The Role of Adjunctive Exenatide Therapy in Pediatric Type 1 Diabetes

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OBJECTIVE — Exenatide improves postprandial glycemic excursions in type 2 diabetes. Exenatide could benefit type 1 diabetes as well. We aimed to determine an effective and safe glucose-lowering adjuvant exenatide dose in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Eight subjects completed a three-part double-blinded randomized controlled study of premeal exenatide. Two doses of exenatide (1.25 and 2.5 μg) were compared with insulin monotherapy. Prandial insulin dose was reduced by 20%. Gastric emptying and hormones were analyzed for 300 min postmeal.

RESULTS — Treatment with both doses of exenatide versus insulin monotherapy significantly reduced glucose excursions over 300 min ($P < 0.0001$). Exenatide administration failed to suppress glucagon but delayed gastric emptying ($P < 0.004$).

CONCLUSIONS — Adjunctive exenatide therapy reduces postprandial hyperglycemia in adolescents with type 1 diabetes. This reduction in glucose excursion occurs despite reduction in insulin dose. We suggest that exenatide has therapeutic potential as adjunctive therapy in type 1 diabetes.

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Intensive insulin therapy delays/prevents complications associated with type 1 diabetes (1,2). However, insulin monotherapy fails to achieve normoglycemia (3). Postprandial hyperglycemia and hypoglycemia (4,5) continue to create impediments to management. Even the closed-loop system fails to normalize postprandial hyperglycemia (6). Additional therapies to insulin are needed to achieve optimal glycemic control.

Glucagon-like peptide (GLP)-1 is an incretin secreted in response to nutrient ingestion (7). Physiological GLP-1 enhances insulin secretion, delays gastric emptying, and suppresses glucagon. But because of its short half-life (8), it is unsuitable for clinical application.

Exenatide is a long-acting GLP-1 receptor agonist and acts similarly to native GLP-1 (9). Exenatide is effective in decreasing postprandial hyperglycemia in type 2 diabetes (10). However, there are few studies using exenatide in type 1 diabetes and none in adolescents. The objective of our study was to examine the effect of adjuvant premeal exenatide and insulin on postprandial glucose in type 1 diabetes and establish an effective and safe glucose-lowering dose.

RESEARCH DESIGN AND METHODS

— Study was performed with Baylor College of Medicine Institutional Review Board approval, and informed consent was obtained in accordance with federal/institutional guidelines.

Subjects with type 1 diabetes using multiple daily injections or insulin pump, aged 13–22 years, with diabetes for ≥1 year, BMI <90th percentile for age, hemoglobin >12 g/dl, and hemoglobin A1C <8.5% were recruited. One subject had treated hypothyroidism with no other chronic conditions. Subjects were not on any concomitant medications, which affected blood glucose concentrations. Pregnant/lactating females were excluded. Two subjects failed screening. One subject had hypoglycemia needing rescue glucose boluses with insulin alone and did not participate in further studies.

Eight subjects completed the three-part study. Followed by a baseline study with insulin alone, subjects were randomized to two different doses of exenatide (1.25 and 2.5 μg), administered in a double-blinded randomized controlled manner. Studies were at least 3 weeks apart. All subjects had type 1 diabetes (antibody positive), with minimal or no endogenous C-peptide response to meals. (A pilot study done previously suggested that higher doses [7–10 μg] of exenatide used in normal BMI subjects with type 1 diabetes resulted in hypoglycemia, and hence the lowered doses were examined.)

Baseline

At 0800 h, the prebreakfast insulin bolus was administered based on patient's usual insulin-to-carbohydrate ratio. Postbolus, subjects drank 12 ounces of a standard liquid meal (Boost High Protein Drink, 360 calories, 50 g carbohydrates, and 12 g fat), enriched with 1 g of [^{13}C]glucose within 10 min. Breath samples for $^{13}CO_2$ analysis were collected in duplicates at 17 time points until 1300 h. Usual insulin basal rates or glargine were maintained during study.

On the days subjects received the study drug of 1.25 μg (~0.02 μg/kg) or 2.5 μg (~0.04 μg/kg) exenatide along with insulin, the prandial insulin was reduced by 20%.

