# Effect of Pramlintide on Prandial Glycemic Excursions During Closed-Loop Control in Adolescents and Young Adults With Type 1 Diabetes

Stuart A. Weinzimer, MD[1]
Jennifer L. Sherr, MD[1]
Eda Cengiz, MD[1]
Grace Kim, MD[1]
Jessica L. Ruiz[1]
Lori Carria, BS[1]
Gayane Voskanyan, PHD[2]
Anirban Roy, PHD[2]
William V. Tamborlane, MD[1]

**OBJECTIVE**—Even under closed-loop (CL) conditions, meal-related blood glucose (BG) excursions frequently exceed target levels as a result of delays in absorption of insulin from the subcutaneous site of infusion. We hypothesized that delaying gastric emptying with preprandial injections of pramlintide would improve postprandial glycemia by allowing a better match between carbohydrate and insulin absorptions.

**RESEARCH DESIGN AND METHODS**—Eight subjects (4 female; age, 15–28 years; A1C, 7.5 ± 0.7%) were studied for 48 h on a CL insulin-delivery system with a proportional integral derivative algorithm with insulin feedback: 24 h on CL control alone (CL) and 24 h on CL control plus 30-μg premeal injections of pramlintide (CLP). Target glucose was set at 120 mg/dL; timing and contents of meals were identical on both study days. No premeal manual boluses were given. Differences in reference BG excursions, defined as the incremental glucose rise from premeal to peak, were compared between conditions for each meal.

**RESULTS**—CLP was associated with overall delayed time to peak BG (2.5 ± 0.9 vs. 1.5 ± 0.5 h; $P < 0.0001$) and reduced magnitude of glycemic excursion (88 ± 42 vs. 113 ± 32 mg/dL; $P = 0.006$) compared with CL alone. Pramlintide effects on glycemic excursions were particularly evident at lunch and dinner, in association with higher premeal insulin concentrations at those mealtimes.

**CONCLUSIONS**—Pramlintide delayed the time to peak postprandial BG and reduced the magnitude of prandial BG excursions. Beneficial effects of pramlintide on CL may in part be related to higher premeal insulin levels at lunch and dinner compared with breakfast.

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External closed-loop (CL) artificial pancreas systems, consisting of insulin infusion pumps, transcutaneous continuous glucose sensors, and controller algorithms to regulate the rate of insulin delivery automatically, have emerged as one of the most promising technologies for the care of people with type 1 diabetes. Short-term, inpatient studies have demonstrated the general feasibility of the CL approach, especially in achieving safe and effective night-time glucose control (1–7). Performance of CL systems for mealtime control has proved more difficult, however, in great part because of the limitations imposed by use of the subcutaneous route of insulin delivery. Systems that respond to meals only when sensor glucose levels begin to rise are inevitably associated with delays in insulin absorption and action and result in exaggerated increases in glucose levels immediately after meals, as well as a tendency toward hypoglycemia in the late postprandial period. Approaches that attempt to anticipate the increased demand for mealtime insulin by giving premeal priming doses of insulin may succeed in reducing prandial glucose excursions (2,5) but require manual inputs, thereby detracting from the goal of a fully autonomous system.

To improve the performance of a CL system around mealtimes, a potential alternative to accelerating insulin appearance would be to delay carbohydrate appearance. This strategy would theoretically slow the gastrointestinal carbohydrate absorption and allow the system to deliver insulin, with its slower absorption characteristics, with a more optimal timing. Pramlintide, an analog of the naturally occurring β-cell peptide amylin, has been introduced as an adjunct to insulin in patients with type 1 diabetes. It has been shown to be effective in reducing postprandial glucose excursions and A1C levels in patients with type 1 and type 2 diabetes (8–15), presumably through the mechanism of delaying gastric emptying and slowing carbohydrate appearance (16,17). An additional mechanism may involve lowering of plasma glucagon levels (18–20). Preliminary studies have suggested similar mechanisms (21–24) and efficacy (25) in adolescents with type 1 diabetes. We hypothesized that the ability of pramlintide to delay gastric emptying and slow carbohydrate appearance would improve the performance of an external CL system in controlling meal-stimulated glucose excursions by enabling a better match between carbohydrate and insulin absorption.

