and type 2 diabetes mellitus (T2DM). We evaluated the effects of single administration of 10 µg sc lixisenatide on glycaemia, insulin secretion and gastric emptying (GE), measured using the ‘gold standard’ technique of scintigraphy following an oral glucose load (75 g glucose).

Methods: Fifteen healthy subjects (nine men, six women; age 67.2 ± 2.3 years) and 15

patients with T2DM (nine men, six women; age 61.9 ± 2.3 years) had measurements of GE, plasma glucose, insulin and C-peptide for 180 min after a radiolabeled 75 g glucose drink on two separate days. All subjects received lixisenatide (10 µg sc) or placebo in a randomised, double-blind, crossover fashion 30 min before the drink. Insulin secretory response (ISR) was determined using the C-peptide deconvolution method.

Results: GE was markedly slowed by lixisenatide compared with placebo in both healthy subjects (1.45 ± 0.10 kcal/min for placebo vs. 0.60 ± 0.14 kcal/min for lixisenatide) and diabetes (1.57 ± 0.06 kcal/min for placebo vs. 0.75 ± 0.13 kcal/min for lixisenatide) (both $P < 0.001$) with no difference between the two groups ($P = 0.42$). There was a moderate to strong inverse correlation between the early insulin secretory response calculated at 60 min and gastric retention at 60 min with lixisenatide treatment in healthy subjects ($r = -0.8$, $P = 0.0003$) and a trend in type 2 diabetes ($r = -0.4$, $P = \text{NS}$), compared with no relationships in the placebo arms ($r = -0.02$, $P = \text{NS}$, healthy subjects) and ($r = -0.16$, $P = \text{NS}$, type 2 diabetes).

Conclusion: The marked slowing of GE of glucose induced by lixisenatide is associated with attenuation in the rise of postprandial glucose in both healthy subjects and diabetes and early insulin secretory response in healthy subjects.

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Key Summary Points

It is now appreciated that the predominant mechanism of glucose lowering of 'short-acting' GLP-1 receptor agonist like lixisenatide is by slowing gastric emptying.

We hypothesized that lixisenatide would attenuate, rather than augment, early postprandial insulin secretory response in healthy subjects as is commonly believed.

We found that glucose lowering by lixisenatide is associated with a reduction in C-peptide and a reduced insulin secretory response, in healthy subjects, related to the slowing of gastric emptying.

INTRODUCTION

Glucagon-like peptide 1 (GLP-1)-based therapy, particularly with GLP-1 receptor agonists (GLP-1RAs), is widely used in the management of type 2 diabetes mellitus (T2DM). While the glucose-dependent insulinotropic and glucagonostatic effects of GLP-1 are well characterised, intravenous administration of GLP-1 also slows gastric emptying markedly and, at least after acute administration in healthy individuals, postprandial insulin levels are reduced, suggesting that slowing gastric emptying may represent the dominant mechanism underlying glucose lowering [1]. Lixisenatide is administered as a 'once-a-day' formulation, both as monotherapy and in combination with insulin glargine. We recently reported that acute administration of lixisenatide (10 µg), in both healthy subjects and T2DM, is associated with a reduction in postprandial glycaemia and a marked retardation of

gastric emptying using the 'gold standard' technique, scintigraphy [2]. It is also known that the effect of lixisenatide on gastric emptying in T2DM is sustained with chronic administration [3]. However, it is uncertain whether lixisenatide has insulinotropic effects postprandially in either T2DM or healthy subjects when changes in gastric emptying are considered. We evaluated the acute effect of lixisenatide on the insulin secretory response (ISR) following an oral glucose load (75 g glucose) in healthy subjects and T2DM.