Measurements

Plasma glucose was measured using a bedside YSI glucose analyzer (2300 Stat Plus; Yellow Springs Instruments, Yellow Springs, OH) throughout the study at regularly timed intervals. Blood samples were collected pre- and postprandially for exenatide, insulin, C-peptide, GLP-1, and glucagon. Blood was processed as previously described elsewhere (11).

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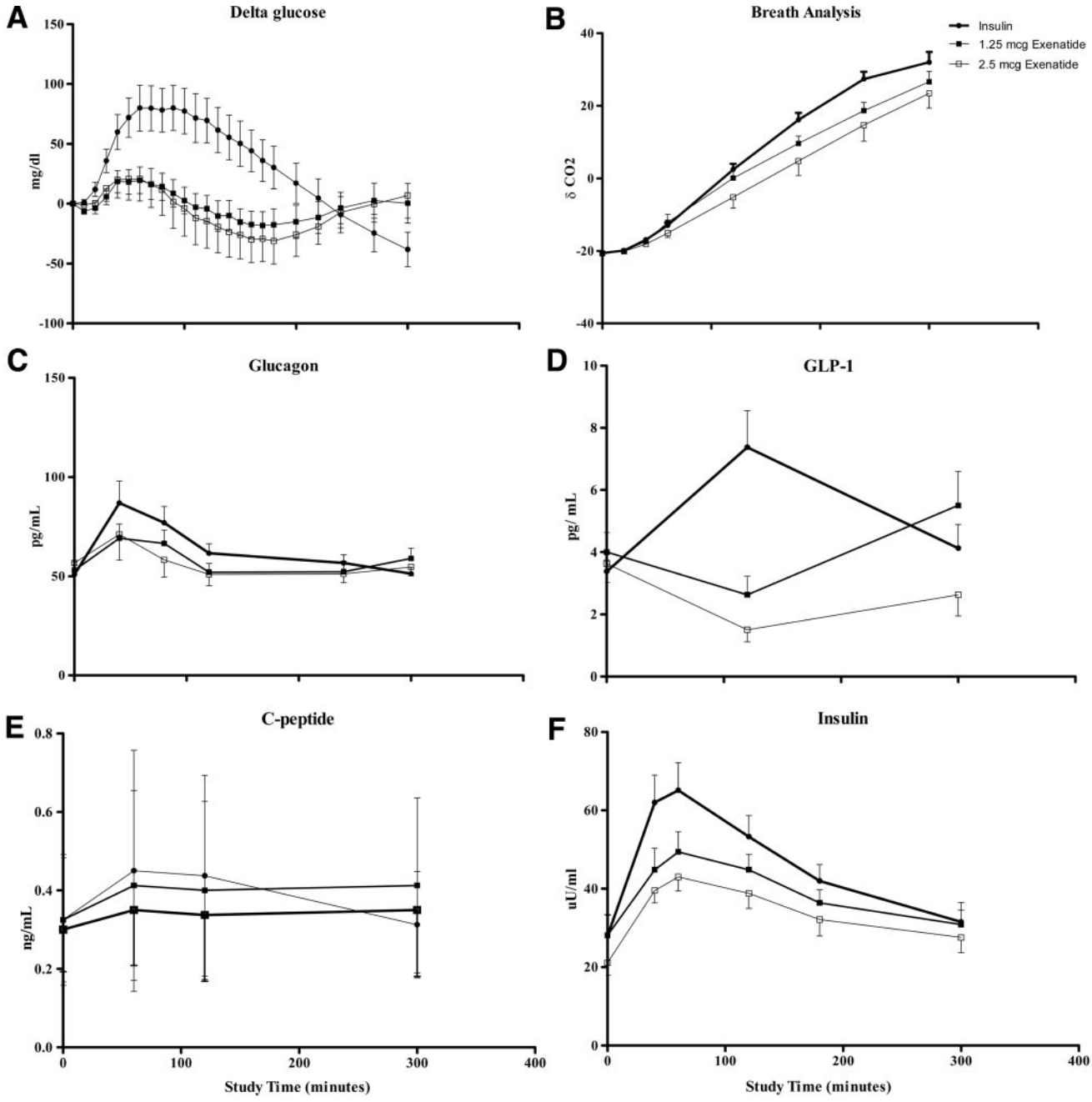