## RESEARCH DESIGN AND METHODS

### Study subjects and enrollment

Eleven subjects meeting the following enrollment criteria were recruited from the Yale Type 1 Diabetes Program and local advertising: age, 15–30 years; clinical diagnosis of type 1 diabetes of at least 1 year's duration; current use of insulin pump

From the [1]Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; and [2]Medtronic Diabetes, Northridge, California.
Corresponding author: Stuart A. Weinzimer, stuart.weinzimer@yale.edu.
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therapy; A1C, <9%; BMI, <95th percentile for age and sex; normal hematocrit and serum creatinine level; no other chronic medical condition (except treated hypothyroidism); no history of celiac disease, gastroparesis, or other disorder of intestinal absorption or motility; and no medications (other than insulin) known to affect blood glucose level (BG) or gastrointestinal motility. After a complete explanation of study procedures, written informed consent was obtained in subjects 18 years or older; for subjects under 18 years of age, written parental permission and subject assents were obtained. The study was approved by the Yale University Human Investigation Committee. Two subjects withdrew consent before any study procedures were conducted, and one subject had ketosis develop as a result of a site failure on the day of admission. The eight subjects (four females) who completed the study ranged in age from 15 to 28 years and had mean ± SD A1C level of 7.5 ± 0.7%.

### Subject preparation for CL studies

Subjects were admitted to the Yale-New Haven Hospital Research Unit in the afternoon on the day before the start of the study to prepare them for the CL experiments to be carried out on study days 1 and 2. Two continuous glucose sensors (the study sensor and a backup sensor) were inserted in the subcutaneous space of the anterior abdominal wall and calibrated; a new insulin infusion set was placed in the hip and buttocks region, and the home insulin pump was replaced by the study pump (Medtronic Paradigm 715). Insulin use during the previous 3–7 days was used to determine algorithm parameters that were programmed into the study computer. An intravenous catheter was placed into an arm vein to facilitate frequent blood sampling. Subjects were continued on open-loop control for dinner. A preliminary test dose of pramlintide, 15 μg by subcutaneous injection, equivalent to half the protocol dose, was given in the right or left deltoid before dinner to assess the effect of pramlintide on meal tolerance in these drug-naive subjects. After dinner, a run-in period of CL control was initiated at approximately 9:00 P.M. to achieve stable, target glucose levels at the start of the CL experiments the next morning (8:00 A.M. of study day 1). During CL control, subjects were free to move about their room and the hallway. During the CLP day, subjects received a 30-μg dose of pramlintide by subcutaneous injection in the deltoid at the time of the meal, consistent with labeled indications.

### CL study procedures

Subjects were randomly assigned to undergo one of two study sequences: CL alone on day 1 and CL with pramlintide (CLP) on day 2 or CLP on day 1 and CL alone on day 2. On both study days, identical meals were provided at 8:00 A.M., 1:00 P.M., and 6:00 P.M. Subjects chose their own meals on day 1, without limitations on calorie or carbohydrate content, and the meals chosen for day 1 were also provided on day 2, to allow accurate comparisons of the two study conditions. No snacks were allowed. For this study, no manual priming doses for meals or any other meal announcements were provided to the controller. Carbohydrate intake averaged 84 ± 26 g/meal (86 ± 22 g at breakfast, 84 ± 32 g at lunch, and 83 ± 27 g at dinner) and ranged between 23 and 138 g. Reference plasma glucose levels were measured at the bedside every 30 min during both study days with the YSI 2300 Glucose Analyzer (YSI Life Sciences, Yellow Springs, OH). Additional plasma samples were collected at 30-min intervals immediately before and for 180 min after each meal for measurement of plasma insulin levels.

### System considerations

The CL system used in this study consisted of four components: a Medtronic Paradigm 715 insulin pump, a Medtronic MiniLink REAL-Time transmitter (MMT-7703) adapted for 1-min transmission, a Medtronic Sof-Sensor (MMT-7002/7003) continuous glucose sensor, and the Medtronic external Physiological Insulin Delivery (ePID) algorithm. Algorithm calculations were performed by a laptop computer that received the glucose sensor signal each minute from a radiofrequency transmitter and delivered insulin commands to the pump by radiofrequency signaling. The ePID controller uses a proportional-integral-derivative algorithm modified to include insulin feedback (26,27). Although the system operates off one sensor, two sensors were used; control of the CL program was set to sensor 1 by default, but it could be switched to sensor 2 at the discretion of the