METHODS

The data presented in this manuscript represent a secondary analysis from an original study evaluating the effect of lixisenatide on gastric emptying and blood pressure, in which power calculations were derived with systolic blood pressure as the primary outcome measure [2]. The study protocol and measurements have been described previously [2]. Fifteen healthy volunteers (nine men/six women; age 67.2 ± 2.3 years) and 15 people with T2DM (nine men/six women; age 61.9 ± 2.3 years, BMI 30.3 ± 0.7 kg/m², duration of known diabetes 5.3 ± 1.2 years, HbA1c 51.8 ± 2.3 mmol/mol [$6.9 \pm 0.2\%$]) underwent concurrent measurements of gastric emptying, and plasma glucose, insulin and C-peptide for 180 min after a radio-labelled 75 g glucose drink on two separate days. On each day, participants attended the laboratory at approximately 0830 hours after an overnight fast and were given a subcutaneous injection of lixisenatide (10 µg) or matching placebo (Sanofi Aventis Deutschland, Industriepark, Höchst, Frankfurt, Germany) in randomised order approximately 30 min prior to ingestion of the drink. $T = 0$ min was defined as the time of drink completion. The ISR (0–180 min) was calculated by C-peptide deconvolution [4]. The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, and each participant provided written, informed consent. Data are presented as mean \pm standard error of the mean (SEM). A P value less than 0.05 was considered significant in all analyses.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Central Adelaide Local Health Network Ethics Committee, Australia.

RESULTS

As reported [2], gastric emptying data were unavailable in one of the healthy subjects. Gastric emptying (% retention) was markedly slowed by lixisenatide in both healthy volunteers (placebo 1.45 ± 0.10 kcal/min, lixisenatide 0.60 ± 0.14 kcal/min, $P < 0.001$) and T2DM (placebo 1.57 ± 0.06 kcal/min, lixisenatide 0.75 ± 0.13 kcal/min, $P < 0.001$) with no difference between the two ($P = 0.42$).

The $AUC_{0-180\text{min}}$ for plasma glucose was markedly reduced by lixisenatide in both healthy subjects and T2DM ($P < 0.001$). The $AUC_{0-180\text{min}}$ for plasma insulin ($P = 0.02$) and the $AUC_{0-180\text{min}}$ for plasma C-peptide ($P = 0.001$) were less after lixisenatide compared to placebo in both groups.

The $ISR_{0-180\text{min}}$ was reduced by lixisenatide in healthy subjects (placebo $42,440 \pm 4876$ nmol/m², lixisenatide $26,431 \pm 3983$ nmol/m², $P = 0.01$) but not in T2DM (placebo $50,036 \pm 5353$ nmol/m², lixisenatide $42,786 \pm 5566$ nmol/m², $P = 0.30$). After administration of lixisenatide, there was a moderate to strong inverse relationship between $ISR_{0-60\text{min}}$ and intragastric retention at 60 min in healthy subjects ($r = -0.80$, $P = 0.0003$) and a non-significant trend in T2DM ($r = -0.40$, $P = 0.10$), but no significant relationships in the placebo arms for either healthy subjects ($r = -0.02$, $P = \text{NS}$) or T2DM ($r = -0.16$, $P = \text{NS}$); Fig. 1.

DISCUSSION

We have shown that glucose-lowering and slowing of gastric emptying following an oral glucose load by a single dose of lixisenatide is associated with (i) a reduction in plasma insulin and C-peptide concentrations in both healthy

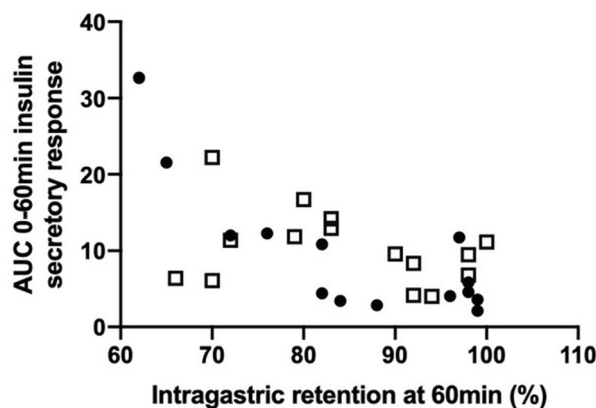


Fig. 1 Relationship between calculated insulin secretory response at 60 min (AUC 0–60) and gastric emptying of a 75-g glucose drink following lixisenatide administration in healthy participants (filled black circles, $r = -0.80$, $P < 0.001$; $n = 14$) and participants with type 2 diabetes (unfilled squares, $r = -0.40$, $P = 0.10$; $n = 15$)

