Subcutaneous Infusion of GLP-1 for 7 Days Improves Glycemic Control Over a Broad Dose Range in Patients with Type 2 Diabetes

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INTRODUCTION

Glucagon-like peptide-1 (7-36) amide (GLP-1) and its analogs are a new class of type 2 diabetes drugs that potentiate glucose-dependent insulin secretion, suppress glucagon release, and exert trophic effects on pancreatic b-cells (1,2). GLP-1 is a peptide hormone secreted by L-cells within the intestinal mucosa in response to food intake (Fig. 1). GLP-1 contributes to the incretin effect, the augmentation of glucose-stimulated insulin secretion after ingestion of a meal (3). GLP-1 also inhibits gastric emptying and reduces appetite and food intake. Importantly, GLP-1 has been shown to stimulate the growth and differentiation of pancreatic β-cells in tissue culture and in animal models of diabetes (4). Some studies have also suggested that GLP-1 may improve insulin sensitivity or increase glucose effectiveness (5,6) (Fig. 2).

The GLP-1 analog Exenatide (exendin-4) was recently approved for the treatment of type 2 diabetes and several other GLP-1 analogs are currently in clinical development (7-10). The optimal therapeutic effect of GLP-1 is achieved with regimens that provide sustained plasma levels of active peptide (11,12). Such regimens include continuous subcutaneous infusion (CSCI) of GLP-1 (7-36 amide) (13-15), and once or twice daily injections of GLP-1 analogs with extended plasma stability (7-10).

Data on the dose-response range for GLP-1 administered by CSCI are sparse. In the present study, we compared the safety and efficacy of four doses of recombinant GLP-1, ranging from 1.25-8.5 pmol/kg/min, given by CSCI over 7 days, to lower fasting, postprandial, and 11-hour serum glucose profiles in subjects with type 2 diabetes.

Figure 1: GLP-1 and the Incretin Axis

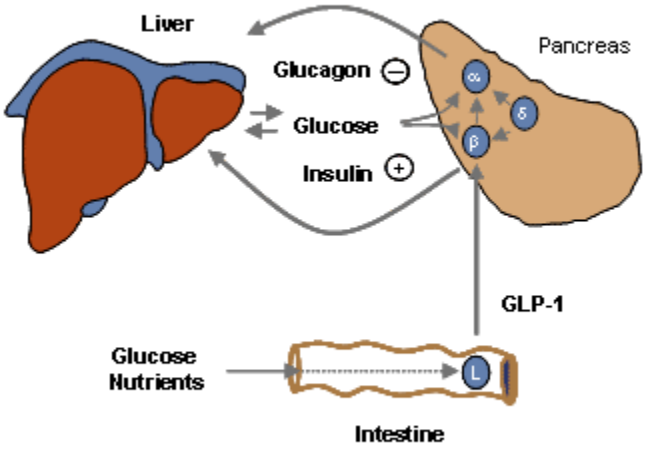
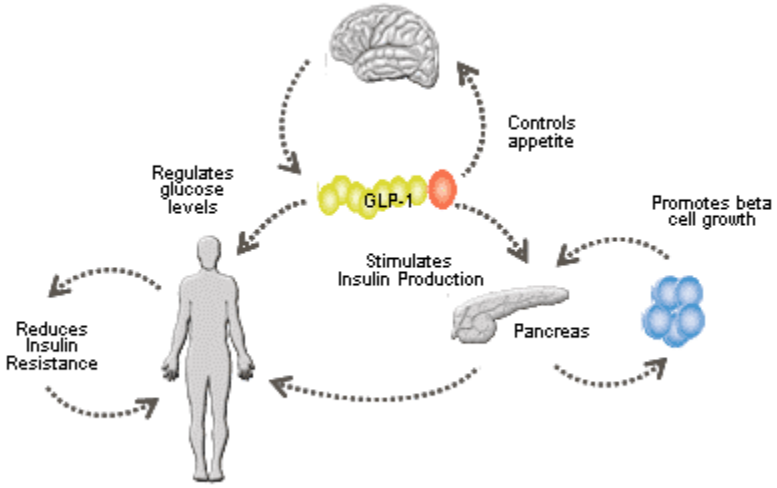