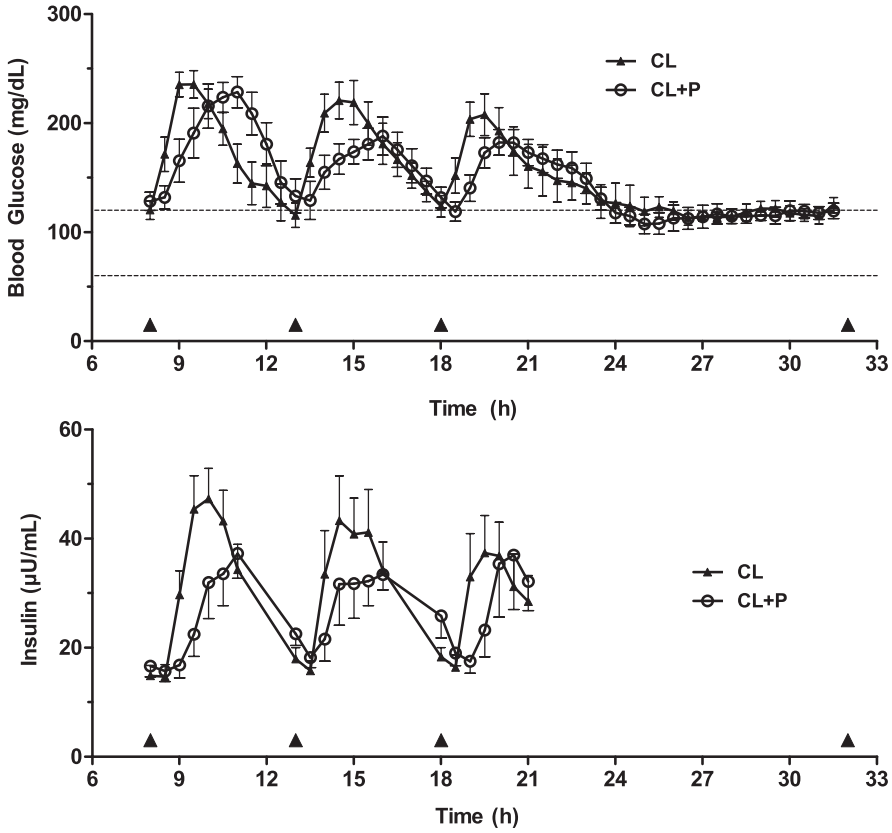


**Figure 1**—*Reference plasma glucose* (upper panel) *and insulin* (lower panel) *profiles over time during CL control (▲) and CLP (CL+P, ○). Meals are indicated by triangles along the x-axis, the system set point is indicated by the upper dashed line, and the hypoglycemia threshold is represented by the lower dashed line. Data are expressed as means with error bars representing SE.*

investigator if sensor 1's performance was noted to deteriorate markedly. Sensors were calibrated at the start of CL control and whenever reference and sensor errors exceeded 20%. Target glucose level was set to 120 mg/dL. Additional description of the CL algorithm is provided in the Supplementary Data online.

### Statistical considerations

Reference plasma glucose concentrations were used to compare differences in glucose control between the two treatment conditions, CL alone and CLP. Differences in sensor glucose levels on the two study days (8:00 A.M. to 8:00 A.M.) were also calculated because these are the glucose levels that are used by the algorithm.

Descriptive statistics were calculated for reference BG values and sensor glucose values in the CL and CLP data groups. Data are expressed as mean ± SD or SEM, as indicated. Sensor accuracy was calculated as the mean absolute relative deviation of the sensor glucose level from the reference venous glucose level for all paired points. Statistical comparisons between CL and CLP groups were accomplished with paired *t* tests for normally distributed data and Wilcoxon matched-pairs signed rank tests for nonnormally distributed data. Plasma insulin levels, available for seven of the eight completed subjects, were determined by an enzyme-linked immunosorbent assay, (Mercodia, Uppsala, Sweden), with an interassay coefficient of variation of 0.038% and an intra-assay coefficient of variation of 1.38 ± 0.4%. Calculations were performed with GraphPad Prism 5 software (GraphPad Software, Inc., San Diego, CA).

**RESULTS**—Reference plasma glucose profiles during the two days of CL control are shown in Fig. 1 (*top*) and Supplementary Fig. 1. As shown in Table 1, the CL system performed extremely well under both study conditions; plasma glucose levels averaged 153 ± 54 mg/dL in the CL condition and 149 ± 48 mg/dL in the CLP condition ($P = 0.07$). Sensor glucose levels (data not shown) were slightly lower than reference BGs in both conditions and demonstrated a significant reduction in mean glucose levels with pramlintide (143 ± 44 vs. 152 ± 47 mg/dL; $P = 0.0003$). Of plasma and sensor glucose levels, 70–75% were within the 70–180 mg/dL range, and <5% of values were <70 mg/dL. Reference plasma and sensor glucose values between 8:00 A.M. and 11:00 P.M. were significantly lower on CLP days than on CL days (Table 1).

