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Effects of lixisenatide once daily on gastric emptying in type 2 diabetes — Relationship to postprandial glycemia

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ABSTRACT

Objectives: To determine the effects of lixisenatide, a new once-daily (QD) glucagon-like peptide-1 receptor agonist, on postprandial glucose (PPG) and gastric emptying, and the relationship between these effects in patients with type 2 diabetes mellitus (T2DM).
Methods: Data were obtained from a randomized, double-blind, placebo-controlled, parallel-group study with treatment duration of 28 days in patients with T2DM receiving ≤2 oral antidiabetic drugs. Lixisenatide was injected subcutaneously using an ascending dose range (5–20 μg) increased every fifth day in increments of 2.5 μg. Blood glucose was determined before and after three standardized meals (breakfast, lunch, and dinner). Gastric emptying of the standardized breakfast was determined by a ^{13}C-octanoic acid breath test at baseline (Day−1) and at Day 28.
Results: A total of 21 and 22 patients were randomized to lixisenatide 20 μg QD and placebo, respectively. With lixisenatide 20 μg QD, there was a reduction in PPG when compared with placebo after breakfast ($p < 0.0001$), lunch ($p < 0.001$) and dinner ($p < 0.05$). Hence, lixisenatide 20 μg administered in the morning exhibited a pharmacodynamic effect on blood glucose throughout the day. Gastric emptying (50% emptying time) increased substantially from baseline with lixisenatide 20 μg QD, but not with placebo (change from baseline ± SD: −24.1 ± 133.1 min for placebo and 211.5 ± 278.5 min for lixisenatide; $p < 0.01$). There was an inverse relationship between PPG area under the curve after breakfast and gastric emptying with lixisenatide 20 μg QD ($n = 17$, $r^2 = 0.51$, $p < 0.05$), but not with placebo.
Conclusions: In this study, lixisenatide at a dose of 20 μg QD reduced postprandial glycemic excursions in patients with T2DM, possibly as a result of sustained slowing of gastric emptying.

1. Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists are now used widely in the management of type 2 diabetes (T2DM) [1]. These agents have beneficial effects on both fasting and postprandial glycemia, with concomitant improvements in 'average' glycemic control, as assessed by glycated hemoglobin (HbA_{1c}) [1–4]. As a class, GLP-1 receptor agonists are known to simultaneously stimulate insulin secretion in a glucose-dependent manner and suppress glucagon release [1–3]. This glucose dependency means that, unlike with insulin or insulin secretagogues (sulfonylurea) therapy, the risk of hypoglycemia is low. Moreover, the use of GLP-1 agonists is associated with weight loss, rather than the weight gain that is often observed with insulin therapy.

There are substantial differences between GLP-1 receptor agonists (currently available or in development) in terms of their duration of action and propensity for gastrointestinal effects following subcutaneous administration [3]. GLP-1 receptor agonists do not improve glycemia solely as a result of their effect on islet cell function in that they also slow gastric emptying [4,5]. The latter is known to be an important determinant of postprandial glycemic excursions in healthy individuals [6] and in patients with T2DM [7,8]. Slowing gastric emptying prolongs absorption of meal-derived glucose and has the capacity to blunt postprandial glucose (PPG) excursions [8,9]. The rate of gastric emptying varies widely between healthy individuals [10], and in patients with long-standing T2DM there is a high prevalence of delayed, and occasionally more rapid, gastric emptying, so that the inter-individual variation is even greater among these patients [11]. Importantly, the effects of exogenous GLP-1 on PPG and insulin appear to be related to the magnitude of slowing of gastric emptying [9,12,13]. Moreover, this slowing is dependent on the baseline rate of gastric emptying, so that when emptying is already slow, GLP-1 has little, if any, effect [9,12]. A recent study suggests that there may be rapid tachyphylaxis to the slowing

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of gastric emptying by exogenous GLP-1 [14]. When two standardized liquid test meals were given to healthy subjects at an interval of 4 h during a continuous, intravenous GLP-1 infusion, GLP-1 delayed emptying of both drinks substantially, but the magnitude of this slowing was less with the second drink [14]. There is evidence for tachyphylaxis of the slowing of gastric emptying with marketed longer-acting GLP-1 receptor agonists, liraglutide once-daily (QD) and exenatide once-weekly (LAR); this is not observed with the shorter-acting agent exenatide twice-daily (BID) [5,15,16]. Hence, there appear to be substantial differences between GLP-1 receptor agonists regarding their effect on gastric emptying, which is relevant to their impact on HbA_{1c} and, particularly, postprandial glycemia.

Lixisenatide is a new once-daily GLP-1 receptor agonist. In a dose-ranging study in patients with T2DM inadequately controlled with metformin, lixisenatide at a dose of 20 μg QD demonstrated the best efficacy-to-tolerability ratio [17]. Lixisenatide has demonstrated efficacy as monotherapy, in combination with oral antidiabetic drugs, and as add-on to basal insulin, with particular efficacy in reducing PPG excursions [18–26]. On February 1st 2013, the European Commission granted Marketing Authorization in Europe for lixisenatide for the treatment of adults with T2DM [27].

The objective of the current analysis was to determine the effects of lixisenatide 20 μg QD administered for 28 days on the blood glucose response to a standardized breakfast, lunch, and dinner, and evaluate the relationship between the effects of lixisenatide on postprandial blood glucose with those on gastric emptying in patients with T2DM.