Figure 2: GLP-1 Key Regulating Peptide in Glucose Metabolism



METHODS

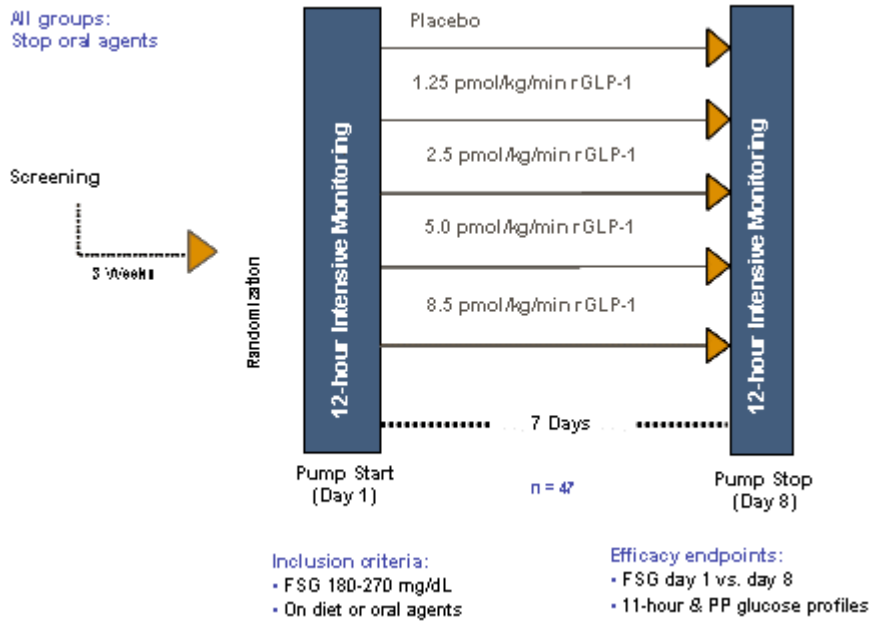
Subjects
Forty-seven subjects with established type 2 diabetes treated by diet, sulfonylurea, metformin, or acarbose, and mean fasting serum glucose (FSG) in the range 180-270 mg/dL, were enrolled in the study. The subjects had a mean (± SD) age of 53.5 ± 9 years, BMI of 31.5 ± 5.1 kg/m2, weight of 196.2 ± 30.3 pounds, and HbA1c of 8.56 ± 0.98%.

Study medication
Recombinant human GLP-1 (7-36) amide (rGLP-1) was produced by Restoragen, Inc. (Lincoln, NE). The formulated peptide was vialed by SP Pharmaceuticals (Albuquerque, NM) at a concentration of 1.0 mg/mL in

a mannitol/acetic acid solution. Placebo consisted of the identical mannitol/acetic acid vehicle but without rGLP-1 peptide.

Study Design and Procedures

The study was a randomized, double-blind, parallel-group, placebo-controlled trial. During a 3-week screening period all oral hypoglycemic agents were discontinued and patients whose mean weekly FSG was 180-270 mg/dL were then randomized into the 8-day study period in which patients received placebo or one of four doses of GLP-1 (1.25, 2.5, 5.0, and 8.5 pmol/kg/min) by CSCI (Fig. 3).