Figure 1— *Glucose* (A)*, breath analysis* (B)*, glucagon* (C)*, GLP-1* (D)*, C-peptide* (E)*, and insulin* (F) *concentrations with insulin monotherapy* (●)*, 1.25 μg* (■) *and 2.5 μg of exenatide* (□) *after a mixed meal.*

The DCA 2000 Hemoglobin A1C System (Bayer, Elkhart, IN) was used for measuring the percentage concentration of hemoglobin A1C.

Hormonal analysis and $^{13}CO_2$ was measured as previously described elsewhere (12).

Statistical analysis

Repeated-measures ANOVA models were applied for each variable. If treatment effect was significant, then pairwise comparisons in treatment means were made among three groups with Tukey's multiple comparison procedure adjustment. The analyses were performed using SAS version 9.2.

Graphs were generated using Graph Pad Prism version 5 (Graph Pad Software, San Diego, CA). Area under the curve was calculated using the trapezoidal rule. Data were considered significant at $P < 0.05$.

RESULTS — Subjects were 17 ± 1 years (range 15.8–18), had diabetes for 5 ± 3.3 years, weighed 67 ± 8.7 kg, had a BMI of 23.8 ± 2.1 kg/m^2, had an A1C of 7.4 ± 0.7%, and had a total daily insulin dose of 0.9 ± 0.2 units/kg/day.

Postprandial hyperglycemia was reduced with 1.25 and 2.5 μg adjunctive exenatide versus insulin monotherapy ($P < 0.0001$) (Fig. 1). Delta plasma glucose area under the curve ($AUC_{0–120}$) was reduced in the early postprandial period in studies with 1.25 μg (49 ± 156 mmol/l per min) ($P < 0.008$) and 2.5 μg (44 ± 281 mmol/l per min) exenatide versus insulin alone (379 ± 259 mmol/l per min) ($P < 0.007$).

Gastric emptying as measured by $^{13}CO_2$ in breath was significantly delayed with 1.25 μg exenatide versus insulin alone ($P < 0.004$) and 2.5 μg exenatide when compared with insulin monotherapy ($P < 0.0001$).

Glucagon and C-peptide concentrations were not statistically different between studies using exenatide versus insulin alone ($P < 0.1$ and $P < 0.06$, respectively). GLP-1 was lower with 2.5 μg exenatide compared with insulin ($P < 0.0001$) but not with 1.25 μg exenatide ($P < 0.2$).

Insulin levels were lower between exenatide groups versus insulin alone ($P < 0.0001$), as expected with a 20% reduction in insulin.

Adverse events

One subject had nausea with both exenatide doses and received ondansetron, and another had nausea with the 2.5-μg dose; none had emesis. One subject who was hypoglycemic at the outset of the study (3.3 mmol/l) had further hypoglycemia after injection of 1.25 μg exenatide, reaching a nadir of 3.1 mmol/l, and received one intravenous bolus of glucose.

CONCLUSIONS

Our study demonstrates reduction in postprandial glucose after exenatide injection in adolescents with type 1 diabetes. These effects were associated with delayed gastric emptying, and the results are consistent with published studies in adults (13,14). However, as opposed to previous reports, glucagon suppression was not noted with exenatide, which could be because of the small sample size of our study.

Both exenatide doses were comparable in reducing postprandial glucose excursions, and hence the lower dose could be tested as an initial dose and titrated to response and tolerability in a larger cohort of subjects. Pharmacokinetic data are included in the online appendix (available at http://care.diabetesjournals.org/cgi/content/full/dc09-1959/DC1), and data are comparable to adults. Caution must be exercised if blood glucose is low to omit exenatide or use lowered insulin and/or exenatide dose.

In conclusion, adjunctive exenatide therapy has therapeutic potential in adolescents with type 1 diabetes. Further studies are ongoing using exenatide for a 4-month period.

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