Sensor accuracy, defined as mean absolute relative deviation, was 10.6 ± 1.6%. Sensors were recalibrated an average of 4 times per subject (range 2–7) during the 48 h of study.

**Table 1—*Reference BG and sensor glucose profiles during CL and CLP***

| | CL | CLP | *P* value |
|---|---|---|---|
| Reference glucose | | | |
| 24-h mean BG | 153 ± 54 | 149 ± 48 | 0.07 |
| <70 | 1 | 2 | |
| 70–180 | 71 | 75 | |
| >180 | 28 | 23 | |
| Mean daytime (8:00 A.M.–11:00 P.M.) BG | 173 ± 56 | 167 ± 49 | 0.04 |
| <70 | 1 | 1 | |
| 70–180 | 57 | 62 | |
| >180 | 43 | 37 | |
| Mean nighttime (11:00 P.M.–7:00 A.M.) BG | 121 ± 29 | 118 ± 26 | |
| <70 | 1 | 3 | |
| 70–180 | 94 | 96 | |
| >180 | 5 | 1 | |
| Sensor glucose | | | |
| 24-h mean sensor glucose | 152 ± 47 | 143 ± 44 | 0.0003 |
| <70 | 0 | 4 | |
| 70–180 | 75 | 76 | |
| >180 | 25 | 20 | |
| Mean daytime (8:00 A.M.–11:00 P.M.) BG | 167 ± 51 | 157 ± 50 | 0.005 |
| <70 | 0 | 5 | |
| 70–180 | 63 | 64 | |
| >180 | 37 | 32 | |
| Mean nighttime (11:00 P.M.–7:00 A.M.) BG | 128 ± 28 | 120 ± 23 | 0.01 |
| <70 | 0 | 2 | |
| 70–180 | 94 | 97 | |
| >180 | 6 | 1 | |

Data are mean ± SD and %. All BG and sensor glucose values are in milligrams per deciliter.

### Effect of pramlintide on prandial glucose excursions

As shown in Table 2, pramlintide delayed the time from meal start to peak plasma glucose level by ~1 h for each individual meal and for all meals combined ($P < 0.0001$). This effect was similar for all three meals.

Pramlintide successfully blunted overall meal-related glucose excursions by an average reduction of 25 mg/dL ($P = 0.006$). This effect was dependent on meal type, with significant reductions in glycemic excursions with pramlintide noted for lunch (average reduction of 47 mg/dL; $P = 0.02$) and dinner (average reduction of 25 mg/dL; $P = 0.04$). Notably, during CL alone, the prandial glucose excursion after dinner was lower than that after the two previous meals and plasma insulin concentrations tended to be lower before breakfast than before the next two meals (Table 2). During CLP, the prandial glucose excursion fell progressively with each meal in association with progressively higher premeal plasma insulin levels. The area under the curve (AUC) of the meal-related glucose excursion behaved similarly, with a significant overall reduction in the AUC seen with the addition of pramlintide relative to CL control alone and with a relatively greater AUC with breakfast than with lunch and dinner during CLP. The carbohydrate, protein, and fat contents of the meals are provided in Supplementary Table 1.

### Plasma insulin levels and insulin excursions

Plasma insulin levels and meal-related insulin excursions are illustrated in Fig. 1 (*bottom*) and also in Table 2. Basal, prebreakfast plasma insulin levels were similar under both study conditions; however, whereas during CL insulin levels returned to near-baseline levels by the next meal, there was a progressive rise in premeal insulin levels during CLP, such that by dinnertime premeal plasma insulin