2. Materials and methods

Presented data were derived from study ACT6011, which was a randomized, placebo-controlled, double-blind, parallel-group design study with a 28-day treatment duration, involving three centers in South Africa. The study was approved by the relevant institutional review boards or ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent prior to their participation. Safety and tolerability were monitored throughout the study. Adverse events reported spontaneously by the subject or observed by the investigator were recorded.

2.1. Study objectives

The objectives of this study were to assess the effect of lixisenatide on postprandial blood glucose after a standardized breakfast, lunch, and dinner, and on gastric emptying, C-peptide, serum insulin and glucagon concentration after a standardized breakfast, fasting blood glucose (FBG), HbA_{1c}, as well as safety and tolerability. The relationship between the change in area under the curve (AUC) for PPG and half-life of gastric emptying were assessed in a post-hoc linear regression analysis.

2.2. Patients

Males and females, 18–70 years old, body mass index (BMI) $\leq$35 kg/m^2, with stable T2DM treated with up to two oral antidiabetic drugs (metformin and/or sulfonylurea) under routine care of a physician for diabetes, with a stable diabetic prescription history (i.e. within the previous 3 months and including adherence to 'reasonable' dietary guidelines), reasonable glucose control and HbA_{1c} $\geq$7.0% and $\leq$10.0% were eligible for inclusion. Exclusion criteria included: evidence or history of renal, hepatic or cardiovascular disease, pancreatitis, gastric surgery, clinically relevant gastrointestinal disease (including known gastroparesis), previous exposure to GLP-1 receptor agonists, insulin use within the preceding 3 months, use of thiazolidinediones or drugs potentially affecting either insulin secretion or gastrointestinal motility (except beta-blockers and sulfonylureas).

2.3. Protocol

Data were derived from participants (hospitalized from the evening of Day−2 to the morning of Day 29) randomized to subcutaneous once-daily lixisenatide or placebo administered in the morning on Days 1 to 28. An additional lixisenatide twice-daily (morning and evening) treatment arm was included in the original study but these data were not included in the current analysis, given that lixisenatide 20 μg QD has been subsequently demonstrated to provide the best efficacy-to-tolerability ratio [17]. Lixisenatide was injected at an initial dose of 5 μg QD and the dose per injection was increased in increments of 2.5 μg every fifth day, to a maximum level of 20 μg QD, administered during the last 4 days (Days 25 to 28). Injections were administered subcutaneously in the morning 15 min before breakfast. Reduction from a given dose level was considered following two or more episodes of vomiting on >2 consecutive days; and/or two or more episodes of marked nausea (of severe intensity for >2 h) on >2 consecutive days. In each subject, decisions relating to dose progression were made by an investigator based on evaluation of blinded safety and tolerability data.

Each subject received three standardized test meals (breakfast, lunch and dinner) on Day−1 (1 day prior to study treatment) and on Day 28. The caloric content of each meal was ~450 kcal with 50% energy as carbohydrate, 23% as fat and 27% as protein. For the determination of gastric emptying rate, ^{13}C-octanoic acid was added to the breakfast meal, as described below. Time zero was considered to be the beginning of the breakfast meal, which was consumed in 10 min. Blood glucose was determined at pre-specified time points with 24-hour profiling.

2.4. Assessments

At baseline, Day−1 and on the fourth day of each dose level, venous blood samples were collected at pre-specified times for measurement of blood glucose before and after the standardized breakfast, lunch and dinner. Blood glucose was determined at the bedside with a Yellow Springs Instruments 2300S glucose analyzer using the glucose oxidase method. Serum samples were analyzed for insulin and C-peptide concentration using radioimmunoassay methods (Linco Research Inc.). HbA_{1c} was analyzed using an immunological assay (Tina-quant® Hemoglobin A1C II, Roche Diagnostics, Germany). Change in HbA_{1c} was recorded from baseline to Day 29.

PPG–AUCs were calculated as the area under the time–concentration curve from 0:14 h after the morning injection, just before breakfast, until 4:55 h after the morning injection ($PPG–AUC_{breakfast}$), from 5:14 h after the morning injection (just before lunch) until 4:55 h after lunch ($PPG–AUC_{lunch}$) and from 10:14 h after the morning injection (just before dinner) until 4:55 h after dinner ($PPG–AUC_{dinner}$). Blood samples for determination of C-peptide, insulin and glucagon were collected on Day−1 and Day 28 after a standardized breakfast and were analyzed as the area under the time–concentration curve from 0:14 until 4:55 h (AUC) relative to the pre-breakfast value.

2.5. Gastric emptying

Gastric emptying at breakfast was determined by a ^{13}C-octanoic acid breath test [28] on Days−1 and 28. Patients received a standardized breakfast consisting of a scrambled egg with the yolk infused with 100 mg of ^{13}C-octanoic acid (manufacturer: Euriso-Top, France). The yolk and egg white were cooked separately, but administered together with two-and-a-quarter slices of white bread, 45 g low-fat cottage cheese, one teaspoon of margarine, a quarter teaspoon mayonnaise or olive oil, 100 g fruit yoghurt, and one apple or peach, followed immediately by 150 mL of non-sparkling water. The meal was consumed in less