Original Research

Once-Weekly Exenatide as Adjunct Treatment of Type 1 Diabetes Mellitus in Patients Receiving Continuous Subcutaneous Insulin Infusion Therapy

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Abstract

Objective: The use of once-weekly exenatide in type 2 diabetes mellitus is well supported, but little is known about its effectiveness in type 1 diabetes. The objective of this study was to determine the clinical efficacy of once-weekly exenatide on glycemic control in patients with type 1 diabetes when added to basal-bolus insulin therapy.

Methods: For this retrospective study, patients with type 1 diabetes, aged 18 years and older, receiving continuous subcutaneous insulin infusion, using a continuous glucose monitoring device or regularly measuring blood glucose levels and receiving 2 mg of exenatide once weekly for at least 3 months were included. Demographic information, glycated hemoglobin (A1C), body weight, body mass index, systolic and diastolic blood pressures, total daily insulin dose, basal and bolus insulin doses, 28-day continuous subcutaneous insulin infusion glucose average and incidence of hypoglycemia were collected at baseline and 3 months after beginning therapy with once-weekly exenatide.

Results: An electronic medical record search identified 11 patients with type 1 diabetes who met the inclusion criteria. Comparing baseline and 3 months after initiation of once-weekly exenatide revealed reductions of 0.6% in A1C ($p = 0.013$), 3.7% in body weight ($p = 0.008$), 1.7 kg/m$^2$ in body mass index ($p = 0.003$), 13% in total daily insulin dose ($p = 0.011$) and 9.3 units in bolus insulin dose ($p = 0.015$).

Conclusions: This study revealed that the addition of once-weekly exenatide to insulin therapy for type 1 diabetes patients leads to significant improvements in A1C, body weight, body mass index and insulin doses.

Résumé

Objectif : L'utilisation de l'exénatide une fois par semaine pour traiter le diabète de type 2 est bien approuvée, mais on en connaît peu sur son efficacité pour traiter le diabète de type 1. L'objectif de cette étude était de déterminer l'efficacité clinique de l'exénatide une fois par semaine sur la régulation glycémique des patients atteints de diabète de type 1 lorsqu'il est ajouté à l'insulinothérapie selon le schéma basal-bolus.

Méthodes : Dans cette étude rétrospective, les patients atteints du diabète de type 1 de 18 ans et plus, qui reçoivent une perfusion sous-cutanée continue d'insuline, utilisent un dispositif de surveillance de la glycémie en continu ou mesurent régulièrement les concentrations de glycémie, et reçoivent 2 mg d'exénatide une fois par semaine durant au moins 3 mois ont été inclus. L'information démographique, l'hémoglobine glyquée (A1c), le poids corporel, l'indice de masse corporelle, les pressions artérielles systolique et diastolique, la dose totale quotidienne d'insuline, les doses d'insuline selon un schéma basal et bolus, la moyenne glycémique de la perfusion sous-cutanée continue d'insuline durant 28 jours et la...
Introduction

The control of glucose homeostasis in patients with type 1 diabetes is difficult as their beta-cell function is negligible. The deficiency in generating insulin or amylin in these patients leads to an inability to naturally compensate for their variable physiological insulin requirements and suppress postprandial glucagon. Their exogenous insulin boluses injected may not match their dosage requirements and bioavailability. Furthermore, in the near absence of insulin and amylin secretion by beta cells, the physiological postprandial inhibition of glucagon secretion by alpha cells likely does not occur in patients with type 1 diabetes, leading to hyper-glucagonemia (1,2). Currently, there are limited data available regarding postprandial glucagon secretion and incretin pathophysiology in patients with type 1 diabetes (1,3). It is essential that this area be investigated further as the erratic and often uncontrollable patterns of glucose concentrations in these patients may be due to hyperglucagonemia (1,2).

Clinically, there is a well-established role for the use of incretin mimetics in patients with type 2 diabetes. However, it is only recently that small studies have begun exploring the role of glucagon-like peptide-1 (GLP-1) agonists in patients with type 1 diabetes. Dupré et al (3) showed that activation of the GLP-1 receptor improves postprandial hyperglycemia in patients with type 1 diabetes, possibly through the suppression of glucagon secretion. Similarly, Raman et al (4) demonstrated a reduction in postprandial glucose after a single twice-daily exenatide injection in adolescents with type 1 diabetes. Kielgast et al (5) demonstrated that a month of treatment with liraglutide (titrated up to 1.2 mg daily after 1 week of 0.6 mg daily) reduced insulin doses without a negative impact on overall glycemic control in patient with type 1 diabetes. Most recently, Varanasi et al (6) showed improved glucose concentrations and less glycemic excursions in adults with type 1 diabetes within 1 week of starting liraglutide 0.6 mg daily.