On day 1, after an overnight fast, patients remained in the clinic for 12 hours of intensive monitoring, including frequent blood sampling after a Sustacal HP meal (8:00 a.m.), a standard lunch (12:00 noon), and a standard dinner (5:00 p.m.). Samples were analyzed for serum glucose, insulin, glucagon, and GLP-1 levels; C-peptide and free fatty acid (FFA) levels were determined at fasting only. After the last blood draw (7:00 p.m.), patients were equipped with a mini-pump (Panomat Infusion Pump, Disetronic Medical Systems, Inc.), infusion of placebo or GLP-1 was commenced, and patients were discharged. On days 2-7, patients returned to the clinic every morning for determination of fasting serum glucose, insulin, glucagon, FFAs, and GLP-1 levels. On day 8, patients were again intensively monitored, except that infusion of placebo or GLP-1 was continued throughout and stopped at 7:00 p.m. Efficacy tests (glucose, glucagon, insulin, C-peptide, FFAs, fructosamine, HbA1c) were performed by Pacific Biometrics, Inc. (Seattle, WA), and plasma GLP-1 levels were measured by LINCO Research, Inc. (St. Charles, MO), using an RIA for total GLP-1.

Statistical analysis

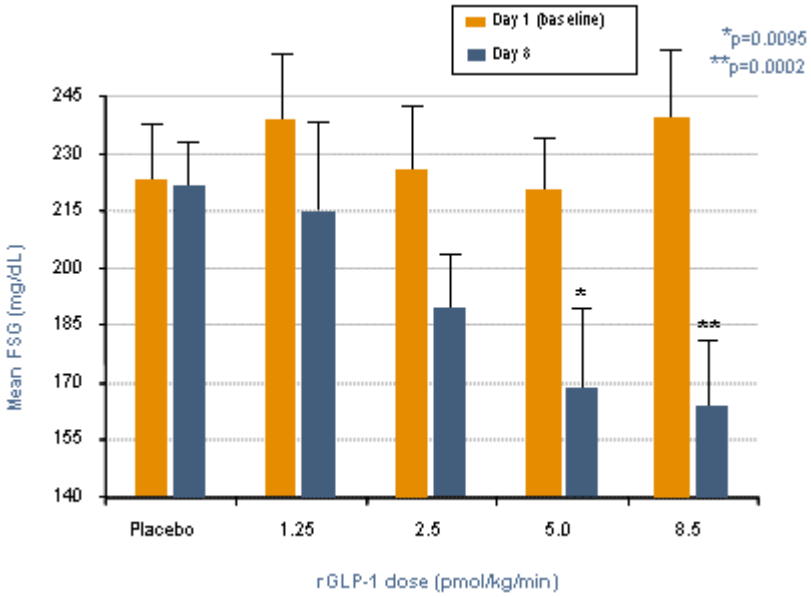
Fasting and postprandial serum glucose levels were analyzed using analysis of variance (ANOVA) with dose as the main factor; generally, the difference between day 1 and day 8 was assessed. Wilks-Shapiro test was used to test for normality of the primary endpoint (FSG) dataset, and Dunnett's t-test (one-tailed) to control for multiple comparisons.

RESULTS

Fasting serum glucose

rGLP-1 administered by CSCI dose-dependently reduced fasting serum glucose (FSG) on day 8 versus day 1 when compared to placebo (Fig. 4). At the highest dose, FSG was reduced by 32%, from 240.4 ± 36.6 mg/dL on day 1 to 164.2 ± 35.7 mg/dL on day 8.

Figure 4: Fasting Serum Glucose



Eleven-hour and postprandial serum glucose profiles

Eleven-hour glucose profiles (starting 15 min before the Sustacal meal at 8:00 AM and ending at 7:00 PM) determined on day 1 and day 8 revealed dose-dependent reductions (Fig. 5). After the Sustacal meal, peak serum glucose values were reduced by 18.6% (p=0.0132) and 33.3% (p=0.0001) in the 5.0 and 8.5 pmol/kg/min dose groups, respectively, and incremental AUCs (8:00-10:00 AM) were reduced by 25.4% (p=0.041) and 34.1% (p=0.0026) (Fig. 6). The 11-hour serum glucose AUCs were reduced by 16.9% (p=0.012), 23.3% (p=0.0019), and 36.3% (p=0.0001) in the 2.5, 5.0, and 8.5 pmol/kg/min dose groups (Fig. 7).