subjects and T2DM, and (ii) a reduction in insulin secretion in healthy subjects which is related to the magnitude of slowing of gastric emptying. Gastric emptying is now appreciated to be a major determinant of postprandial glycaemia in healthy subjects and T2DM, such that relatively more rapid gastric emptying is associated with a greater initial postprandial glycaemic excursion. Accordingly, short-acting GLP-1RAs, such as lixisenatide and exenatide BD, diminish postprandial glycaemia, at least in part, by slowing gastric emptying [5]. As reported, plasma insulin and C-peptide were diminished, rather than elevated, when plasma glucose was lowered with lixisenatide [2], translating into a statistically significant reduction in the insulin secretory response in healthy subjects. We recently reported [3] that slowing of gastric emptying was associated with a reduction in the postprandial C-peptide response following 8 weeks' administration of lixisenatide in T2DM, without a significant reduction in the insulin secretory response. Accordingly, it appears that glucose lowering by lixisenatide is not always by stimulating insulin secretion postprandially in either healthy subjects or T2DM. That insulin secretion was suppressed in healthy subjects but not significantly

in T2DM is likely to reflect the more effective blood glucose counter-regulation, particularly beta cell sensitivity, in healthy subjects. The observation that insulin secretion after lixisenatide was significantly less when the slowing of gastric emptying was more marked in healthy subjects, and tended to be less in T2DM, attests to the importance of gastric emptying as a determinant of postprandial glycaemia. The relationship of postprandial glycaemia with gastric emptying appears to be non-linear [5]. Accordingly, it is possible that acute administration of lixisenatide, by slowing gastric emptying, induces 'beta cell rest' which would, intuitively, benefit long-term beta cell function. This hypothesis warrants further evaluation.

Our study has some limitations. First, we employed half the recommended clinical dose of 20 µg lixisenatide to reduce the potential for gastrointestinal adverse effects and only evaluated the effects of acute administration. Thus, 20 µg lixisenatide may potentially slow gastric emptying more; the slowing of gastric emptying by the 10-µg dose was profound but, as shown, the variability in slowing of emptying between individuals impacted on insulin secretion. Second, we employed a 75-g glucose drink as the test 'meal' rather than a physiological meal, since this was a 'proof-of-principle' study, and also because 75 g of glucose is traditionally used to determine glucose tolerance. Finally, we studied only well-controlled T2DM.

CONCLUSIONS

To summarise, plasma glucose-lowering induced by acute administration of lixisenatide is associated with a reduction in C-peptide and, at least in healthy subjects, a reduced insulin secretory response. The latter is related to the magnitude of slowing of gastric emptying.

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Author Contributions. C.S.M. was involved in data analysis and interpretation, statistical analysis and writing of the manuscript. H.P. and L.G.T. assisted with data collection and were involved in data interpretation. R.S.R. and S.H. were involved in subject recruitment, data collection and data interpretation. M.D.M.B. and S.H. were involved in scintigraphic data analysis. K.L. performed the statistical analysis and was involved in data interpretation. M.H., C.K.R. and T.W. were involved in the conception and design of the study and data interpretation. All authors critically reviewed the manuscript and have approved the publication of this final version of the manuscript. K.L.J. was involved in the conception, design, and coordination of the study, data interpretation, K.L.J. and M.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with Ethics Guidelines. This study was performed in line with the principles

of the Declaration of Helsinki. Approval was granted by the Central Adelaide Local Health Network Ethics Committee, Australia. Informed consent was obtained from all individual participants included in the study.

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Data Availability. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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