The aim of our study was to determine the clinical effects of once-weekly exenatide as add-on therapy to insulin in patients with type 1 diabetes. In addition to enhanced glycemic control, we hypothesized that the administration of once-weekly exenatide would lead to improvements in other markers of diabetes management, such as blood pressure and body weight.

Methods

This retrospective observational study was conducted at an ambulatory care endocrinology office affiliated with the Rochester General Health System located in Rochester, New York. After obtaining appropriate protocol approval from the Institutional Review Boards at both Rochester General Health System and St. John Fisher College, subjects were identified, and all pertinent information was gathered utilizing an electronic medical record system search. Patients with type 1 diabetes aged 18 years and older, who were receiving continuous subcutaneous insulin infusion (CSII) and using a continuous glucose monitoring system (CGMS) device or regularly (at least 3 times daily) measuring their blood glucose levels, and who received 2 mg of exenatide once weekly for at least 3 months were included. Patients were excluded if they had been diagnosed with type 1 diabetes for less than 6 months, had lack of documented C-peptides or glumatic acid decarboxylase (GAD) antibodies or documented detectable C-peptides or negative GAD antibodies, use of once-weekly exenatide for less than 3 months or a lack of follow-up data.

For patient records meeting all study criteria, data were collected at the initiation of once-weekly exenatide (baseline) and 3 months after once-weekly exenatide initiation. Data collection included demographic information (age, gender, ethnicity, height, duration of type 1 diabetes, C-peptide and GAD antibody levels) and the following medical information: body weight (in kg) using a calibrated in-office scale, body mass index (BMI), glycated hemoglobin (A1C) obtained from one of the Rochester General Health System laboratories, blood pressure (BP) measured manually by office nurses, total daily insulin dose (TDD), basal and bolus insulin doses (in number of units and as a percentage of TDD) (data obtained from 28-day Carelink upload at baseline and 3-month follow-up appointment), CSII blood glucose average over 28 days and hypoglycemia incidence over 28 days (obtained from 28-day Carelink upload as above). Hypoglycemia was defined as a documented blood glucose of <3.9 mmol/L.

Statistical analysis

Differences in each variable were determined using a paired t test and SigmaPlot 11.0 software (SyStat Software, San Jose, CA) and expressed as mean ± SD. Changes were considered statistically significant with a p value of less than 0.05. Body weight and TDD were each expressed as a percentage of baseline, as baseline values for individual patients were highly variable.

Results

The electronic medical record search identified 101 patients receiving once-weekly exenatide therapy. Of these, 29 patients had type 1 diabetes, and the remaining 72 patients had type 2 diabetes. Eleven of the 29 patients with type 1 diabetes met the remaining study criteria. The average duration of follow up was 90 ± 8 days, mean age was 53 ± 11.1 years, average duration of diabetes was 39 years (range 11 to 49 years), median age at diagnosis was 17 years (range 2 to 54 years), 4 patients used a CGM device, 8 patients were female and all 11 were Caucasian. All patients had documented negative (<0.1 ng/mL) C-peptide and positive (>5 IU/mL) GAD antibody levels.

Eighteen of the 29 patients with type 1 diabetes did not meet the inclusion criteria owing to either multiple daily insulin injections (n = 2), never having started treatment with
Table 1

Combined results of all measures at each time point

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>3 Months</th>
<th>p Value (paired t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A1C, %</td>
<td>7.7±0.95</td>
<td>7.0±0.62</td>
<td>0.013</td>
</tr>
<tr>
<td>Body weight, % of baseline</td>
<td>100±0</td>
<td>96±3.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.8±5.1</td>
<td>28.1±4.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Total daily insulin dose, % of baseline</td>
<td>100±0</td>
<td>87±1.29</td>
<td>0.011</td>
</tr>
<tr>
<td>Bolus insulin, units</td>
<td>24.4±12.4</td>
<td>16.6±7.7</td>
<td>0.015</td>
</tr>
<tr>
<td>Basal insulin, units</td>
<td>22.1±13.5</td>
<td>25.4±21.7</td>
<td>0.312</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121.6±12.8</td>
<td>115.3±17.0</td>
<td>0.217</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>69.5±11.0</td>
<td>62.5±9.3</td>
<td>0.055</td>
</tr>
<tr>
<td>28-day CSII blood glucose average, mmol/L</td>
<td>10.4±1.4</td>
<td>9.8±2.2</td>
<td>0.114</td>
</tr>
<tr>
<td>28-day hypoglycemia incidence, number of episodes</td>
<td>9.3±5.3</td>
<td>13.0±10.9</td>
<td>0.251</td>
</tr>
</tbody>
</table>

CSII, Continuous subcutaneous insulin infusion.