**Table 2—*Prandial changes in glucose and insulin with meals***

| | CL | CLP | *P* value |
|---|---|---|---|
| Time to peak prandial BG (h) | | | |
| Breakfast | 1.4 ± 0.5 | 2.4 ± 0.6 | 0.04 |
| Lunch | 1.5 ± 0.5 | 2.3 ± 0.8 | 0.03 |
| Dinner | 1.5 ± 0.5 | 2.8 ± 1.3 | 0.03 |
| All meals | 1.5 ± 0.5 | 2.5 ± 0.9 | <0.0001 |
| Prandial BG excursion (mg/dL) | | | |
| Breakfast | 123 ± 39 | 120 ± 40 | 0.84 |
| Lunch | 122 ± 33 | 75 ± 32 | 0.02 |
| Dinner | 93 ± 32 | 68 ± 39 | 0.04 |
| All meals | 113 ± 32 | 88 ± 42 | 0.006 |
| BG excursion AUC (mg/dL · $h^{-1}$) | | | |
| Breakfast | 288 ± 101 | 291 ± 143 | 0.94 |
| Lunch | 313 ± 122 | 159 ± 117 | 0.05 |
| Dinner | 218 ± 119 | 156 ± 107 | 0.38 |
| All meals | 273 ± 117 | 202 ± 134 | 0.04 |
| Premeal insulin level (μIU/mL) | | | |
| Breakfast | 14.9 ± 5.0 | 16.6 ± 5.2 | 0.69 |
| Lunch | 17.9 ± 5.5 | 22.5 ± 5.5 | 0.16 |
| Change from breakfast | 3.1 ± 4.3 | 5.9 ± 6.6 | 0.58 |
| Dinner | 18.3 ± 4.6 | 25.8 ± 10.7 | 0.05 |
| Change from breakfast | 3.4 ± 3.5 | 9.2 ± 11.9 | 0.22 |
| All meals | 17.0 ± 5.0 | 21.7 ± 8.2 | 0.005 |
| Prandial insulin excursion (μIU/mL) | | | |
| Breakfast | 34.3 ± 12.6 | 24.0 ± 9.5 | 0.11 |
| Lunch | 29.2 ± 19.0 | 18.1 ± 13.3 | 0.22 |
| Dinner | 24.9 ± 18.2 | 15.8 ± 17.9 | 0.22 |
| All meals | 29.4 ± 16.4 | 19.3 ± 13.8 | 0.01 |
| Insulin excursion AUC (μIU/mL · $h^{-1}$) | | | |
| Breakfast | 47.8 ± 27.0 | 38.3 ± 24.1 | 0.38 |
| Lunch | 44.0 ± 44.7 | 25.6 ± 20.6 | 0.47 |
| Dinner | 31.8 ± 33.0 | 20.6 ± 21.3 | 0.47 |
| All meals | 41.2 ± 34.5 | 28.2 ± 22.3 | 0.11 |

Data are mean ± SD.

levels were significantly higher during CLP than during CL (25.8 ± 10.7 vs. 18.3 ± 4.6 μU/mL; $P = 0.05$). Combined for all meals, premeal insulin levels were higher during CLP than during CL (21.7 ± 8.2 vs. 17.0 ± 5.0 μU/mL; $P = 0.005$). Despite the higher premeal plasma insulin concentration, however, the magnitude of the meal-related insulin excursions was significantly less during CLP condition than during CL. The AUC of the insulin excursions were also lower during CLP, but these differences did not reach statistical significance (Table 2).

### Hypoglycemia and other adverse effects

There were no episodes of hypoglycemia (defined as BG <60 mg/dL, with or without symptoms) during the two study days. None of the subjects reported nausea, abdominal pain, bloating, distension, diarrhea, headache, or any other symptoms in response to pramlintide administration.

**CONCLUSIONS**—In this initial study of the effect of pramlintide on the performance of a CL system, we demonstrated that premeal injections of 30-μg doses given in conjunction with fully automated CL insulin delivery consistently delayed the peak postprandial glucose level and reduced the magnitude of the meal-stimulated glucose excursions in comparison with CL alone. These data are consistent with those of Chase et al. (23), who described a similar 2-h delay in the time to peak postprandial glucose in a pharmacokinetic and pharmacodynamic study of pramlintide in adolescents with type 1 diabetes who received the same 30-μg dose used in the current study. Under both of the current study conditions, glucose control was excellent. Despite meal-related increases in glucose levels, average BGs during CL and CLP were 149 and 153 mg/dL, respectively, equivalent to an A1C of about 6.8–7.0%, a clinically desirable target (28). In considering that the CL system "sees" the sensor glucose values, not the BG values, the beneficial effect of pramlintide becomes more apparent: whereas average BGs were 4 mg/dL lower during CLP than during CL, average sensor glucose levels were 9 mg/dL lower during CLP. Meal-related sensor glucose excursions were also slightly lower than corresponding BG excursions. The tendency of continuous glucose sensors to underestimate BGs during hyperglycemia has been observed in our previous study (2) and in other CL studies with other sensors. It may be reasonably argued that improvements in current sensor technologies would improve the performance of CL systems, with or without the addition of pramlintide.