Figure 5: 11-Hour Glucose Profiles

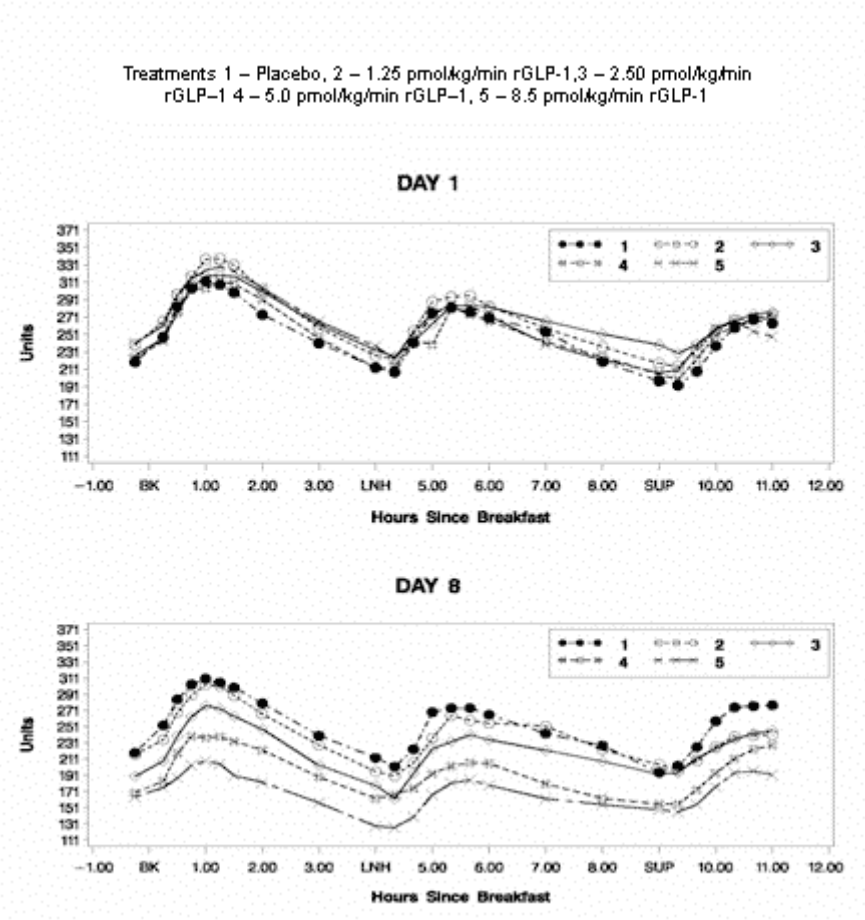


Figure 6: Post-prandial Glycemia

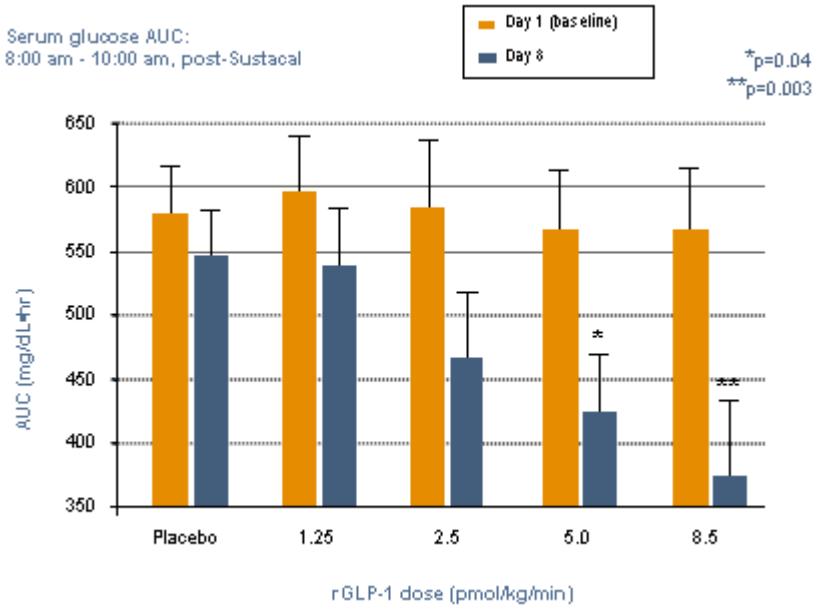
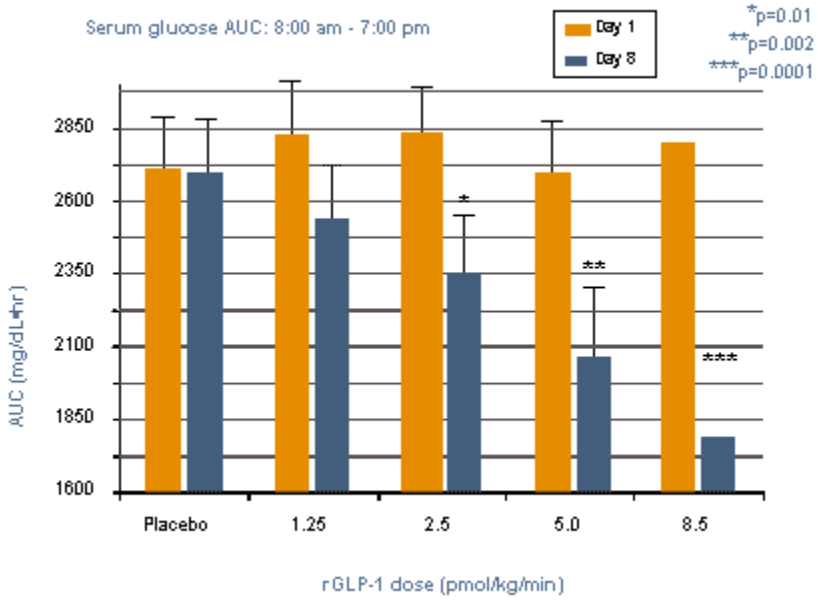


Figure 7: 11-hour Integrated Glycemia



Fasting hormone and FFA levels

Treatment with rGLP-1 did not significantly change fasting insulin, glucagon, or FFA levels when compared to placebo. However, fasting insulin levels did not decline despite an up to 32% decrease in FSG; in fact, at the 8.5 pmol/kg/min dose, there was a numerical increase of 31% in fasting insulin, suggesting a relative increase in insulin secretion (Fig. 8). Similarly, fasting C-peptide levels revealed a dose-dependent increase of up to 39% at the highest dose (Fig. 8). As expected, fasting GLP-1 levels were unchanged in the placebo group, but increased 4.0 x, 3.8 x, 6.5 x, and 7.0 x in the 1.25, 2.5, 5.0, and 8.5 pmol/kg/min dose groups, respectively (Fig. 9).