- All comparisons are baseline versus 3 months after initiation; p < 0.05 considered statistically significant.

once-weekly exenatide despite it being prescribed (n = 4), less than 3 months of treatment or lack of follow-up data (n = 12). Of these 12 patients, 3 discontinued once-weekly exenatide before completing 3 months of therapy. Their reasons for discontinuation varied: bothersome nodule formation (n = 1) gastrointestinal intolerance (n = 1) and discontinuation with no additional explanation (n = 1).

Statistically significant reductions in A1C, body weight and BMI were observed at 3 months after once-weekly exenatide initiation in comparison with baseline values (Table 1). The A1C was reduced by 0.6% at 3 months (p = 0.013). The average reduction in body weight and BMI at 3 months was 3.7% (p = 0.008) and 1.7 kg/m² (p = 0.003), respectively. In addition, there was a statistically significant reduction of 13% in the TDD of insulin compared with baseline dose (p = 0.011). The average reduction in the dose of bolus insulin was 7.8 units (p = 0.015), with an average increase in the required basal insulin dose of 3.3 units (p = 0.0312) over the 3-month study duration. There were no statistically significant changes in mean systolic BP (6.3 mm Hg; p = 0.217) or diastolic BP (7 mm Hg; p = 0.055), and during this time there were no changes in any antihypertensive medication regimens. In addition, the 28-day CSII blood glucose average decreased by 0.684 mmol/L (p = 0.114) and the 28-day incidence of hypoglycemia increased by 3.7 episodes (p = 0.251); average hypoglycemic blood glucose 2.6 mmol/L [range 2 to 3.3 mmol/L] and 2.5 mmol/L [range 2 to 3.7 mmol/L] at baseline and follow up, respectively), neither of which were statistically significant. There were no documented hospitalizations, emergency department visits or third-party interventions for hypoglycemia of any of the study patients during the follow-up period.

Discussion

To our knowledge, this is the first study evaluating the use of once-weekly exenatide as adjunct treatment of patients with type 1 diabetes. Incretin therapy has been shown to reduce glycemic variability, insulin doses or weight in both type 1 diabetes and type 2 diabetes (1.4–8). Despite these promising data, incretin therapy for type 1 diabetes is not standard of care. On an individualized basis, patients were prescribed once-weekly exenatide based on clinical indication (glycemic variability, n = 10; consistent postprandial hyperglycemia, n = 7; gastrointestinal intolerance to liraglutide or twice-daily exenatide, n = 4; or glycemic improvement on previous incretin therapy with the desire for once-weekly administration, n = 2).

Given the elevated baseline A1C level of our patients (7.7±0.95%) and delayed onset of action of once-weekly exenatide, we did not perform any empiric reduction in insulin doses as was done in previous studies of liraglutide in patients with type 1 diabetes (5–7). Before receiving a prescription for once-weekly exenatide and training on proper administration technique, all patients had documented in their medical records that they were well versed in carbohydrate counting, the use of their CSII (without or with CGM) devices and performed blood glucose testing a minimum of 4 times daily. As is standard practice for our patients with type 1 diabetes, all patients were instructed to decrease their basal rates, carbohydrate counting ratios and correction factors as needed to avoid or minimize hypoglycemia (9 patients made at-home adjustments) and to call our triage nurse during business hours or the on-call physician after hours should they need any assistance adjusting their doses (1 patient called for assistance). In addition, adjustments to CSII settings were made at their 3-month follow-up appointment as needed (n = 10).

The results of our study showed rapid reductions in A1C, body weight and BMI at 3 months after initiation of once-weekly exenatide. These results are consistent with previous reports of incretin therapy in patients with type 1 diabetes (3–6). In addition, there was a significant reduction in TDD of insulin with a significant reduction in bolus insulin (as a percentage of TDD) at 3 months after once-weekly exenatide initiation. Because of the highly variable baseline insulin doses for analysis, we calculated the change in TDD as a percentage of baseline. There was an average reduction of 9.3±9.1 units in bolus dose and little change in the number of basal units (average increase of 0.9±9.7 units). It is documented that GLP-1 receptor agonists reduce postprandial glucagon secretion from alpha cells, resulting in lower postprandial glucose concentrations (8). This effect may have played a key role in the significant reduction in bolus insulin seen in this study.