It is particularly noteworthy that overall prandial glucose excursions with CLP were significantly reduced compared with CL alone, even though the slower rise in postprandial glucose levels during CLP resulted in a slower rise in postprandial insulin levels and an approximate 33% reduction in peak postprandial insulin concentrations. These data suggest that the potential benefit of pramlintide in a CL system is somewhat mitigated by corresponding reductions in insulin delivery responses of the ePID controller used in this study and that alterations in algorithm gains in the ePID controller to account for the delayed gastric emptying effect of pramlintide, such as more aggressive derivative gain, might enhance the performance of the system. The safety and effectiveness of premeal pramlintide in a "hybrid" CL system, consisting of a small manual premeal priming bolus of insulin, also remain to be established, in that potential benefits relating to earlier appearance of insulin may be offset by the risk of early prandial hypoglycemia.

Although overall glucose excursions were reduced with pramlintide, pramlintide failed to reduce the magnitude of the rise in glucose levels after breakfast, despite the similar magnitude of carbohydrate content ingested at breakfast compared with lunch and dinner. It is possible that the quality of the meal content is at least in part responsible for the differing response, as the relative contribution of calories from protein and fat were lower at breakfast than at lunch and dinner. It may be even more important that premeal plasma insulin concentrations with pramlintide were higher at lunch and dinner but not at

breakfast. Thus the delay in carbohydrate absorption induced by pramlintide after breakfast led to delays in meal-stimulated insulin delivery, resulting in higher premeal plasma insulin concentrations before lunch and dinner. Such elevations in plasma insulin levels above basal, prebreakfast values are likely to have played a key role in the blunted glucose excursions after lunch and dinner during CLP control, even if the peak glucose absorption at the next meal was similarly delayed by the effect of pramlintide. This would explain why the effect was not seen at breakfast, in which the long overnight period would have allowed insulin levels to reach a true basal state.

In the current study, the frequency of low glucose concentrations was much lower and there was less of a tendency toward hypoglycemia after dinner (the last meal of the day) than in our previous observations with the Medtronic ePID system. These differences in hypoglycemia exposure may relate to the higher daytime target glucose level that was used in this study (120 vs. 100 mg/dL) or to the addition of the insulin feedback modification to the ePID controller that reduces insulin delivery when predicted plasma insulin levels exceed desired thresholds (27,28). Insulin feedback is analogous to the "insulin on board" feature of current commercial insulin pumps by functioning as a "brake" on insulin delivery specifically to avoid late postmeal hypoglycemia. The success of the insulin feedback modification to the ePID algorithm to prevent overshoot hyperinsulinemia and late postprandial hypoglycemia might enable subsequent trials to target lower glucose set points, thereby further improving the glucose control in this CL system.

Only treatment-naive subjects were enrolled in this study of adolescents and young adults with type 1 diabetes to avoid the need to wash out pramlintide before admission to the clinical research unit. A negative aspect of this study design was that the protocol was designed to evaluate adolescent subjects, so we were limited to the lower 30-μg dose of pramlintide, as used in other adolescent studies, to minimize gastrointestinal problems and food intolerance issues. Other limitations of this study include the small sample size and the failure to measure plasma glucagon levels at mealtimes. To correct these deficiencies, a follow-up study is currently underway to assess the effects of pramlintide on CL system performance after a 2- to 3-week period of open-loop dose titration aimed at achieving maximum doses of 60 μg of pramlintide before meals. In this experiment, meal-related changes in plasma glucagon are also being compared during CL alone and during CLP.

It is obvious that manual injection of pramlintide at mealtimes markedly detracts from the convenience of a CL system and from a compliance perspective may not be well accepted by many patients. If subsequent modifications to the controller algorithm or higher doses of pramlintide demonstrate superior glucose control or glucagon suppression with pramlintide, however, strategies to incorporate pramlintide into a CL system, either with dual pump delivery, coformulation, or delayed-release preparation, may prove to be both practical and beneficial.

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S.A.W. researched data and wrote the manuscript. J.L.S. and E.C. researched data, contributed to discussion, and reviewed and edited the manuscript. G.K. and L.C. researched data. J.L.R. and G.V. researched data and reviewed and edited the manuscript. A.R. and W.V.T. contributed to discussion and reviewed and edited the manuscript. S.A.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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