Figure 8: Changes in Fasting Hormones

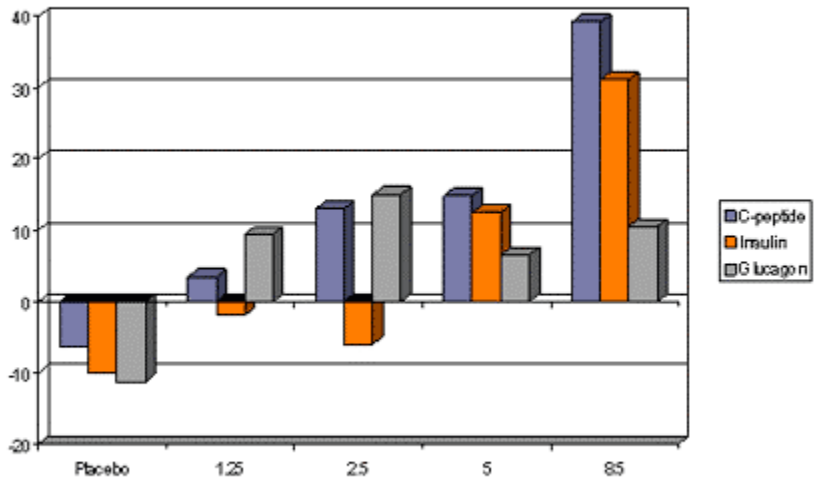
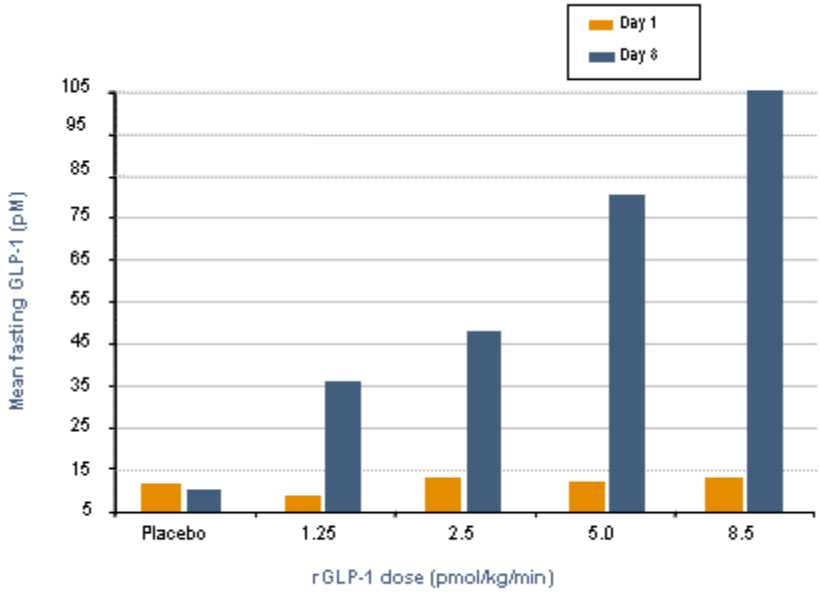


Figure 9: Changes in Fasting Hormones



CONCLUSIONS

GLP-1 and its analogs are promising drugs for the treatment of type 2 diabetes, but questions remain about the optimal dose and mode of administration of these peptides (16). Our results indicate that rGLP-1 administered by CSCI for 7 days decreased serum glucose across a broad dose range. We found no evidence for a flattening of the dose response from 4.5 to 8.5 pmol/kg/min. The 8.5 pmol/kg/min dose was substantially more effective than the 4.5 pmol/kg/min dose in terms of all parameters of glycemic control that were studied (Figs. 3-7). Thus, higher doses of GLP-1 by CSCI may be effective in poorly controlled type 2 diabetics.

However, the 8.5 pmol/kg/min dose elicited the highest incidence of gastrointestinal AEs, which may be dose-limiting. Interestingly, even at the highest dose, the GI events occurred during the first 48-72 hours and then spontaneously abated, suggesting a form of tachyphylaxis of the GI effects of GLP-1; this has also been noted with exenatide and liraglutide (8,10). It might therefore be possible to titrate patients to a higher dose over a period of days or weeks, thereby limiting the GI effects.

Insulin and glucagon levels were not significantly different from the placebo group. However, for insulin this reflects a substantial relative increase because mean serum glucose levels decreased by up to 36%, concordant with previous results (10,14). There was also a relative suppression of glucagon, since hyperglycemia per se inhibits glucagon secretion and glucagon levels were unchanged in the rGLP-1-treated patients despite substantial reductions in glycemia.

No instances of hypoglycemia were recorded. The insulinotropic action of GLP-1 is glucose dependent, but concurrent treatment with oral agents, such as sulfonylureas and metformin, has resulted in episodes of mild-to-moderate hypoglycemia (8,15).

In summary, the 7-day administration of recombinant GLP-1 (7-36) amide by CSCI significantly reduced mean fasting, postprandial, and 11-hour serum glucose levels in type 2 diabetic patients. Administration of rGLP-1 by CSCI was effective over a broad dose range, with no evidence of tachyphylaxis or a flat dose-response curve, and treatment was safe and generally well tolerated.

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