Although no significant changes were seen in systolic BP, diastolic BP or 28-day CSII blood glucose average, downward trends were observed after once-weekly exenatide initiation. In addition, 28-day incidence of hypoglycemia, measured by the number of episodes, showed a nonsignificant trend upward after initiation of therapy. With a sample size of only 11 patients, it is likely that our study was underpowered to detect significant changes in any of these measures.

Although not the original intention of this study, we believe it is important to consider the tolerability of once-weekly exenatide in patients with type 1 diabetes. Of the 11 patients included in our study, 5 patients discontinued therapy before 6 months of treatment. Their reasons for discontinuation included complaints of bothersome nodule formation (n = 4; 1 of these 4 patients also complained of gastrointestinal intolerance) and discontinuation with no additional explanation (n = 1). There are no head-to-head studies comparing the tolerability of GLP-1 agonists in patients with type 1 diabetes, but studies with liraglutide have shown low discontinuation rates due to adverse reactions (5,6). The 45.5% discontinuation rate seen in this study by 6 months of treatment with once-weekly exenatide may indicate poor tolerability by this patient population despite the positive changes in glycemic control. Future studies including expanded patient populations with a longer treatment duration are warranted to better evaluate the effect of once-weekly exenatide on tolerability and nonglycemic parameters in patients with type 1 diabetes.

The mechanism of once-weekly exenatide’s efficacy in type 1 diabetes is likely 3-fold. First, exogenous incretin therapy decreases postprandial glucagon secretion from alpha cells. In the absence of beta-cell function, insulin and amylin secretion in patients with type 1 diabetes, there is likely a loss of inhibition of postprandial glucagon secretion, leading to severely elevated postprandial glucagon and blood glucose levels that cannot be accounted for by...
carbohydrate intake alone (1,8). Exogenous incretin therapy is also known to delay gastric emptying and increase satiety (8). By slowing the rate of carbohydrate absorption after a meal, post-prandial blood glucose levels do not rise as high or as rapidly. That could potentially allow the onset, peak and duration of exogenously administered rapid-acting insulin to more closely mimic that of the postprandial glycemic excursion and further minimize hyperglycemia. Lastly, increasing satiety and subsequent appetite suppression allows for less carbohydrate intake and consequently lower insulin requirements, attenuated postprandial blood glucose excursions and ultimately weight loss. The roles of glucagon secretion, delayed gastric emptying and increased satiety in the treatment of type 1 diabetes provide additional areas for research, as these appear to be promising new targets in the management of type 1 diabetes.

We acknowledge that this study may have potential limitations. First, as it was a retrospective observational study, we are unable to conclude cause and effect; however, our results are similar to those previously published on the use of exogenous incretin treatment in type 1 diabetes (5,6). Secondly, potential significant changes in some measures may have been missed owing to our small sample size. Lastly, given the entirely Caucasian study population, it would be difficult to generalize these observations to a more diverse population. Future research, ideally prospective, double-blind, randomized, placebo-controlled studies with a larger patient population, is needed to evaluate patients with type 1 diabetes from a variety of ethnicities and for treatment duration beyond 3 months.

In conclusion, once-weekly exenatide added to insulin therapy for patients with uncontrolled type 1 diabetes leads to significant reductions in A1C, body weight and BMI. It also leads to a significant reduction in TDD and bolus insulin dose. These results corroborate the need for further investigation into the long-term safety and efficacy of adjunct incretin mimetic therapy for patients with type 1 diabetes.

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Author Disclosures

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Author Contributions

ANT contributed substantially to conception and design, acquisition of data, analysis and interpretation of data, drafted the article, revised it critically for important intellectual content and gave final approval of the version to be published. MEL contributed substantially to conception and design, analysis and interpretation of data, revised the article critically for important intellectual content and gave final approval of the version to be published. ACH contributed substantially to the acquisition of data, analysis and interpretation of data, drafted the article, revised it critically for important intellectual content and gave final approval of the version to be published. TMZ contributed substantially to conception and design, revised the article critically for important intellectual content and gave final approval of the version to be published. JL-P contributed substantially to conception and design, revised the article critically for important intellectual content and gave final approval of the version to be published.

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